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AGARD LECTURE SERIES No. 105

Sleep, Wakefulness and Circadian Rhythm

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NORTH ATLANTIC TREATY ORGANIZATION

ADVISORY GROUP FOR AEROSPACE RESEARCH AND DEVELOPMENT

(ORGANISATION DU TRAITE DE L'ATLANTIQUE NORD)

(11) Sep 79

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SLEEP, WAKEFULNESS AND CIRCADIAN RHYTHM

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The material in this publication was assembled to support a Lecture Series under the sponsorship of the Aerospace Medical Panel and the Consultant and Exchange Programme of AGARD, presented on 1–2 October 1979 London, England; 4–5 October 1979 Paris, France; 9–10 October 1979 Toronto, Canada

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FOREWORD

This Lecture Series No.105 on the subject of Sleep, Wakefulness and Circadian Rhythms is sponsored by the Aerospace Medical Panel of AGARD and implemented by the Consultant and Exchange Programme.

The Lecture Series is intended for those concerned with the management of civil, and particularly military personnel, who have to cope with irregular work and rest. It will provide an understanding of the physiological processes involved in the adaptation of man to disturbed sleep and wakefulness, and consider approaches to the problem of management including the use of drugs.

The lectures will fall into three subject categories:

Sleep, wakefulness and circadian rhythms. Physioiogical and psychological aspects.
Adaptation of man to disturbed sleep and circadian rhythmicity.
Managment of irregular rest and activity.

In the first part attention will be given to the physiological basis of sleep, wakefulness and circadian rhythms and the psychological correlates including performance relevant to personnel in.olved in skilled activity. The second part will review studies on the adaptation of man to unusual patterns of rest and activity with special reference to present day situations, and the third part will attempt to provide a basis for the management of disturbed rest and the rationality for the use of drugs.

The series is designed for a wide range of interests in both the civil and military context, and for the land, sea and air environments. It is intended that the participants will include managers and operations staff as well a. medical officers.

Wing Commander A N.NICHOLSON

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RYTHMES CIRCADIENS ET CIRCANNUELS CHEZ L'HOMME ADULTE SAIN

par

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RESUME

Les résultats des mesures de processus physiologiques chez les êtres vivants, y compris l'Homme, ne sont pas constants en fonction du temps: des variations régulières et prévisibles ayant une période τ d'environ 24 heures (rythmes circadiens), d'environ 1 an (rythmes circannuels), etc. peuvent être détectés objectivement. Chaque rythme mis en évidence peut être caractérisé par l'estimation de paramètres qui sont: l'acrophase Φ (situation temporelle du sommet), l'amplitude $\underline{A}$, le mésor M (moyenne ajustée du rythme).

L'estimation de τ, Φ, $\underline{A}$ et M d'un ensemble de variables étudiées dans des conditions expérimentales, spécifiées, conduit à représenter un aspect de l'organisation temporelle ou de la structure temporelle biologique. Les buts de la chronobiologie sont de quantifier et de rechercher objectivement les mécanismes des structures temporelles biologiques. Les rythmes biologiques et l'organisation temporelle qui en dépend, ont une origine génétique. Cependant, un ou plusieurs paramètres des rythmes peuvent être influencés par les variations cycliques de facteurs de l'environnement (synchroniseurs ou Zeitgeber). Ce dernier fait a des conséquences pratiques puisqu'un changement de phase des synchroniseurs peut résulter de vols transméridiens, du travail de nuit ou du travail posté.

La chronobiologie appliquée comprend aussi l'étude des variations rythmiques d'activités endocriniennes (chronoendocrinologie) et des effets des médicaments (chronopharmacologie).

LES RYTHMES BIOLOGIQUES CONSIDERES COMME UN PHENOMENE ADAPTATIF AUX VARIATIONS PREVISIBLES DE FACTEURS DE L'ENVIRONNEMENT

L'étude quantitative des rythmes biologiques montre que tout processus biophysique ou biochimique varie en fonction du temps de manière périodique et prévisible (Aschoff[1], Bünning[2], Halberg[3]). Nous savons aujourd'hui que l'activité rythmique est une propriété fondamentale de la matière vivante (Reinberg, Ghata[4]). Des rythmes biologiques peuvent être démontrés chez tous les êtres vivants depuis les unicellulaires nucléés jusqu'à l'Homme et à tous les niveaux: l'organisme entier, les systèmes d'organes, les organes, les tissus, les cellules et le matériel sub-cellulaire. Les rythmes biologiques montrent des propriétés fondamentales similaires chez les plantes et les animaux:

- ils ont une origine génétique;
- ils persistent en l'absence de signaux et d'informations temporelles;
- ils peuvent être caractérisés pour une espèce donnée (par exemple le Rat, la Souris, l'Homme) tout en gardant à l'esprit que des différences inter-individuelles peuvent être démontrées (par exemple différences entre des souches génétiques de souris. Halberg et al.[5], différences entre jumeux dizygotes et monozygotes chez l'Homme (Barcal et al.[6])

Ils peuvent être influencés par les variations cycliques de certains facteurs de l'environnement appelés synchroniseurs ou Zeitgeber.

Tout se passe comme si ces changements biopériodiques résultent au moins en partie, de phénomènes d'adaptation à des variations prévisibles d'un ensemble de facteurs directement liés à la rotation de la terre autour de son axe (en environ 24 heures) ou autour du soleil (en environ 365,25 jours). En fait, les exemples illustrant l'organisation temporelle d'êtres vivants concernent principalement (mais non exclusivement) les domaines circadiens et circannuels des rythmes biologiques. (Des phénomènes biopériodiques avec une période τ d'environ 7 jours, d'environ 1 mois, etc. ont été mis en évidence. Halberg[3]; Smolensky et al.[7], mais de manière moins étendue que celle des rythmes circadiens et circannuels).

Quand on considère les rythmes biologiques comme un phénomène adaptatif aux variations prévisibles des facteurs de l'environnement, deux possibilités doivent être prises en considération. La première concerne une espèce donnée, sa survie à travers de nombreuses générations et son évolution probable. La seconde concerne un individu donné de l'espèce considéré, ce sujet étant confronté aux manipulations cycliques et non cycliques de facteurs de l'environnement, y compris celle des synchroniseurs. Une meilleure compréhension des rythmes biologiques peut être obtenue en comparant, d'une part les propriétés des rythmes à travers les espèces (Edmunds[8], Bünning[9]) et en étudiant, d'autre part, la tolérance individuelle aux effets des manipulations des synchroniseurs (Halberg et al.[3,5,10], Hayes[11], Aschoff[12,13], Reinberg: tolérance au travail posté: Cf. le rapport consacré à ce problème dans le présent ouvrage).

L'organisation circadienne de l'Homme (et probablement son organisation circannuelle) est l'expression d'une population d'oscillateurs auto-entretenus qui sont interconnectés (avec une certaine hiérarchie) et influencés par un ensemble de synchroniseurs.

L'intérêt biologique pour un individu d'ajuster son organisation temporelle aux changements cycliques de facteurs de l'environnement a été aussi formulé par Ehret et al.[14]: ".... une créature avec tous ses systèmes circadiens fortement synchronisés a en quelque sorte appris comment "mettre tout cela ensemble" de manière à ce que les multiples profits de l'environnement et la multitude des appétits internes se distribuent dans le temps pour donner une harmonie circadienne satisfaite. De telles créatures heureuses sont récompensées par leurs capacités fonctionnelles et leur longévité".

LA VARIATION BIOPERIODIQUE ET SES PARAMETRES

La modification cyclique régulière de toute variable biologique peut faire l'objet d'une approximation par une fonction sinusoidale. Cela peut être fait grossièrement en reportant les résultats bruts en fonction du temps (chronogramme) ou peut être fait avec précision, en utilisant la méthode des moindres carrés pour obtenir la fonction cosinus qui donne la meilleure approximation de l'ensemble des résultats bruts constituant la série temporelle (cosinor). Pour ce dernier, Halberg et al.[15,16] a proposé d'utiliser l'équation classique.

$$y_{(t)} = M + A \cos(\omega t + \Phi) .$$

Où $\underline{M}$ est le mésor (moyenne ajustée du rythme); $\underline{A}$ est l'amplitude du rythme; ω est la fréquence angulaire; t est le temps et Φ l'acrophase. La fréquence angulaire $\omega = 2\pi/\tau$, ou τ est la période et $1/\tau$ la fréquence.

Un exemple illustrant la caractérisation d'un rythme biologique est donné à la figure 1.

La période τ est la durée d'un cycle complet d'une variation rythmique. τ est habituellement exprimé en unité de temps (secondes, minutes, heures, jours, années).

L'amplitude $\underline{A}$ correspond à la moitié de la variation totale du changement rythmique pour la période τ considérée. $\underline{A}$ peut être exprimé en unités conventionnelles (Celsius pour la température, mg/h pour les 17-OHCS urinaires etc.) ou en pour cent de $\underline{M}$.

Le mésor M est la moyenne ajustee du rythme pour la période τ considérée.

L'acrophase Φ est la localisation temporelle du sommet pour la période considérée. Φ doit être donné par rapport à un point de départ ou phase de référence $\Phi = 0$.

Le cosinor et les méthodes voisines sont largement utilisées par les chronobiologistes. Ils peuvent être programmés aujourd'hui pour des petits calculateurs de bureau. L'hypothèse d'une amplitude $\underline{A}$ différant de zero (avec $P < 0,05$) peut être éprouvée par la méthode du cosinor ce qui permet de savoir si un rythme est détecté pour une période τ donnée.

LE SPECTRE DES RYTHMES BIOLOGIQUES

La logique aussi bien que la méthodologie demandent que l'analyse d'un rythme détectable commence toujours par l'estimation de sa période. En effet, la connaissance de la période d'un rythme biologique est indispensable pour estimer son amplitude et son acrophase.

Considérons les changements périodiques d'une variable physiologique, la température de l'homme par exemple. Si la série temporelle des mesures est suffisamment longue (plusieurs jours, mois ou années) et avec des points demesure faits à courts intervalles de temps (plusieurs secondes, minutes ou heures) on peut détecter un rythme avec un τ d'environ une minute (rythme ultradien), un rythme avec un τ d'environ 24 heures (rythme circadien), un rythme avec un τ d'environ 7 jours, et d'environ un an etc., (rythme infradiens). En d'autres termes, pour le même processus biologique, plusieurs variations cycliques peuvent être mises en évidence, chacune d'entre elles ayant une période différente. Comme le montre le tableau I es périodes ultradiennes, circadiennes, et infradiennes existent chez l'enfant, la femme et l'homme sain pour un ensemble de variables biologiques.

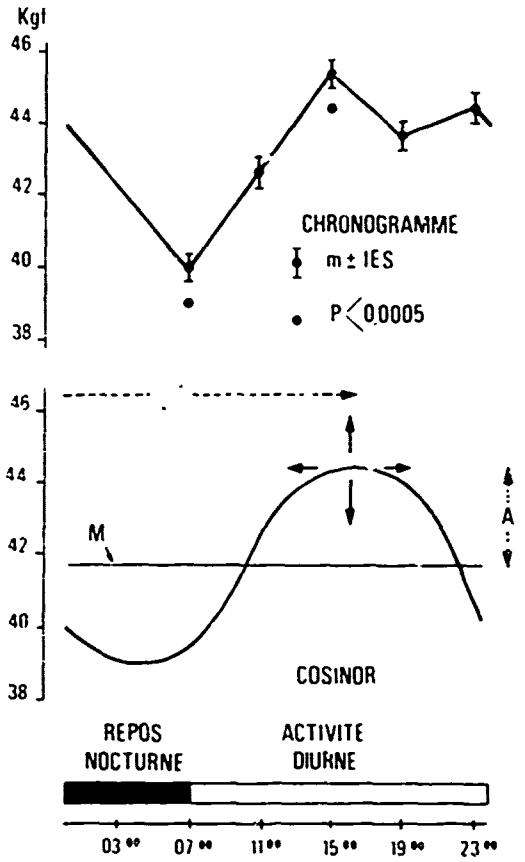


Fig.1 Exemple d'analyse d'un rythme biologique dans la force musculaire de la main droite: méthode du chronogramme en haut, méthode du cosinor en bas

L'étude porte sur 9 sujets, apparemment en bonne santé, âgés de 19 à 29 ans; ils sont synchronisés par une activité diurne de 7 h à minuit et un repos nocturne. Ils mesurent eux-mêmes (autométrie) la force musculaire de la main droite à l'aide d'un dynamomètre (Colin-Gentile, Paris) dans des conditions normalisées, toutes les 4 heures, pendant 24 heures, sauf pendant le sommeil.

L'analyse de cette étude transversale d'un rythme circadien (τ = environ 24 heures) peut se faire de deux manières:

(1) *Chronogramme* On reporte, en fonction du temps, les moyennes des valeurs obtenues avec leurs limites de confiance (pour une erreur-type, par exemple). Il apparaît, dans ces conditions, que la force musculaire a son maximum vers 15 h et son minimum vers 7 h, la différence étant statistiquement significative ($p > 0.0005$). On voit aussi que la variation, au cours des 24 heures, affecte grossièrement la forme d'une sinusoïde.

(2) *Méthode du cosinor* Dans l'exemple choisi, la période est égale à 24 h, ce qui correspond à la synchronisation des sujets. L'acrophase de la force musculaire de la main droite se situe ici à 1611 (16 h et 11 mn); si l'on étend les limites de confiance à 95% de sécurité, elle peut se localiser entre 12 h 36 et 19 h 46. L'amplitude est de 2,7 kgf (de 1,1 à 4,2 kgf pour 95% de sécurité). Le mésor se situe à 41,8 kgf ± 1,8 kgf.

Cela signifie que la force musculaire peut s'élever au voisinage de 46 kgf au moment de l'acrophase et se situer aux environs de 37 kgf 12 heures plus tôt ou 12 heures plus tard.

TABLEAU

Analyse Spectrale de Rythmes Biologiques Humains

Exemples de rythmes	*Domaines du spectr*		
	Haute fréquence ou ultradien ($\tau < 16$ h) τ	*Moyenne fréquence ou circadien* ($\tau \simeq 24$ h) τ	*Basse fréquence ou infradien* ($\tau > 2,5$ j) τ
Pouls radial	~ 1 s (E, F, H)	~ 24 h (E, F, H)	~ 1 an (E, F, H)
Température (digitale = dig.; orale = or.; rectale = rec.)	~ 1 mn (H) (dig.)	~ 24 h (E, F, H) (dig., or., rec.)	~ 30 j (F) ~ 7 j et 1 an (F et H) (or., rec.)
Cortisol plasmatique	~ 45 et 90 mn (E, F, H)	~ 24 h (E, F, H)	~ 30 j (F) et ~ 1 an (H)
Testostérone plasmatique	~ 90 mn (H)	~ 24 h (H)	~ 1 an (H)
Comportement sexuel	~ 8 h (H)	~ 24 h (H)	~ 1 an (F, H)
Comportement alimentaire	~ 3 h (E, F, H)	~ 24 h (E, F, H)	~ 1 an (E, F, H)

τ = période en secondes (s), en minutes (mn), en heures (h), en jours (j). Fréquence $f = 1/\tau$. F = femme adulte, H = homme adulte; E = enfant.

D'après les résultats de N.Kleitmann, F.Halberg, M.Gautherie, E.van Cauter, A.Reinberg, J.Ghata, M.Lagoguey, G.Debry, E.Weitzman.

La période τ est souvent considérée comme connue dans l'exemple d'un homme synchronisé par une alternance stable d'activité diurne et de repos nocturne (tous deux liés aux contraintes de la vie sociale et de la niche écologique) avec une période moyenne de 24 heures. Il est hautement probable et dès lors attendu que, dans ces conditions, les rythmes circadiens de ce sujet auront une période moyenne τ de 24 heures.

L'ORGANISATION TEMPORELLE

Pour n'importe quelle espece (y compris la nôtre) la connaissance des rythmes de toutes sortes de variables biologiques permet une représentation précise de son organisation temporelle pour un domaine spectral donné. Mais, même chez les espèces les plus étudiées (Homme, Souris, Rat, Acetabulaire) nous ne possédons encore qu'une représentation imparfaite et très incomplète de cette organisation temporelle.

De manière à simplifier la présentation de cette structure temporelle, celle de l'Homme par exemple, on peut faire apparaître les relations des acrophases de différents rythmes (et leur amplitude respective) pour les périodicités circadiennes et circannuelles. La schématisation de l'organisation temporelle circadienne (fig.2) et circannuelle (fig.3) de l'homme adulte a été faite à partir de résultats obtenus, autant que possible dans des conditions expérimentales contrôlées et standardisées. Soulignons que tous les sujets étudiés étaient synchronisés de manière similaire pour ce qui concerne les rythmes circadiens. Cette necessité methodologique, aussi élémentaire qu'elle puisse paraître, est parfois oubliée, bien qu'elle soit indispensable

LES SYNCHRONISEURS SOCIO-ECOLOGIQUES

Il n'est pas exagéré de dire que nous sommes nés avec une certaine structure temporelle exactement comme nous sommes nés avec une certaine anatomie (structure spatiale). Un ensemble d'arguments indirects sont en faveur du caractere héréditaire des rythmes biologiques chez l'homme. (Des arguments directs resultent d'expériences faites chez les végétaux et les animaux. Bünning[2], Aschoff[1], Pittendrigh[17], Reinsing[18], Hastings[19], Vanden Driessche[20]) Par exemple, les rythmes biologiques persistent durant l'isolement de l'Homme vivant ainsi à l'abri des variations rythmiques de facteurs de l'environnement (Halberg et al.[9], Aschoff[13], Reinberg[21], Mills[22]), les variations circadiennes des rythmes biologiques sont presque similaires chez les jumaux monozygotes mais ne le sont pas chez les jumaux dizygotes[6].

Toutefois, les rythmes biologiques sont influencés par les variations périodiques d'un ensemble de facteurs de l'environnement. Le terme synchroniseur (ou Zeitgeber) s'applique a tout facteur de l'environnement qui présente

des variations cycliques capables de modifier un ou plusieurs des paramètres qui servent à caractériser un rythme biologique (τ, $\underline{Q}$, $\underline{A}$, $\underline{M}$). Pour de nombreuses espèces végétables et animales, l'alternance périodique de la lumière et de l'obscurité suivant une période d'environ 24 heures est un des synchroniseur les plus puissants Cependant, l'alternance périodique du bruit et du silence, du chaud et du froid etc... agit aussi comme un synchroniseur circadien pour certaines espèces et/ou certaines conditions expérimentales. Chez l'Homme, le synchroniseur le plus efficace est de nature socio-écologique (Halberg et al.[3,10], Aschoff et al.[23], Apfelbaum et al.[24]). Cela signifie que l'alternance de l'ensemble, activité-lumière-bruit-chaleur et de l'ensemble de repos-obscurité-silence-froid, liés tous deux à notre vie sociale et à notre niche écologique, jouent un rôle prépondérant dans notre synchronisation.

La manipulation d'un synchroniseur prépondérant peut concerner par exemple sa période. Il est possible entre certaines limites étroites – d'imposer aux rythmes circadiens de l'homme une période différente de 24 heures, par exemple 23 ou 25 heures (Aschoff[12,13]). Mais il n'a pas été possible d'imposer une période de 21 heures (Simpson[25]) ou 30 heures (Gouars[26]) par la manipulation de τ des synchroniseurs socio-écologiques.

Quand la manipulation du synchroniseur est dirigée essentiellement sur sa phase, un déplacement de l'acrophase circadienne se produit. Des aspects de cet important phénomène sont discutés dans le présent livre par K.Klein, E.Weitzman, P.Hartman, A.Reinberg.

En ce qui concerne les rythmes circannuels de l'Homme, il existe très probablement un synchroniseur, sa nature est encore inconnue. Il a été montré, par des expériences animales, que, (a) les rythmes circannuels persistent pendant l'isolement et (b) que les variations circannuelles (saisonnières) de la photofraction circadienne sont capables de jouer le rôle d'un signal (Cf. Bünning[2]; Benoit et Assenmacher[27]; Pengelley[28]; Assenmacher et Farner[29]).

EXEMPLES DE L'ORGANISATION TEMPORELLE CIRCADIENNE DE L'HOMME (CONCERNANT EN PARTICULIER LA LIBERTE BRONCHIQUE DE SUJETS SAINS ET ASTHMATIQUES) (Figure 2)

L'acrophase des différents rythmes circadiens chez des sujets synchronisés, ne sont pas distribués au hasard dans l'échelle des 24 heures; au contraire, cette distribution, à tous les niveaux d'organisation, représente une structure temporelle spécifique. La relation causale classique entre diverses fonctions physiologiques doit être complétée par des informations concernant leurs relations temporelles. Les relations de phase entre des phénomènes biopériodiques ainsi considérées, conduisent à décrire des systèmes circadiens cohérents.

Les rythmes circadiens de variables physiologiques utilisées pour caractériser la liberté bronchique (le calibre des bronches) la motricité bronchique etc. ont été mis en évidence chez des enfants et des adultes sains aussi bien que chez des enfants et des adultes souffrant d'asthme allergique. Le débit expiratoire de pointe, la capacité vitale, le volume expiratoire maximum par secondes (VEMS), la résistance pulmonaire, la compliance dynamique, en re autres variables étudiées, évoluent dans le temps suivant des rythmes circadiens. Ces derniers ont une relativement grande amplitude (de 10 à 35% au-dessus et en-dessous de la moyenne ajustée des 24 heures) et ont une localisation temporelle de l'acrophase montrant que la plus petite liberté bronchique se situe aux environs du début du repos nocturne (fig.2) Les rythmes biologiques pouvant être considérés comme un processus adaptatif, il n'est pas surprenant d'observer que les acrophases des variables permettant d'apprécier la liberté bronchique se situent dans l'espace de temps d'activité des sujets.

Ces variations circadiennes de la liberté bronchique peuvent être liées à celles des hormones surrénaliennes et des catécholamines entre autres substances secrétées capables d'agir sur le calibre des bronches. Il a été montré que le creux du rythme circadien du cortisol plasmatique, des 17-OHCS urinaires, de l'adrénaline, de la nor-adrénaline et du VMA coincident avec le début du repos nocturne aussi bien chez les sujets allergiques que chez les adultes sains (fig 2) En outre, les recherches chronopharmacologiques mettant en oeuvre un agent béta-stimulant et un agent vagolytique ont montre que le tonus vagal predomine durant le repos nocturne, cependant que le tonus sympathique prédomine durant l'activité diurne en ce qui concerne la bronchomotricité (Gaultier et al.[30]).

La réactivité de la peau et de la bronche humaine à differentes substances a été explorée au cours du nycthémère Il apparaît que le pic circadien de la susceptibilité est à nouveau trouve durant la première partie du repos nocturne Cela est vrai pour, (1) la réaction cutanée à l'histamine aussi bien chez les sujets sains que les malades allergiques Chez ces derniers, l'acrophase de la sensibilité cutanée vis-à-vis d'allergènes spécifiques (extraits de poussière domestique, de plume, de pollens de graminées, de pénicilline, etc.) se situe, comme celle de l'histamine, dans la première partie du repos nocturne, cela est vrai. (2) pour la réactivité bronchique à l'inhalation d'histamine, (3) pour le seuil de la réponse bronchique a l'inhalation d'acétylcholine et (4) pour le test de provocation bronchique vis-à-vis d'un aérosol contenant un extrait de poussière domestique chez les patients spécifiquement sensibilisés (Reinberg[31]).

Il est logique d'admettre que l'apparition nocturne de la crise d'asthme est le résultat de changements biopériodiques dans la reactivite des patients. Ces changements sont liés aux rythmes physiologiques du cortisol, des catécholamines, de la susceptibilite des broncho-récepteurs et sont liés d'autre part, aux changements individuels du niveau moyen de la tolérance aux allergènes (Cf. McGovern, Smolensky, Reinberg[32]).

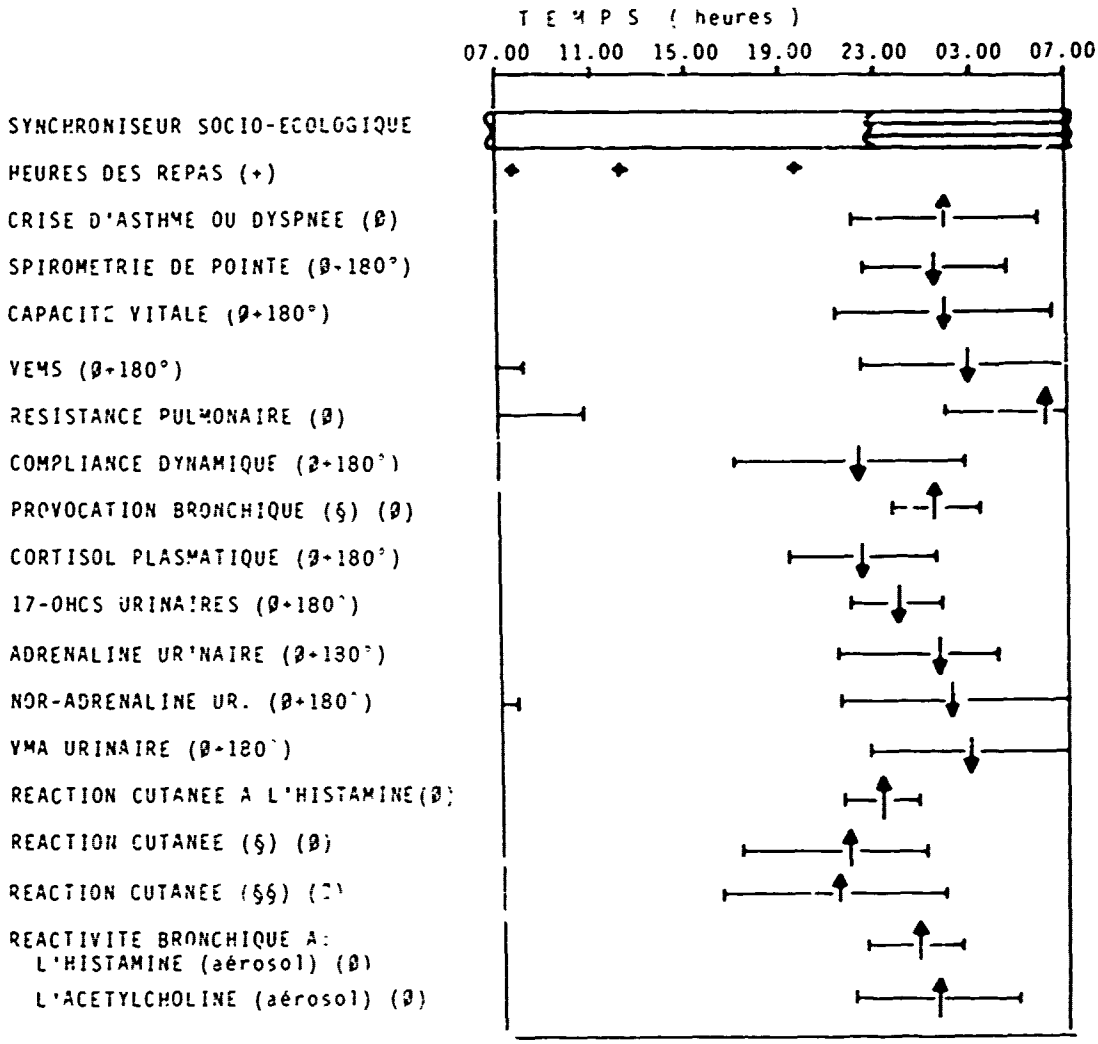


Fig.2 Aspect de l'organisation temporelle de l'homme

La relation temporelle entre l'acrophase de la crise d'asthme (ou du pic circadien de la dyspnée) de malades souffrant d'asthme allergique et l'acrophase (ou la batyphase) circadienne de variables physiologiques considérées comme des rythmes composants possibles chez des sujets asthmatiques et ou des sujets sains. L'acrophase -‡- et la batyphase ‡- qui sont respectivement le pic et le creux de la fonction sinusoïdale donnant la meilleure approximation du rythme sont donnés avec leurs limites de confiance pour une sécurité de 95% (la batyphase diffère de l'acrophase O par 180° ou 12 heures) Il y a une bonne coincidence entre (1) l'heure du pic des manifestations cliniques et (2) l'heure des acrophases circadiennes (ou des batyphases) de variables qui sont considerees habituellement comme ayant un rôle à jouer dans les manifestations cliniques de l'asthme allergique

Crise d'asthme (A.Reinberg et al 1963), spirométrie de pointe (F Haïberg et al 1966, H.Chai et al. 1968, J.Reindl et al 1969, A.Reinberg et al 1970, U Serafini et al 1974), capacité vitale (A.Reinberg et al 1970), VEMS ou volume expiratoire maximum par secondes (G.De Vries et al. 1962, A.Reinberg et al 1971, G Tammeling et al 1974), resistance pulmonaire et compliance dynamique (C Gaultier et al 1975), test de provocation bronchique à l'extrait de poussière domestique (Gervais, Reinberg et al 1974), 17-OHCS urinaires (A.Reinberg et al. 1963, Vanden Straten 1964), cortisol plasmatique (Reinberg et al 1975), catécholamines urinaires (Reinberg et al 1975), reactions cutanees a l'histamine et aux allergènes (A Reinberg et al 1965, 1969, M Smolensky et al 1974), réactivité bronchique aux aérosols d'histamine (De Vries et al 1962, G Tammeling et al 1974), reactivité bronchique aux aerosols d'acetylcholine (A Reinberg et al 1971) La figure originale A.Reinberg[31] a été completee par de nouveaux resultats

EXEMPLES DE L'ORGANISATION TEMPORELLE CIRCANNUELLE DE L'HOMME (CONCERNANT EN PARTICULIER LES ACTIVITES ENDOCRINIENNES OU ENDOCRINO-DEPENDANTES)

Trois remarques préliminaires peuvent être utiles:

(a) Les rythmes circadiens et circannuels doivent être étudiés au cours de la même expérience. Le fait que la biopériodicité d'une variable physiologique donnée peut s'exprimer suivant plusieurs domaines de fréquence a été vérifié pour plusieurs espèces animales, en particulier la Souris (Haus et Halberg[33]), la Grenouille (Dupont et al.[34]), et l'Homme (Reinberg[35]). Quand les collectes d'échantillons sont faites une fois par jour (par exemple tous les deux mois), des heures différentes ou même a la même heure, les valeurs obtenues peuvent refléter une variation circadienne plutôt qu'une variation circannuelle. En effet, non seulement le niveau moyen des 24 heures mais aussi l'emplacement temporel de l'acrophase circadienne d'une variable physiologique peut présenter un rythme circannuel.

(b) La situation géographique (ville état) ou l'étude a été faite doit être donnée. L'acrophase circannuelle peut dépendre chez l'homme de cette situation ainsi que cela a été mis en évidence pour certaines variables par Batschellet et al.[36] et par Simpson et Bohlen[37], par Ghata et al.[38]. Les changements annuels de la durée du jour, par rapport à la latitude semblent être un des facteurs prépondérants (ou signal) qui doit être pris en considération pour diverses espèces animales. Les résultats résumés dans ce papier ont été obtenus chez des sujets vivants dans l'hémisphere nord.

(c) Une relation temporelle entre deux variables ne démontre pas en elle-même une relation causale directe. Cette dernière peut être suspectée si en plus de la relation temporelle un ensemble d'autres arguments peut être donnée[10, 35].

VARIATIONS ENDOCRINIENNES CIRCADIENNES ET CIRCANNUELLES DE 5 PARISIENS ADULTES JEUNES ET SAINS (Figure 3)

Pendant 14 mois, 5 parisiens jeunes, adultes et apparemment sains (examens cliniques et biologiques de routine) vivant à Paris ont été volontaires pour étudier un certain nombre de rythmes circadiens. Au début de l'étude, ils avaient respectivement: 26, 26, 28, 29 et 31 ans. Au moment des tests qui duraient 28 heures (tous les 2 mois pour les collectes de sang et tous les mois pour les collectes d'urines), les sujets ne prenaient aucun médicament et n'avaient pas d'activité sexuelle. Les apports d'eau et d'aliments ne furent pas contrôlés, les repas furent pris aux environs de 07, 13 et 20 heures. La périodicité circadienne des sujets fut synchronisée par une activité diurne de 07.00 (± 1 h) à 23.00 (± 1,5 h), pendant toute l'année (Reinberg et Lagoguey[39]).

Les rythmes circadiens des concentrations plasmatiques en hormones ont été explorés simultanément chez les 5 sujets pendant les mêmes nombres de jours de janvier, mars, mai, juillet, septembre, novembre 1973 et à nouveau en février 1974. Les jours des tests, le sang veineux était pris à heures fixes toutes les 4 heures, pendant 28 heures, en commençant à 8 heures du matin, le premier jour.

Le plasma (après centrifugation) et les échantillons d'urine ont été conservés à −25°C à raison de 10 tubes par échantillon pour faciliter les contrôles et les dosages multiples, chaque tube n'étant dégelé qu'une seule fois. Les dosages ont été faits en large séries à la fin de l'étude. Des méthodes radioimmunologiques ont été utilisées pour les variables plasmatiques et l'aldostérone urinaire. La spécificité, la sensibilité et la précision ont été éprouvées suivant la meilleure méthodologie de routine. Les séries temporelles ainsi obtenues ont été analysées du point de vue statistique, suivant des méthodes conventionnelles et suivant celles du cosinor.

Rythmes Circadiens

Il n'a pas été détecté de rythmes circadiens pour la FSH plasmatique. Le rythme circadien de LH n'a été mis en évidence que pendant les mois de juillet à novembre. Les autres variables étudiées ont un rythme circadiens statistiquement significatifs.

Variations Annuelles de l'Acrophase Circadienne

(quand les rythmes sont mis en évidence pour tout ou presque tous les mois considérés). La prolactine plasmatique a une acrophase remarquablement fixe, tout le long de l'année. Elle se situe aux environs de 04.00. Les acrophases circadiennes de l'activité sexuelle et des 17-OHCS urinaires ne se déplacent pas le long de l'année par opposition à ce qui se passe pour les acrophases circadiennes de la testostérone et du cortisol plasmatique. Les acrophases circadiennes de la testostérone plasmatique, de la thyroxine, se situent le plus tôt, dans l'échelle des 24 heures, au printemps et, le plus tard, dans l'échelle des 24 heures, en automne. Au contraire, l'acrophase des rythmes circadiens liée à l'activité cortico-surrénalienne (cortisol plasmatique, aldostérone urinaire etc.) se situe plus tôt, dans l'échelle des 24 heures, en automne et en hiver, et plus tard, dans l'échelle des 24 heures, au printemps. La fixité de l'acrophase circadienne des 17-OHCS urinaires pourrait être due au fait que les valeurs obtenues étaient assez dispersées.

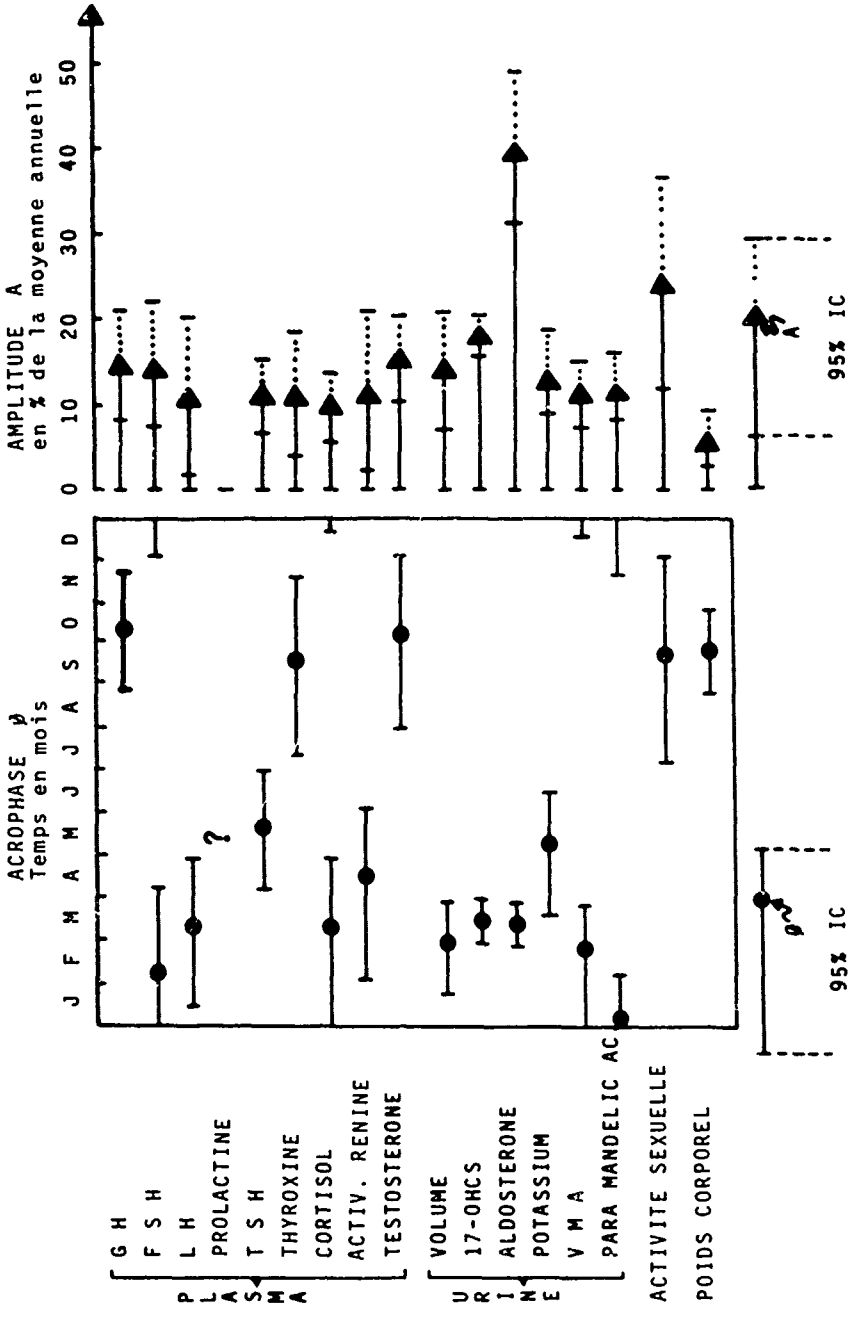


Fig.3 Aspect de l'organisation temporelle circannuelle de l'homme adulte sain

Rythmes circannuels de 5 parisiens jeunes, adultes et sains de sexe masculin: analyse par la méthode du cosinor singulier. Pour chacune des variables considérées, le mésor circadien a été utilisé pour l'analyse des séries temporelles. L'acrophase annuelle ϕ (sommet de la variation) et l'amplitude $\underline{A}$ (moitié de la variabilité totale annuelle) sont données avec leurs limites de confiance (IC) pour une sécurité de 95%. $\underline{A}$ est exprimé en pour cent de la moyenne annuelle de 24 heures. L'amplitude annuelle est relativement grande pour l'excrétion urinaire d'aldostérone et relativement petite pour le poids corporel. L'amplitude ne diffère pas de zéro pour la prolactine plasmatique (pas de détection de rythme circannuel pour cette dernière variable).

La figure originale A.Reinberg et M.Lagoguey[39] a été complétée par de nouveaux résultats.

Variations Annuelles du Niveau Moyen des 24 Heures M

La méthode du cosinor singulier a été utilisé pour résumer tous les résultats dans la figure 3. La prolactine n'avait pas de variations circannuelle chez ces hommes jeunes. Des rythmes circannuels statistiquement significatifs ont été observés pour les autres variables considérées. FSH, LH et TSH atteignent leur sommet en hiver. L'activité cortico-surrénalienne (cortisol plasmatique, 17-OHCS urinaires et aldostérone) ont aussi leur sommet en février et mars. Les acrophases respectives de l'activité rénine plasmatique et du potassium urinaire se localisent un peu plus tard en avril-mai. L'acrophase annuelle de la thyroxine plasmatique apparaît en septembre, en phase avec l'acrophase annuelle de la testostérone plasmatique de l'hormone de croissance, de l'activité sexuelle et du poids corporel. Les excrétions urinaires des catécholamines atteignent leur acrophase en hiver. Les variations individuelles des variables considérées sont similaires à celles qui ont été observées pour le groupe. Un certain nombre de rythmes circannuels ont été déjà rapportés chez l'homme adulte sain (Cf. Reinberg[35]; Reinberg et Lagoguey[39]). En dépit des différences qui peuvent être liées aux méthodes, à la localisation géographique etc., ces résultats et les nôtres sont en bon accord.

Commentaires

Les relations de phase circannuelles entre la testostérone plasmatique et l'activité sexuelle peuvent être le reflet d'une relation causale ainsi que cela est le cas pour diverses espèces de vertébrés (Cf. Benoit et Assenmacher[27]; Pengelley[28]), y compris chez les primates non humains (Conaway et Sade[40]; Gordon et al.[41]; Peng et al.[42]; Mendoza et al.[43]).

Cela ne signifie pas que le rythme circannuel de la testostérone plasmatique est la seule variable mais seulement une des variables qui peut jouer un rôle dans le rythme circadien de l'activité sexuelle. Entre autres, FSH et LH plasmatiques doivent être pris en considération même si une différence d'environ 6 mois apparaît entre les acrophases reflétant les activités pituitaires et gonadiques. Une différence similaire dans les acrophases circannuelles de ces hormones plasmatiques a été observée chez le Canard mâle par Assenmacher[29].

Une des hypothèses pour expliquer ce fait est l'existence d'une rythme circannuel de la susceptibilité gonadique vis-à-vis des hormones gonadotropes. La seconde hypothèse, qui n'exclut pas la première, prend en considération des phénomènes chronopharmacologiques (Reinberg et Halberg[44]; Reinberg[45]). L'éfficacité d'un agent (y compris les hormones) varient en fonction du temps de son administration ou de son acrophase circadienne de concentration plasmatique. Un essai pour éprouver cette deuxième hypothèse a été fait et rapporté dans la dernière partie du présent papier.

Ajoutons que chez les filles aux environs de la puberté, une variation circannuelle de la ménarche a été observée (Cf. Revue par Reinberg[21]), avec un pic qui se situe à la fin de l'automne et au début de l'hiver et un creux qui se situe au printemps pour l'hémisphère nord.

La question doit se poser de savoir si ces rythmes annuels sont endogènes ou ont une composante endogène. Un ensemble cohérent de connaissances peut être obtenu d'autres expériences animales. Les rythmes circannuels endogènes (par exemples ceux de l'activité gonadique et des fonctions reproductives) s'ils ne sont pas créés par des modifications de l'environnement peuvent cependant être influencés par des changements annuels de facteurs externes tels que la durée du jour (qui joue le rôle de signal temporel) au moins pour certaines espèces (Farner[46]; Pengelley[28]). Si la généralisation de l'animal à l'Homme peut être faite, notre espèces aurait certaines propriétés des animaux à jour court (ou à nuit longue) pour ce qui est des fonctions reproductives. Rappelons dans cette discussion la remarque faite par Conaway et Sade[50]. "... il se pourrait bien que tous les primates y compris l'Homme soient fondamentalement des espèces à reproduction annuelle ...". En outre, les variations circannuelles des activités endocrines peuvent jouer un rôle dans l'apparition des variations annuelles de la résistance de l'organisme humain à des facteurs potentiellement nocifs. Plus précisément, il y a une coincidence frappante, dans le temps, entre l'acrophase annuelle de l'activité cortico-surrenalienne et le haut risque de certaines infections pulmonaires et de maladies cardio-vasculaires. Par référence à ces dernières, ajoutons que non seulement l'acrophase annuelle de l'aldostérone et de l'activité rénine plasmatique peut être interessées, mais aussi l'acrophase annuelle des catécholamines.

CHRONOPHARMACOLOGIE CLINIQUE

Les effets désirés et non désirés d'un agent physique ou chimique dépend, entre autres choses, de l'heure à laquelle l'organisme est traité; ou, plus précisément, de l'état des systemes circadiens du sujet étudié, à l'heure du traitement (Halberg, Reinberg[10]; Reinberg, Halberg[44]; Reinberg[45]).

La chronopharmacologie comprend à la fois des recherches concernant les effets des médicaments en fonction du temps biologique et des investigations des effets des médicaments sur les caractéristiques des phénomènes biopériodiques.

(1) Un grand nombre d'exemples concernant la chronopharmacologie humaine été publié et synthétisé. variations circadiennes de la réactivité de la peau à l'histamine et à d'autres substances, réactivité bronchique à l'histamine, à des agents béta stimulants, à l'acétylcholine, rythmes circadiens de la durée de l'excrétion du salicylate etc. Une grande variété d'autres médicaments et agents chimiques a été étudié chez l'homme d'un point de vue chronopharmacologique.

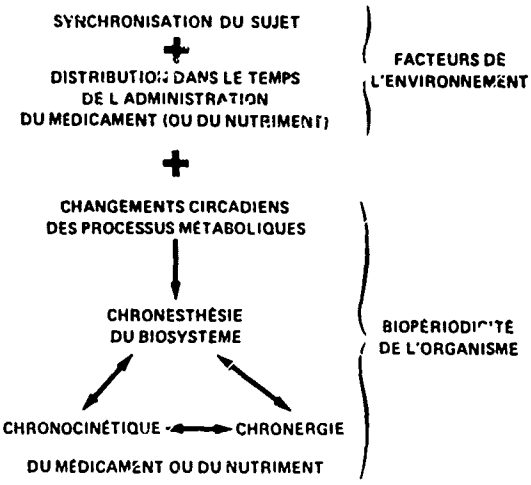


Fig.4 Concepts de chronopharmacologie

La chronesthésie d'un biosystème correspond aux variations rythmiques de sa susceptibilité; elle inclut les phénomènes de membranes et les phénomènes moléculaires liés aux processus métaboliques. La chronesthésie intéresse les cellules, les tissus, les organes et les systèmes d'organes de l'hôte aussi bien que la susceptibilité de parasites, de bactéries, de tumeurs etc. La chronopharmacocinétique d'un agent chimique correspond aux variations rythmiques de sa biodisponibilité aussi bien que de sa pharmacocinétique et/ou de son excrétion urinaire ou autre (fécès, sueurs, salive etc.) Des rythmes circadiens statistiquement significatifs ont été démontrés pour les paramètres qui servent à caractériser la pharmacocinétique de plusieurs agents. La chronergie d'un agent chimique (ou physique) correspond aux variations rythmiques de ses effets, qu'ils soient désirés (chronoefficacité) ou non désirés. La chronergie d'un agent chimique fait intervenir sa chronopharmacocinétique aussi bien que la chronesthésie de plusieurs biosystèmes. L'acrophase (sommet) de la chronergie d'un agent chimique ne coincide pas nécessairement avec la chronesthésie des biosystèmes intéressés ni avec l'acrophase des concentrations plasmatiques de l'agent chimique dans le sang.

(2) La chronopharmacologie n'est pas limitée aux rythmes circadiens mais peut être étendue aux rythmes dont la période est supérieure à 24 heures, par exemple, une chronopharmacologie mensuelle chez les femmes: (a) variations de la réponse à un agent chimique en fonction des jours du cycle mensuel et (b) altérations du rythmes mensuels par un certain nombre de médicaments. Cependant, seule la chronopharmacologie circadienne est actuellement bien étudiée

(3) Trois nouveaux concepts peuvent être pris en considération (fig.4).

(a) La *chronocinétique* d'un médicament qui comprend à la fois les variations rythmiques de sa biodisponibilité (ou de sa pharmacocinétique) et de ses excrétions (urinaires entre autres).

(b) La *chronesthésie* d'un biosystème vis-à-vis d'un médicament: par exemple, les variations circadiennes de la susceptibilité d'un biosystème vis-à-vis d'une substance y compris les systèmes d'organes, les parasites, les tumeurs etc. La chronesthésie bronchique et cutanée vis-à-vis de divers agents a été étudiée chez l'homme.

(c) La *chronergie* d'un médicament. Elle prend en considération sa chronocinétique et les chronesthésies des biosystèmes intéressés de l'organisme. Le terme chronergie comprend les variations rythmiques de tous les effets et bien entendu, de l'efficacité du médicament.

(4) La chronopharmacologie clinique est utile pour résoudre le problème de l'optimisation des médicaments Par exemple, pour augmenter l'efficacité désiré d'un médicament et/ou pour réduire ses effets non désirés. Cela a déjà été réalisé pour les corticostéroides, conduisant à une chronocorticothérapie. Donnons un nouvel exemple illustrant : fait qui intéresse la chronopharmacologie clinique aussi bien que la chrononendocrinologie. Il concerne la réponse testiculaire simulée par HCG chez des hommes adultes sains (Lagoguey et al.[47]). 4 hommes adultes jeunes synchronisés avec une activité diurne de 07.00 à minuit et un repos nocturne ont été volontaires pour cette expérience. Ils avaient déjà participé à l'étude des rythmes circadiens et circannuels endocriniens (Cf. figure 3). Les sujets ont subi 6 différents tests centrés sur le mois de juin 1978. 2500 unités internationales dans 0,5 ml de HCG (Organon) ont été injectés par voie intramusculaire à une semaine d'intervalle et respectivement aux heures suivantes: 07.00, 14.00, et 20.00 heures. Une solution de sérum physiologique fut injectée dans les mêmes conditions expérimentales à trois reprises. Les jours et l'heure des débuts des 6 tests ont été randomisés. Du sang veineux fut recueilli 30, 60, 90, 150 et 240 minutes après chaque injection (solution saline ou HCG). La testostérone plasmatique (pT) a été dosée par une méthode radio-immunologique.

Les changements résultant d'une injection unique d'HCG, en fonction du temps peut être exprimée (1) par le rapport: pT après HCG sur pT de contrôle, (2) le rapport, hauteur du pic de pT après HCG sur pT de contrôle. La réponse testiculaire à l'HCG semble plus forte à 20.00 qu'à 07.00. Par exemple, le rapport hauteur du pic sous stimulation/pT de contrôle est 8 fois plus grand à 20.00 qu'à 07.00 ($p < 0.01$). En outre, l'espace de temps pour atteindre le pic est le plus court à 20.00 (90 mn ± 21 = 1 E.S) qu'à 07.00 (218 ± 23; $p < 0.005$).

Dès lors, il semble que la reponse testiculaire de l'homme à une stimulation spécifique varie suivant un rythme circadien de grande amplitude. Ces résultats peuvent etre utilises pour une meilleure compréhension de changements biopériodiques en endocrinologie et en chronopharmacologie humaine.

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CIRCADIAN AND CIRCANNUAL RHYTHMS IN HEALTHY ADULTS

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SUMMARY

Physiologic processes in any living organism including man are not constant as a function of time : regular and predictable variations with period, τ, of about 24 hours (circadian), about 1 year (circannual) etc. can be detected. Each rhythm can be characterized by estimating such parameters as : acrophase ϕ (crest time), amplitude A and mesor M (rhythm adjusted mean).

The estimation of τ, ϕ, A and M of a set of variables under specified experimental conditions enable us to visualize an aspect of the temporal organization (or biologic time structure). Aims of chronobiology are to quantify and investigate mechanisms of biological time structures. Biological rhythms and the related temporal organization are gentic in origin. However, one or several rhythm parameters may be influenced by cyclical variations of environmental factors (synchronizers or Zeitgeber). The latter has practical implications since phase shift of synchronizers may occur with transmeridian flights, night-working and shift-working.

Chronobiology also involves the study of rhythmic changes in endocrine activities (chronoendocrinology) and in drugs effects (chronopharmacology).

BIOLOGICAL RHYTHMS AS ADAPTATIVE PHENOMENA TO PREDICTABLE CHANGES OF ENVIRONMENTAL FACTORS

The quantitative study of biological rhythms shows that any biophysical and biochemical process varies with respect to time in a periodic, regular and predictable manner. (Aschoff 1, Bünning 2, Halberg 3). We know today that rhythmic activity is a fundamental property of living matter (Reinberg, Ghata 4). Biological rhythms can be demonstrated in all living beings from nucleated unicellular organisms to man, and at all levels : the entire organism, organ-systems, organs, tissues, cells, sub-cellular material. Biological rhythms exhibit similar basic properties in plants and animals :

- they are genetic in origin;
- they persist without time clue and cue;
- they can be characterized for a given species (e.g. Rat, Mice, Man) bearing in mind that interindividual differences can be demonstrated (e.g. differences between strains of mice : Halberg et al 5; MZ versus DZ twin studies in man : Barcal et al 6).

They can be influenced by cyclic variations of certain environmental factors called synchronizers or Zeitgeber.

These bioperiodic changes are likely to result from adaptative phenomena to predictable variation of a set of factors directly related to the Earth's rotation around its axix (in $\sim$ 24 h) and around the Sun (in $\sim$ 365,25 days). In fact, examples of the temporal organization of living beings were reported mainly (but not exclusively) in both circadian and circannual domains of biological rhythms. (Bioperiodic phenomena with period τ = 7 days, = 1 month etc. have been documented as well (Halberg 3, Smolensky et al 7) but to a lesser extent than circadian and circannual rhythms).

When refering to biological rhythms as adaptative phenomena to predictable changes of environmental factors two possibilities must be considered. The first one concerns a given species, its survival troughout many generations and its presumable evolution. The second concerns a given individual of the considered species this subject being subjected to cyclic or non-cyclic manipulations of environmental factors, including synchronizers. A better understanding of biological rhythms may be reached both when comparing rhythm properties among species (Edmunds 8, Bünning 9) and when studying the individual tolerance or effects of manipulation of synchronizers (Halberg et al 3,5, 10, Hayes 11, Aschoff 12, 13, Reinberg : tolerance to shift-work : this lecture series).

The circadian (and presumably the circannual) organization of man consists of a population of self-sustaining oscillators which are interconnected (with a certain hierarchy) and influenced by a set of synchronizers.

The biological interest for an individual in adjusting his temporal organization to cyclic changes of environmental factors has been also formulated by Ehret et al 14 : "....a creature with all of its systems in strong circadian synchrony has somehow learned how to "put it all togetner" so that the multiple environmental amenities and the multitude of inner appetites mesh in a satiable and circadian harmony. Such fortunate creatures are rewarded by functional proficiency and longevity".

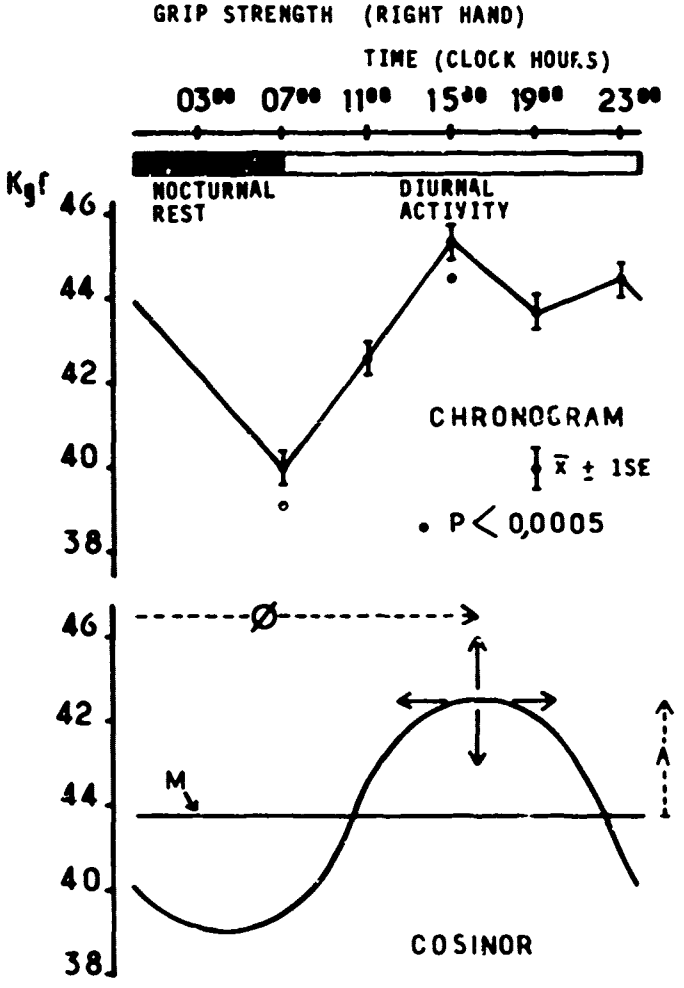


Figure 1 . Example of the time series analysis of a biological rhythm : circadian changes in grip strength (right hand).

9 healthy male volunteers (19 to 29 years) synchronized with a diurnal activity from 07.00 to 00.00 (midnight) and a nocturnal rest. The period τ = 24 h.
Chronogram (top). Raw data were plotted as a function of time. Measurements (in kg-force) for each time point (07.00, 11.00, 15.00, 19.00 and 23.00) are expressed as $\bar{X} \pm 1$ SE. The waveform of the curve showed a maximum at 15.00 and a minimum at 07.00; the difference was statistically significant ($P<0.0005$). The circadian variation is obvious and its characteristics may be quantified.
Cosinor (bottom). The rhythm was approximated by the least squares method with the 24 h cosine function best fitting all data. A statistically significant circadian rhythm was detected with A differing from zero ($P < 0.005$). It was then characterized by the point estimation of several of its parameters with their respective 95% confidence limits (CL).
Acrophase Ø was 16.11 (4 p.m. and 11 min.) from 12.36 to 19.46 with 95% CL.
Amplitude A was 2.7 kgf; from 1.1 to 4.2 kgf with 95% CL.
Mesor M or rhythm adjusted mean was 41.8 kgs ± 1.8 (1 SE).
Therefore at the time of the circadian Ø grip strength may be as high as 46 kgf whereas 12 h later (or earlier) the corresponding value may be as low as 37.6 kgf.

SPECTRAL DOMAINS OF HUMAN BIOLOGICAL RHYTHMS

DOCUMENTED EXAMPLES	HIGH FREQUENCY OR ULTRADIAN RHYTHMS τ < 20 h	MEDIUM FREQUENCY OR CIRCADIAN RHYTHMS $\tau \simeq$ 24 h	LOW FREQUENCY OR INFRADIAN RHYTHMS τ > 30 h
HEART RATE	~ 1 s (c,m,w)	~ 24 h (c,m,w)	~ 1 y (c,m,w)
TEMPERATURE	~ 1 min. (m)	~ 24 h (c,m,w)	~ 30 d (w)
			~ 7 d; 1 y (m&w)
PLASMA CORTISOL	~ 45 & 90 min. (c,m,w)	~ 24 h (c,m,w)	~ 30 d (w)
			~ 1 (m&w)
PLASMA TESTOSTERONE	~ 90 min. (m)	~ 24 h (m)	~ 1 y (m)
SEXUAL BEHAVIOUR	~ 8 h (m)	~ 24 h (m)	~ 1 y (m & w)
FEEDING BEHAVIOUR	~ 90 min. & ~ 3 h (c,m,w)	~ 24 h (c,m,w)	~ 1 y (c,m,w)

PERIOD τ IN SECONDS (s), MINUTES (min.), HOURS (h), DAYS (d) AND YEARS (y). FREQUENCY F = $1/\tau$. DOCUMENTED AS YET IN CHILDREN (c) INCLUDING NEW BORNS AND ADULT GONADALLY ACTIVE MEN (m) AND WOMEN (w).
DATA FROM J. DAVY, N. KLEITMAN, M. GAUTHERIE, A. REINBERG, F. HALBERG, E. VAN CAUTER, J. GHATA, M. LAGOGUEY, F. SARGENT, G. DEBRY, E. WEITZMAN, J. UDRY.

Table 1

THE BIOPERIODIC VARIATION AND ITS PARAMETERS

The regular cyclic variation of any biological variable can be approximated by a sinusoidal function. This can be done roughly by plotting raw data as function of time (chronogram) or accurately by using the least squares method to obtain the best fitting cosine function (cosinor) approximating all data. For this latter Halberg et al (15,16) proposed employing a classical equation of the form.

$$y_{(t)} = M + A\cos(\omega t + \phi)$$

were M is the mesor : rhythm adjusted mean; A is the rhythm amplitude; ω is the angular frequency; t is the time and ϕ is the acrophase. The angular frequency $\omega = 2\pi/\tau$, were τ is the period and $1/\tau$ the frequency.

An illustrative example of a biologic rhythm characterization is given figure 1.

The period τ is the duration of one complete cycle in a rhythmic variation. It is customarily expressed in units of time, (e.g. seconds, minutes, hours, days, years).

The amplitude,A corresponds to one half the extent of rhythmic change for the considered τ. It can be expressed in conventional units (e.g. Celsius for temperature, mg/h for the 17-PHCS urinary excretion etc.) or as percent of M.

The mesor,M is the rhythm adjusted mean for the considered τ.

The acrophase, ϕ is the crest time location for the considered τ. ϕ must be given with respect to a starting point or a phase reference $\phi = 0$.

The cosinor and related methods are widely used by chronobiologists. They can now be programmed for small desk computers. The hypothesis of the amplitude A differing from zero (e.g. with $P < 0.05$) can be tested by the cosinor method in order to know whether or not a rhythm is detectable for a given τ.

THE SPECTRUM OF BI LOGICAL RHYTHMS

Logic as well as methodology demands that analysis of a rhythm always begin with an estimate of its period. In fact, knowledge of the period of biological rhythm is indispensable in estimating its amplitude and its acrophase.

Let us consider the periodic changes in a physiologic variable, the temperature of man. Beginning with sufficiently lengthy time series (several days, months or years) and with measurements made at relatively short time intervals (several seconds, minutes or hours) one can detect a rhythm τ = 1 minute (ultradian rhythm), a rhythm with τ = 24 h (circadian rhythm), a rhythm with τ = 7 days, τ = 1 year etc. (infradian rhythm). In other words, for the same biological process one can demonstrate several cyclic variations, each having a different period. As shown in table 1 ultradian, circadian and infradian periodicities have been shown in healthy children, men and women for various biological variables.

Knowledge of τ is often taken for granted. Take, for example, the case of a man who is synchronized by a stable alternation of diurnal activity and nocturnal rest (related to both the social constraint and the ecological niche) with an average period of 24 h. It is highly predictable and then expected that, under these conditions, the circadian rhythms of this subject will also have an average τ of 24 h.

THE ORGANISM'S TEMPORAL ORGANIZATION

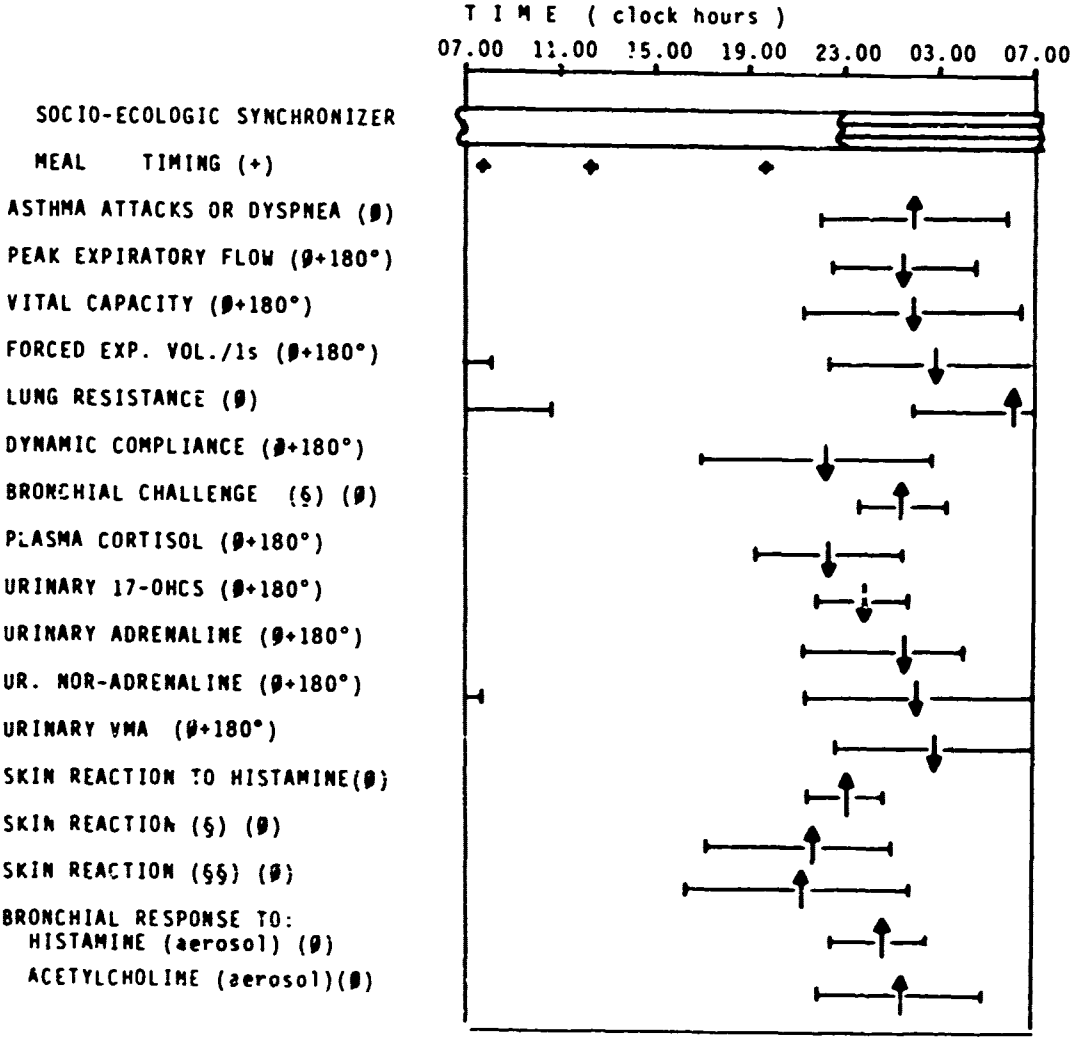
In any one species (including ours), knowledge of rhythms in all kind of biological variables permits a precise representation of its temporal organization for given domains. But even for the most extensively studied species (man, mouse, rat, acetabularia) we possess as yet only imperfect and very incomplete representation of this temporal organization.

In order to simplify the presentation of the time structure for man for example, one may for the circadian and the circannual periodicities show the acrophase relationships of different rhythms as well as their respective amplitude. The schematization of the circadian (figure 2) and the circannual (figure 3) temporal organization of adult men was made with results obtained, as far as possible under controlled and standardized experimental conditions. Emphasizing that all the subjects under the study were synchronized in a similar manner with regard to circadian rhythms. This latter methodological requirement although elementary is sometimes forgotten despite the fact it is essential.

SOCIO-ECOLOGIC SYNCHRONIZERS

We are born with a certain time structure, just as we are born with a certain anatomy (spatial structure). A set of indirect arguments are in favor of the hereditary character of biological rhythms in man. (Direct evidences result from plant and animal experiments : Aschoff 1, Bünning 2, Pittendrigh 17, Rensing 18, Hastings 19, Vanden Driessche 20). For example, biological rhythms persist during the isolation of men from known rhythmic variation of environmental factors (Halberg et al 9, Aschoff 13, Reinberg 21, Mills 22); their pattern are almost similar in MZ twins but not in DZ twins (6).

Nevertheless, biological rhythms are influenced by certain periodic variations of a set of environmental factors. The term synchronizer (or Zeitgeber) is applied to all environmental factors which present cyclic variations and which are capable of modifying one or more parameters which serve to characterize a biological rhytnm (τ,ϕ, A, M). For many plant and animal species, the cyclic alternation of light and darkness within a 24 h period for example, is one of the most powerful synchronizers. However, the periodic alternation between noise and silence, between heat and cold, etc. also act as cir-



(§)=House dust extract; (§§)=Pollen and/or Feather extracts.

Figure 2 . Aspect of the circadian temporal organization of men.

Temporal relationship between the timing of a) asthma attacks (or circadian peak in dyspnea) of patients suffering from allergic asthma and b) circadian acrophase or bathyphase timing in a set of these patients and/or healthy subjects physiological variables, considered as possibly component rhythms. Both acrophase —•— and bathyphase —|— -- respectively peak and trough of the best fitting cosine function used to approximate each of the rhythms -- are given with their 95% confidence limits. (The bathyphase differs from the acrophase Ø by + 180° or 12 hr). There is a good agreement in 1) the peak time of the clinical symptoms and 2) the timing of the circadian acrophase (or bathypase) of rhythms of variables usually considered as having a role in symptoms of allergic asthma. Asthma attacks (A. Reinberg et al 1963); Peak expiratory flow (F. Halberg et al 1966; M. Chai et al 1968; J. Reindl et al 1969; A. Reinberg et al 1970; U. Serafini et al 1974); Vital capacity (A. Reinberg et al 1970); Forced expiratory volume/1 sec. (G. de Vries et al 1962; A. Reinberg et al 1971; G. Tammeling et al 1974); Lung resistance and dynamic compliance (C. Gaultier et al 1975); Bronchial challenge to house dust extracts (Gervais, Reinberg et al 1977); Urinary 17-OHCS (A. Reinberg et al 1963; Van der Straeten 1964); Plasma cortisol (Reinberg et al 1975); Urinary catecholamines (Reinberg et al 1975); Skin reaction to histamine and allergens (A. Reinberg et al 1965, 1969; M. Smolensky et al 1974); Bronchial response to histamine (de Vries et al 1962; G. Tammeling et al 1974); Bronchial response to acetylcholine (A. Reinberg et al 1971).
New data has been added to the original figure - . . Reinberg : 31.

cadian synchronizers for certain species, under certain conditions. In man, the most effective synchronizer appears to be socio-ecological in nature (Halberg et al 3, 10, Aschoff et al 23, Apfelbaum et al 24). This means that the alternation of activity-light-noise-heat/rest-darkness-silence-cold related to both our social life and our ecological niche plays the major role in our synchronization.

The manipulation of a prominent synchronizer may be directed for example, at its period. It is possible -- within certain narrow limits --to impose a period other than 24 h, upon the circadian rhythms of men, e.g. 23 h or 25 h (Aschoff 12, 13). But is was not possible to impose a period of 21 h (Simpson 25) or 30 h (Gouars 26) by the manipulation of socio-ecologic synchronizers.

When the manipulation of a synchronizer is directed primarly at its phase, a shift in circadian rhythm acrophase is produced. Aspects of this important phenomenon are discussed in the present book by K. Klein, E. Weitzamn , B. Hartman, A. Reinberg.

With regard to circannual rhythms in men, the nature of the presumably existing synchronizer remains unknown. It has been shown in animal experiments : a) that circannual rhythms persist during isolation and b) that circannual (so-called seasonal) changes in the circadian photofraction are able to play the role of a signal (Cf. Bünning 2, Benoit et Assenmacher 27, Pengelley 28, Assenmacher et Farner 29.

EXAMPLE OF THE CIRCADIAN TEMPORAL ORGANIZATION IN MEN WITH SPECIAL REFERENCE TO THE BRONCHIAL PATENCY OF HEALTHY AND ASTHMATIC SUBJECTS (figure 2).

The acrophases of different circadian rhythms, in synchronized subjects, are not randomly distributed in the 24-hour-scale; on the contrary this distribution, at all level of organization, represents a specific time structure. The causal relationship between several physiological functions must be complemented by information concerning their temporal relationship. The phase relations between bioperiodic phenomena thus considered lead to describe coherent circadian systems.

Circadian changes in physiological variables used to characterize the bronchial patency, the bronchial motricity etc. has been demonstrated in healthy adults and children, as well as in adults and children suffering from allergic asthma. Peak expiratory flow, vital capacity, forced expiratory volume/1/sec, lung resistance and dynamic compliance among other investigated variable were shown to have circadian rhythms : a) with a large amplitude (10 to 35% above and below the 24 h adjusted mean or mesor) and b) with an acrophase timing that shows the smallest broncnial patency occuring around the beginning of the nocturnal rest (figure 2). When biological rhythms are viewed as an adaptative process one is not surprized to observe that the acrophases of the airway patency indexes occur during the activity span.

These circadian changes can be related to circadian rhythms in adrenal hormones and catecholamines among other secreted substances influencing the bronchial activity. It has been shown that, the trough in circadian rhythm of plasma cortisol, urinary 17-OHCS, adrenaline, noradrenaline and VMA coincide with the early nocturnal rest in both allergic patients and healthy adults (figure 2). In addition, chronopharmacologic studies with both a β-stimulating agent and a vagolytic agent have shown that the vagal tone predominates during nocturnal rest while the sympathetic tone predominates during diurnal activity with regard to the bronchomotricity (Gaultier et al 30).

Human susceptibility (skin and bronchial reactivity) to various substances has been explored around the clock. It has been demonstrated that, the circadian peak of susceptibility is found again during the first part of nocturnal rest. This is true for : 1) skin reaction to histamine, both in healthy and allergic subjects and to allergens (house dust, feathers, grass pollens, penicillin etc.) in sensitized subjects; 2) bronchial reactivity to inhaled histamine; 3) threshold of bronchial response to inhaled acetylcholine and 4) bronchial challenge to inhaled house dust extract in specifically sensitized patients. (Reinberg 31).

It would therefore appear that the usually nocturnal occurence of the asthmatic attack is a result of bioperiodic changes in the patient's reactivity, related : a) to physiological rhythms in cortisol and catecholamine secretion in bronchoreceptor susceptibility etc. and b) individual changes in the mean level of tolerance to allergens (Cf. McGovern, Smolensky, Reinberg 32).

EXAMPLE OF THE CIRCANNUAL TEMPORAL ORGANIZATION IN MEN WITH SPECIAL REFERENCE TO ENDOCRINE AND RELATED ACTIVITIES

Three preliminary remarks may be useful :

Three preliminary remarks may be useful :

a) Circadian and circannual rhythms must be investigated in the same experiment. The fact that bioperiodicity of a given physiologic variable can be expressed in several frequency domains has been documented in various animal species, including mice (Haus and Halberg 33), frogs (Dupont et al 34) and men (Reinberg 35). When sampling once daily (e.g. every other month) at different or even at the same clock hour(s), collected data may reflect circadian rather than circannual rhythmicity. Moreover, not only the 24 h mean level M, but also the circadian crest time Ø of a physiologic variable can be the subject of a circannual rhythm

b) The location (city and/or state) of the study must be given. The circannual acrophase can be geographically dependent in men, as demonstrated for certain variables by Batschelet et al (36) and by Simpson and Bohlen (37), Ghata et al (38). Annual changes in the day length with respect to the latitude, seem to be some of the major environmental factors (signals) to be considered in various species. Results summarized in this paper were obtained from subjects living in the northern hemisphere.

c) A temporal relationship between changes of two variables does not demonstrate in itself a direct causal relationship. This latter can be suspected if, in addition to the

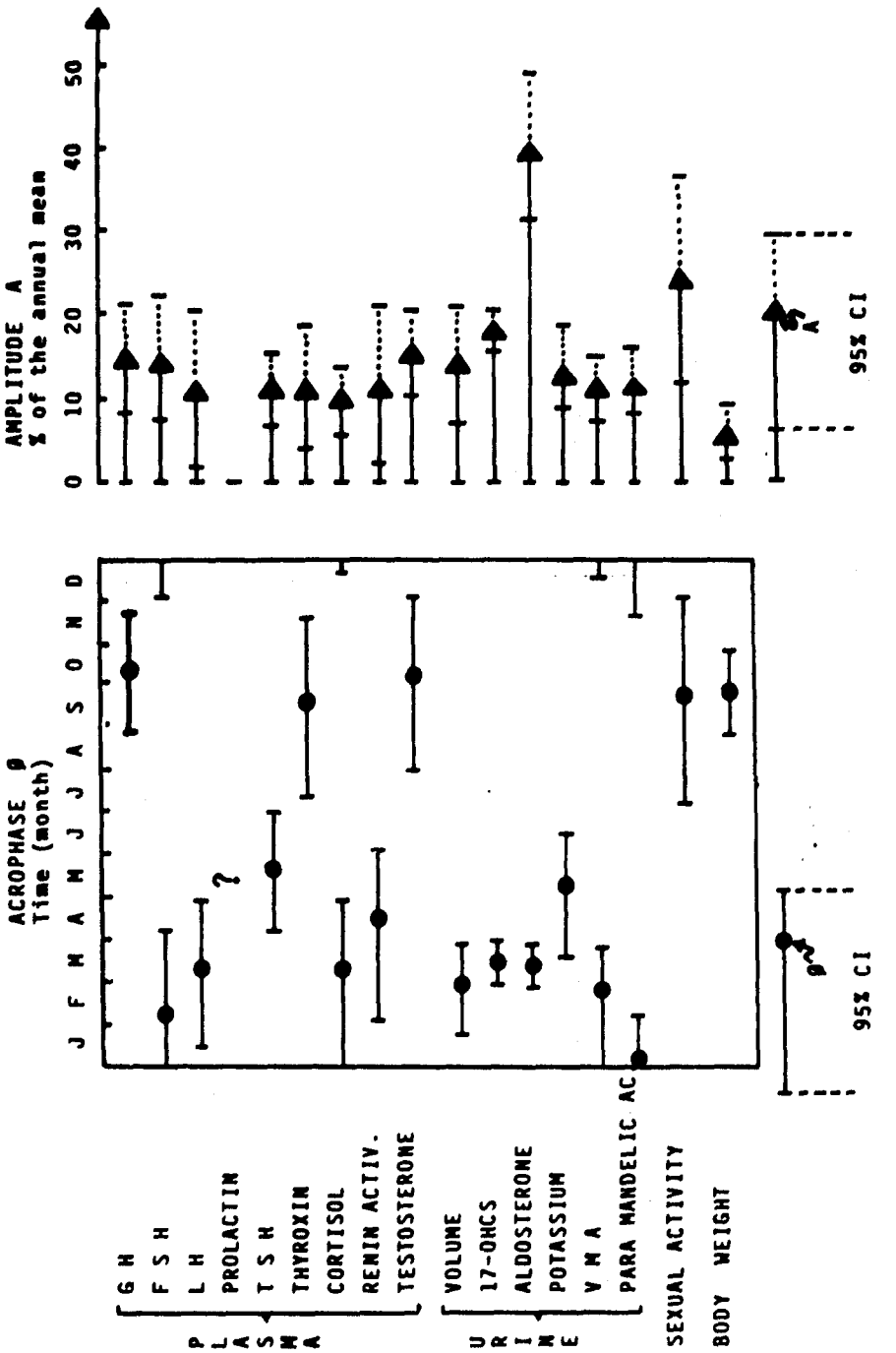


Figure 3 . *Aspect of the circannual temporal organization of healthy men.*

Circannual rhythms of 5 healthy young Parisian males : single cosinor summary. In any of the variables circadian mesors have been used for time series analyses. Annual acrophase, φ (crest time) and amplitude A (1/2 of the total variability/year) are given with their 95% confidence limits. A is a percentage of the annual 24 h mean. The annual A is relatively large for urinary aldosterone and relatively small for body weight. A does not differ from zero for plasma prolactin (no annual rhythm detected in the latter).
New data had been added to the original figure -- A. Reinberg and M. Lagoguey : 34 --

temporal relationship, a set of other arguments can be given (10, 35).

ENDOCRINE CIRCADIAN AND CIRCANNUAL CHANGES IN FIVE HEALTHY PARISIAN MALES (Figure 3)

For 14 months, five mature, apparently healthy (routine clinical examinations and biologic tests were normal) young males (medical students and biochemists) living in Paris, volunteered to document circadian change. At the beginning of the study they were 26, 26, 28, 29 and 31 years old. At the time of the 28-h tests (every other month for plasma sampling; monthly for urine sampling) the subjects were not taking any medication and had no sexual activity. Food and water intake was not controlled; meals were taken at about 07.00, 13.00 and 20.00. The subjects' circadian periodicity was synchronized with light-on at 07.00 (7 a.m.) + 1 h and light-off at 23.00 (11 p.m.) ± 1.5 h during the year (Reinberg and Lagoguey 39).

Circadian rhythms of levels of plasma hormone were investigated simultaneously in the five subjects during the same two days in January, March, May, July, September, November 1973 and again in February 1974. On test days, venous blood samples were withdrawn at fixed 4-h intervals for 28 h, starting at 08.00 on day 1.

Plasma (after centrifugation) and urine samples were stored at -25°C, ten tubes per sample to allow control and multiple determinations, each tube was defrosted only once. Determinations were performed in a large series, at the end of the entire study. Radioimmunoassay procedures were used for plasma variables and urinary aldosterone determinations. Specificity, sensitivity, and precision were tested according to the best current methodology. Both conventional and single cosinor (Halberg et al 15) methods were used for the statistical analysis of the time series thus obtained.

Circadian rhythms. No circadian rhythm in plasma FSH was detected in any monthly time series or in pooled data. Circadian rhythm in LH was detected only from July to November and in pooled data, with a small amplitude. Other variables showed statistically significant circadian rhythms.

Annual changes of circadian acrophase (when rhythms are measured in most if not all months). Plasma prolactin has remarkably fixed acrophases, located in the vicinity of 04.00 throughout the year. Circadian Ø's of sexual activity and urinary 17-OHCS do not exhibit detectable annual change, in contrast with circadian Ø's of plasma testosterone and plasma cortisol, respectively.

Both circadian Ø's of plasma testosterone and thyroxin have an early location in Spring and a late location in Autumn. On the contrary, Ø's of circadian rhythms related to the adrenal activity (plasma cortisol, urinary aldosterone, etc.) occur earlier in autumn (first half) winter and later in (second half) winter-spring. The fixation of circadian Ø of 17-OHCS could be due to noisy data.

Annual changes of circadian 24-h mean M. The single cosinor method was used to summarize all findings in figure 3. Prolactin has no circannual periodicity in these adult men. Statistically significant circannual rhythms are observed in the other documented variables. FSH, LH and TSH reach their maximum in Winter. Cortico-adrenal activity (plasma cortisol, urinary 17-OHCS and aldosterone) is also highest in February to March. Respective acrophases of plasma-renin activity and urinary potassium occur somewhat later, in April to May. The annual Ø's for thyroxin occurs in September in phase with annual Øs of plasma testosterone, GH, sexual activity and body weight. Urinary excretion of catecholamines reach their peak in Winter. Individual changes of the considered variables were similar to those depicted for the group. A set of circannual rhythms have been already reported in healthy men (Cf. Reinberg 35, Reinberg, Lagoguey 39).

Despite differences in methods of data acquisition, geographic location, etc. these results are in good agreement with ours.

Comments

The annual phase relationship between plasma testosterone and sexual activity may reflect a causal relationship, as is the case in various vertebrate species (Cf. Benoit and Assenmacher 27; Pengelley 28), including nonhuman primates (Conaway and Sade 40; Gordon et al 41; Peng et al 42; Mendoza et al 43).

This does not mean that the circannual rhythm of plasma testosterone is the sole variable, but only one of the variables that may play a role in the circannual rhythm of sexual activity. Plasma FSH and LH must also be considered even if a difference of about 6 months occurs between Ø's reflecting pituitary and gonadal activity. A similar time difference between annual peaks of these plasma hormones was observed in the Mallard drake by Assenmacher (29).

One explanation could be the existence of an annual cycle in gonadal sensitivity to gonadotropic hormones.

The second hypothesis, which does not exclude the first, takes into account chronopharmacologic phenomena (Reinberg and Halberg 44; Reinberg 45). The effectiveness of an agent (including hormones) varies as a function of the time of its administration (or of its circadian crest time in plasma concentration). An attempt to test this second hypothesis has been carried out as reported in the last part of present paper.

In addition, a circannual change of menarche has been observed (Cf. review in Reinberg 21), with a peak in late autumn-early-winter and a trough in Spring for the northern hemisphere.

The question arises whether or not these annual rhythms are endogenous or have an endogenous component. A coherent body of knowledge is available from other animal expe-

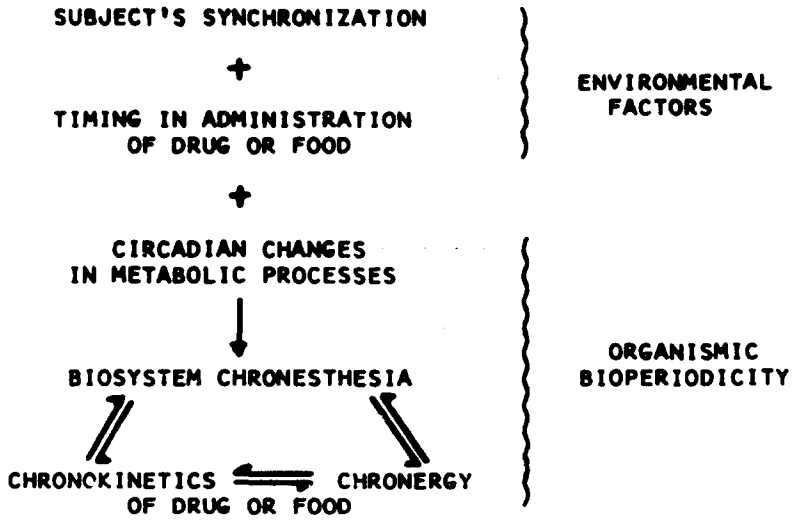


Figure 4 . *Concepts in chronopharmacology.*

Chronesthesia of a biosystem : rhythmic changes in its susceptibility; it includes both molecular and membrane phenomena and related metabolic processes. The chronesthesia involves cells, tissues, organs and organ systems of the host as well as the susceptibility of parasites; bacteria, tumours, etc. Chronopharmacokinetics of a chemical agent : rhythmic changes in either its bioavailability or its pharmacokinetics and/or in its excretion in the urine or by other routes (faeces, sweat, saliva, etc.). Statistically significant rhythms have been demonstrated in parameters used to characterize the pharmacokinetics of several agents. Chronergy of a chemical (or physical) agents; rhythmic changes in any of its effect(s) either desired ("chronoeffectiveness") or undesired activities. The chronergy of a chemical agent involves its chronopharmacokinetics as well as the chronesthesia of some biosystems. The acrophase (peak time) in the chronergy of a chemical agent does not necessarily coincide with the acrophase of its blood level.

riments : endogenous circannual rhythms (e.g., in gonadal activity and reproductive functions) are not induced by environmental information, but can be entrained by annual changes of external factors such as day length (Farner 46; Pengelley 28) at least in certain species. If the extrapolation from animals to man is acceptable, our species should have certain properties of short-day (or long-night) animals, with reference to reproductive functions in this context. The remark of Conaway and Sade (40) may be relevant : " .... it may well be that all primates including the human should be regarded as basically seasonal breeders".

In addition, circannual changes in endocrine activities could play a role in the occurence of annual changes in the resistance of the human organism to potentially noxious factors. More precisely, there is a striking coincidence in time between annual Ø's of adrenal activity and the high risk of certain lung infections and cardio-vascular diseases. With reference to the latter, it may be added that not only annual Ø's in aldosterone and plasma renin activity might be involved, but also annual Ø's in catecholamines.

CLINICAL CHRONOPHARMACOLOGY

The desired or undesired effects of a chemical (or physical) agent depend, among other things, upon the hour at which the organism was treated and especially, upon the circadian system stage of the subject under study(Reinberg, Halberg 10; Reinberg, Halberg 44; Reinberg 45).

Chronopharmacology involves both the investigation of drug effects as a function of biologic timing and the investigation of drug effects upon rhythm characteristics.
1. A large number of examples related to human chronopharmacology have been published and reviewed : circadian changes of skin reaction to histamine or allergens, of airways reactivity to histamine, a β-stimulating agent and acetylcholine; circadian rhythm in the duration of salicylate excretion, etc. A wide variety of other drugs and chemical agents have been studied in man, from a chronopharmacologic point of view.
2. Chronopharmacology is not restricted to circadian rhythms but can be extended to rhythms with period $\tau > 24$ h, e.g. mensual chronopharmacology in women : a) days of changing responsiveness to chemical and physical agents, and b) drug-induced circamenstrual rhythm alteration.However, only circadian chronopharmacology is well documented.
3. Three new concepts must be considered (figure 4).
a) The chronokinetics of a drug embracing both rhythmic (circadian) changes in the drug bioavailability (or pharmacokinetics)and its excretion (urinary among others).
b) The chronesthesy of a biosystem to a drug, i.e. circadian changes in the susceptibility of any biosystem to a drug (including organ systems, parasites etc.). Both skin and bronchial chronesthesy to various agents have been documented in men.
c) The chronergy of a drug taking into consideration its chronokinetics and the chronesthesies of the involved organismic biosystems. The term chronergy includes rhythmic changes in the overall effects and in the effectiveness of some drugs.
4. Clinical chronopharmacology is useful to solve problems of drug optimization, i.e. to enhance the desired efficiency of a drug and/or to reduce its undesired effects. This has been done already for corticosteroids, leading to a chronocorticotherapy.

Let us give a new illustrative example of clinical chronopharmacology which is also pertinent for chronoendocrinology. It deals with the HCG-stimulated testicular response of healthy human males (Lagoguey et al 47). Four healthy human males synchronized with a diurnal activity (from ~ 07.00 to ~ midnight) and a nocturnal rest volunteered for the experiment. They were already involved in the study of endocrine circadian and circannual rhythms (cf. figure 3). The subjects were submitted to 6 different tests (June 78). 2500 IU/0.5 ml HCG (Organon) IM injections were done one week apart at 07.00, 14.00 and 20.00, as well as control IM injections of saline. Days and fixed clock hours of the 6 tests were randomized. Venous blood was sampled 30, 60, 90, 150 and 240 min. after each injection of both saline and HCG. Plasma testosterone (pT) was measured by radioimmunoassay.

Mean control pT levels are relatively high at 07.00-11.00 and relatively low at 20.00-00.00. These changes correspond to the circadian rhythm reported previously for the same subjects.

Changes resulting from a single HCG injection, as a function of time can be expressed as : 1) HCG-stimulated pT/control pT ratio; 2) pT peak height/control pT ratio; pT peak height being the highest level after the HCG stimulation. The testicular response to HCG seems to be stronger at 20.00 than at 07.00. In example, pT peak height/control pT ratio is ~ 8 times greater at 20.00 than at 07.00 ($P < 0.01$). In addition, the span of time to reach the peak (time to peak) is shorter at 20.00 (90 min $\pm$ 21 = 1 SE) than at 07.00 (218 min. $\pm$ 23; $p < 0.005$).

Therefore, it seems that the response of the human testis to a specific stimulation has a circadian rhythm of large amplitude. These results may be useful for a better understanding of bioperiodic changes in both human endocrinology and clinical chronopharmacology.

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CIRCADIAN RHYTHMS OF HUMAN PERFORMANCE AND RESISTANCE: OPERATIONAL ASPECTS *

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SUMMARY

Circadian rhythmicity of mental and physical efficiency as well as of resistance to noxious hazards is reviewed, the interaction with internal and operational factors analyzed, and implications are given for management of human operations; in an append· the significance of the "Biorhythms" concept for the prediction of human behaviour an· the occurrence of man-related accidents is discussed.

INTRODUCTION

Man's functional capacity during mental and physical activity is the result of multiple endogenous and exogenous determinants, one of them being their daytime-related oscillation. It has been documented that circadian rhythmicity as a basic principle of biological systems does not only control physiological functioning at rest but also the responses of the body during loading, thus involving performance and efficiency.

Already more than 20 years ago, a certain section of the circadian cycle has been characterized as the "minimum of readiness for efficiency" (67) and as the "hours of diminished resistance" (32). In animals, it was shown that even death and survival in a hazardous environment could be made experimentally a function of circadian system phase (39). In 1966, we first presented data demonstrating in man rhythms in indices of physical fitness and operational stress resistance (63). Since then, the applied aspect of variations and oscillations of human performance efficiency has been subject of extensive research and analyzation (15, 17, 38, 43, 61, 62). It is the purpose, now, to summarize and update information on this topic and discuss its significance for human operations.

RHYTHMICITY OF MENTAL PERFORMANCE EFFICIENCY

In the beginning of research irregular findings with respect to the shape of the 24 hours performance curve - often due to poor methodology and inappropriate techniques - have caused scepticism as to the genuineness and significance of the relation between time of day and mental performance. Then, in well-controlled studies, using relatively short and simple tests Kleitman (66) established an association of diurnal variations of human performance with body temperature which appeared so close that temperature for a while was used as an indirect measure of performance efficiency in studies on circadian rhythm and shift work. However, in the last decade it became increasingly clear that this relationship does not hold for mental performance in general, but different tasks show different circadian variations in terms of "shape", or better phase and amplitude of rhythm, and that - where such a relationship originally exists - it may dissociate as consequence of changes in the temporal organisation of the environment or in response to shift work.

"Normal" Performance Rhythms

It is obvious from Figure 1 that body temperature as well as the scores of performance tests, with some variations, rise during the day to a peak, or kind of a plateau, between 1200 and 2100 hours and decline to a minimum which usually occurs between 0300 hours and 0600 hours. This is true for flying an F-104 simulator (56, 57), for cancelling symbols or adding two-digit numbers (65), and for the highly paced psychomotor performance on the "Kugeltest" (64). Similar curves have been described for many other tasks (46), like latency and detections in a vigilance test, for card sorting, and for the scores in a choice reaction test, to mention only a few.

The range of oscillation, i.e. the difference between the maximum and minimum score within a circadian cycle, for mental performance measured under standardized laboratory conditions, varies (for the group averages) between 10 % to 30 % of the 24-hour mean (1, 5, 8, 16, 44, 46, 57, 65, 66, 68, 88).

Factors Controlling or Modifying Performance Rhythms

Some factors of internal, operational or environmental character have been identified to control or modify mental performance rhythms of which the following proved to be the most significant: sleep, task variables, personality, motivation, sustained operation, physical exertion, and changes in the relationship between the temporal organisation of the body and the environment. (Of these factors the last will not be discussed in this paper but later in the Lecture Series.)

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* (Part of this lecture was presented by one of the authors (K.E.K.) as 11th "Harry G. Armstrong Lecture" to the 47th Annual Scientific Meeting of the Aerospace Medical Association on May 13, 1976, in Bal Harbour, Florida)

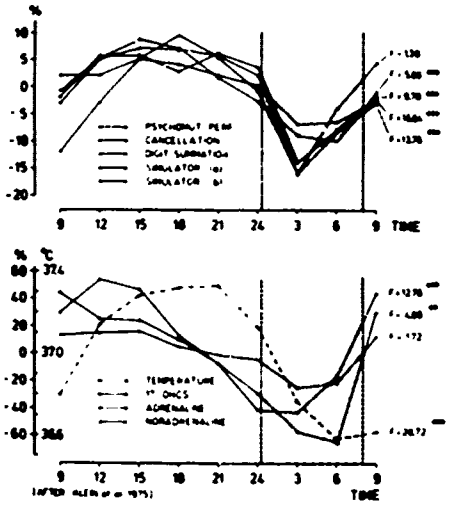


Figure 1: Circadian rhythms of behavioural and physiologic functioning in percent of the 24-h mean, body temperature in °C. (F-values for within day variation; ** $p \leq 0.01$; *** $p \leq 0.001$)

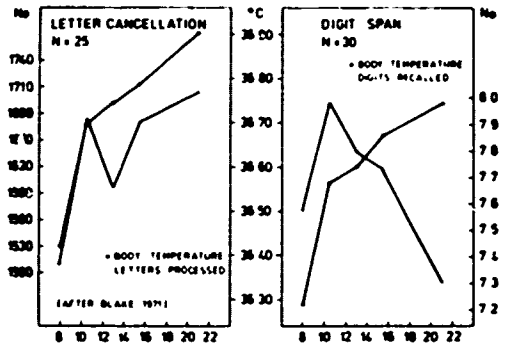


Figure 2: Mean body temperature and mean performance sores in the Letter Cancellation and the Digit Span test.

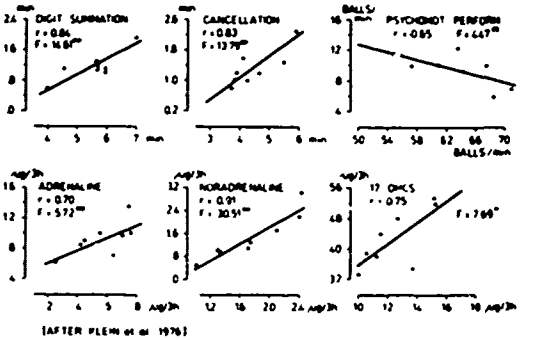


Figure 3: Correlation of circadian range of oscillation and 24-h mean for behavioural and physiologic rhythms. (F-ratio for significance of correlation; (*) $p \leq 0.1$; *$p \leq 0.05$; ** $p \leq 0.01$).

Sleep. If subjects are not aroused from sleep for testing but stay awake during the night, the phase of rhythm drifts towards later hours. The range of oscillation, in comparison to controls, during the first night awake is smaller but becomes increasingly larger as sleep deprivation continuous; at the same time the 24-hour mean of performance decreases (1, 28). (For sleep loss effects see also section "Sustained Operation".)

Task variables. Blake (8) seems to be the first who presented evidence for the assumption, that memory - with respect to the phase of the circadian curve - may be a "notable exception"(46) since the peak score in a memory task, inversely to body temperature, occurred in the morning and scores dropped off steadily during the day (Figure 2), thus resembling more the variation of some stress-related hormones like 17-OHCS, or more, yet, adrenalin (Figure 1). Later, some authors have established that "immediate memory" peaks in the morning, deteriorates through the early afternoon (1400 to 1500 hours) and rises again to the evening (35, 70). Others found the correlation between performance rhythm and temperature rhythm to change from a significant positive value to a significant negative one as the memory load of the task was increased (29, 30).

Memory functions not only exhibit pecularities in phase but also lower ranges of oscillation (70). This is of particular interest in view of the negative correlation between amplitude and speed of adjustment of physiologic rhythms to shift work (84) and to shifts of artificial "Zeitgebers" (103). In fact, it was demonstrated (70) that a higher memory loaden task adapted faster to night work conditions simulated in a laboratory and to time shift following transmeridian flight.

Personality. Several investigators have described an influence of habitual and personality factors on behavioural periodicity (9, 10, 66, 73, 74). The results may be summarized as follows: In extraverts as compared to introverts (and similar in evening types against morning types) maximum and minimum of performance efficiency came later within the circadian cycle and the spontaneous period length in the free running state is longer. If extraverts and introverts are tested in one group, circadian rhythm is synchronized and the differences are masked (13). In addition, "neuroticism", as compared to "stability", seems to increase the rate of internal desynchronization in isolation from time cues (102), as well as to hasten phase adjustment during shift from day to night work or after transmeridian flight (19).

Motivation. In their extensive studies on various demanding work-rest schedules, Alluisi, Chiles and their collaborators (1, 2, 12) demonstrated that motivation may reduce circadian variation of mental performance through "extra effort". They concluded that together with motivation, workload, that is the stress imposed by the task, had determinated the extent of cycling in so far, as the range of oscillation was low, if motivation was good or the task simple; or, on the other hand, periodicity was pronounced when motivation was low or the task very complex. In context with the load of the task, the reduction of the circadian amplitude during practicing (2, 31) and its increase

during sleep deprivation (12, 28) can be understood as effects of relative workload alterations.

Changes in the range of oscillation, as just described, must alter the 24-hour mean. Since, in general, the trough of the circadian cycle is more susceptible to influences of the kind mentioned above, the 24-hour mean will be inversely related to the range of oscillation. Indeed, we have been able to demonstrate such an inverse relationship for the performance level of pilots in a flight simulator (57), as well as for some other mental performance tasks (62) for which the regression lines and correlation coefficients (together with those for some "stress-related" hormones) are shown in Figure 3. Since practicing on the task was finished and each subject had reached his optimal level of performance, the interpretation of this phenomenon leaves open, yet, two possibilities: the reason could be seen in different levels of motivation; but also a particular "disposition" manifesting itself as a higher susceptibility to the performance depressing influence during night could have been the cause for the higher range of oscillation in individuals with the lower performance level.

Sustained operation. Of particular interest are the interaction of circadian cycling of performance efficiency with the behavioural effects of sustained activity or sleep deprivation. As was shown earlier (1, 14), and recently was demonstrated again (3), the extent of performance degradation caused by sustained operation depends on the actual phase of the circadian cycle it coincides with (Figure 4). When an extended duty period began at noon, the performance degradation (commencing in this group of subjects after about 16 hours of operational activity), amounted to -10 % to -15 %, while, when the same operation began at midnight, the maximum decrement of performance amounted to -35 %. In the former case the effect of fatigue was obviously compensated in part by the increasing level of arousal during the day; in the latter case operational fatigue evidently added to the depression of alertness naturally occurring at night. It is clear that in managing human operations one should possibly prevent a coincidence of the final section of a long-haul activity period with the nocturnal low of behavioural rhythms.

Colquhoun (20) has proven the benefit of the injection of a sleep section into a period of sustained operation (Figure 5): Two operational periods which took place between 2000 and 2400 hours and 0400 and 0800 hours were separated in one case by a (non-operational) wake period, in the other case by a sleep section. The difference between the two conditions, obviously caused by sleep, was (a) a reduction in performance degradation at the circadian trough of about 10 %, and (b) a "normal" increase of performance in the early morning hours, leading to a difference of more than 20 % in performance efficiency at 0800 hours. The significance for crew management, for instance, in reinforced crew operation is obvious, again.

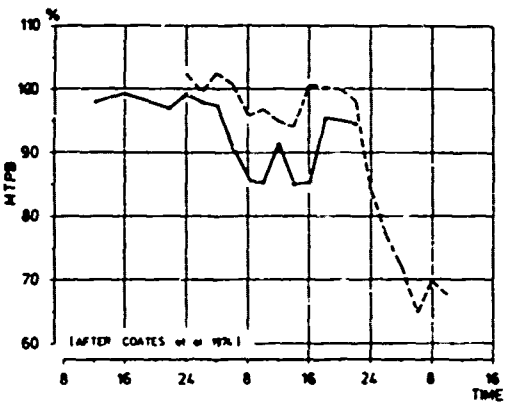


Figure 4: Sustained operation and circadian performance rhythm: Dependence on starting time.

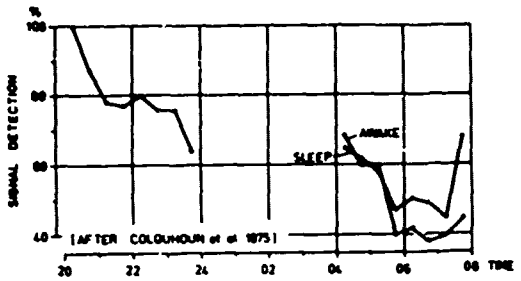


Figure 5: Effect of sleep injection into a period of sustained operation. (Relative changes in auditory vigilance).

As Wilkinson (104) has shown, the effect of sleep reduction is, also, dependent on the time of day (Figure 6): if sleep was reduced by only 2.5 hours in each of two consecutive nights, for instance, impairment of performance on a vigilance task was 13 % in the morning, but only 8 % in the afternoon and evening of the following day; the daytime dependent difference in performance degradation was the more pronounced the more sleep was reduced.

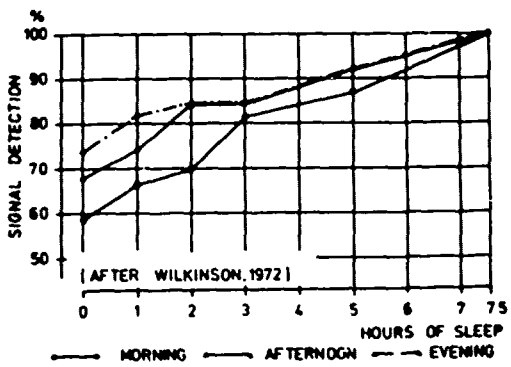


Figure 6: Sleep deprivation effect on performance depending on time of day.

Physical exertion. Physical activity may influence mental performance through changes in the level of arousal: Light to moderate physical work increases it, heavy;

work has the opposite effect. It has recently been demonstrated (113) that this effect depends on time of day as well as on a task specialty. A physical load of about 30 % of the maximum aerobic work capacity improved the scores of a visual-motor coordination test in the morning and afternoon but not in the late evening and early night. However, the same exercise regimen impaired performance in a memory test at all hours of the day, in comparison with (non-exercise) control conditions. The results were explained with differences in the relative load of physical exertion: the load seemed to be beyond the optimum of arousal for memory functions in general, and for psychomotor performance at the specific time of the day. (The relativity of physical exercise load in dependence on the time of day is furhter discussed in the chapter "Rhythmicity of Physical Exercise Efficiency".)

The Arousal Theory and Performance Rhythms

The modification of behavioural rhythm can be explained quite well by the "inverted-U" shaped relation between arousal and mental efficiency (Figure 7). Colquhoun (16) has pointed to the fact that a given fluctuation in arousal will result in a more pronounced variation in performance efficiency when the overall level of arousal is low than when it is relatively high or even near the optimal point. Accordingly, increase of arousal by task-complexity and/or by higher motivation will decrease the circadian range of oscillation of performance rhythms while a reduction in arousal through loss of sleep, lack of interest etc. will have the opposite effect. Arousal beyond the optimum (hyperarousal), for instance through extreme motivation and/or task overload, increasingly causes pronunciation of circadian rhythmicity the more arousal is shifting towards the (opposite) end of the curve.

Performance Rhythms in Field Studies

Behavioural rhythms evaluated in field studies like work output, frequency of failures and number of errors (7, 11, 37, 45, 82), in principle, follow the circadian characteristics observed in laboratory research on human performance efficiency; there are, however, two differences, at least, worth mentioning (Figure 8): (a) the range of oscillation is much higher and often comes up to 100 %, or more, of the 24-hour mean, and (b) a second (minor) peak of performance degradation, the "post-lunch dip", is often found shortly after noon.

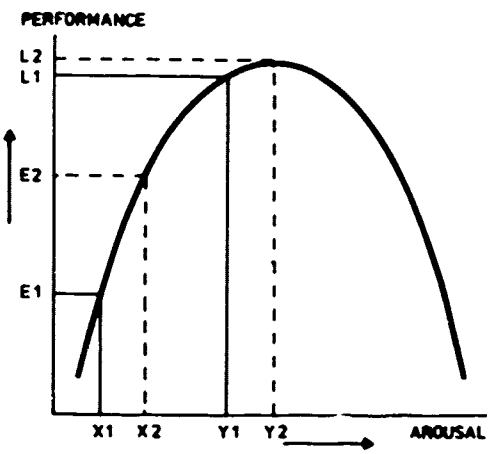


Figure 7: Postulated relationship between level of arousal and performance efficiency. (After Blake, 1971).

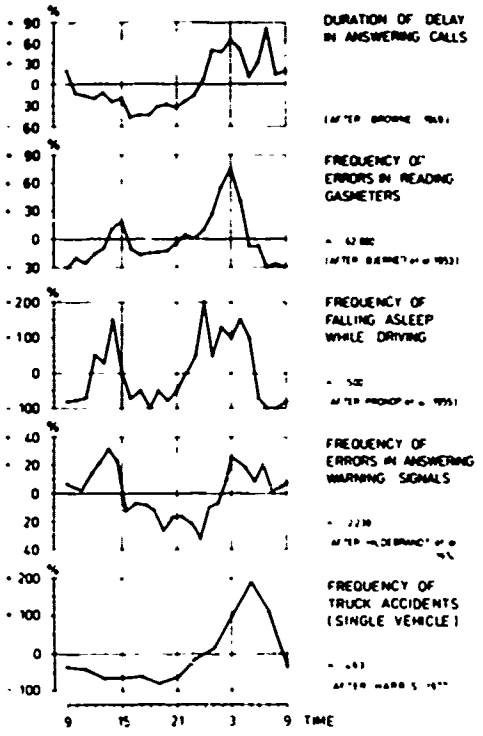


Figure 8: Behavioural circadian rhythmicity in field studies.

The pronounced circadian oscillation is usually explained with the fatigue caused by continuous duty and its interaction with the circadian depression at night. Other reasons could well be lack of interest and/or motivation, or, in comparison to the laboratory, unfavourable environmental conditions, for instance, with respect to noise or temperature levels.

The "post-lunch" phenomenon is not necessarily related to the meal usually taken at that time of the day (16). It has been attributed, also, to the duration of the preceding duty period; however, this does not explain, why the performance increases, again,

towards later hours,even during continuous activity. It nas been speculated (45) that a 12-hour rhythm of "susceptibility" or "readiness" for mental performance might be superimposed on the basic 24-hour cycle and could be responsible for the accumulation of performance failures in the early afternoon. In this context it is of interest to know that the post-lunch depression of performance, in contrary to the responses at night, is not accompanied by a decrease in body temperature.

Behavioural circadian rhythmicity may favour an accumulation of nocturnal mishaps. As Harris (37) did demonstrate, recently, this is the case in single-vehicle road accidents, in particular, if "dozing" of drivers was reported (Figure 8). In analyzing the situation leading to accidents of that kind for which "coming off the road" is typical,he emphasized that "the truck driving task is likely one of the most demanding vigilance tasks" where the driver must maintain a "continual vigil", "keep his truck positioned in a traffic lane", "constantly monitor the lane", and "a momentary lapse of attention could have and often has had disasterous consequences". Harris, in the same material confirmed the effect of fatigue: fewer accidents than expected occurred early in trips and more than expected during second half of trips; the "crossover" from less than expected to more than expected occurred between the fourth or fifth hour of driving time. So, there was, again, evidence for an interaction or a superimposition of the natural decrease of arousal through circadian rhythmicity and the operational induced fatigue effect causing a depression of arousal, too.

Circadian influence could hardly be demonstrated for accidents in which a vehicle crashed into the rear end of another one (37): the percentage followed rather closely the "exposure" data i.e. the relative number of trucks on the highway by time of day, though accident rates are slightly higher than expected by exposure between midnight and 0800 hours (Figure 9).

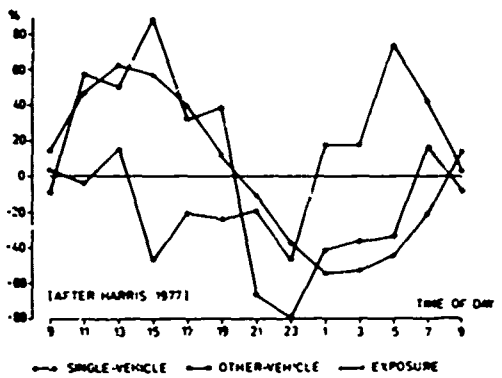


Figure 9: Percentage of accidents by time of day and type of accident. (Exposure: normalized percentage of trucks on the highway for a random sample of interstate drivers).

RHYTHMICITY OF PHYSICAL EXERCISE EFFICIENCY

It seems that we were the first to experimentally repeat standardized physical fitness tests around the clock. We found cardiovascular responses at mild (55) and medium (63) exercise intensities to be subject to periodic variations: heart rates and blood pressure were lowest between 0300 - 0600 hours and highest at 1200 - 1800 hours. If exercise heart rates were used in the conventional manner to predict maximal oxyger uptake ($\dot{V}O_2max$) by means of nomograms we came to the result that aerobic work capacity was higher at night than during the day. This finding was unexpected but compulsory since the prediction of $\dot{V}O_2max$ from exercise heart rates rests on the assumption of an inverse proportional relationship between the two parameters according to which lower heart rates at a given work intensity indicate a higher aerobic work capacity. This principle has been proven to be valid in comparison of individuals with different work capacities, i.e. trained and untrained subjects, and, intraindividually, if muscular exercise capacity, in parallel to $\dot{V}O_2max$, increased in the course of an athletic training. However, we have always expressed doubts (55, 63, 64) that this principle was applicable to intraindividual differences in exercise heart rate response due to circadian cycling, and have pointed to the fact that older and starving individuals have lower heart rates without having higher work capacities, at the same time.

In the following years, circadian differences of cardio-vascular responses - mainly heart rates - were confirmed for various tests (Leistungspulsindex, Physical Work Capacity 170,etc.) at different submaximal exercise levels (22, 97, 98). At the same time, it became obvious that oxygen consumption oscillates with the time of day only at rest and at mild exercise loads; no day-time dependent $\dot{V}O_2$-differences were found at submaximal work intensities (22, 98). In 1971, the status of knowledge induced the statement (42): "The maximum of physical efficiency is not found during the day but around 3 a.m. at night".

Up to that time, however, direct measurements of aerobic capacity at different day times were still lacking. Then, between 1973 - 1975, five papers from different groups of investigators were published on this topic (23, 49, 99, 100, 112). Additionally, it was demonstrated that actual athletic performance was significantly better between 1600 and 1800 hours as compared to 0700 - 0800 hours (21, 86); the same was shown for exercise training (6).

In one of the laboratory studies (23) maximal aerobic work capacities compared at 0800 and 1800 hours were not different. For the other experiments, with respect to day-night differences, the results can be summarized as follows:

- Maximal oxygen uptake was not different (99), was 3.9 % higher at night (100), was 5.7 % (49) and 5.2 % (112), respectively, higher around noon, all differences being statistically significant.
- Maximal work output was higher for 1.1 % (100) and for 12.4 % (49), respectively, during the day as compared to the night, both differences were significant.
- Maximal heart rate was not significantly different in most studies (99, 100, 112); only in one case (49) it was 3.4 % higher during the day.

For the evaluation of circadian differences of physical work capacity it is of particular interest that in the two studies where it was indicated work output was higher during the day than at night. From the figures given in these papers we have computed for the circadian extremes of work output the ratio of oxygen consumption to work output and found that "efficiency" was 5 % lower at 0400 hours as compared to 1600 hours (100) and was 11 % lower at 0300 hours than at 0700 hours (49), respectively. For rest and mild exercise levels, in principle, the opposite, a higher efficiency at night, is true, since oxygen consumption under these conditions shows a clear cut circadian rhythm with a maximum during the day and a minimum at night. The differences of "efficiency" for physical labour performed either at 1600 or at 0400 hours are best demonstrated through the linear regression of oxygen consumption on workload (Figure 10): At 11 mkp/s, e.g., oxygen consumption is 3.6 % higher during the day, in the medium range of workload (at about 14 mkp/s - 16 mkp/s) there is no day-night difference and at 27 mkp/s the oxygen consumption is 4.6 % higher during the night. These figures are taken from an investigation performed in our laboratory on 16 untrained students (100); since "workload" is also a relative term, the absolute values of this correlation may depend on properties of test subjects, like status of training, age, etc. Typical intraindividual differences in the physiological responses to an increasing workload observed in one subject in a day- and night-test are presented in Figure 11.

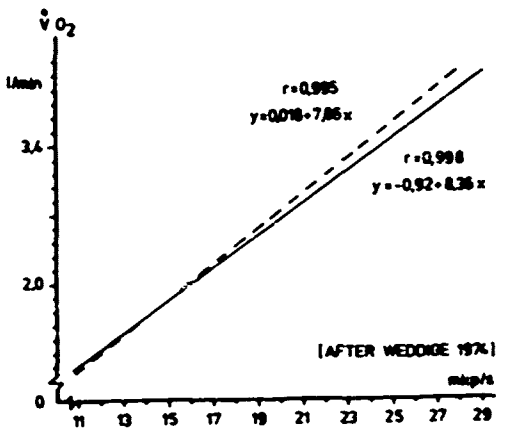


Figure 10: Linear regression of maximum oxygen uptake on workload, as evaluated at night (dashed line) and during the day (solid line).

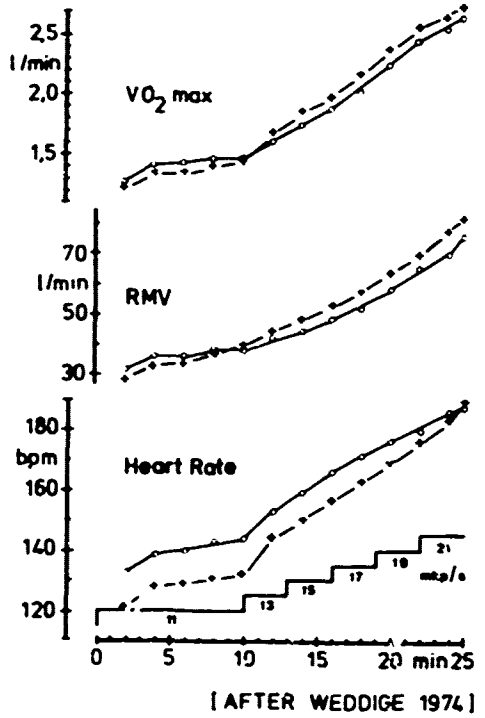


Figure 11: Intraindividual day-night differences in heart rate, respiration, and oxygen uptake under different workloads. (o-o day, +-+ night).

In context with the subject discussed here, Östberg und Svensson (74) recently pointed to the fact that older individuals have lower heart rates but perceive workload higher than younger ones; they compared this with day and night responses to physical exercise and concluded that the "functional age" increases during the night. They took this phenomenon as indication for a minor efficiency of man for physical work at night.

Similar as with mental efficiency, in physical performance, also, there was an interaction demonstrated between the effects of sustained operation and time of day (111): If subjects pedaled on an ergometer continuously for an 8 hours shift with a workload of 30 % of $\dot{V}O_2$max there was no significant difference in oxygen uptake 30 min after commencement of shift at 0830 hours, 1630 hours or 0030 hours; however at the end of shift oxygen uptake was higher than at the beginning, for 2.7 % at 1600 hours, for 11.5 % at mid-

night and for 4.9 % at 0800 hors, thus efficiency for a medium workload being lowest at midnight.

The present knowledge on circadian variations of physiological responses to physical work is best summarized and interpreted as follows (Figure 12):

- Heart rates at rest (in parallel to other cardiovascular and metabolic variables) show a circadian oscillation with a difference of about 8 - 12 % between the diurnal maximum and nocturnal minimum. This difference becomes smaller with increasing workload and approaches zero at maximum effort. The day-night difference in heart rate is not identical with the trained-untrained difference (Figure 13); it is therefore not possible to predict aerobic work capacity correctly from heart rate level at submaximal exercise with nomograms set up in sports medicine.
- Similar as with heart rate, oxygen uptake at night as compared to the day, is lower at rest and at mild exercise; however, there is no circadian difference anymore at medium workload and at submaximal and maximal work output nocturnal oxygen consumption seems to be higher (Figure 10). This is also different from what was observed as typical for trained and untrained subjects (Figure 13).
- In accordance with the nocturnal low of "readiness for efficiency" spontaneous maximal work output or maximal oxygen consumption seems to be somewhat lower at night; however, depending likely on motivation, it is possible to reach the same level of maximal oxygen uptake at night as during the day through "extra effort".
- "Efficiency", that is oxygen consumption in relation to work output, at maximum efforts, is significantly lower at night, consequently equivalent work outputs as during the day can only be produced with higher "physiological cost"; this is in the order of magnitude of 5 - 10 % extra oxygen uptake. The lower efficiency could explain the subjective feeling of temporary night workers that nocturnal labour is relatively more stressful.

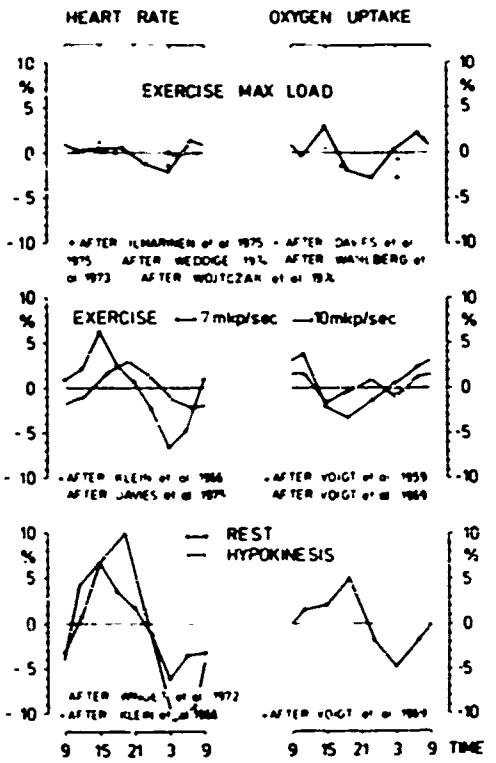


Figure 12: Circadian rhythms of heart rate and oxygen uptake during hypokinesis, rest, and physical exercise of different loads.

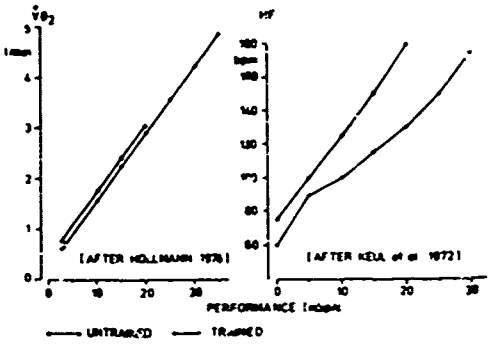


Figure 13: Dependence of heart rate and oxygen uptake on workload in untrained and trained subjects.

RHYTHMS OF SUSCEPTIBILITY TO HAZARDOUS FACTORS

Susceptibility to noxious stimuli. Rhythms of susceptibility or resistance have been investigated, mostly, in animals. Many authors were able to demonstrate circadian cycling already more than 15 years ago for a variety of noxious stimuli like ethanol (40), anaesthetics (24, 77), bacterial endotoxine (32), cuabain (34), and for convulsions experimentally induced through audogenic (36) and chemical (25) stimulation or electroshock (110). Also, a circadian sensitivity of mice and rats to irradiation has been shown (80), with a possible relation to periodic hemopoetic cell responses (41, 81, 96), and to the circadian amplitude of hypophyseoadrenal activity (26).

Though phase differences were quite apparent among drug susceptibility rhythms, it seemed that the lowest resistance for a standard dose in the lethal range frequently was more easily obtained in the natural activity period, while during the same period the largest dose was needed to produce the specific therapeutic drug effect (e.g. anaesthesia with an anaesthetic); thus, the therapeutic index seems to be the lowest during the activity, and the highest during the resting period of rodents. Meanwhile, circadian periodicities in toxicology and pharmacology have been intensively explored and implications are being introduced into clinical practice for man (33, 71, 83, 92).

Decompression sickness. More than the therapy-oriented susceptibility rhythms, the periodic oscillations of resistance to environmental stressors seem to be of significance for aerospace operations; and here, indeed, exist some observations on man. Already in 1944, a dependency on the time of day of the frequency of symptoms of decompression sickness in man during altitude chamber rides has been observed (13): Between 0900 and 1200 hours 11 % out of approximately 2 000 subjects experienced signs of decompression sickness while between 1300 and 1600 hours only 29 % out of a similar number of subjects suffered from the same symptoms. Differences in peripheral blood flow which is higher in the afternoon '52) could be the reason.

Altitude (hypoxia) tolerance. We evaluated human tolerance to decreased PO_2 (hypoxia), measuring the time of useful consciousness (TUC) in healthy male subjects in an altitude chamber at a barometic pressure of 287 mm Hg or 7.500 m (63): With a TUC of 6.3 min at 0300 hours, altitude tolerance was about 34 % better at night than at 1500 hours (TUC = 4.7 min) and 1800 hours (TUC = 4.8 min) during the day (Figure 14). In mice (93) mortality during exposure to a hypoxic gas mixture of 5.5 % oxygen in nitrogen was significantly higher (66.7 %) in the dark (activity period) than in the light span (36.1 %). Independently from the time of day, mortality was always higher when mice came from the dark (activity) before being exposed to hypoxic conditions (94), so that the circadian rest activity cycle seems to be one strong determinant of hypoxic resistance.

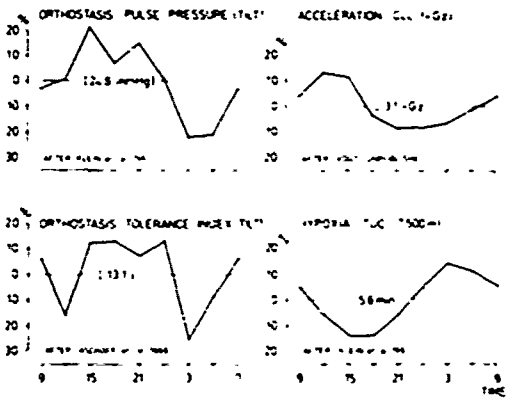


Figure 14: Circadian rhythm of susceptibility to stressors in man.

In man altitude tolerance is highly correlated in a negative way with the individual response of the adrenal cortex to an acute altitude exposure (101): Higher resting values and smaller responses of the 17-OHCS plasma level were found in relation with relatively better altitude tolerances in unadapted (58, 60), as well as in altitude-adapted (50, 59) subjects. This is exactly the functional state of the adrenal cortex during the night in man with normal social habits: A higher level of 17-OHCS and a smaller response of the same hormone to a standardized stress or ACTH dose, so that the circadian periodicity in the activity and reactivity of the adrenal cortex in connection with the circadian rhythm of basic oxyge.. consumption could be the reason for the particular day-night fluctuations found in the altitude tolerance.

Oxygen toxicity. A circadian rhythm has also been established for the susceptibility to oxygen toxicity seizures (47): In rats during exposure to hyperbaric oxygen the time preceding the first convulsion, was more than 100 % longer between 0700 and 1100 hours, i.e. during the early sleep phase than at the other times of the 24-hour cycle; it was speculated that the protective mechanism against cerebral oxygen toxicity effects might be seen either in a decrease in sympathetic tone due to a decrease in epinephrine, or in the circadian rhythm in the CNS level of serotonin which is high at the onset of sleep.

Orthostatic tolerance. Another physical factor for which circadian rhythmicity of tolerance has been demonstrated in man is orthostasis (Figure 14). Pulse pressure during tilt (63) as well as an "Index of Orthostatic Tolerance" (4) computed from heart rate and blood pressure responses to tilt were more favourable in the afternoon and evening than between 0300 and 0600 hours; sleeping subjects between tests during the nocturnal period seemed to pronounce the differences. The reason was seen in the nightly trough of cardiac output and of venous pressure at the lower extremities which is accompanied by a high of the extracellular fluid volume (4). We could recently confirm the idea of daytime dependent responses to orthostasis for "Lower Body Negative Pressure (LBNP)" tolerance which, again, was markedly higher in the afternoon than in the morning (unpublished results).

Acceleration tolerance. On the same line, we should see preliminary data obtained in our laboratory by Vogt (unpublished results) which indicate central light loss (CLL) during $+G_z$ centrifugation to occur at an acceleration level about 0.8 G higher in the early afternoon than at night (Figure 14). However whether this finding reflects a "true" circadian rhythmicity of cardiovascular responses to a $+G_z$ stimulus is presently difficult to decide, since the light-threshold itself shows a similar periodicity without centrifugation.

SYNOPSIS

There can be not doubt that endogenous circadian rhythmicity is one determinant of mental performance, physical exercise capacity and the resistance to noxious hazards.

With the exception of altitude (hypoxic) tolerance - which peaks at night when tonic physiologic levels are set for sleep - in man the better performance efficiency is found during the day. However, by no means did phasing concur; even for mental performance alone there is a dependency on task specifity: Memory loaden tasks peak earlier than psychomotor or vigilance oriented elements of mental efficiency.

Amplitude of efficiency rhythms is smaller when subjects stay awake than when they are aroused from sleep. The same is true if an individual is more disposed, better trained and more highly motivated for a task. By motivation, mental as well as physical performance at night may be brought up to similar levels than those encountered during the day; this requires "extra effort" and higher physiological costs.

Fatigue, as consequence of sustained operation and sleep loss, intensifies circadian rhythmicity of mental efficiency. This seems to be one reason that in field studies the nocturnal maximum of human failures and errors is much more pronounced than in comparable laboratory research; differences in motivation and in interest for the task as well as unfavourable environmental conditions "at the work bench" might be other factors.

As observed in road traffic, a heavy continuous call on vigilance in an otherwise monotonous environment may give rise to a higher nocturnal accident rate by way of interaction of fatigue and the circadian variation of arousal.

Moderate exercise as well as injection of sleep sections into periods of sustained operation seem to be beneficial with respect to fatigue and circadian effects on arousal.

Night duty should only be commenced well rested. Since it is more stressful, maximum permissible duty hours should be shortened. If possible, maximum efficiency (like landing an aircraft after a long-haul flight) should not be demanded at the time of maximum behavioural depression.

A P P E N D I X

THE "BIORHYTHM" THEORY

The concept of Biorhythm was first brought up at the end of the 19th and the beginning of the 20th century by W. Fliess, a German ENT specialist in Berlin, H. Swoboda, an Austrian psychologist from Vienna, and by the engineer A. Teltscher from Innsbruck, Austria. In the thirties it was further developed mainly by mathematicians and engineers like A. Judt from Germany and H.R. Früh from Switzerland; it finally gained general public interest, in particular in the Anglo-American sphere, through G. Thommen's book (95) on "Biorhythm".

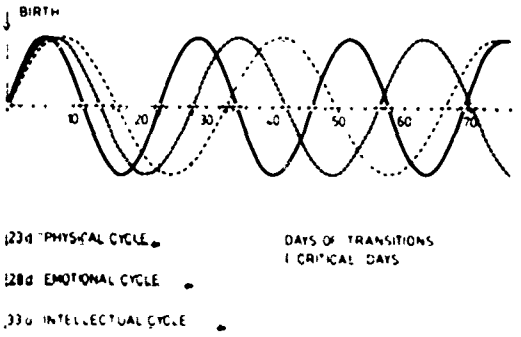


Figure 15: The "Biorhythm" concept (After Sacher, 1974)

The concept claims that each human being's performance is governed by three basic cycles of different period lengths (Figure 15): a 23-day "male" or "physical" cycle involving changes in strength and endurance, a 28-day "female" or "emotional" cycle covering changes in sensitivity and emotional reactions, and a 33-day "intellectual" cycle enclosing changes in intelligence, alertness or awareness. It pretends to be able to predict human behaviour in terms of "bad" or "good" days at any time of any person's life. This is done by a mathematical model which rests on a number of indispensable premises, some of the most important being the following:

- Each cycle is described by a sine curve having a positive and negative phase with two cross-over points.
- The cycling begins at the moment of birth always with a positive phase.
- In all individuals on earth, at all times, cycles must run with precisely the length of 23, 28 and 33 days; deviations of only minutes or even fractions of seconds from the assumed period length, through internal or external factors, are not compatible with the theory.
- The positive phase of all cycles corresponds to periods when performance is best, the negative to poorer performance, the cross-over points are termed "critical"; when two cycles cross the medium line criticality is doubled, and three curves crossing simultaneously is even more critical or dangerous.
- According to the theory, performance would be poor, vulnerability high, and accidents more likely to occur, on critical days, on days when more than one cycle is in a critical phase and the other cycles are in a negative phase, or on days when all cycles are in a negative phase.

The fascinating possibility of predicting human performance capacity was eagerly picked up by man-intensive industries in order to lower accident rates and/or increase efficiency and productivity. At the same time, Biorhythm companies grew up offering consulting services for human labour management or selling Biocalculators for computing one's own "bad" or "good" days. The Biorhythm concept, thus, was commercialized before it had been tested seriously for its biological and mathematical foundations. It was in 1972, yet, when G. Schönholzer stated (90): "Besides some recent expert statements which have not been published and, therefore, are not available, there are an endless number of press-releases, propaganda-brochures, mass-media commentaries, courtesy certificates etc. The very few regularly published papers which allow a scientific review more or less belong to the past. New sound and scientific publications do not exist. Therefore, there is no really controllable base".

Meanwhile the Biorhythm theory has been investigated independently in different scientific laboratories; mainly by comparison of actual events (accidents, deaths, athletic records etc.) with those expected by a random distribution. A second method applied was computing correlation of actual performance of a laboratory task with the phases of the Biorhythms' cycles. We have reviewed 15 reports, 13 of which appeared between 1971 and 1979; the results are briefly summarized:

- Papalcîzos et al. (75), Psychological Service d'Ebauches, Neuchâtel, Switzerland (1960): The theory was tested on 500 drivers who caused an accident; the occurrence of an accident could not be predicted by the theory better than by chance.
- Kallina (51), Verkehrspsychologisches Institut des Kuratoriums für Verkehrssicherheit, Vienna, Austria (1961): From birth-dates of 100 drivers who caused accidents, the "Austrian Society for Biorhythm" calculated Biorhythm phases; the authors then correlated expected and actual frequency distribution of accidents and found that there were no significant differences; they concluded that there was no influence of Biorhythm phases on the disposition to cause an accident.

- Mason (69), Workman's Compensation Board of British Columbia (1971): Over 13 000 industrial accidents have been investigated without a statistical significant correlation to Biorhythm phases.
- Pircher (79), Fliegerärztliches Institut, Dübendorf, Switzerland (1972): More than 3 000 air and road accidents were investigated; the actual frequency was not significantly different from the expected frequency of accidents; it was concluded that Biorhythm is useless as a mean for accident prevention.
- Schönholzer et al. (90), Forschungsinstitut der Eidg.Turn- und Sportschule, Magglingen, Switzerland, and Sandoz-Wander, Inc., Hanover, New Jersey, USA (1972): The biorhythmic characteristics of more than 1 000 athletic records were calculated by the "Biorhythm Research Center, Switzerland"; then the authors computed the level of significance for differences between the actual events and their theoretical probability, special attention was given to the critical periods; the results demonstrated that Biorhythms have no influence on the frequency of such events; they concluded that the idea of Biorhythm is a theory without biological and mathematical foundations.
- Steinmetz (91), Master Thesis, Technical University Darmstadt (1972): The winner of Olympic records in track and field sports in 1968 and the German members of the European championship in track and field sports in 1971 were investigated; no correlation between physical athletic performance and Biorhythms' favourable and unfavourable periods were found; the hypothesis of proponents of the Biorhythm theory that the status of the physical cycles decides defeat or victory in a competition where athletes physically and technically are equal was not supported; the author quotes Russian investigations of 2 500 cases of athletic world and Russian records coming to the same results.
- Sacher (89), Master Thesis, Naval Post Graduate School, Monterey, Calif., USA (1974): The author investigated the probability of biorhythmic criticality and its influence on human error and accidents based on data from more than 4 300 naval aircraft mishaps; by straightforward application of critical days or critical periods there was no significant influence from Biorhythms; however, a significant lower number of accidents than expected in pilots younger than 30 were found when a critical physical day was accompanied by a positive state of the emotional cycle (what is against the Biorhythm theory!), and in pilots older than 30 when physical critical days coincided with the negative state of the emotional cycle; with these results it is not easily comprehended that the author recommends "Biorhythmic Criticality" to be incorporated into a "Sortie System Safety Evaluation".
- Rodgers et al. (87), Wyoming State Hospital and University of Wyoming, USA (1974): Predictive validity of Biorhythm theory was tested with three rating tests of a) general feeling b) job performance and c) sleep quantity and quality; critical days did not relate above chance to any test criterion; it was concluded that the critical days hypothesis was not shown to be a meaningful concept.
- Feinleib et al. (27), National Heart, Lung and Blood Institute, Bethesda, MD, USA (1974): The hypothesis claimed in the literature that abnormally higher deaths rates occur on critical days was tested on 960 deaths from a long-term longitudinal study; the results appeared to contrast sharply with claims made by proponents of Biorhythm theory, they suggest that it is higly unlikely that biorhythmic cycles influence when men will die.
- Rey et al. (85), Institut für mathematische Statistik und Versicherungslehre, Universität Bern, Switzerland (1976): More than 10 000 cases of suicide in Switzerland from 1961 to 1970 were used to test the hypothesis that Biorhythms cause differences in the frequencies of suicides at the various days of the cycles, in particular, at critical days; the results did not support the hypothesis; there was no indication of a verification of the Biorhythm theory.
- Neil et al. (72), Man-Machine System Design Laboratory, Naval Post Graduate School, Monterey, Calif., USA (1976): For 70 days,information processing was followed in 3 subjects; the set of performance data was subjected to Fast Fourier Transforms in an attempt to identify significant harmonics; from 12 significant harmonics 9 were found to be within one day of one of the cycles hypothesized by the theory of Biorhythms; the results were interpreted as suggesting the possibility of a biorhythmic influence in the performance of the tasks; however, no attempt was made to correlate these rhythms to birthdates.
- Khalil et al. (54), Department of Industrial Engineering, University of Miami, Florida, USA (1977): In 63 aircraft accidents, 105 cases of unscreened deaths, 181 traffic accidents where a driver was at fault, performance and scores in 23 members of a swimming team, and in 25 members of a bowling league, Biorhythm had no significant influence; it was concluded that no evidence in support of the theory of Biorhythm had been found.
- Wolcott et al. (108), Aerospace Pathology Division, Armed Forces, Institute of Pathology, Washington, D.C., and National Transportation Safety Board, Washington, D.C.; Accident Investigation Branch, Office of Aviation Medicine, FAA, Washington, D.C. (1977): In more than 5 000 "pilot-involved" accident cases no correlation was found between any aspect of the Biorhythm theory and the occurrence of accidents.
- Persinger et al. (78), Environmental Psychophysiology Laboratory, Department of Psychology, Laurentian University, Sodbury, Ontario, Kanada (1978): Analysis of 400 mining accidents demonstrated that the number of employees who are involved with accidents on their individual critical days of the different cycles did not differ significantly from chance expectancy; furthermore the number of employees involved in accidents when their cycles were in ascending phases did not differ significantly from the number of employees who were involved in accidents when their cycles were in the descending phases; neither empirical nor theoretical support for the Biorhythm model was found.
- Wolcott et al. (109), Aerospace Pathology Division, Armed Forces, Institute of Patho-

logy, Washington, D.C., USA (1979): In 10 individuals efficiency at a choice reaction time did not correlate with the phases of the Biorhythm cycle; it was concluded that performance was not influenced by Biorhythms.

The obviously complete failure to verify the Biorhythm theory with scientific methods contrasts to a certain degree with some reports on its successful application in reducing accident rates in industry (95, 105, 106). Where such conclusions are not due to a false use of mathematical models they bring up the question of a potential suggestive power of such a concept once the persons concerned have confidence in its (pretended) predictive power. In this context Schönholzer (90) has pointed out a possible "Placebo-effect" which might be positive or negative; he mentioned athletes who failed in competitions obviously since Biorhythmic criticality had been suggested to them for this day, and others who performed very well in a kind of "stubborn" reaction since they knew they were supposed to be bad. Wolcott et al. (108) conclude their study with the warning: "Although it has been suggested by many advocates of the theory that briefing the theory to flying personnel might reduce accidents rates, briefing a theory not proven by fact is fraught with danger. It could bring about a psychosis by association that, indeed, might make pilots reluctant to fly on a critical day, especially a multiply critical day. Individuals do have "good" and "bad" days; their occurrence, however, is not predictable by the Biorhythm theory".

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SLEEP STAGE ORGANIZATION: NEURO ENDOCRINE RELATIONS

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INTRODUCTION

During the past 25 years, the field of biological rhythms has made great strides and has emphasized that all single and multi-cell organisms and a wide variety of biological functions within these organisms demonstrate endogenous oscillatory behavior. The disciplines of sleep research and neuroendocrinology have been at the forefront of these issues because of the critical interface relationships of the central and peripheral nervous system and the endocrine secretory system. The cross fertilization of the disciplines of biological rhythms, sleep physiology and neuroendocrinology has led to a series of important observations which have challenged 24 hour homeostatic and steady state concepts. The use of the techniques of frequent serial blood sampling, sophisticated microchemical assay techniques, and polygraphic sleep stage analysis have allowed studies to be carried out in man correlating large numbers of sequential multiple hormone measurements with sleep-waking functional states. The results of these studies have demonstrated that hormonal control is related to a temporally "programmed" series of events, endogenous circadian rhythmic processes and central nervous sytem complex "state" relationships. In this review, I will emphasize both the circadian and shorter term episodic patterns of those hormone systems that have been most extensively studied. These include ACTH-cortisol; Growth Hormone (GH); Prolactin; and the Gonadotrophins, Luteinizing Hormone (LH) and Follicle Stimulation Hormone (FSH).

THE CIRCADIAN ACTH-CORTISOL SECRETORY PATTERN

In order to study the relationship between sleep stage patterns and the plasma cortisol concentrations an indwelling venous catheter technique was devised to obtain plasma samples at frequent intervals with a minimum of disturbance to the sleeping subject (1). With sampling done at 30 minute intervals during the sleeping period, it was found that the rise in plasma 17-OHCS which occurred during the latter half of the sleep period, was characterized by a series of episodic peak evaluations, indicating that cortisol was being secreted in a series of episodic secretory bursts. This finding was confirmed using ^{14}C labelled cortisol and was extended to 24 hour studies (2). A specific one to one relationship between the nocturnal episodes of cortisol secretion and the Non-REM-REM sleep cycle however, was not supported by the previous findings in relation to sleep deprivation, (67) nor by the dissociation between sleep stage and plasma cortisol patterns when the sleep-waking cycle was inverted (3). In detailed studies of the 24 hour pattern of cortisol secretion it was found that the cortisol secretory pattern was an episodic one throughout the 24 hour day with a greater clustering of the episodes during the latter half of the sleep period and the subsequent morning waking time(4, 5). Further confirmation of an episodic pattern was found when adrenal vein blood was sampled at 15 minute intervals in man and spontaneous pulses of cortisol secretion were measured (6).

Utilizing a 20 minute sampling technique (72 samples/24 hour period), it was found that only about 25% of the 24 hours was spent in active secretion with 9 to 11 discrete episodes (4). There were four unequal temporal phases defined, with approximatrely 40% of the total daily secretion taking place during a four hour period in the early morning. During the 4 hour period in proximity to the usual nocturnal sleep onset time (e.g. 10PM to 2AM), the cortisol concentration was usually extremely low (frequently 0) and less than 5% of the daily cortisol output occurs during that time period.

It is important to emphasize that in normal man, a "basal level" or "steady state" of cortisol is not presesnt for any extended time period of the day and there is considerable variability in the lag time and concentration values between secretory episodes. These findings indicate that a closely controlled homeostatic feedback system is not the mechanism for the normal control of the 24 hour plasma cortisol secretory pattern but rather indicates that the sequence of episodic secretory events is "programmed" as part of a stable repetitive daily pattern in concert with the sleep-waking cycle and the general program of biological rhythms (7,8).

The 24 hour episodic pattern of cortisol has been correlatred with plasma ACTH measurements in man. These studies have indicated that appropriate temporal correlations are present for the major secretory episodes (9,10,5). When a 5 minute sampling frequency was used, it was found that several

ACTH episodes of short duration in close temporal juxtaposition may produce only one cortisol secretion episode with a smoothly rising concentration.

The stability of the circadian episodic pattern of cortisol secretion is demonstrated by several recent studies. In a group of normal subjects who were placed on a 3 hour sleep-wake schedule for ten days, there was no significant difference in the average 24 hour cortisol output, number of secretory episodes and total secretory time and all demonstrated a clear circadian rhythm of plasma cortisol compared with the baseline pattern (11). However, a 3 hour cycle of secretory episodes was entrained to the 3 hour sleep wake cycle. A study of seven totally blind subjects revealed that 5 had a definite circadian pattern of episodic secretion whereas two had atypical patterns without a clear 24 hour pattern (12). The results of a study of the 24 hour cortisol, and growth hormone patterns and sleep stage patterns during the four seasons of the year in a group of Norwegian air force pilots in Tromso, Norway (above the arctic circle) demonstrated no differences in the circadian pattern of cortisol, although there was a small increase in the mean daily plasma concentration and amount secreted during the autumn - winter compared with the spring - summer seasons (13). A comparison of the 24 hour cortisol and GH pattern was made between two different behavioral schedules of healthy medical students; an "active" day with full, normal activities (classes, meals, driving a car, etc.) compared with a "basal" day of strict bed rest (lights on) without reading, conversing or other external stimulation (14). An episodic cortisol secretory pattern was clearly present for all subjects during both the "activity" and basal 24 hour periods and all had the typical circadian clustering of episodes during both behavioral conditions. However, higher peak concentrations were found during the noon to 8 PM waking portion of the 24 hour day on the "activity" as compared to the "basal" day. In a recent psychoendocrine study, utilizing the frequent (20 min) 24 hour sampling technique, Czeisler (15) compared four patients on the day before major elective cardiac surgery with normal control subjects. The only difference found between the two groups was that a major pulse of cortisol was secreted between 9 PM and 11 PM for each patient in the presurgery group, clearly caused by the preoperative preparation (body shaving, wash and enema). The rest of the 24 hour period, including the nocturnal episodic pattern, was otherwise the same in the two groups.

These results taken together indicate that most of the episodes of cortisol are endogenous and have a "programmed" circadian pattern of secretion. Indeed the inter-episode intervals and therefore, clustering of the episodes appear to be the major determinant of the circadian distribution. The 24 hour pattern is quite resistant to major shifts in the sleep-waking cycle, on a short term basis, but when the sleep-wake cycle is persistently phase shifted, the 24 hour cortisol pattern will entrain to it. In the discussion of "Biological Rhythms of Man Living in Isolation from Time Cues" data will be presented demonstrating that a new phase relationship is established when a "free running" sleep-wake cycle takes place. Differences in waking behavior, particularly those associated with strong emotional anxiety will produce selective but transient episodes of cortisol secretion.

There have been a number of studies applying these new concepts to clinical problems. Abnormalities of the 24 hour plasma cortisol concentration have been found in older patients with psychotic depression (16). Significantly more cortisol was secreted during both the dayt me waking and nocturnal hours of sleep with both an increase in the number of secretory episodes and in the minutes of secretion. After treatment and clinical improvement, the patients' secretory patterns approached normality. The authors suggest that these findings support the concept of a dysfunction of CNS monoaminergic neuretransmitter systems in this psychiatric disease.

TWENTY-FOUR HOUR PATTERN OF GROWTH HORMONE (GH) SECRETION

It is now well established that GH is secreted in substantial amounts during the first 2 hours of sleep at night when the subject has a normal sequence of nocturnal sleep stages (17,18,19,20). Following sleep onset at night and with the characteristic progression of sleep stage patterns (Stage 1-Stage 2-Stage 3-4), the rapidly rising concentration of GH can be detected within the first 30 to 45 minutes, usually reaching a peak between one to two hours. Following this major episode of secretion, the concentration rapidly falls to extremely low concentrations, usually zero by the third hour of the sleep period. In some cases a second or rarely a third smaller secretory episode may occur during the remaining hours of the nocturnal sleep period. In repeated studies, this sleep induced release has been found to be the most consistent time of GH secretion for the 24 hours. In the study of the Norwegian pilots described earlier (13), in only two of the twenty-eight 24 hour GH measurements did a daytime GH peak exceed the peak at sleep onset at night. During the waking portion of the 24 hour period, infrequent short episodes of secretion occur but no consistent temporal pattern has been found. For most of the 24 hours in normal subjects, the plasma GH is either undetectable or at very low concentration (3 ng/ml). If sleep onset is delayed or prevented for many hours, the expected GH release will also be delayed and will then occur in relation to the delaved sustained sleep period (21). This sleep related release has been correlated to the Stage 3-4 sleep in several studies (20,21,22). Stage 3-4 sleep characteristically occurs within the first 3 hours after sleep

onset at night. In a study carried out by our group (23), we found that the release of GH coincided with the development of the EEG patern characterized by slow synchronous activity ("slow wave" sleep) in the period after sleep onset at night. However, "slow wave" (stage 3-4) sleep is not always correlated with GH release since it has been found that especially during the latter portion of the night, Stage 3-4 occurred without an associative GH secretory episode (20). In a study of the ontogeny of the 24 hour pattern it was reported that in four prepubertal males (ages 8-15) GH was secreted only during sleep and not during the waking portion of the day (24). In pubertal adolescents (ages 9-20) however, there were frequent secretory episodes (1 to 4) during waking, as well as several episodes (1 to 4) in sleep. There was a 7.5 fold increase in estimated total amount secreted in pubertal children, compared with the prepubertal group. In young adults (ages 23-42) GH was secreted during both waking and sleep, although less so than in the pubertal group, and in an older adult group (ages 47-62) there was a great reduction in GH secretory episodes, with 3 of the 5 normal subjects showing no GH at any time during a 24 hour study period.

In several more recent reports (25,26,27), using the technique of integrated sampling (continuous pump withdrawal of blood with sampling at 30 minute intervals), it is reported that prepubertal children do secrete GH during the waking state as well as sleep, but the amounts are less in prepuberty compared to puberty; adult subjects were also found to secrete less hormone than pubertal children. In infants it has been shown that GH has a high plasma concentration range throughout the 24 hour day, although a sleep-wake relationship has not been well documented (28,29,30).

The relation between daytime napping and GH secretion (31,32) was clearly shown in a study recently carried out by our group (33,34) in which 15 of 18 secretory episodes during the daytime for the 6 subjects on a "basal" day (see previous section) were clearly related to a polygraphically defined daytime nap. In the "activity" day group without naps, there were 11 daytime secretory episodes.

It is, of course, well known that other stimuli will induce a GH secretory episode during the day, in man (35). These include, arginine infusion, insulin hypoglycemia, venipuncture, nonspecific stress, L-Dopa (68,51,70-72). It has been considered that there is a relationship of GH secretion to meals (post-prandial rise); recent work has challenged that concept with evidence that there was no reproducible GH secretion temporally related to meals (36). Although an earlier study did not report an increase in GH secretion during nocturnal sleep after heavy daytime exercise (37), a more recent study did show an increased amount and earlier rise of the sleep related GH secretion, but without a concomitant increase in stages 3-4 sleep in ten of twelve subjects studied after heavy daytime exercise in non-athletes (38).

We studied the GH secretion during sleep in a group of seven blind subjects, and found that six had clear sleep related release of GH (12). The two subjects with low or absent sleep GH release had the most abnormal sleep pattern with markedly reduced stage 3-4 sleep. The importance of relating GH secretion during sleep at night or during daytime naps to polygraphically defined sleep stages is strongly emphasized.

The application of these findings to clinical problems has been increasing. In each of 5 patients with acromegaly, the 24 hour pattern of GH differed from normal (39). The GH concentration never reached undetectable levels during the 24 hour sampling period (every 20 minute sampling). In addition, rapid changes in concentration were found indicating frequent distinct episodic secretions. Therefore, although GH concentrations in several patients were found to be within the normal range, the 24 hour pattern was grossly abnormal and resulted in markedly increased GH production over a 24 hour period. In these patients the 24 hour curve appeared to have a circadian pattern, with high values at approximately 4 AM and low values at 4 PM, although a clear sleep related release was seen in only one patient.

THE PATTERN OF PROLACTIN SECRETION DURING SLEEP AND WAKING IN MAN

A specific and sensitive radioimmunoassay for the measurement of human prolactin in plasma has been available for only a few years (40,41). Therefore, the analysis of the 24 hour pattern of its secretion has only begun. Nevertheless, it has been clearly demonstrated that there is a relation to the sleep-wake cycle (42,43). In all adult subjects studied a large increment in the plasma prolactin concentration takes place between 60 to 90 minutes after the sleep onset period at night and is generally followed by a series of even larger secretory episodes resulting in progressively higher plasma concentratrions during the night with peak values occurring at the end of the sleep period, generally at 5 to 7 AM. Upon awakening, a rapid fall in concentration occurs with plasma concentration reaching the lower daytime waking values by 10 AM. Although the pattern of release of prolactin during both waking and sleep is clearly episodic, the pattern differs from that of

cortisol and GH in that prolactin never falls to undetectable values in normal subjects . When the sleep time is shifted or the sleep-wake cycle is inverted, it has been shown that prolactin immediately is dependent on the occurrence of sleep and not on an inherent rhythmic secretion pattern such as is the case for the ACTH-Cortisol system (44).

In a recent study, (45) analysis of the relationship between the episodes of prolactin secretion during sleep and the Non-REM-REM sleep stage cycle demonstrated that a sharp rise of prolactin takes place at the beginning of the Non-REM period and then falls prior to the onset of the next REM period. Lowest concentrations are present during REM sleep and highest values occur in the middle of the Non-REM period. They confirmed the very rapid decrease in prolactin concentration upon awakening and found no difference whether awakening took place from a REM or Non-REM sleep stage. It has also been shown that prolactin is secreted in larger amounts during the daytime naps (43).

The hypothalamic mechanism of control of prolactin is considered to be primarily via an "inhibitory" rather than a "releasing" factor. Prolactin concentrations are frequently quite elevated in patients with pituitary and hypothalamic tumors (46). Like GH and the ACTH- Cortisol hormones, prolactin will be released in response to a variety of stimuli. These include stress, hypoglycemia, suckling in post partum women, strenuous excercise and a number of psychotropic drugs. However, L-DOPA administered to man will consistently produce a decrease in prolactin secretion (47,48,49) whereas it characteristically stimulates GH secretion (50,51).

THE RELATIONSHIP OF GONADOTROPHIN HORMONE LH AND FSH SECRETION TO SLEEP-WAKING PATTERNS

The application of the 24 hour frequent plasma sampling technique to the gonadotropin system has been quite fruitful and has demonstrated that there are important sleep-wake relationships. Perhaps the most significant finding is that in normal pubertal boys and girls a major increment in plasma LH concentrations occurs in an episodic pattern during the nocturnal sleep period (52). No sex difference was found. In pre-pubertal children this sleep LH augmentation was not found and the values are in a low range of concentration. In general, a relation was noted between the number of LH episodes and the number of sleep cycles; the LH episode interval of 70 to 90 minute Non-REM-REM cycle. The temporal relation to sleep stages suggests that LH secretion is initiated during Non-REM sleep and terminates in relation to the REM sleep stage. As puberty proceeds the sleep related enhanced secretory episodes also occur during the waking portion of the 24 hour period so that by the completion of sexual maturation, the sleep and waking patterns are equivalent with respect to both the mean concentration and the episodic pattern. The sleep augmented LH release has been shown to be associated with a corresponding increase in testosterone (53).

Acute inversion of the sleep-wake cycle in a group of pubertal boys demonstrated a concomitant and immediate shift of the augmented secretory pattern of LH and testosterone during daytime sleep (54). Although the mean LH and testosterone concentration was higher during daytime sleep as compared with the nocturnal waking values, the latter values were significantly greater than the daytime waking values obtained prior to the sleep-wake phase shift.

These findings indicate that the relationship between CNS sleep processes and LH hormonal release via hypothalamic-pituitary control, is the major mechanism for the initiation and subsequent maturation of sexual pubertal changes. In normal adult men, we found that LH was secreted episodically (approximately 12 episodes for a 24 hour period), but we were unable to demonstrate a 24 hour sleep-wake relationship (55). Rubin, et al (56) reported that in men LH values were 14% greater during REM periods when compared to other sleep stages combined. Nankin and Troen (57) reported that LH serum values were highest in men between 3 and 7 AM during the sleep period compared with earlier evening values. In a recent report, concomitant measurement of Luteinizing Hormone-Releasing Factor (LRF) with LH in man indicated that there was an overal correlation between the two assays, but at times there was a discordant relationship (58,59). A nocturnal rise in plasma testosterone in normal men has been found (60,61) with a temporal relation with LH secretory episodes (62). This testosterone augmentation is probably of testical origin since it can be dissociated from the cortisol correlated pulses of androstenedione and dehydroepiandrosterone (72). It is therefore possible that the enhanced secretion of testosterone during sleep may be due to local changes in testosterone during sleep may be due to local changes in testicular function such as alteration in blood flow-related to autonomic nervous svtem changes (59,62).

There have been a series of studies in sexually mature women investigating the 24 hour pattern of LH and FSH secretion during selected portions of the menstrual cycle. The gonadotropin hormones have been shown to be secreted in an episodic manner, however, the pattern, frequency and amplitude differ depending on the phase of the cycle. During the early follicular phase, LH is

secreted by a sequence of 10 to 15 episodes during the 24 hour period (63). Instead of a major increment of LH during sleep such as is found in pubertal children, a significant decrease in the plasma LH concentration was found during the first 3 hours after sleep onset. When the onset of the first stage 2 was used as reference point, a 33% decrease from the mean LH was found for the 3 hours of sleep. This was not found in an age matched normal male group. Acute inversion of the sleep-waking cycle in women during the follicular phase demonstrated that this early sleep LH concentration decrease was present during the daytime sleep period as well (54). These findings suggest that transient inhibition of LH secretion occurs shortly after sleep onset and that the sequence of sleep stages 2, 3 and 4 may be an important factor.

During the peri-ovulatory phase of the menstrual cycle at the time of the LH "surge", large recurrent secretory episodes were present, superimposed on a progressive elevation of the baseline concentration (64). In three subjects, the presumptive onset of the LH surge appeared to take place in close proximity to the end of the nocturnal sleep period.

During the mid and late luteal phases, a diminished frequency of secretory pulses have been found with an interval of 3 to 4 hours (65). Although pulsatile secretion of FSH is not as prominent as LH, nevertheless similar changes were found during the early follicular and mid-cycle phases.

Coincidental pulses of FSH and LH are found in postmenopausal women and in patients with gonadal dysgenesis in which the feedback loop from ovarian steriods is absent (66).

CONCLUSION

It is not well established that hypothalamic-pituitary hormonal systems have temporal patterns of secretion that are clearly related to the 24 hour sleep-waking activity in man. Each of the four hormonal systems (ACTH-cortisol, Growth Hormone, Prolactin and Gonadotropin hormones) discussed in this report has its own temporal organization and response pattern to alterations of the sleep-wake cycle and no single principle or mechanism can explain these patterns. Previous concepts of constancy of blood levels in regard to closed loop feedback control are challenged by data that demonstrates widely fluctuating hormone concentrations produced by episodic secretory activity.

Cortisol and ACTH are clearly secreted in an episodic manner with the episode frequency occurring on a 24 hour basis. The 24 hour cortisol pattern is relatively resistant to shift of the sleep-wake cycle and can be dissociated from sleep in spite of a highly correlative relationship under normal, stable circadian conditions.

Growth hormone secretion at night is intimately related to sleep and closely associated with the specific sleep stages 3 and 4, particularly in relation to the period immediately after sleep onset. In contradistinction to the cortisol pattern, the secretion of GH can be readily shifted by shifting the time of sleep.

Prolactin is also secreted in larger amounts during the night's sleep period, with initiation just following sleep onset and increasing in an episodic manner throughout the sleep period. There is an abrupt fall in concentration upon awakening in the morning. An immediate shift of this pattern occurs with a shift of sleep time.

The findings for gonadotropin hormones strongly suggest that in man CNS sleep mechanisms are intimately involved in the initiation and maturation of normal pubertal hormonal changes. In pubertal boys and girls, there is an augmented release of LH with sleep at night and if sleep is shifted, the LH increment is also shifted. During the follicular phase of the menstrual cycle in sexually mature women, there appears to be a transient decrease in LH plasma concentration. Although the data in general does not support a clear sleep-wake relationship for LH in men, nevertheless there does appear to be a nocturnal increase in testosterone. In pubertal boys there is a clear increase in testosterone concentration accompanying the sleep rise of LH.

The findings from these studies have begun to provide new diagnostic and mechanistic insight and emphasize the potential usefulness of applying a chronobiologic analysis to the relations between 24 hour neuro-endocrine events and sleep-wake cycling in man.

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SLEEP DISTURBANCES IN HUMANS

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SUMMARY

Disturbed sleep results in feelings of fatigue and, usually, in impaired performance regardless of whether the disturbed sleep is due to excessive noise or a chronic sleep disorder. In addition to noise, some other environmental factors that disturb sleep are temperature, unscheduled operational demands that fragment sleep time, rotating shift-work schedules, and operational requirements that result in air travel across several time zones. While appropriate attention to sleep logistics may minimize the environmental causes of disturbed sleep, resolution of the disturbed sleep of those with sleep disorders is more difficult. The focus in sleep disorders must be on the individual. The major sleep complaint is insomnia, not enough sleep, usually due to prolonged sleep latency. A more serious medical problem, however, may be the complaint of excessive daytime sleep or hypersomnia. Most patients with complaints of hypersomnia are usually diagnosed as having narcolepsy or sleep apnea. Relative to narcolepsy, sleep apnea (episodes of respiratory arrest during sleep) has only recently received attention. In addition to a sleep problem, sleep apneic patients may have hypertension and/or cardiac arrhythmia.

INTRODUCTION

The suggested title of my first talk was, initially, "Sleep Disturbances in Man." Since, in the United States, there is a concerted effort to remove all reference to sex (in fact, the Defense Department has a task force to survey all manuals and writings to make sure that references to men and women are not used), my first act in preparing this lecture was to change the title to "Sleep Disturbances in Humans." After this decision was made, then the problem became, how was I going to define sleep disturbances? Further, with respect to performance, is there a difference between disturbed sleep and sleep disturbances? One person may be unable to go to sleep because of excessive outside noise, another may stay awake for 2 hours as thoughts keep racing through his/her mind, or another person may have problems staying awake. All three have a sleep problem. Persons who have problems staying awake could have a problem of excessive daytime sleepiness because (1) the noise kept them awake during the night, (2) they have chronic insomnia and cannot sleep, (3) they may be having sleep apneic attacks and thus are not getting restful sleep, or (4) they may be suffering from narcolepsy.

There have been numerous ways of classifying sleep problems, but none have yet gained universal acceptance. In the United States, the Association of Sleep Disorders Centers is working on the classification of sleep disorders, but no conclusions have yet been reached. Traditionally, sleep disorders have been classified into: the insomnias, a complaint of not enough sleep; the hypersomnias, where there is excessive sleep; and the dyssomnias. The latter category includes miscellaneous sleep disturbances such as enuresis, sleepwalking, bruxism, or night terrors. There are many problems with such a classification even though the simplicity is appealing. For example, excessive daytime sleepiness, the hallmark of hypersomnia, could also be an outcome of chronic insomnia. Narcoleptics, on the other hand, generally complain of hypersomnia, and also of poor nighttime sleep, or insomnia. Hauri,[1] in a very readable pamphlet on the sleep disorders, first separates the problem into primary and secondary sleep disorders. For Hauri, primary sleep disorders include the disorders in which disturbances or abnormalities of sleep are the principal or only symptoms of the problem. In this category, he includes sleep apnea, narcolepsy, and primary insomnia. It is interesting that patients with night epilepsy are diagnosed as nocturnal epileptics, while those who have problems breathing only at night are considered to have a sleep disorder. Secondary sleep disorders are those in which the sleep problem is only part of a symptom complex belonging to a more widely ranging clinical problem. Among the secondary sleep disorders, Hauri lists sleep disorders secondary to psychiatric problems, secondary to medical problems, or secondary to behavioral problems. In a third category, the parasomnias, Hauri includes sleepwalking, nightmares, enuresis, and bruxism. Others have referred to these as dyssomnias, but Hauri points out that Dorland's Illustrated Medical Dictionary has preempted that term by defining dyssomnia as any disorder of sleep. Hauri's classification will help those who are attempting to bring some order into the emergence of a new clinical subspecialty concerned exclusively with problems of sleeping and waking.

While later on in this lecture I will discuss what is now being referred to as the sleep disorders, such a focus on the more medical aspects of those with sleep problems would not, I believe, accurately reflect the range of interests of this audience. For some in this group, the most important sleep problem may be that produced by the operational requirements of the mission; *e.g.*, the irregular hours for sleep during extended periods of semicontinuous performance or the severe environmental factors present in the sleep environment. Thus, before looking at sleep disturbances which would be grouped under the category of sleep disorders and thus requiring attention by sleep experts, let's quickly look at mission requirements or environmental factors that might produce disturbed sleep. The alleviation of these operational and environmental causes of sleep

disturbances rests more with the operational commanders than with sleep disorder experts. In an early article entitled "Sleep Starvation and You," Harold Williams, then a Lieutenant Colonel in the United States Army, emphasized that the commander should plan the logistics of sleep with the same attention he gives to supplying food, ammunition, and other essentials.[2]

Environmental Factors

Whether we are talking about sleep logistics or sleep disorders, we are concerned with determining the amount of sleep necessary for efficient daytime functioning. We know that sleep needs vary, and insomnia cannot be defined in terms of absolute hours of sleep. A person who needs 9 hours, but is chronically unable to obtain more than 5, would probably say he has a sleep problem. But a person who only needs, and obtains, 5 hours of sleep each night does not complain. For the operational commander, a person has a sleep disturbance whenever the amount of sleep obtained during a 24-hour period is insufficient to maintain effective waking performance. The type of sleep—*i.e.*, sleep stage components—does not appear to be important.[3] Even in those instances where all-night sleep recordings have been obtained, there are no commonly accepted criteria for the electroencephalographic (EEG) classification as to quality of sleep. Some researchers spend a great deal of their efforts defining how much rapid eye movement (REM) sleep was obtained, and others focus on the amount of slow wave sleep (SWS), stages 3 and 4, that was present. Others are preoccupied with the latency to the first stage REM or the latency to SWS or the number of REM periods that occurred during sleep or with REM density, the number of eye movements. Although these may be important basic questions for sleep researchers, at the present time, there are no data to indicate that one type of sleep has any unique recuperative value than another.[3] In this lecture, outside of noting the effects of sleep loss on sleep stages, I will not focus on the amount of stage REM or the amount of stage 4 obtained, or not obtained, as an indicator of a sleep disturbance. Instead, I will concentrate on findings with respect to total wake time, total sleep time, sleep latency (time to first stage 2), number of awakenings, number of stage changes, and the number of movements. These values were used successfully as a measure of "goodness" of sleep to measure the withdrawal effects in a group of chronic alcoholics.[4] These measures also have been found to separate good and poor sleepers and to be useful in measuring the effects of various drugs on sleep.

Environmental Influences on Sleep

Noise. The effects of noise on sleep have been extensively studied,[5] and Lukas[6] has done a literature review. Muzet[7] presented a paper at the Third European Congress on Sleep Research entitled "Environment and Human Sleep," which reviewed the problem of noise as well as temperature and altitude. The effects of noise on sleep are not necessarily determined by the loudness, in decibels, of the noise. Lukas, in his review, cites studies which show that the older the individual, the more likely he is to be awakened or to change sleep stage as a result of environmental noise. Thiessen,[8] in a comparison of young, middle-aged, and old subjects, found that the younger subjects (those between 16 and 25 years) were as easily aroused by truck noise as the older subjects who ranged from 55 to 77 years. Middle-aged subjects, those between the ages of 46 and 51, were less disturbed by truck noise. Lukas reports that women generally have a lower arousal threshold than men, citing studies by Wilson and Zung,[9] Steinicke,[10] and Lukas and Dobbs.[11] However, Muzet, Schieber, Oliver-Martin, Ehrhart, and Metz[12] found that men were more responsive than women, though the differences were not statistically significant.

In addition to the loudness of the tone, the difference between the peak and background levels of the noise has been found to be important. The greater the difference between the background and peak noise levels, the greater are the sleep modifications observed.[12,13] Several investigators have also found that the effects of noise depend on its personal significance for the sleeper.[14-18] The more significant the stimuli with respect to either personal meanings or to survival of a subject, *i.e.*, indications of danger, the lower the decibel level required to bring about awakening.

To those who have slept in a noisy environment, personal observations indicate that one can eventually sleep. However, the question of habituation to noise during sleep is, as yet, unanswered. While the number of awakenings clearly decreases with repeated noise, studies of long-term exposure to noise have all found that, while awakenings to repeated noise may not occur, there are clear autonomic changes indicating phasic sympathetic nervous system activation and EEG indications of a change to a lighter stage of sleep to many of the noises.[8,19-22] Also, even after 30 days of 24-hour exposure to brief, clearly audible pings, there was a measurable brain-evoked response during sleep.[20] Muzet and Ehrhart[23] have noted a similar failure of the heart rate response to habituation to noise during sleep. Although changes in sleep quality may diminish with repeated exposure to noise, the physiological responsivity does not habituate and the physiological changes to chronic noise are unknown.

Ambient temperature and sleep. The effects of ambient temperature on human sleep have not been extensively studied. Most of the work in this area has been reported by Muzet and his colleagues at the Centre National de la Recherche Scientifique (CNRS) in Strasbourg, France, where they have very well-controlled climatic chambers. The results obtained at the present time seem to indicate that when sleeping either at too low or too high an ambient temperature, sleep is disturbed, with an increase of wakefulness and body movements.[24-26]

Altitude and sleep. Reite, Jackson, Cahoon, and Weil,[27] studying 6 subjects at 50 and 430 meters, noted that the intense subjective complaints of sleepiness were disproportionate to the sleep observed during EEG recordings. Reite *et al.* also found that the few EEG changes that were initially observed in sleep soon returned to low-altitude levels. Joern, Shurley, Brooks, Gunter, and Pierce[28] and Natani and his colleagues,[29,30] in a study at high altitude (2804 meters) at Admundsen Scott, of Americans stationed at the South Pole, reported little variability in total sleep time. They, however, did find an increase in sleep latency.

Variability in Work/Sleep Schedules and Sleep Disturbances

Except for missions that require continuous or semicontinuous operations, such as the 9-day mission of Exercise "Early Call"[31] and that concerned with the team efficiency of a Fire Direction Center Team in simulated sustained operations,[32] total sleep loss is not the major sleep disturbance produced by operational requirements. Fragmented sleep and partial sleep loss are the most common findings. While regular sleep habits do not necessarily insure an adequate amount of sleep, irregular sleep habits almost always lead to a sleep debt and may cause disturbances in chemical and physiological rhythms which are normally on a 24-hour schedule. In the U.S. Navy, it is difficult to maintain a regular sleeping schedule and still man the various shipboard watches. About 3 years ago, Paul Naitoh, Ph.D., a psychologist on our staff, compared sleep schedules aboard the carrier, USS Kitty Hawk, and the destroyers, USS Tucker and USS Roark, with the sleep of men in land-based barracks, called "Ping B" in this comparison. Under Ping B

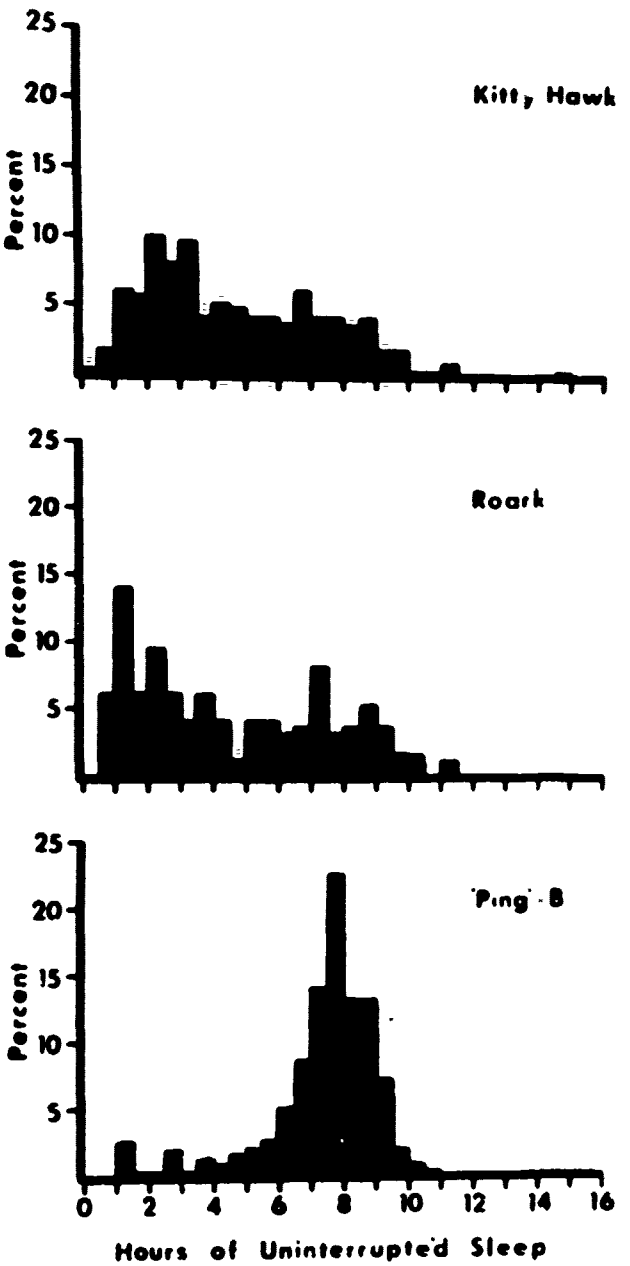


Fig. 1. Profiles show periods of uninterrupted sleep for crew members aboard three U.S. Navy ships and for shore-based Navy personnel.

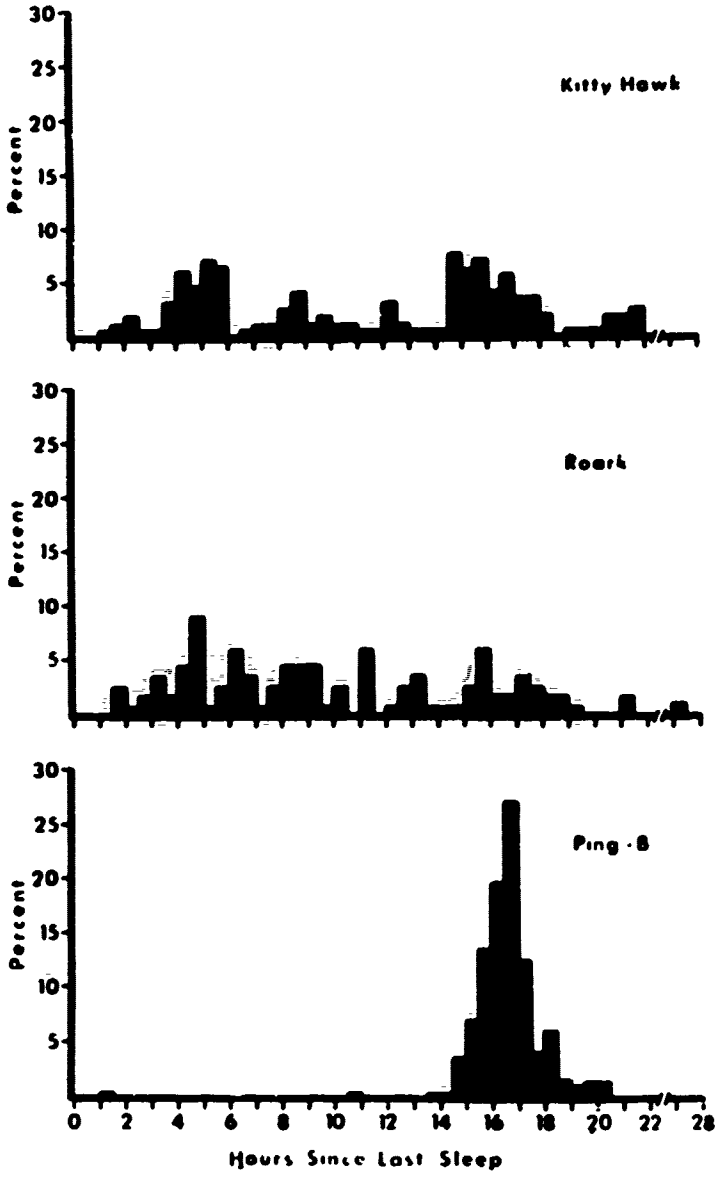


Fig. 2. Profiles of shipboard and shore-based sleep/wake cycles reflect fragmentation of shipboard sleep.

conditions, 75% of the men's sleep was uninterrupted for 6 to 9.5 hours, and the group's sleep pattern was symmetrical (Figure 1). But shipboard sleep differed considerably; only about 30 to 35% of the crew obtained 6 to 9 hours of uninterrupted sleep, while approximately 50% of the crew got less than 4 hours of uninterrupted sleep. Even more striking was the disruption of the sleep/wake cycle in shipboard sleep (Figure 2). Most of us prefer a schedule of 8 hours of sleep, followed by 16 hours awake. Ping B conditions reflect this preference, with most subjects reporting 16 to 18 hours between sleep periods. Again, shipboard sleep was dramatically different. The sleep/wake cycle was clearly fragmented, with the time between sleep ranging from 1 to 22 hours. Foret and Lantin[33] have reported on the sleep of 10 train drivers of mainland trains on the Southwest Network in France. While the average duration of their sleep was 6 hours and 22 minutes for working days, and 7 hours and 59 minutes for rest days, the variability of their sleep was almost as great as that reported by Naitoh for the sailors aboard ship. Foret and Lantin found that the starting time of the sleep period was particularly important in determining the duration of the sleep. Sleep that began after 6 o'clock in the morning, and before 11 o'clock at night, ranged from 1 to 5 hours in duration, while the sleep that began between 11:00 at night and 6:00 in the morning ranged from 6 to 10 hours (Figure 3). Foret and Lantin concluded that the duration of unbroken sleep periods is an inverse function of bedtime and an almost linear one at that.

Shift work. Although, for most shift workers, sleep is not as fragmented as that reported by Foret and Lantin,[33] sleep is a major concern in the life of shift workers, particularly when they work at night. Maurice and Monteil, cited by Rutenfranz, Colquhoun, Knauth, and Ghata,[34] showed that whereas 50% of the people with normal daywork sleep for 7 to 8 hours, of 3 shift workers in afternoon, morning, and night teams, only

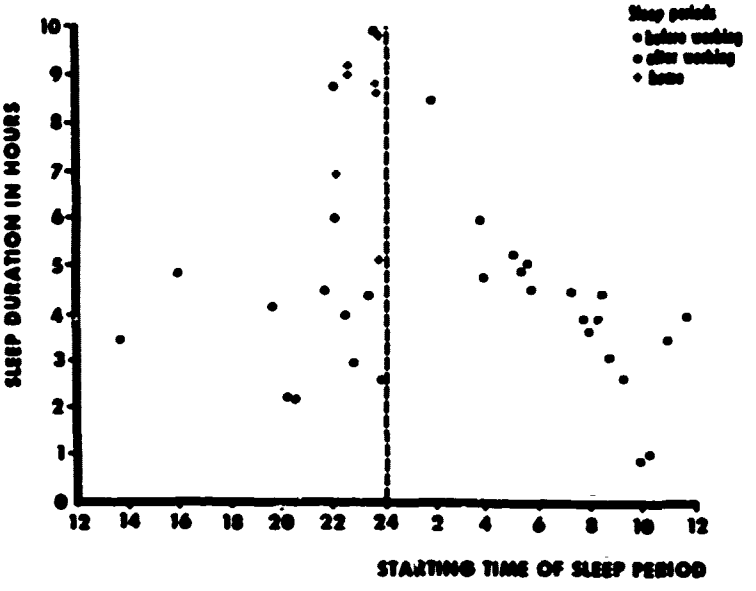


Fig. 3. Relation of recorded sleep duration to the starting hour of sleep (from Foret & Lantin[33]).

40, 35, and 15%, respectively, sleep as long. Matsumoto[35] found that 5 nurses who slept days averaged only 295 ± 51 minutes compared to their nocturnal average of 453 ± 29. It is generally agreed that the average sleep of day sleepers is less than 7 hours.[36,37] In a more recent study, Tepas and his colleagues, working with shift workers in the Saint Louis area, have commented on the objective and subjective signs of insufficient sleep in shift workers.[38,39] Both steady shift workers and changing-shift workers reported 5.97 and 5.98 hours of sleep, respectively. The data suggest that the relative sleep duration of changing-shift workers parallels that of steady shift workers on comparable shifts, but sleep problems and napping appear more frequently among third and the changing-shift workers. The changing-shift workers reported that they had more trouble falling asleep, and staying asleep, than did the steady shift workers. In their EEG analysis of changing-shift workers, Tepas and his colleagues commented that their findings were very similar to that reported in long-term, partial sleep-deprivation studies.[40,41] Dr. Reinberg will discuss further the adjustment to shift work in his lecture.

Time-zone crossings. I do not wish to dwell on this area at great length because other lecturers in this series will adequately discuss the topic of circadian rhythms. It is, of course, obvious that when one varies the natural sleep time, sleep and waking are desynchronized relative to the other biological rhythms. In addition to the noise and psychosocial problems, the desynchronization of biological rhythms, of course, plays a major part in the sleep disturbances experienced by shift workers.

Perhaps in no other group is the problem of displacement of sleep from its usual time, compounded with the desynchrony of biological rhythms, more apparent than that seen in aircrew members who fly across several time zones during their routine flight schedules. After reviewing the work reported prior to their 1974 AGARDograph, Johnson and Naitoh[42] concluded that most aircrew personnel flying worldwide schedules suffered from sleep loss. Depending on the length of the "tours," the sleep could be reduced by 1 to 3.75 hours. When EEG recordings have been made of sleep after time-zone changes, the pattern of sleep is usually similar to that seen after sleep deprivation. For example, Evans, Christie, Lewis, Daly, and Moore-Robinson,[43] in a study of 4 healthy male subjects before and after transatlantic flights in both directions, found that on the first night after a London-San Francisco flight, stage 4 sleep was enhanced and REM sleep was depressed. Early morning awakening was a feature of the first 5 nights in a new time zone, particularly in the older subjects. Similar changes occurred after their return flight. A similar elevation in SWS was found by Endo, Yamamoto, and Sasaki[44] when EEG changes in sleep were recorded after a flight from Tokyo to San Francisco. The amount of SWS was significantly elevated and REM sleep was markedly depressed. After arrival in San Francisco, it took 8 days for the sleep rhythms to synchronize with Japan time and about 5 days for pulse rate. To control for the effect of sleep loss *per se*, in their EEG findings Endo *et al.* compared the sleep after southward and northward flights, *i.e.*, from Japan south to Australia. Again, they found marked enhancement of SWS on the first night in Sydney, after the Tokyo to Sydney flight, without time-zone changes. On the first night after the return flight, Sydney to Tokyo, there was enhancement of SWS but no change in REM sleep.

There appears to be little doubt that a rapid jet flight, which takes the traveler across several time zones in a brief period of time, leads to desynchronization of not only the sleep/wake cycle but also other biological rhythms. The changes in sleep,

however, appear to also be influenced by the sleep loss during these flights. The increase in SWS and the decrease in REM sleep are a typical finding of the first recovery sleep following relatively brief periods of sleep loss.

Although brief, this review indicates that both environmental factors and work/sleep schedules, and changes in these work/sleep schedules, can lead to a sleep disturbance. This disturbance is usually reflected in reduced sleep, either due to fragmentation of the sleep period and to brief periods or to reduced length of single episodes of uninterrupted sleep. While those so deprived would feel that they had a sleep problem, they would not consider that they had a sleep disorder that required consultation by a sleep expert. Instead of complaining to the doctor, they would probably take their complaints to the company commander, union steward, or whatever appropriate managerial agent was available.

Sleep Disorders

I would now like to turn to a discussion of those who also complain of inadequate sleep, but whose sleep disturbance is not due to environmental factors or work schedules. Those who complain of insufficient sleep, and especially the chronic complainers, are generally classified as insomniacs. The sleep problems of insomniacs are of three types. The most common, regardless of age, is the complaint of being unable to fall asleep. With increasing age, there is an increase in the complaint of waking up and having difficulty in returning to sleep; *i.e.*, a problem of maintaining sleep. The third problem, referred to as early morning awakening, is waking up in the morning before the desired time for arousal and being unable to go back to sleep. Most insomniacs would fall into the classification that Hauri[1] has labeled as secondary sleep disorders. The sleep disorders are most often secondary to psychiatric problems, but may also be secondary to medical problems, or secondary to behavioral problems or to situational problems. There may be some instances in which the inability to sleep is the only complaint and no associated psychological, physical, or situational factors are present, but these cases are infrequent. Hauri refers to these patients as having primary insomnia.

Most sleep researchers would agree that insomnia, the inability to fall asleep and the problems of being unable to maintain sleep, could be best viewed as similar to a fever; *i.e.*, a symptom of some other problem. It has been reported that insomnia was the second most common symptom of psychological distress. Several surveys of sleeping habits and incidence of sleep problems have been made, with somewhat varying results. In a 1959 to 1960 sample of adults from 30 to over 90 years of age, selected for low mobility and excluding those who reported they had "ever had" diabetes, heart disease, strokes, or high blood pressure, 5.6% of the males and 13.6% of the females reported insomnia either "fairly often" or "often."[45,46] In a sample from 1,000 Los Angeles households, 14.4% reported trouble falling asleep, 22.8% reported waking up during the night, and 13.7% reported early final awakenings.[47] In a survey of the population in Alachua County, Florida, 45% of the individuals reported trouble getting to sleep and staying asleep, 31% "sometimes," and 14% "often."[48] In a 1970 to 1971 national household survey of a population aged 18 to 74, 11% of the men and 17% of the women reported "a lot of trouble getting to sleep and staying asleep," and an additional 19% reported "not much trouble."[49] All of these studies indicated that with increasing age, there were increasing complaints with respect to sleep problems, and, generally, the percent of women reporting sleep difficulties exceeded those of men.

The different results highlight the measurement problem inherent in the use of subjective responses with respect to sleep quality. Webb, Bonnet, and Blume[50] illustrated the methodological measurement problems in a class demonstration. In a class on "Sleep and Dreams," 12 students were first asked, "Was last night's sleep good or bad?" After this answer, they were asked, "Was last night's sleep good or bad or both good and bad?" They were next asked, "Was last night's sleep good, bad, both good and bad or neither good nor bad?" Finally, they were allowed to answer, "Was last night's sleep good, bad, both good and bad, neither good nor bad, or I don't know." When the choice was good or bad, 67% of the students said their sleep was good; 33% said it was bad. As the number of alternatives increased, the percent describing their sleep as good and bad decreased; for example, when given three choices (*i.e.*, either good, bad, or both), 42% said their sleep was good, 13% said it was bad, and 45% said it was both. When given five choices, 30% said their sleep was good, 9% said it was bad, both good and bad was 29%, neither good nor bad 10%, and 21% said they didn't know how to evaluate the quality of their sleep.

We asked a sample of 1,043 young adult sailors to rate their sleep as "very good," "good," "average," "poor," or "very poor." Eleven percent rated their sleep as "poor," 1% rated their sleep as "very poor," and 25% said their sleep was "very good." In a college sample of 303, 5% said their sleep was "poor," 0.8% "very poor," and 40% said "very good."

From all of the surveys that have been made relative to sleep quality, it is probably safe to assume that one-third of the population report having had sleep problems at one time or another, but, when given a number of alternatives and specifically asked to evaluate their sleep in terms of "bad" or "poor," 5 to 15% would classify themselves as poor sleepers.

In addition to the measurement problem with respect to estimating the subjective quality of sleep, there is often a great discrepancy between the subjective reports of total sleep time and sleep latency when compared to the sleep obtained in the sleep

laboratory. Poor sleepers generally overestimate the length of time it takes them to go to sleep and underestimate the total sleep time. In a study of drug-free subjects with complaints of chronic insomnia, Carskadon, Dement, Mitler, Guilleminault, Zarcone, and Spiegel[51] clearly demonstrated the discrepancies between reported, estimated, and laboratory-recorded sleep latency and sleep length. Figure 4 is a comparison of average sleep latencies reported in prerecording interviews, estimated after sleeping in the laboratory, and actually recorded in the laboratory, in a group of subjects complaining of insomnia. It is clear that the reported and estimated sleep latencies are different from those actually recorded. The usual sleep latency criterion for insomniacs is 30 minutes, but approximately 80% of these insomniacs have sleep latencies of less than 30 minutes. The average recorded latency was 26.2 minutes and the average estimated latency was 61.7 minutes. Dement and his group use stage 1 for indication of sleep onset, while in our laboratory we use the appearance of the first spindle or K-complex of stage 2 as sleep onset. Regardless of the criteria used for sleep onset, similar results are obtained.

In our sample of 12 subjects who described themselves as "very poor" sleepers, their estimated sleep latency was 91 ± 35 minutes.[52] The actual sleep latency in the laboratory averaged 36 ± 18 minutes. In contrast, 12 good sleepers estimated their sleep latency was 8 ± 4 minutes, and their actual sleep latency was 10 ± 4 minutes. To obtain 12 sleepers

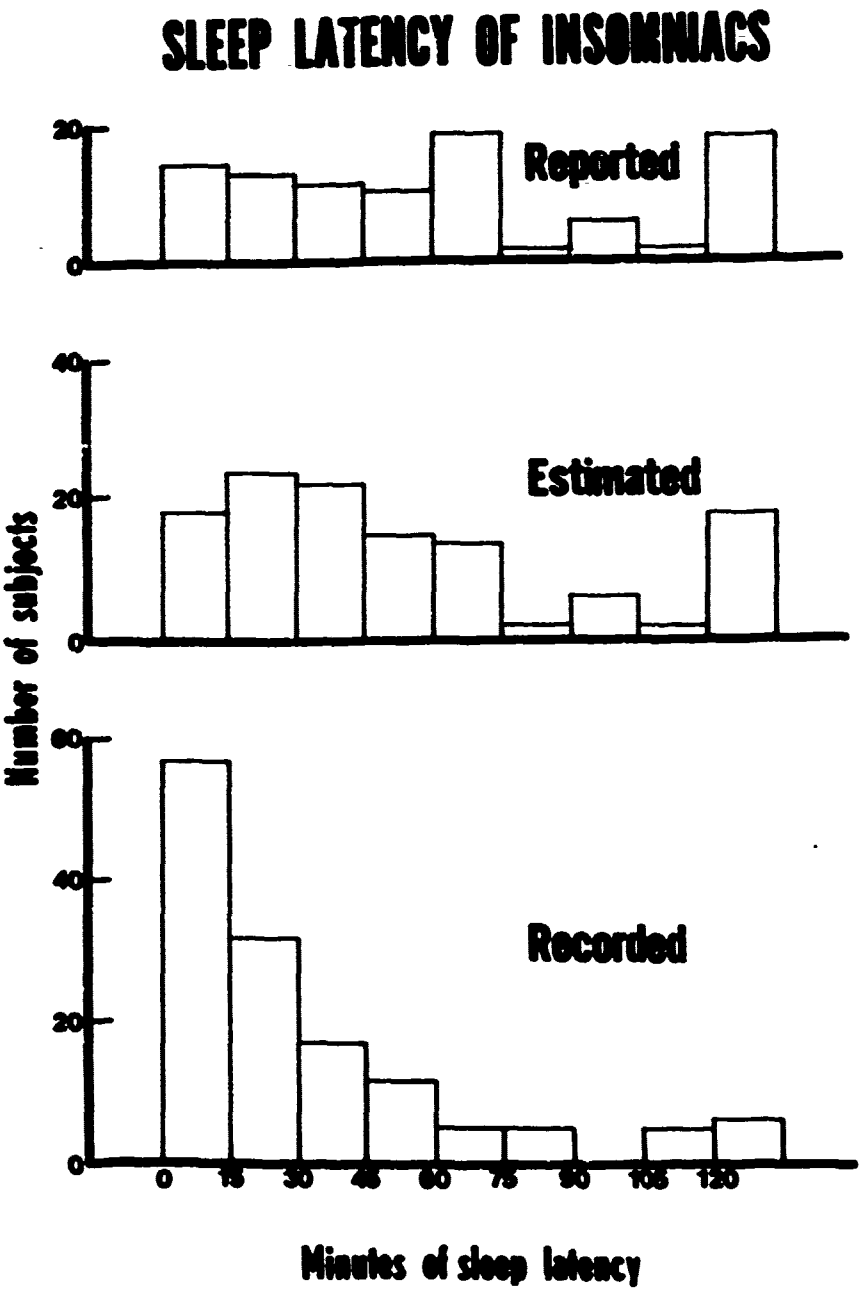


Fig. 4. Comparison of average sleep latencies of subjects with insomnia complaints reported in prerecording interview (N = 89), estimated after sleeping in laboratory (N = 119), and recorded in laboratory (N = 122) (from Carskadon *et al.*[51]).

who would meet the 30-minute sleep latency requirement on each of 2 consecutive nights, we had to screen in the laboratory 31 subjects who reported sleep latencies of over an hour.

Carskadon *et al.*[51] also compared the reported, estimated, and recorded average sleep times of subjects with insomnia complaints. Their findings are reported in Figure 5. The reported and estimated sleep lengths tend to be skewed toward shorter sleep times, where the actually recorded sleep length forms a more symmetrical distribution. Carskadon *et al.* concluded that approximately half of the subjects with complaints of insomnia could not be distinguished from normal subjects by total sleep time or sleep latency. Not only are these findings of interest in terms of how does one classify an insomniac versus the non-insomniac, but they also have relevance for the treatment of patients complaining of long sleep latencies or inadequate total sleep. It would seem inappropriate to give a sleeping pill to a patient who consistently shows sleep latencies of less than 30 minutes and total sleep times of over 7 hours in the sleep laboratory.

Several studies have pointed out that sleep complaints are associated with psychological problems.[53,54] Insomniacs seen at sleep disorder clinics generally show elevated scores indicative of neurotic difficulties on the Minnesota Multiphasic Personality Inventory (MMPI). The scales with the highest scores were hysteria (Hy), depression (D),

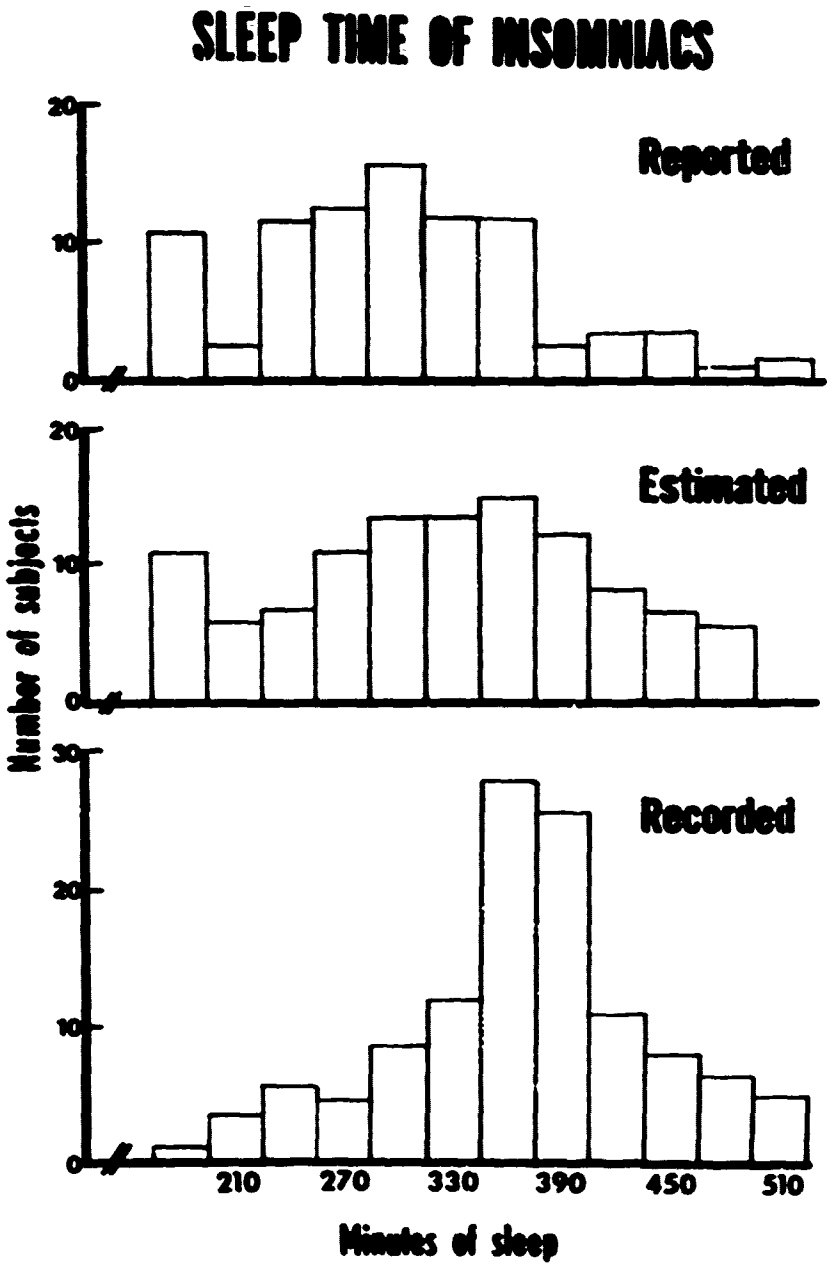


Fig. 5. Comparison of average sleep times of subjects with insomnia complaints reported in prerecording interview (N = 101), estimated after sleeping in laboratory (N = 115), and recorded in laboratory (N = 122) (from Carskadon *et al.*[51]).

and hypochondriasis (Hs). These three scales are sometimes referred to as the neurotic triad. The insomniac patients also reported a higher number of medical complaints on the Cornell Medical Index than those reported by normal subjects or neurotic outpatients.

While it was not too surprising that insomniacs should have psychological problems, the finding that, with few exceptions, all sleeping pills cause insomnia or make it worse was not anticipated.[55] In a study of chronic hypnotic drug use, Kales, Bixler, Tan, Scharf, and Kales[56] reported that patients who were receiving sleep medication had as great or greater difficulty in falling asleep or staying asleep, or both, than insomniac controls who were not using medication. Dement and his group have estimated that a third of all the insomniac patients seen in the Stanford Clinic are drug-dependent due to overuse of hypnotic drugs, particularly the barbiturates; other compounds that produce drug-dependent insomnias when taken chronically include glutethimide, methyprylon, and ethchlorvynol.

In addition to psychological/psychiatric or other medical conditions and to overuse of sleeping medications, insomnia can also be related to acute situational life stresses. Examples of kinds of acute situational stresses will immediately come to your mind (job related, marriage, etc.), and, once the life stress is resolved, the insomnia usually disappears. Occasionally, a person has a sleeping problem not because of psychological or medical problems or a situational life stress, but because of an unusual circadian rhythm problem. In these patients, the biological rhythms, particularly sleep/wake rhythm cycles, are not well entrained with the environmental time givers, or zeitgebers. These subjects are often attempting to go to sleep when their biological clocks indicate they should be awake and active. For these free-running persons, an *ad-lib* sleep schedule usually solves their sleep problem.

Sleep Disorders and Disorders that Occur during Sleep

While insomnia is the most frequent sleep disorder seen, there are other conditions that are also called sleep disorders. In Table 1 are listed some of the sleep disorders. While these conditions are generally called sleep disorders, it seems more appropriate to refer to some of them as "disorders of sleep" or "disorders during sleep."

Somnambulism, enuresis, night terrors. The first three sleep disorders in Table 1 are more common in children than in adults, and occur out of stage 4 sleep. Kales and Kales have found that when these three continue into adulthood, they are usually associated with severe psychological problems.[57] The impression is that the sleepwalking and night terrors are rare in adults. While I have no exact data as to the incidence of sleepwalking and night terrors in our Navy population, I have been impressed with the number of cases, particularly sleepwalking, which have been referred to me. The history of these sleepwalkers usually does not include childhood sleepwalking, and psychiatric evaluation and psychological studies have shown there are no severe psychological difficulties. Many of these sleepwalkers have been reported to carry out rather complex activities while "asleep." One sailor was referred after having set the lifeboats adrift and opening a valve that flooded the captain's cabin, all while asleep. One of the problems we have in a naval setting is to determine the motivation behind such acts. If this sailor had not flooded the captain's cabin, there probably would have been less concern over whether he was a "true somnambulist." Dr. Karacan,[58] Baylor University, has also studied cases of adult somnambulists without psychiatric complaints and with a negative childhood history. He has found that some of these patients have frontal and temporal lobe spiking in their EEGs. He raises the question of whether some of these patients might have psychomotor-type seizures.

Excessive daytime sleepiness. The complaint that we give most attention to in our laboratory is that of excessive daytime sleepiness. In the military setting, we find that the patient is often referred because he has been reported for sleeping on duty or has been described as unmotivated or as lazy. The fact that these patients are referred for evaluation in our sleep laboratory, however, reflects the increasing sensitivity to sleep disturbances by military commanders and, in particular, by medical officers. Previously, these men would have been given some disciplinary action and, if the problem persisted, they would probably have been given a discharge from the service. Patients complaining of chronic excessive daytime sleepiness not associated with primary or secondary insomnia should be evaluated for narcolepsy, sleep apnea, as well as hypersomnia. While narcoleptics and sleep apneics usually complain of excessive daytime sleepiness, one should not overlook the fact that these patients are often poor sleepers and, in about 10 to 15% of the cases, they may also complain of insomnia as well as the complaint of excessive daytime sleepiness.

Narcolepsy. Narcolepsy is a highly specific sleep disorder. Usually, the patient suffers from two or more of the four symptoms referred to as the narcoleptic tetrad:

(1) Short but almost irresistable daytime sleep attacks. This is the primary and most disabling symptom of classical narcolepsy. Sleep attacks can occur at the most inappropriate times, and they usually last 10 to 15 minutes, but they have been reported to last 2 to 3 hours.

(2) Cataplexy. This symptom can range from a very transient weakness in the knees to total paralysis of all voluntary muscles while the patient is fully conscious. Attacks of cataplexy are often triggered by emotions, laughing, crying, excitement. Usually the attacks last only seconds.

TABLE 1. Sleep Disorders (from Kales & Kales[57])

Disorder	Sleep-Laboratory Findings	Psychologic Evaluation	Management & Treatment
Somnambulism	Incidents occur out of stage 4 sleep; critical skills & reactivity are impaired during the incident.	Psychiatric disturbances infrequent in children & frequent in adults	Prophylactic measures; children frequently outgrow disorders, so parents should be reassured; psychiatric evaluation for adults.
Enuresis	Occurs out of all sleep stages; misconception of dreaming as a frequent causal factor is explained.	Psychiatric disturbances infrequent with primary enuresis; psychologic evaluation often indicated for secondary enuresis.	Parental counseling & reassurance critical so that parental mishandling does not create psychiatric problems; pharmacologic treatment (imipramine) may be indicated in older children.
Night terrors	Occur out of stage 4 sleep; characterized by extreme vocalizations, motility & autonomic response; recall minimal or absent.	Psychiatric disturbances infrequent in children & frequent in adults	Parents reassured that children frequently outgrow the disorder; for adults, psychologic evaluation often indicated; use of stage 4 suppressants under investigation.
Nightmares	Occur out of REM sleep; characterized by less motility & autonomic response; recall frequent & elaborate.	Frequent nightmares in children or adults may indicate psychopathology; rule out drug withdrawal as a possible cause of nightmares	Parents reassured that nightmares in children are often transient; if episodes are frequent in children or adults, psychologic evaluation is indicated.
Narcolepsy	Sleep attacks of narcolepsy may be accompanied by 3 auxiliary symptoms: cataplexy, sleep paralysis & hypnogogic hallucinations (cataplexy is accompanied by sleep-onset REM periods).	Sleep attacks may be misinterpreted for laziness, irresponsibility or emotional instability	Establishing diagnosis critical; stimulants effective for sleep attacks; imipramine effective for auxiliary symptoms; danger in using imipramine & amphetamines simultaneously.
Hypersomnia	Sleep-stage patterns normal, but sleep is extended; associated with post dormital confusion & difficulty in awakening; autonomic variables are increased.	Often a symptom of psychologic disorder (e.g., depression).	Stimulant drugs effective; neurologic & psychologic evaluation important in establishing diagnosis.
Insomnia	Complaints of patients have been verified in the sleep laboratory; sleep is more aroused (i.e., heart rate & respiration are increased); most hypnotic drugs lose their effectiveness within 2 wk.	Insomnia most often symptom of psychologic disturbance, & not a primary disorder; depression a common feature.	When insomnia is secondary to medical conditions, pharmacologic treatment may be useful; if psychologic factors are primary, pharmacologic therapy should be combined with psychotherapy.

(3) Sleep paralysis. This symptom occurs when falling asleep or upon awaking. The patient feels he cannot move any muscle except those controlling his eyes. Sleep paralysis usually lasts from a few seconds to several minutes and the patient can sometimes break the paralysis by vigorously moving his eyes, and then the eyelids, then the facial muscles, gradually restoring movement throughout the body. The paralysis is broken immediately if somebody touches the patient.

(4) Hypnogogic hallucinations. When falling asleep, narcoleptic patients occasionally experience vivid dreams while still fully conscious. Both sleep paralysis and hypnogogic hallucinations are less frequent than sleep attacks and cataplexy.[1]

As Hauri[1] notes, there is a fair amount of confusion in the current literature concerning the term "narcolepsy." Following the discovery of Rechtschaffen, Wolpert, Dement, Mitchell, and Fisher[59] that many narcoleptic subjects had sleep-onset REM periods, some authors tried to distinguish "classical" narcolepsy involving REM sleep from idiopathic narcolepsy involving NREM mechanisms (see Figure 6). Caution should be exercised, however, in diagnosing narcolepsy from the presence of sleep-onset REMs in the absence of other narcoleptic symptoms. It is well known that sleep-onset REM can occur during naps in subjects with no history of narcoleptic symptoms. When the sleep is fragmented, such as in those studies reported by Carskadon and Dement,[60] Moses, Hord, Lubin, Johnson, and Naitoh,[61] and Weitzman, Nogiere, Perlow, Fukushima, Sassin, McGregor, Gallagher, and Hellman,[62] it is not unusual to get several episodes of sleep-onset REM

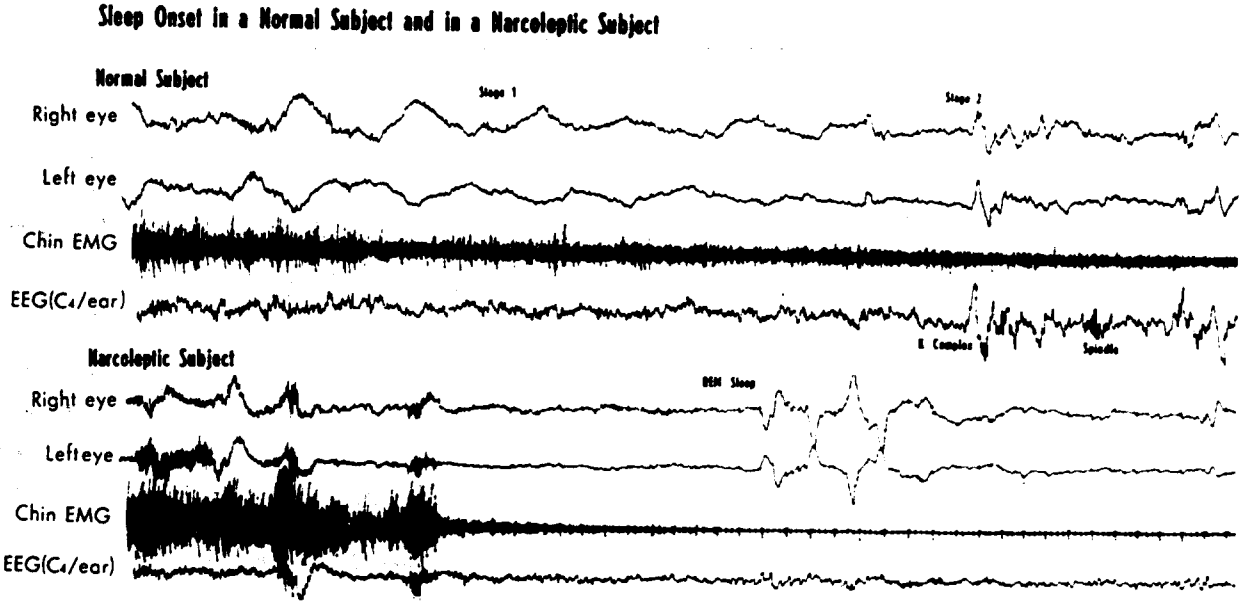


Fig. 6. In normal sleep, the transition is from awake to drowsiness, stage 1, and then to spindle sleep, stage 2. In the narcoleptic, the transition may be from awake to stage REM sleep (from Hauri[1]).

during episodes of repeated napping. Hauri[1] believes that it is conceptually much clearer to limit the term "narcolepsy" to the sleep disorder with the primary complaint of sleep attacks and which may involve sleep-onset REM, and at least one auxiliary symptom such as cataplexy. He would reserve the term "hypersomnia" for disorders involving excessive sleep attacks without at least one of the other aspects of narcolepsy.

Sleep apneas. As previously mentioned, patients with sleep apnea literally stop breathing whenever they fall asleep. Sleep then lightens to the point where breathing resumes after 10 to 180 seconds, or the patient may wake up. Patients are seldom aware of their sleep apneas, even when they are awakened literally hundreds of times each night. The 15- to 45-second episodes of sleep apnea may last a few minutes to a few hours, or they may occur throughout the entire night with over a hundred awakenings. In a milder form, sleep apnea, hypopnea, and oxygen desaturation have been observed in normal subjects, especially in males.[63] There are also more male than female patients with sleep apnea associated with hypersomnolence.[64]

Relative to narcolepsy, sleep apnea has been described only recently.[65,66] Sleep apneas have been reported in the cardiopulmonary syndrome of obesity (Pickwickian) and in other syndromes involving hypersomnia such as narcolepsy. They are most often associated with a complaint of hypersomnia, but, as noted earlier, complaints of insomnia are present in roughly 10% of the population.

Three distinct types of sleep apnea have been defined. They include a "central" type characterized first by cessation of breathing and then, after the apnea, by simultaneous resumption of diaphragmatic movements and oral air flow; an obstructive peripheral type characterized by the interruption of air flow secondary to upper airway obstruction, but with continuance of diaphragmatic and thoraxic muscle contraction; and a mixed type characterized by initial central apnea followed by temporary upper airway obstruction at the subsequent resumption of diaphragmatic movements. Illustrations of the central and obstructive apneas are presented in Figures 7 and 8. Guilleminault and Dement[67] list several medical complications that are usually associated with severe sleep apnea. Some complications appear to be secondary to the extreme respiratory effort of trying to breathe against the upper airway obstruction; others seem to be the result of chronic hypoxemia associated with apnea, or they may be related to the same CNS dysfunction that initially caused the apneas. Hemodynamic complications are also prevalent. During sleep, most apneic patients show marked elevations of blood pressure and they gradually may develop essential hypertension during wakefulness. Other complications involve the heart. Tilkian, Guilleminault, Schroeder, Lehrman, Simmons, and Dement[68] report that severe arrhythmias are commonly observed in association with sleep apnea, such as sinus arrhythmias, second-degree heart block, ventricular tachycardia, and sudden systolies lasting up to 6 seconds. Dement and Guilleminault describe sleep apnea as a serious and sometimes life-threatening disorder.[55]

At present, there are no medications that can be used to effectively treat sleep apnea. In patients suffering from obstructive sleep apnea, where the problem is so severe that awake behavior is severely impaired, tracheostomy is usually recommended. If the patient is overweight, a diet-reduction program is first tried as loss of weight is often helpful to the apneic patient. Although obesity is often a problem with



Fig. 7. Note there is a cessation of respiratory activity during the apneic episodes.

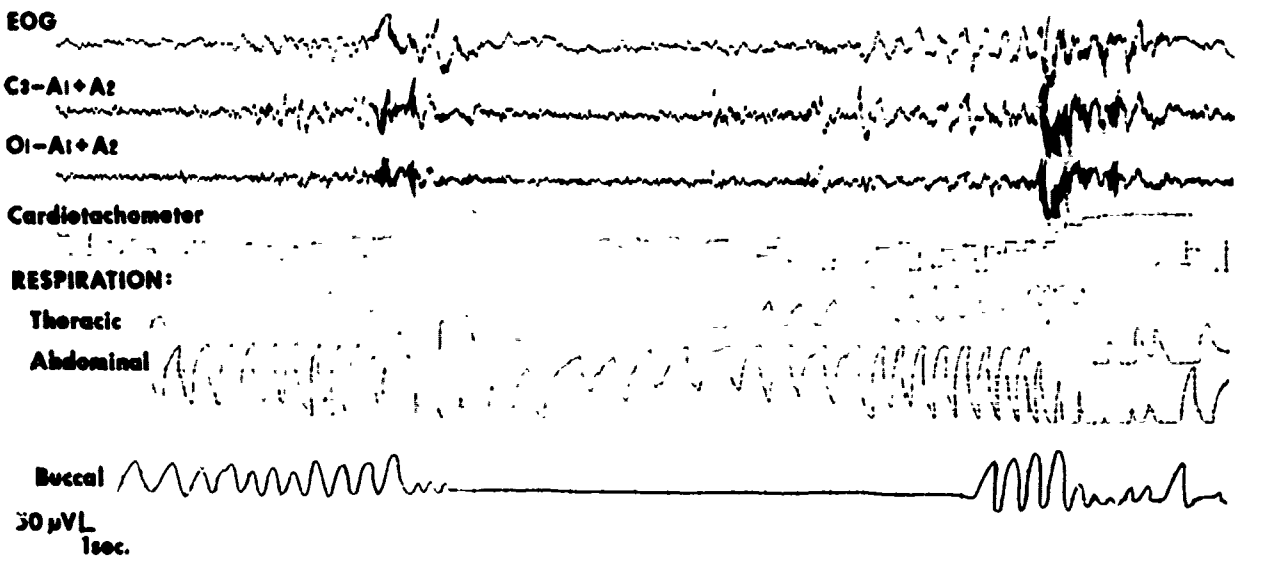


Fig. 8. In obstructive apnea, respiratory movements are seen in the abdomen and thoracic leads, but no passage of air is recorded from the buccal therma couple.

patients with obstructive sleep apnea, there are also many apneic patients whose obesity is not a problem.

Hypersomnia. Patients without symptoms of narcolepsy or sleep apnea, with complaints of excessive daytime sleep, are generally referred to as having idiopathic hypersomnia, essential hypersomnia, or just hypersomnia. To clearly document the hypersomnia, 24-hour recordings are recommended.

Recently, Richardson, Carskadon, Flagg, Van den Hoed, Dement, and Mitler[69] have reported that in classical narcoleptics, those with sleep attacks and REM-onset sleep when given frequent opportunities to nap, sleep latency data differentiated narcoleptic subjects from control subjects with enough clarity to be useful diagnostically. As a preliminary guideline, Richardson *et al.* are using a mean sleep latency of less than 5 minutes as a minimum cutoff for documentation of the complaint of pathological sleep.

Restless legs syndrome and nocturnal myoclonus. These complaints are less frequent causes of sleep disturbances but have been reported by Dement and Guilleminault.[55] Patients with restless legs usually say they feel as if there is something crawling inside their legs. These sensations occur during the day as well as during the night. Walking eliminates these tingling sensations, so, at night, patients must get out of bed to walk around.

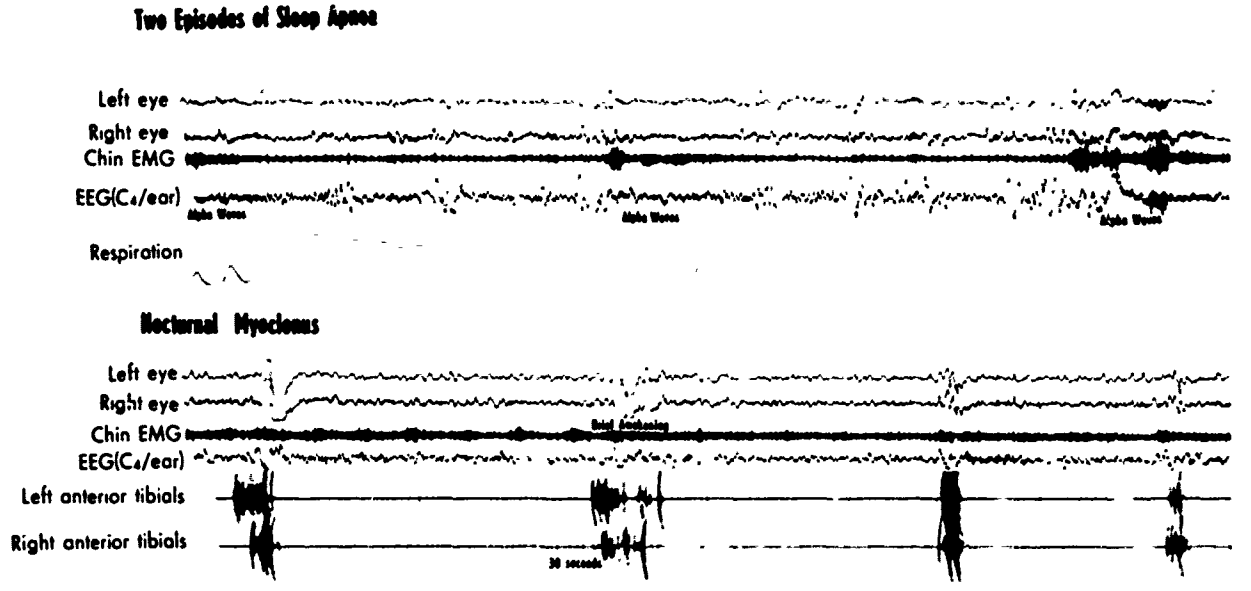


Fig. 9. Two episodes of sleep apnea (type unknown) and an illustration of leg movements in a patient with nocturnal myoclonus (from Hauri[1]).

Nocturnal myoclonus may occur alone or in association with the restless legs syndrome. Nocturnal myoclonus is exhibited by pronounced jerks simultaneously in both legs, with a tendency for flexion to occur at the ankle, knee, and hip. The jerks may be pronounced enough to awaken the sleeper. In Figure 9 is an illustration from Hauri's Sleep Disorders booklet[1] illustrating two sleep apneic episodes on the top of the figure and myoclonic jerks in the lower half.

Although the discussion of each was brief, I have attempted to list some of the causes of disturbed sleep, including the external environmental factors as well as those classified as sleep disorders. Time does not allow for a discussion of treatment. I will briefly mention the effects of benzodiazepine hypnotics tomorrow, but Wing Commander Nicholson will give a more extensive presentation of the efficacy and performance sequelae of hypnotics. The reader is referred to "Sleep Apnea Syndromes,"[70] "Narcolepsy,"[71] and "Sleep Disorders: Diagnosis and Treatment."[72]

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VIGILANCE ET ATTENTION

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RESUME

Les rapports entre la vigilance et l'attention sont envisagés à partir d'approches informatiques, psychologiques et physiologiques. Après avoir envisagé les différents types de mesures disponibles, les facteurs influant sur l'attention des sujets sont passés en revue. On envisage successivement les caractéristiques des signaux, les conditions d'ambiance, les caractéristiques individuelles et les interactions possibles entre ces facteurs.

Les différentes théories sont passées en revue et suivies de la proposition d'un modèle mathématique intégrant l'activation, la capacité de traitement et celle de filtrage, en tenant compte des données relatives à l'environnement et à la motivation.

En conclusion, différentes voies d'action sont envisagées dans les directions ergonomiques, psychotechniques, psychologiques et pharmacologiques.

1 - INTRODUCTION

La plupart des études sur la vigilance portent sur l'alternance veille-sommeil, ainsi que l'attestent plusieurs exposés qui ont été ou seront présentés au cours de ces journées. Or, l'homme répartit approximativement son temps entre le sommeil, le repos et le travail. C'est ce troisième point qui nous retiendra ici. En effet, il ne suffit pas de ne pas dormir pour être efficace, l'attention requise pour l'exécution des tâches requiert plus qu'un simple éveil. En effet, le progrès technologique a modifié les rapports que l'homme entretient avec les outils qu'il utilise - rappelons les principales étapes historiques qui nous aiderons à mieux fixer le rôle croissant que joue l'exercice des fonctions mentales les plus élevées, au détriment des aspects énergétiques purs. Le fait le plus évident est que l'accroissement du rendement tant sur le plan qualitatif que quantitatif s'accompagne d'une distance plus grande entre la tâche et l'homme qui l'exécute :

- La manipulation directe de l'outil est une prolongation de l'action elle même, elle lui est isomorphe et les conséquences de l'acte sont immédiatement perceptibles ; en terme cybernétique, la boucle de rétroaction milieu → tâche → modification du milieu est évidente.

- L'apport de l'énergie artificielle n'a pas modifié fondamentalement ce rapport, il s'agit en effet essentiellement d'une amplification des forces appliquées à une commande dont la manipulation est directement compréhensible, et du même ordre de complexité que le système moteur de l'homme. L'utilisation d'un tour entraîné par un moteur n'est pas fondamentalement différent du tour de potier ; il en est de même pour la visée à l'aide d'une arme à feu et celle effectuée avec une arbalète.

- La première rupture a lieu avec l'apparition de la notion d'actionneur : il s'agit de dispositifs qui permettent la commande indirecte de la mise en œuvre et de l'utilisation de l'énergie. Ainsi, une vanne est une commande directe : le volant est situé sur le point d'application, une électrovanne peut être commandée à distance avec un dispositif quelconque, interrupteur, poussoir ou potentiomètre. La logique de la commande cesse d'être immédiatement perceptible.

Parallèlement à ces actionneurs, on voit apparaître des moyens indirects d'information permettant à l'homme de connaître l'état de sa machine. La vision directe du processus est remplacée par une information issue d'une autre machine, une vitesse par une déviation angulaire d'une aiguille, une pression par une longueur, la présence d'un avion par un spot lumineux, etc... Le rôle de l'homme est alors de prélever ces signaux et de répondre par des actes, les uns et les autres étant arbitraires.

- Le stade suivant est celui de l'asservissement qui a consisté à court-circuiter l'homme en réinjectant directement dans les actionneurs l'information provenant de la machine, c'est la classique boucle de rétroaction négative qui décharge l'homme des tâches simples de surveillance : la vitesse de rotation d'un moteur est maintenue constante malgré la quantité de travail fournie, le canon se dirige automatiquement vers la cible ... L'homme qui était déjà déchargé de l'effort physique l'est maintenant théoriquement de la surveillance de routine. Il lui reste à veiller au bon fonctionnement des systèmes de régulation eux-mêmes et à prendre des décisions de suppléance, ou de modifications éventuelles de stratégie de fonctionnement.

- Le dernier stade est celui de l'informatique où des dispositifs sont capables de prendre en charge des activités jusque là réservées aux fonctions les plus intellectualisées, tels que calculs complexes, résolution de problèmes, etc...

Il semblerait qu'à ce niveau l'intervention humaine soit superflue et que la machine se suffise à elle-même pour assurer à la fois son fonctionnement et sa régulation. Elle est, en effet, plus fiable, infatigable, plus précise, plus rapide dans ses réponses et est capable de traiter de nombreuses données quasi simultanément.

Toutefois, pour certaines questions, l'efficacité de l'homme reste supérieure à celle de la machine, tout au moins dans l'état actuel de la technique : c'est le cas de l'aptitude à reconnaître une forme au milieu d'informations non pertinentes et de la capacité de décider en l'absence de la totalité des informations. Dans les deux cas, la fiabilité n'est pas totale, mais mieux vaut une réponse probablement vraie plutôt que pas de réponse du tout.

Il existe donc une sorte de paradoxe, il semblerait à première vue que le rôle de l'homme s'amenuise et cependant, plus la machine se substitue à lui, plus les conséquences d'un dysfonctionnement sont graves en raison de la complexité croissante des systèmes et des énergies mises en jeu. L'homme se trouve donc n'avoir à exercer que rarement des capacités qui impliquent les processus les plus élaborés de son psychisme, et ceci avec des conséquences qui peuvent être catastrophiques. Il faut donc qu'à tout instant il soit capable d'un haut niveau de performance, qu'il risque de ne jamais avoir à mettre en œuvre.

Ajoutons que ces activités peuvent se dérouler dans des conditions très éloignées des conditions normales. Les dispositifs technologiques déchargent l'homme de ses activités mais créent ou permettent des nuisances : bruits, ambiances thermiques, vibrations, pollutions chimiques, rythmes de travail.

2 - NOTIONS THEORIQUES

Le problème de l'attention peut être abordé selon trois optiques complémentaires.
La première l'étudie en tant que condition du traitement de l'information, la seconde utilise les concepts des psychologues pour l'analyser sur le plan du comportement, la dernière enfin est d'inspiration physiologique.

2.1 - Approche informatique.

On a vu depuis plusieurs années naître plusieurs modèles qui rendent compte des processus de traitement de l'information par l'homme. On peut les classer en deux catégories : l'une structurale, inspirée du modèle informatique, construit des organigrammes de processus, l'autre fonctionnelle se centre sur les propriétés générales de ces processus.

2.11 - Modèle structural.

Il s'articule sur un schéma qui distingue plusieurs stades correspondant : à la prise d'information, son stockage à court et à long terme, son traitement et enfin l'exécution de la réponse.

a) La prise d'information comporte plusieurs étapes :

Le codage sensoriel : transformation de l'énergie de l'input en influx nerveux structurellement organisé
La mémoire sensorielle immédiate qui est une rémanence très labile de ce code
L'extraction des informations pertinentes
L'identification par comparaison avec le contenu d'un "lexique" contenu dans une mémoire à long terme
La dénomination qui consiste à leur attribuer un code verbal ou non

b) Le stockage comprend deux aspects :

Le premier consiste à emmagasiner l'information, il s'effectue en deux temps successifs : la mémoire à court terme est de durée limitée à quelques secondes ; elle serait supportée par une rémanence des patterns de l'excitation nerveuse correspondant au code envisagé précédemment. Lui ferait suite un stockage à long terme qui ferait intervenir des processus biochimiques.

A ce temps d'accumulation succède celui de l'évocation qui implique la recherche de l'information stockée pertinente au milieu de toutes les autres, c'est un problème d'adressage de mémoire. On admet que la mémoire est organisée selon deux critères, l'un sémantique ou conceptuel, l'autre perceptif. Le premier fait intervenir les analogies de sens, le second les analogies de forme.

c) Le traitement

Il peut être conçu comme un programme combinant des opérations élémentaires en vue de transformer les informations stockées.

Les opérations élémentaires sont du type logique (union, intersection, négation, débouchant sur des niveaux déjà plus complexes de classifications sériation, implication, etc...) ou arithmétique qui en sont des dérivés (PIAGET). La succession de ces opérations représente un programme dont la finalité est de réduire la quantité des informations afférentes.

Une des caractéristiques des comportements des organismes est qu'en présence d'une même constellation des stimuli, plusieurs programmes débouchant sur des solutions sont disponibles, il est donc nécessaire d'effectuer un choix tenant compte à la fois du coût du traitement et du bénéfice escompté. Cette fonction de décision joue un rôle primordial, elle permet en effet la modification des stratégies en fonction des fluctuations possibles du milieu et des possibilités instantanées de l'individu.

d) Exécution

Une fois la décision prise, le schéma d'action est transposé en programmes d'exécution verbaux ou gestuels. Il en résulte deux conséquences : d'une part, une modification du milieu extérieur, d'autre part, une information interne qui l'une et l'autre constituent une nouvelle constellation de données afférentes à traiter. On peut imaginer que grâce à ce bouclage, des opérations de plus en plus efficaces soient mises en œuvre à tous les niveaux et voir là le support des apprentissages perceptifs intellectuels et moteurs.

2.12 - Modèle fonctionnaliste.

A cette vision discrète du déroulement des opérations qui reproduit en gros le schéma input → boîte noire → output, on peut opposer une approche plus globale qui recouvre non plus les processus mais les propriétés plus générales qui conditionnent leur exécution.

a) Capacité de traitement

Cette capacité représente l'aspect quantitatif, elle n'est pas infinie, ni pour l'homme ni pour la machine. Cette limitation intervient à tous les niveaux, qu'il s'agisse de la mémoire sensorielle ou du nombre des propositions qu'il est possible de traiter.

La capacité de traitement est très faible par rapport à la complexité des informations afférentes ; celles-ci doivent donc être fragmentées en sous-ensembles qui une fois traités constituent eux-mêmes des éléments à recombiner séquentiellement. Selon l'expérience passée des sujets, certaines données peuvent être considérées comme prétraitées. La complexité subjective est donc toujours plus faible que la complexité objective.

Deux propriétés complémentaires permettent ce déroulement séquentiel, le filtrage et les stratégies.

b) Filtrage

Il va consister à prélever dans la totalité des afférences les sous-ensembles considérés comme utiles en éliminant l'information non pertinente. Ce filtrage est nécessaire à tous les niveaux.

- Direction des organes des sens vers la partie utile, qui sera mise en mémoire sensorielle
- Choix des caractères à retenir à l'exclusion des autres
- Valorisation des données prélevées dans la mémoire à long terme qui va permettre l'identification et l'exécution des traitements

c) Stratégies

Ce sont des sous-programmes d'opérations élémentaires que l'on retrouve également au niveau perceptif (exploration visuelle, recherche dans le lexique d'identification) au niveau du traitement (mode de résolution de problèmes logiques) et de l'exécution (séquences gestuelles) ; il semble que ces stratégies puissent être classées en deux groupes :

- Les unes sont du type analytique séquentiel et correspondent à la pensée discursive supportée par le langage
- Les autres sont synthétiques simultanées et seraient plus liées à une appréhension globale du type spatial

d) Décision

Elle est rendue nécessaire par la multiplicité des stratégies possibles. A un niveau très global, l'existence évoquée plus haut de deux modes d'appréhension implique soit un choix, soit une dynamique qui les fait alterner, avec prédominance éventuelle de l'un sur l'autre. Les décisions interviennent à tous les stades de l'activité mentale ; au niveau le plus élémentaire, le seuil absolu d'une sensation dépend d'une décision, il en est de même des choix du mode d'exploration et des caractéristiques pertinentes, et enfin, du mode de résolution des problèmes et des actes à effectuer.

Deux facteurs rationnels déterminent les choix : l'un est relatif à la distribution des informations (probabilités subjectives) et l'autre à la valeur qui leur est attribuée, leur produit représente le gain escompté. D'autres fois, la décision relève à des stéréotypes plus ou moins conscients, conditionnés par des habitudes mentales, des facteurs socio-culturels ou affectifs.

2.2 - Approche expérimentale.

Les études sur l'attention traitent principalement de deux aspects de l'attention qui recouvrent en partie les aspects fonctionnels envisagés au précédent paragraphe.

2.21 - L'aspect quantitatif recouvre la notion de capacité de traitement. Dès 1871, JARVIS avait remarqué qu'en un temps très bref, il est possible de compter des objets dans la mesure où leur nombre est inférieur à 7. Les diverses études menées dans ce sens montrent une assez grande cohérence : 6,9 lettres pour GLANVILLE et DALLENBACH (1929), 8 objets par WOODWORTH et SCHLOSBERG (1954). MILLER en 1956, constatant que cette capacité limitait l'exercice de nombreux processus aux niveaux perceptuel, mnémonique, jugement absolu, etc..., posa t l'hypothèse que le nombre 7 (plus ou moins 2) fixait la limite possible du traitement de l'information par l'homme. Il convient de noter que cette valeur concerne des informations traitées comme des unités. Si, en effet, on ne peut traiter que 7 lettres ou 7 chiffres, il est possible d'appréhender la même quantité de mots ou de nombres signifiants, représentant un plus grand nombre d'éléments pris isolément. Des informations redondantes sont dans ce cas condensées en 1 seule. On retrouve ici la différence entre informations objectives et subjectives, les dernières étant conditionnées par l'expérience des regroupements déjà effectués par le sujet. C'est en définitive non le nombre des objets mais la quantité d'informations qu'ils représentent pour l'observateur qui constitue la variable importante.

Outre la notion de quantité d'information traitable en une seule opération, il faut tenir compte de la durée requise pour la traiter. A l'origine, limitées aux problèmes simples de temps de réaction (DONDERS 1868), ces recherches s'appuyèrent sur la théorie de l'information et dès 1952, HICK montrait que, pour une tâche apprise, la fonction qui reliait le nombre des signaux à traiter au temps de réponse était de forme logarithmique. WELFORD, en 1967, assimile le fonctionnement de l'opérateur humain à celui d'un ordinateur obéissant à un programme séquentiel où, à chaque pas requerrant une durée de l'ordre de 100 millisecondes, ne peut être traitée qu'une quantité limitée : c'est la théorie du canal unique. Dans le cadre de ce modèle, on comprend la relation entre complexité des données et temps de résolution. Le problème doit être fragmenté et chaque partie traitée isolément, puis une fois condensée, reconfrontée aux autres. Le découpage peut être plus ou moins efficace, l'idéal étant une partition, mais il n'est réalisable que dans la mesure où intervient une sélection efficace des informations.

2.22 - La sélection des données.

Dès 1904, KULPE avait montré que lors de la présentation tachystoscopique de figures, les éléments sur lesquels l'attention des sujets avait été orientée étaient mieux perçus que les autres.

NEISSER, en 1962, distingue deux aspects : le contrôle préattentif et l'attention focale. Le premier serait très précoce et filtrerait l'information dès son acquisition ; par contre, l'attention relèverait de processus plus intégrés et plus tardifs. La même distinction est faite par BROADBENT (1971) qui oppose une sélection portant sur les propriétés objectives des stimuli (stimulus-set) à celle qui met en oeuvre leur signification (response-set).

Récemment, KEREN (1976) a substitué à ces dichotomies un continuum : les deux aspects agiraient simultanément et seul, leur dosage différerait selon les situations. Le modèle structualiste a amené à se poser des problèmes quant au site de filtrage. Etait-il pré-perceptif, mnémonique, conceptuel, verbal ? Pour

intéressantes que soient ces discussions, elles ne sont pas directement en rapport avec notre sujet. Bien que NORMAN (1969) ait nié l'utilité de l'intervention d'un filtre, il semble que le concept soit pertinent. Il apparaît chez BROADBENT, en 1958, sous forme d'un dispositif agissant en tout ou rien : l'information pertinente est retenue, les autres bloquées. Ce modèle ne permettant pas d'expliquer la prise de conscience d'informations non utiles, TREISMAN (1960) a proposé un modèle plus souple faisant intervenir un atténuateur, les informations non pertinentes ne sont plus éliminées mais affaiblies. Ces informations affaiblies seraient ensuite prises en compte en fonction des besoins requis pour traiter l'information. SELFRIDGE (1960) a pu montrer que les caractères importants d'un stimulus que l'on cherche à détecter étaient essentiellement négatifs. On reconnait plus vite une information par ce qu'elle n'est pas, que par ce qu'elle est.

Ce caractère hiérarchique des processus d'attention est confirmé par les études portant sur les caractéristiques des stimuli les plus difficiles à filtrer (HINES - 1978). Ce sont essentiellement la similarité avec les stimuli pertinents, tant physique que sémantique et leur caractère soudain, aléatoire.

Le premier caractère s'explique par la nécessité de mettre en œuvre des niveaux hiérarchiques plus élevés en raison du plus faible nombre de caractères négatifs, et le second correspondant à un phénomène d'alerte et de désinhibition qui sera abordé en fin de cet article.

Un dernier point doit être envisagé quant au filtrage, c'est son aspect dynamique, c'est-à-dire la possibilité de passer d'un point de focalisation à un autre : cette mobilité conditionne tous les processus de stratégies. La durée minimale de commutation est de l'ordre de 80 millisecondes (WELFORD - 1967).

2.3 - Approche physiologique.

Nous passerons rapidement sur ce point qui est largement développé ailleurs ; seules seront retenues les informations utiles aux discussions ultérieures. C'est en 1949 que MAGOUN et MORUZZI décrivent le rôle important de la substance réticulée du tronc cérébral. Cette structure reçoit de façon indifférenciée toutes les informations qui parviennent au système nerveux, et exerce une action excitatrice sur l'ensemble des fonctions corticales. Sa destruction chez l'animal le rend incapable d'intégrer les données sensorielles bien que celles-ci parviennent au cortex : à l'inverse son excitation crée un phénomène d'éveil chez l'animal endormi. Sa fonction est donc celle d'un centre non spécifique de l'attention diffuse. Plus tard, en 1957, HUGELIN et BONVALET découvrent une formation située dans la région thalamique dont l'excitation aboutit à l'activation sélective de régions corticales, en les entourant d'une zone d'inhibition. Cette structure hiérarchiquement plus élevée que la précédente correspondait à une fonction plus différenciée. SOULAIRAC (1978) ajoute à ces deux aspects qu'il nomme vigilances de base et focalisée, un troisième volet qu'il nomme vigilance affective qui aurait pour support anatomique la région rhinencéphalique répondant au cortex archaïque. Cette approche anatomique devait se compléter de données biochimiques. La vigilance de base serait sous la dépendance de médiateurs de type adrénergiques dont la répartition anatomique recouvre le système réticulaire mésencéphalique, certaines structures hypothalamiques et les formations amygdaliennes du rhinencéphale. La vigilance focalisée mettrait en œuvre le système cholinergique qui regrouperait les formations réticulaires thalamiques et leurs projections dans les deux sens avec le cortex cérébral. Enfin, la vigilance affective semble être à la fois dépendante du système cholinergique et de l'effet modulateur des médiateurs sérotoninergiques.

Ce bref rappel nous a permis de retrouver la distinction entre les aspects global et focalisé et de mettre l'accent sur les facteurs affectifs de la vigilance ainsi que sur l'aspect longitudinal de ces différentes fonctions qui ne sauraient se contenter d'une localisation, mais agissent en tant que systèmes interconnectés. Ces différents niveaux constituent les conditions de l'attention. Chez l'homme, où prédominent les fonctions corticales, elle s'exerce grâce à la mise en œuvre de structures plus élaborées et notamment la région préfrontale, qui conditionnerait les stratégies en fonction des besoins affectifs. PRIBRAM a montré le rôle qu'elle pourrait jouer comme détecteur de nouveauté.

3 - MESURE DE L'ATTENTION.

Deux approches sont possibles :

La première fait appel à l'observation directe de performance impliquant certains niveaux d'attention. Il peut s'agir de l'exécution d'une tâche réelle ou plus souvent d'épreuves standardisées ou tests. Cet abord psychométrique peut à son tour s'adresser à l'attention en tant qu'aptitude caractéristique stable d'un individu ou à ses fluctuations.

La seconde est indirecte et porte principalement sur les paramètres physiologiques concomitants de l'attention.

3.1 - Mesures de performances

Nous nous arrêterons peu sur les performances en situations réelles, celles-ci se prêtent mal aux mesures, seules sont en effet disponibles les estimations de rapidité et les fautes ou incidents.

a) L'attention - Aptitude

L'importance de l'attention dans l'exécution des tâches a vite amené les psychologues à construire des épreuves psychométriques destinées à la mesurer, et ceci souvent dans un but de sélection ou d'orientation professionnelle.

L'attention est ici envisagée sous son aspect statique et considérée comme une aptitude. L'épreuve type est représentée par les tests de barrage : dont le prototype est celui de PIERON. Il consiste à détecter dans un ensemble de signes graphiques ceux qui correspondent à un modèle donné. La forme d'attention qui est estimée ici est la focalisation et plus particulièrement la résistance à la distraction. La mesure des temps de réaction simple constitue également une mesure de l'aptitude à se tenir prêt à répondre à un stimulus. A ces épreuves simples s'en adjoignirent rapidement d'autres, où un choix devait s'effectuer entre stimuli et réponses. Citons pour mémoire les temps de réaction de choix, les tests d'attention diffusée. Une revue de ces tests a été récemment faite par BREMOND (1978). Pour ces tests, ce sont la mobilité des processus de filtrage et l'empan de l'attention qui sont en cause. Enfin, il faut se

souvenir que l'attention est la condition nécessaire à l'exécution de toute tâche, et donc de tout test, dans la mesure où la familiarité n'en fait pas une réponse automatique. Toute épreuve peut donc être considérée comme test de vigilance : en particulier les tests de mémoire immédiate, ceux qui mettent en œuvre des stratégies nouvelles à découvrir, et principalement les techniques qui utilisent un matériel non verbal. Toutes ces épreuves sont celles que les psychométriciens utilisent pour le diagnostic de la détérioration mentale, qui est une diminution de l'efficience liée à un processus pathologique ou de vieillissement. Il s'agit donc déjà d'une mesure des fluctuations de l'attention.

b) L'attention - Etat

Lors des études portant sur les prédispositions aux accidents, S. PACAUD avait déjà remarqué que l'irrégularité des temps de réaction était un meilleur prédicteur que leur valeur moyenne. BILLS, en 1931, constatait également que lors des mesures de temps de réaction apparaissaient des périodes brèves (blocs) où les réponses étaient anormalement longues, compensées par des réactions rapides qui masquaient le phénomène, lorsque seule était prise en compte la moyenne.

Mais il faut attendre les travaux sur les tâches de surveillance lors de la deuxième guerre mondiale (DITCHBURN - 1943) et leur systématisation par MACKWORTH en 1950, pour que le problème de l'évolution de l'attention donne lieu à un ensemble cohérent de recherches. Elles dérivent de la constatation d'une diminution de l'efficience des opérations Sonar et Radar au cours de veilles prolongées. Ces tâches se caractérisent par la détection de signaux faibles, peu fréquents et imprévisibles. MACKWORTH les a nommé tâches de vigilance, par contamination avec le terme utilisé en physiologie. Les tests tendent à reproduire artificiellement de telles situations, et le premier conçu par MACKWORTH (clock test) consistait en une aiguille se déplaçant par à coups sur un cadran, le signal à détecter était un saut double. Les variables mesurées étaient le temps de latence, le pourcentage de détections correctes et celui des détections erronées ; la combinaison des deux derniers permettant, en s'appuyant sur la théorie de la décision (SWETS et TANNER - 1954), de déterminer deux nouvelles mesures : le coefficient de discrimination (d') qui rend compte de la capacité à détecter le signal et le critère (β) qui traduit l'attitude prudente ou risquée du sujet dans sa décision à considérer qu'il s'agit ou non d'un signal.

Peuvent être rattachées à ces épreuves, celles qui concernent des informations plus facilement détectables, plus fréquentes, mais se répétant pendant des durées de l'ordre de l'heure. Les épreuves de mémoire immédiate de détection d'identité de nombre en sont un exemple.

A l'opposé de ces tâches peu complexes, on a réalisé des dispositifs simulant l'exécution de missions à forte charge informationnelle, surveillance de nombreux cadrans ou compteurs, poursuite ou alignement en position ou en vitesse (ADAMS - 1959 ; ALLUISI - 1967). Le développement de la microinformatique a permis de réaliser des dispositifs faciles à utiliser, légers et sans mécanismes mobiles - les signaux étant présentés soit sous forme de chiffres ou de symboles, soit par affichage (LED ou CLD) ou sur écran. C'est ainsi qu'on a pu envisager l'emploi de tels dispositifs pour juger du niveau d'attention de conducteurs de véhicules (ATTWOOD D.A. - 1975) et interdire la mise en route en cas de défaillance. Nous avons nous-mêmes adapté sur calculatrice imprimante (HP 97) une épreuve composite (VIGIL 97) d'attention couplant un subtest de mémoire de chiffres auto-adaptatif et un subtest de détection de dissimilarité de nombres. La correction est immédiate et les résultats fournis en fin de chaque période de quatre minutes.

KALSBEEK en 1965 proposa une technique de mesure de l'attention de sujets en situation réelle : il s'agit de la méthode des doubles tâches. Elle consiste à surajouter à l'exécution normale du travail une épreuve en général peu complexe, et à mesurer l'évolution des performances à ce test. On peut utiliser à cet effet des épreuves de détection d'éclairs présentés en vision périphérique, de comptage à rebours, d'estimation de durées, etc... Ces mesures donnent une idée de la quantité d'attention résiduelle disponible.

L'utilisation des mesures des fluctuations de l'attention implique un certain nombre de précautions méthodologiques notamment dans leur emploi au cours de situation de travail réel. L'application d'un test constitue en effet un stimulus nouveau qui lui-même constitue une source d'éveil pour le sujet (BROWN - 1977) ; les mesures obtenues traduisent donc plus une estimation de l'attention éveillable par le test que celle de son état actuel.

Parmi les mesures de performances, une part doit être réservée aux estimations subjectives des niveaux d'attention ; il existe des échelles d'observation standardisées, mais surtout orientées vers le phénomène "fatigue" et des questionnaires d'autonotation, comme celui de THAYER qui demande aux sujets de cocher les adjectifs qui correspondent à ce qu'il ressent. Récemment, TURNER (1977) n'a pu mettre en évidence une corrélation entre cette échelle et les performances objectives à des tests.

3.2 - Mesures psychophysiologiques.

Le parallélisme des évolutions de certains paramètres physiologiques et de l'attention les rend utilisables comme indicateurs, et ceci pour deux aspects : l'un quantitatif, le niveau général de vigilance, et l'autre qualitatif, l'attention sélective (BUSER - 1976).

a) Aspect quantitatif

On connaît bien les caractéristiques physiologiques du sommeil (KLEITMAN - 1953). On distingue quatre stades correspondant à un sommeil de plus en plus profond auquel on ajoute le R.E.M. (Rapid Eye Movements) Seul nous intéresse ici le versant correspondant à l'éveil. A ce stade, la fréquence cardiaque, le tonus musculaire et la température centrale sont plus élevés que durant le sommeil, la résistance cutanée plus faible, mais c'est l'électroencéphalogramme qui traduit le mieux ce niveau d'attention diffuse du sujet.

On sait que, les yeux fermés, le tracé présente un rythme de 8 à 12 Hertz d'une amplitude minimale de 40 microvolts au niveau de la région parieto-occipitale : c'est le classique rythme alpha. Lorsque l'attention devient plus intense, on observe la disparition de ce rythme : c'est la réaction d'arrêt. Dans les états d'hypervigilance, on rencontre ce même tracé plat, mais d'une façon permanente. La quantité de rythme alpha peut donc être considérée comme une mesure de la non concentration de l'attention. Estimée à l'origine par le pourcentage du temps d'occurence de l'alpha (index α), elle peut être maintenant appréciée à l'aide de techniques plus élaborées, permettant de chiffrer l'amplitude relative des différentes fréquences.

A partir de ces faits, on a pu proposer des systèmes de contrôle continu de la vigilance : à partir de l'E.E.G. chez les pilotes, de la force d'agrippement chez les conducteurs de train, de la résistance cutanée pour les automobilistes, etc...

Il s'en faut toutefois que le problème soit si simple, en effet, ce tableau n'est pas le même pour tous les sujets, ainsi que l'a montré LACEY (1958). D'autre part, le système circulatoire entre autre, présente sa propre régulation qui, consécutivement à une élévation tensionnelle, peut aboutir à un ralentissement cardiaque paradoxal. Un tracé d'éveil E.E.G. peut accompagner un état de non disponibilité de l'attention et à l'inverse, on a vu des surveillants radars efficaces présenter des signes électriques de sommeil. Tous ces faits incitent à la plus grande prudence, bien que ces mesures présentent un intérêt en recherche fondamentale.

b) Focalisation de l'attention

La plupart des mesures portent sur les potentiels évoqués cérébraux qui sont la succession des événements électriques recueillis sur le scalp consécutivement à l'application de stimuli. La technique d'extraction est disponible depuis maintenant une quinzaine d'années ; elle consiste à sommer les portions d'E.E.G. en prenant pour chacune le stimulus comme origine. On obtient alors une courbe qui présente un certain nombre de pics, caractéristiques. On peut distinguer en gros les composantes précoces situées à moins de 150 milli-secondes du stimulus et les composantes tardives après 200 milli-secondes. Dès 1964, CHAPMAN a pu montrer que l'amplitude des phases tardives des potentiels évoqués était augmentée lorsque l'attention est dirigée vers le stimulus et réciproquement la même année GARCIA AUSTT constatait leur diminution lorsque le sujet était orienté vers d'autres stimuli. Les recherches récentes (SCHWATZ 1978, ont confirmé cette spécificité des phases tardives et principalement l'onde positive située à 300 milli-secondes dans la focalisation de l'attention. Elle serait principalement sensible aux situations dans lesquelles une incertitude existe quant à la survenue des stimuli, et où le sujet doit décider de l'utilité de l'information. Certains auteurs ont montré que les phases précoces pouvaient rendre compte également de la focalisation (PICTON - 1974) et seraient plus ample pour les signaux attendus que pour les non attendus. Les potentiels évoqués peuvent donc être considérés comme des phénomènes liés à l'attention sélective, toutefois, "ils sont plus le résultat de la sélection d'un signal qu'un signe d'un état antécédent conditionnant cette solution" (POSNER - 1975). De plus, ils ne sont pas seulement en rapport avec l'attention sélective, ils évoluent également avec le niveau de vigilance global (DEFAYOLLE - 1971 et ceci pour les phases précoces et tardives.

Outre ces aspects électroencéphalographiques, d'autres signes électrophysiologiques accompagnent les processus de filtrage : ainsi, une augmentation des mouvements oculaires dans les tâches visuelles traduit l'exploration, elle-même conditionnée par la sélection des informations. Un paramètre cardiaque peut également être révélateur, il s'agit de l'arythmie sinusale décrite par KALSBEEK (1963) ; cet auteur a montré que souvent, les états d'attention focalisée s'accompagnaient outre d'une accélération cardiaque, d'une augmentation de la régularité des pulsations. De même, on peut observer une diminution de la fréquence respiratoire qui peut elle-même être la cause du phénomène.

4 - FACTEURS INFLUANT SUR L'ATTENTION.

Le point de départ de toutes ces recherches est la constatation d'une diminution des performances de détection lorsque celles-ci se prolongent au delà de 45 minutes (BROADBENT). Cette dégradation a tout d'abord été envisagée sous son aspect quantitatif, et MACKWORTH J.F. (1964) la relie au temps écoulé par une fonction linéaire de la racine carré de celui-ci. Une analyse plus fine, à partir du modèle de la détection de SWEETS et TANNER, montre que cette détérioration n'est pas liée à l'aptitude à détecter le signal (d') mais à une augmentation de la prudence dans la prise de décision (BROADBENT et GREGORY 1965).

A l'origine centrée sur les tâches de surveillance peu complexes, les recherches se sont étendues à d'autres aspects :

- Tâches motrices répétitives (MURRELL - 1971)
- Tâches à fortes charges mentales (ALLUISI - 1967)
- Tâches psychomotrices (HAUTY - 1955)

Dans tous les cas, les caractéristiques des détériorations ont été identiques à une constante près. L'attention lors d'un enseignement atteindrait son maximum après 15 minutes et décroitrait ensuite (STUART et RUTHERFORD - 1978). Les erreurs de détection surviendraient après 90 minutes chez les conducteurs de train à grande vitesse (ENDO et KOGI - 1975).

Un certain nombre de facteurs sont susceptibles d'exercer une influence sur cette détérioration normale. Nous les classerons en trois catégories : ceux relatifs aux caractéristiques des tâches, ceux qui relèvent des conditions d'environnement et enfin les facteurs dépendant des sujets.

4.1 - Caractéristiques de la tâche

On n'a pas observé de différences relevant de la modalité sensorielle : les tâches visuelles et auditives se dégradent identiquement (CHENEY - 1968). Plus une tâche est constituée de signaux de faible intensité (ADAM - 1956), courts (BAKER - 1963), plus elle tend à se détériorer rapidement. La distribution des informations joue également un rôle important. Une faible fréquence s'accompagne d'une plus grande dégradation (DEESE et ORMOND - 1953) et d'un ralentissement des réponses (MARTZ - 1967). Le facteur important serait la durée qui sépare les détections successives et non les signaux eux-mêmes (JENKINS - 1958). A l'inverse, TAUB et OSBORNE (1968) trouvent que la dégradation est plus rapide lorsque la fréquence totale des informations devient trop grande. Cette divergence n'est qu'apparente, un certain optimum semble exister auquel correspond une dégradation minimale (JOHNSTON et Coll. - 1966). La prévisibilité des signaux constitue, elle aussi, un élément favorisant le maintien des performances (BUCKNER - 1961). Enfin, la complexité de la tâche doit être prise en compte. Plus le nombre des sources de signaux s'accroit, plus la dégradation est sensible (ROBEY - 1963), bien que GRUBER (1963) ait montré que l'alternance les modalités sensorielles pouvait exercer un effet favorable. Les tâches impliquant une activité physique (poursuite) ou mentale tendent à mieux résister à la dégradation que les tâches passives.

Il semble qu'au niveau de la complexité, on retrouve un phénomène analogue à celui de l'optimum que nous avons évoqué précédemment : les tâches trop simples ou trop complexes résistent mal lorsqu'elles sont trop prolongées.

4.2 - Conditions d'exécution

Dans cette partie, on regroupe les facteurs non directement liés à la tâche et à l'opérateur : les conditions d'ambiance, l'environnement psycho-social et les facteurs chronologiques.

a) Facteurs d'ambiance

Il s'agit de l'influence des nuisances sur l'exécution des tâches impliquant un bon niveau d'attention. Deux aspects ont été plus particulièrement étudiés : ce sont les bruits et la température. Les effets du bruit ne sont pas univoques : de nombreux facteurs, en effet, les conditionnent. Une forte intensité (supérieure à 95 dB) tend à dégrader les performances, mais le silence complet est également défavorable. La nature du stimulus sonore intervient également : un bruit constant exerce un effet moindre qu'un bruit présentant des caractéristiques aléatoires (modulation en fréquence ou en intensité, présence de transitoires). La signification du signal sonore est également un facteur important : on a dans l'ordre décroissant : parole, bruit et musique (TARRIERE et WISNER - 1962). Mais ces effets propres aux ambiances sonores peuvent entraîner des effets différents selon les variations des autres facteurs. C'est ainsi que les tâches à faible complexité peuvent être améliorées par l'adjonction de stimuli sonores, alors que ceux-ci amènent la détérioration d'une tâche complexe. Le travail en musique est favorable pour éviter la dégradation des performances lors d'un travail répétitif peu informatif.

Pour la température, on observe également une valeur optimale de 26 degrés. Une augmentation de la température extérieure à 36° ou une diminution à 21° amènent l'une et l'autre une dégradation des performances (MACKWORTH - 1950). Pour WILKKISON (1964), les effets de la chaleur dépendent du type de tâche : elle dégraderait les tâches complexes et faciliterait celles de surveillance passive. La chaleur augmente les erreurs de détection et le froid ralentit les réponses (MACKWORTH - 1969).

Les effets du bruit et de la chaleur sont susceptibles de se potentialiser, c'est ainsi que PAPIN (1973) a pu montrer que dans une tâche de pistage, les performances étaient moins bonnes à 34 degrés centigrades, par contre, bien qu'appliqué isolement, le bruit n'entraînait pas de dégradation, sa combinaison avec la chaleur amenait une plus grande détérioration. Les mêmes remarques pourraient être faites à propos de la pression athmosphérique : en deça et au-delà des conditions normales, les performances se dégradent. Lorsque l'on envisage les effets des conditions d'ambiance, il faut garder à l'esprit qu'elles s'exercent de deux façons : d'une part, elles agissent sur le niveau général d'activation, et d'autre part, elles constituent en elles-mêmes un stimulus qui peut entrer en compétition avec l'information pertinente.

b) Facteurs psycho-sociaux

Dès le début des études sur les tâches de surveillance, les auteurs ont pris conscience de l'importance de la connaissance que les sujets avaient de leur performance. Cette information en retour retarde en effet notablement la dégradation des performances au cours du temps (MACKWORTH N.H. - 1950). Une analyse plus fine a permis de préciser les caractéristiques de cette rétroaction.

La récompense pour une bonne réponse et la punition pour une fausse auraient le même effet (BEVAN - 1965), il vaut mieux punir pour une omission que pour la détection d'un signal absent (SMITH - 1967). Une information fausse sur les résultats a, malgré tout, un effet bénéfique, bien qu'à moindre degré, qu'une information correcte (MACKWORTH - 1964)et l'information verbale est préférable à une présentation visuelle (HARDESTY - 1963). Enfin, les jugements évaluatifs sont plus efficaces que ceux qui ne font état que de l'aspect quantitatif (HARDESTY - 1964).

Tous ces faits traduisent l'importance des renforcements sociaux. La présence réelle de l'observateur n'est d'ailleurs pas indispensable ; PUTZ a pu montrer, en effet, le même effet favorable, que celui-ci se trouve dans la même pièce, vu à travers une fenêtre ou même sur un écran de télévision. Un autre aspect de la facilitation sociale est attesté par la moindre détérioration lorsque plusieurs opérateurs sont dans la même salle et peuvent converser.

c) Facteurs chronologiques

Ils vont nous permettre d'effectuer la transition avec l'influence des caractéristiques propres aux opérateurs. Nous serons bref, ce point ayant été exposé ailleurs. On sait l'influence néfaste des heures du milieu de la nuit, l'existence de rythmes hebdomadaires et annuels, sans oublier le rythme menstruel de la femme : la période postovulatoire se traduisant souvent par des troubles de l'attention. La désynchronisation des rythmes par franchissement horaires a fait l'objet d'études nombreuses depuis la généralisation des vols long courrier : elles ont révélé une détérioration plus importante pour les vols ouest-est, que pour ceux de direction inverse.

4.3 - Facteurs liés aux sujets

Certains sont permanents ou semi-permanents, d'autres au contraire revêtent un caractère accidentel ; les premiers constituent les traits, les autres les états.

a) Caractéristiques stables

Il ne semble pas, en ce qui concerne l'aptitude à effectuer des tâches nécessitant de l'attention, qu'il existe de corrélation avec le niveau intellectuel. Par contre, un haut niveau de performance dans une tâche la rend plus résistante aux dégradations. C'est ainsi que KLEIN et Coll. (1975) ont pu montrer que les effets des décalages horaires étaient plus faibles chez les sujets qui avaient les meilleures performances et ceux qui étaient le mieux entraînés. Avec PAPIN (1972), nous avons mis en évidence une liaison entre le niveau intellectuel des sujets et leur résistance aux effets dégradants du bruit et de la chaleur dans une tâche de poursuite ; ici, l'intelligence joue vraissemblablement au niveau de la facilité d'apprentissage, celui-ci étant dans l'expérience très bref.

Sur le plan des variables de personnalité, l'école britannique d'EYSENCK a cherché les relations entre intro - extraversion et l'attention. Les introversifs se caractériseraient par un haut niveau d'excitation du système nerveux central et résisteraient mieux à la dégradation des performances de surveillance (CORCORAN - 1965). Récemment, EYSENCK M.W. (1976) a montré que les meilleures performances seraient liées à un niveau moyen d'introversion. Ce résultat est confirmé sur des malades dépressifs

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par BYRNE (1976) qui oppose les psychotiques sous-activés aux névrotiques suractivés. En estimant l'activation par la technique de SHAGASS (seuil d'endormissement sous barbituriques), il trouve que les niveaux moyens correspondent aux meilleurs taux de détection. D'autres facteurs de personnalité ont été envisagés : SCHLESINGER (1964) oppose les sujets à large empan d'attention à ceux qui ont un champ réduit, et WITKIN (1954) classe ses sujets en fonction de leur aptitude à se détacher des informations non pertinentes constituées par le fond (opposé à la figure pertinente). SCHLESINGER s'oriente donc vers l'aspect quantitatif et WITKIN sur la sélection des informations.

Etat du sujet :

Nous avons vu précédemment le rôle des rythmes biologiques, le plus souvent leurs effets se combinent avec la privation de sommeil : cette dernière se manifeste également par des troubles de l'attention et ceci d'autant plus que la tâche est familière, monotone (WILKINSON - 1968). La dégradation liée à la prolongation de l'épreuve est alors plus marquée. Elle se traduit par une attitude plus prudente pour les privations modérées, puis par une augmentation des fausses alarmes lorsque la privation est sévère (plus de 3 nuits). La connaissance des résultats, et le bruit minimisent les effets de la privation de sommeil.

La fatigue physique entraîne également une dégradation des performances aux épreuves d'attention (DEFAYOLLE - 1978). Il en est de même de la maladie : ALLUISI, en 1969, observe au cours d'une maladie infectieuse, la Tularemie, une détérioration de 25 % des performances lors de tâches d'attention prolongée. Nous citerons pour mémoire les effets des produits psychotropes qui seront abordés au cours de la deuxième journée de cette série de conférences : les hypnotiques entraînent une dégradation de l'attention à l'inverse des stimulants, ceux-ci à forte dose ont toutefois un effet négatif.

La motivation pour la tâche constitue un des plus importants facteurs : la connaissance des résultats est un des moyens de l'entretenir. Un excès de motivation ou la présence d'anxiété ou de préoccupation exercent un effet défavorable.

Les effets isolés de tous ces facteurs sont susceptibles de se conbiner soit en se potentialisant, soit en compensant leurs effets adverses. Ainsi, la motivation peut compenser les effets dégradants d'une tâche répétitive, de la privation de sommeil, etc... Par contre, le bruit dégrade plus les tâches complexes exécutées avec forte motivation. La chlorpromazine diminue les effets négatifs du bruit (HARTLEY - 1977). L'effort physique favorise les tâches simples et détériore les plus complexes (SJOBERG 1977).

5 - MODELES EXPLICATIFS.

Le contraste existant entre la multiplicité des facteurs influant sur l'attention et la relative simplicité de leurs effets conduit à proposer des théories explicatives. Pour certaines, un seul facteur suffit à expliquer les faits observés. Trois grandes théories ont été avancées :

- MACKWORTH (1950) s'appuie sur le modèle du conditionnement pavlovien et impute la détérioration au développement de l'inhibition interne par non renforcement.

Mc CORMACK (1962) fait intervenir à côté de ces phénomènes d'inhibition le rôle de la motivation.

- BROADBENT, en 1953, propose la théorie du filtre. Celui-ci a pour rôle de sélectionner pour un traitement ultérieur, les stimuli importants, en raison de leur intensité, leur signification biologique et leur caractère de nouveauté. C'est la diminution de celle-ci au cours de l'épreuve qui expliquerait la dégradation des performances. En 1963, ce même auteur fait jouer un rôle prépondérant aux processus décisionnels.

- La dernière tendance fait appel au concept physiologique d'activation qui relie le niveau d'éveil et la performance. Nous avons vu précédemment que les différents niveaux d'attention s'accompagnaient de modification des paramètres psychophysiologiques, traduisant la mise en fonction du système réticulaire non spécifique. La théorie de l'activation considère ce parallélisme comme une causalité, reprenant sur le plan psychologique les idées de CANNON (1936) qui attribuait une fonction de préparation à l'attaque ou à la fuite, aux réactions végétatives. Les différents facteurs envisagés au paragraphe précédent, entraînant généralement des phénomènes végétatifs, il était logique de considérer leurs effets comme une conséquence de l'activation qu'ils induisent.

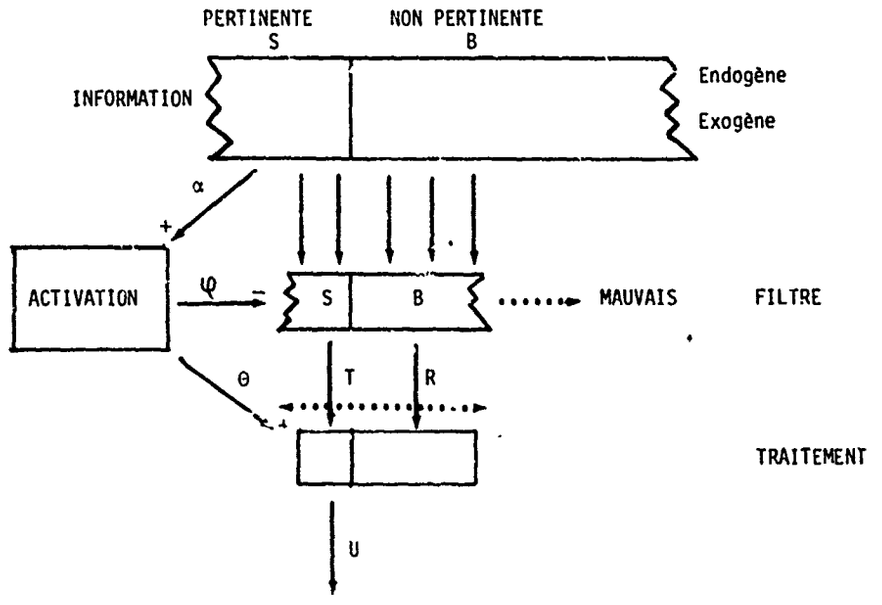
Les données expérimentales révèlent souvent qu'entre activation et performance la liaison est non monotone, mais revêt la forme curvilinéaire d'un U renversé ; il existerait donc un point optimal d'activation tel que, en deçà et au delà, on observerait une diminution de l'efficacité (MALMO - 1962). Ce phénomène avait été décrit dès 1908 par YERKES et DODSON à propos de l'apprentissage. Nous l'avons déjà rencontré pour les effets de la complexité du bruit, des psychotropes et de la typologie. L'explication de la partie ascendante de la courbe apparaît simple, par contre, il est plus difficile de comprendre comment un surcroit d'activation peut induire une diminution de l'efficience. BROADBENT (1965) fait intervenir le modèle de décision et relie l'activation à l'augmentation de la prise de risque (β), la dégradation serait alors due à une attitude imprudente qui augmenterait les fausses détections. EASTERBROOK (1959) attribue le phénomène de dégradation rencontrée lors de l'hyperactivation à un excès de la focalisation. Mc GRATH (1963) propose de combiner deux facteurs : l'activation et le filtrage, idée reprise et complétée récemment par POSNER (1975) qui distingue trois composants : l'alerte, la sélection et les processus conscients de choix de stratégie.

C'est dans cette optique que nous avons proposé un modèle (cf. CROCQ - 1978) faisant intervenir deux facteurs : la capacité de traitement et celle de filtrage, placés l'une et l'autre sous l'influence du niveau général d'activation. L'information que le sujet est susceptible de traiter à chaque instant peut être répartie en quatre sous-ensembles répondant à deux critères :

- son origine : elle peut être externe, véhiculée par les organes sensoriels, ou interne et être constituée par l'ensemble des images et représentations que le sujet est susceptible d'évoquer
- sa pertinence vis-à-vis de la tâche : les informations externes pertinentes (S) sont celles qui correspondent aux modifications de l'environnement en rapport avec la tâche à effectuer, les consignes, les règles de traitement et l'expectation des gains ou coûts, sont également des informations pertinentes. Par contre, sont non pertinentes (B) les données externes relatives à l'environnement (bruit, chaleur) et internes, constituées d'évocations non pertinentes (soucis, conscience des nuisances, etc....).

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Pour fixer un ordre d'idée, les informations externes correspondent à 10^7 bits répartis en 87% et 9% respectivement pour les canaux visuels et auditifs. Cette masse de données est considérablement plus grande que la capacité de traitement global de l'homme qui se situe à environ 15 bits. La solution à cette disparité va consister à trier les informations à l'aide d'un filtre de façon à ne traiter, à chaque instant, que ce qui est utile. Le processus pourrait se schématiser de la façon suivante. Face à un signal qui excède la capacité de traitement, le filtre (F) se positionne de façon à en prélever une partie qui soit compatible avec les possibilités du système de traitement (T), compte tenu de l'information interne correspondant au programme de traitement. Celui-ci condense les éléments sélectionnés en une unité d'ordre supérieure stockée en mémoire.



Le filtre se replace alors sur une autre portion de l'information. Chaque repositionnement est défini par le programme d'exploration et par les résultats du traitement précédent selon un processus de type markovien. Un problème ou partie de problème non résolu est donc susceptible de bloquer toute la succession des opérations à moins de changer de programme, donc d'en sélectionner un nouveau. On retrouve ici la notion de processus vicariant (REUCHLIN - 1978).

Les deux facteurs T et F sont sous la dépendance du niveau d'activation (A). L'accroissement de ce dernier entraîne une augmentation de la capacité de traitement et une diminution de la valeur du filtre. Cette dernière hypothèse est inverse de celle proposée par EASTERBROOK, le sujet suractivé n'est pas trop focalisé, mais au contraire ne peut assurer un filtrage correct. Ce point de vue rejoint celui de HAATÄNEN (1975) qui attribue la dégradation des performances des sujets suractivés à des "demandes divergentes", c'est-à-dire à des informations internes non immédiatement pertinentes pour l'exécution de la tâche. Quant au niveau d'activation (A), il est déterminé par la quantité d'informations à traiter, pertinentes ou non, l'état physiologique du sujet et sa motivation (M). Cette dernière joue un rôle très important, elle représente la vigilance affective (SOUIRAC - 1978). BAILEY (1976) a montré la relation qui existe entre ennui et éveil et MURRELL (1974) a développé la notion d'AUTOAROUSAL, où les informations internes sont utilisées comme génératrices d'éveil.

La fonction croissante de A et donc de T sous l'influence de l'état de besoin et de la quantité d'information à traiter représente un mécanisme d'autorégulation adaptative. La décroissance de la valeur sélective peut apparaître paradoxale ; en réalité, dans les limites normales, elle est aussi adaptative : une focalisation trop importante lorsque le problème à résoudre atteint une certaine complexité, aboutit à se priver d'informations qui pourraient être pertinentes. C'est seulement dans les conditions extrêmes que le phénomène devient gênant.

Pour figurer les relations existant entre S.B.M et A d'une part, A et T.F d'autre part, on a choisi une fonction exponentielle. Celle-ci outre son caractère très général dans les systèmes vivants présente l'intérêt de rendre compte de la rapidité d'évolution vers une valeur maximale.

La capacité de traitement T qui correspond à l'information traitable dans chaque unité de temps peut s'écrire :

$$T = T_{MAX} (1 - e^{-\theta A})$$

- T_{MAX} qui représente la quantité maximale traitable est un paramètre propre à l'individu. C'est un des aspects de l'aptitude
- θ indique la rapidité à laquelle T croît lorsque l'activation augmente, c'est une valeur également propre aux individus.

La valeur de filtrage, ou plutôt de sa réciproque se traduit par la quantité d'information non pertinente (B), non filtrée : nous la nommons information résiduelle (R).

$$R = B (1 - F_{MAX}) (1 - e^{-\psi A})$$

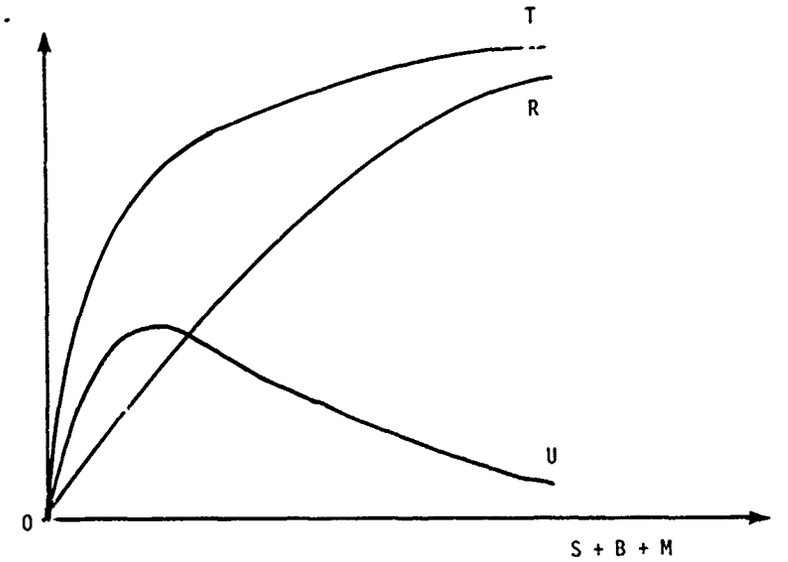
- F_{MAX} variant de un à l'infini donne la valeur maximale du filtrage que l'on peut escompter d'un sujet donné et φ est le paramètre qui rend compte de la dégradation du filtre en fonction du niveau d'activation.

Ce niveau d'activation A obéit au même type de fonction :

$$A = A_{MAX} (1 - e^{- \alpha (S + B + M)})$$

A_{MAX} correspond à l'activation maximale qui peut présenter le sujet dans son état actuel (sommeil, drogue, fatigue), α est un paramètre de réactivité à l'accroissement de la quantité d'information S, B et de la motivation M.

Confronté à chaque instant avec une quantité globale d'information (S, B), présentant certaines caractéristiques personnelles de base (T_{MAX} F_{MAX}) et d'état (A_{MAX} M 0 φ), le sujet ne va pouvoir en traiter qu'une partie réduite qui correspond à la différence existant entre sa capacité T et l'information résiduelle non traitée R.



Cette différence que nous nommerons capacité utile U = T - R, conditionne l'efficacité de l'attention. Plus sa valeur sera grande, plus d'informations pourront être traitées. Dans le cas d'une tâche où les signaux sont discontinus, ils se surajoutent au bruit de fond non pertinent et risquent surtout, s'ils sont de durée brève, de ne pas être traités et donc perçus.

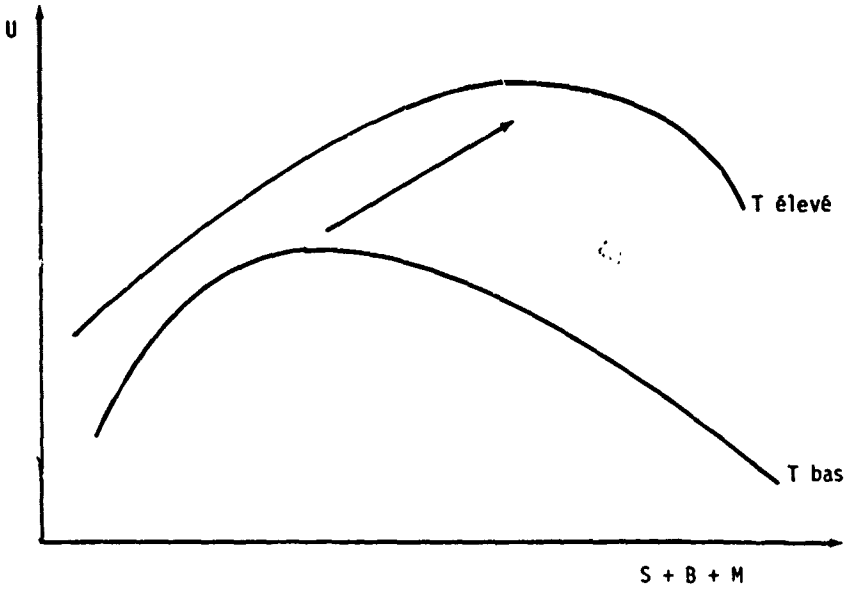
La simulation de l'équation complète va nous permettre d'estimer la valeur du modèle. Nous discuterons successivement l'influence des caractéristiques de l'information pertinente de l'environnement, des variables de personnalité et de leurs effets conjoints.

Tout ce qui va accroître l'information contenue dans S va se traduire par un accroissement de A : ainsi, la complexité, le caractère de nouveauté et la fréquence.

Inversement, la repetition monotone, la simplicité, tous facteurs qui se développent avec la prolongation de la tâche se traduiront par une diminution de l'activation. Il en est de même de la motivation et des stimuli pertinents ou non, S, B et M ayant le même effet pouvant se compenser mutuellement.

L'activation résultante sera fonction des paramètres A_{MAX} et α ; un sujet privé de sommeil ne pourra atteindre un niveau d'éveil aussi élevé qu'un sujet reposé. Les valeurs des différents paramètres définissent les propriétés de la courbe d'efficacité. Pour des valeurs croissantes de l'activation, U tend vers une valeur asymptotique $T_{MAX} - B (1 - F_{MAX})$.

Si cette valeur est négative, la tâche ne peut être effectuée, le bruit non filtré afférent étant supérieur à la capacité de traitement. Pour $0 = \varphi$, la courbe est croissante à accélération négative. Pour $0 > \varphi$, on a une courbe qui passe par un maximum qui correspond au niveau d'activation le plus favorable. Au delà et en deçà, les performances sont moins bonnes. Pour une tâche simple, ce maximum requiérera un plus haut niveau de motivation que pour une tâche complexe qui pourra, à son tour, se détériorer si cette motivation est trop intense. Le "bruit" qui augmente l'activation a un effet plus complexe puisqu'il doit être filtré, là aussi, on peut observer que pour des niveaux de complexité faibles pour la tâche et une faible motivation, il peut exercer un effet favorable.



Le paramètre F_{MAX} qui correspond à l'aptitude joue lui aussi un rôle très important. Plus sa valeur est grande, meilleure est l'efficacité en présence de stimuli non pertinents, et plus l'optimum d'activation se déplace vers des valeurs élevées. Elle serait une des conditions de la fiabilité de l'opérateur et pourrait correspondre à la dimension introversion d'EYSENCK.

Ce rapide survol des propriétés du modèle permet de voir qu'il rend compte d'un assez grand nombre de faits concernant l'influence de la tâche, de l'ambiance et des facteurs de personnalité. Il ne doit toutefois pas être considéré comme possédant une valeur explicative, mais plutôt comme un moyen descriptif utile pour cerner les facteurs importants : quantité d'information Activation et Filtrage.

Nous n'avons pas abordé le problème des stratégies des sujets qui jouent un rôle également très important dans l'efficacité. Nous avons vu, que pour une situation donnée plusieurs stratégies peuvent être disponibles, leur choix dépend des coûts et gains relatifs à chacune d'elles. MORAY considère qu'une part non négligeable de la capacité de traitement est occupée par les programmes eux-mêmes. Un optimum doit donc être trouvé qui concilie économie de données à traiter et lourdeur du programme qui la permet, l'un et l'autre variant souvent en sens inverse.

CONCLUSION.

La vigilance considérée comme état de disponibilité à la réponse et l'attention comme la capacité à traiter et filtrer l'information apparaissent intimement liées, elles sont l'une et l'autre les deux aspects de la dualité psychologique et physiologique de l'homme.

Elles recouvrent en réalité trois processus distincts : l'activation, la capacité de traitement et l'aptitude au filtrage, qui rendent compte d'effets parfois paradoxaux de la facilitation ou de dégradation de l'attention.

Sur le plan pratique, quatre types de solutions sont envisageables pour éviter la détérioration de ces processus :

a) La voie ergonomique consiste à aménager les signaux et l'environnement de l'opérateur afin de le situer vers son optimum d'activation

b) la voie psychotechnique chercherait à détecter les sujets les plus aptes. Nous avons vu la difficulté qu'il y avait à définir une aptitude à l'attention, il semblerait plus intéressant de s'orienter vers les aspects sélectifs centrés sur les processus de filtrage ; il est possible que sur ce point les mesures physiologiques soient utilisables

c) La voie psychologique consisterait à optimiser la motivation des sujets, en fonction du type de tâche. Un travail à faible charge nécessitant un plus haut niveau de motivation, on conçoit l'utilité d'informer d'autant plus les exécutants de l'importance de leurs actes que ceux-ci apparaissent inintéressants

d) Enfin, la voie pharmacologique ferait appel aux aides chimiques susceptibles d'agir sur les trois grands systèmes : catecholaminergique, serotoniergique et cholinergique, qui seront abordés au cours de la prochaine journée.

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VIGILANCE AND ATTENTION

by

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SUMMARY

The relations between vigilance and attention are considered using computer analyses and psychological and physiological techniques. After considering the different types of available measures, the factors influencing attention are reviewed. The characteristics of signals, the environmental conditions, the individual features and the possible interactions between these factors are then considered.

The various theories are reviewed and followed by a proposed mathematical model which integrates activation, the use of processing ability and filtering, taking into consideration the data relative to the environment and to motivation.

In conclusion, different methods are envisaged from ergonomical, psychological and pharmacological directions.

1 - INTRODUCTION

Most studies on vigilance relate to the alternation of sleep and wakefulness. This is shown by numerous papers which have been or will be presented in the course of these lectures. Now, man distributes his time between sleep, rest and work. It is this third point which we will consider here. Indeed, simply staying awake is not sufficient to be effective. The attention required to perform tasks needs more than simple wakefulness. In effect, technological progress has modified man's relations with the tools he uses. Let us recall the principal historical background which will help us understand the increasing role played by the highest mental functions, to the detriment of purely physical aspects. The most obvious fact is that the increased efficiency, both on a qualitative and quantitative level, is accompanied by a greater distance between the task and the person who performs it:

- The use of instruments is a lengthening of the action itself. It is its dual, and the consequences of the action are immediately perceptible. In cybernetic terms, the feed-back loop environment → task → modification of environment is obvious.

- The use of energy from external sources has not fundamentally modified this relationship. It is essentially a question of increasing power applied to the control, the management of which is directly understood, and of the same order of complexity as the human motor system. The use of a motor-driven lathe does not differ fundamentally from a potter's wheel, similarly for aiming with a firearm or with a cross-bow.

- The first breakthrough occurred with the introduction of the concept of an actuator: that is of systems which allow the indirect control of energy. Thus, a sluice is a direct drive: the fly-wheel being situated at the point of application. An electrosluice can be operated from a distance with any device, circuit-breaker, push-button or potentiometer. The control logic is no longer immediately perceptible.

Parallel to these actuators, one has seen the appearance of indirect methods of information allowing man to know the state of his machine. Direct view of the process is replaced by information coming from another machine, speed by the movement of a needle, pressure by length, and the presence of an airplane by a luminous spot, etc. The role of man is to perceive these signals and to act upon them, both of these being arbitrary.

- The next stage is that of servo-control which consists in by-passing man by directly feeding the information from the machine into the actuators. This is the classical negative feed-back loop which relieves man of simple surveillance tasks. The rotational velocity of a motor is constantly maintained despite the quantity of work supplied, the gun aims itself automatically towards the target ... Man, who was already free of physical effort, is now theoretically free of routine control. He is left to look after the running of the regulation systems themselves and to take decisions for substitutions, or for eventual modifications of function strategy.

- The last stage is that of computer control where devices are capable of controlling activities which up til now have been reserved for the most intellectual functions, such as complex calculations, solution of problems, etc.

It appears that at this level human intervention is superfluous and that the machine is sufficient in itself for ensuring both its running and its regulation. Indeed it is more reliable, untiring, more precise, more rapid in its responses and is capable of treating numerous data almost simultaneously.

However, in some instances, the efficiency of man remains superior to that of the machine, at least in the present state of the art. Such is the case with aptitude in recognizing form amongst irrelevant information and with the ability to make decisions in the absence of all the information. In both cases, reliability is not complete, but a probably correct response is better than no response at all.

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There is, therefore, a sort of paradox. It would seem at first glance that man's role is reducing, and yet, the more the machines are substituted for him, the more serious are the consequences of dysfunction because of the increasing complexity of systems and of the energies energies used. Man finds himself, therefore, having only rarely to exercise capabilities which involve the most elaborate processes of his psyche, and with consequences which can be catastrophic. It is thus necessary that he should be capable at any time of a high level of performance which he may never never have to use.

Let us add that these activities can take place under conditions far removed from normal. Technological devices free man from some activities, but create or allow harmful effects: noises, thermal environments, vibrations, chemical pollution, shift work.

2 - THEORETICAL NOTIONS

The problem of attention can be approached according to three complementary points of view.

Firstly, it is a subject for information processing, secondly for psychological concepts for behavioural analysis, and lastly it is physiologically based.

2.1 - Informational Approach

We have seen the rise, during the last several years, of numerous models which take into account the processes by which man treats information. They can be classified into two categories: one structural, prompted by the information model and based on flow diagrams of processes; the other is functional, based on the general properties of these processes.

2.11 - Structural model

This hinges on a plan which characterises several connected stages: to the acquisition of information, its short and long-term storage, its processing and finally carrying out the response.

a) Acquisition of information comprises several stages:

Sensory coding: transformation of the input energy into a structurally organized nerve impulse
Immediate sensory memory which is a very unstable retention of the code
Extraction of pertinent information
Identification by comparison with the contents of a "glossary" contained in the long-term memory
Naming which consists of attributing a verbal code or not to them.

b) Storage comprises two aspects:

The first consists of storage of information. It takes place in two successive phases: short-term memory is of limited duration of a few seconds; it would be supported by a retention of the patterns of nerve excitation which correspond to the code seen previously. Following this would be long-term storage which calls for the intervention of biochemical processes.

This accumulation period is followed by that of recall which implies a search for the relevant stored information amongst the rest, is a problem of memory arrangement. The memory is organized according to two criteria: one of them semantic or conceptual; the other, perceptive. The first calls for the use of sensory analogies; the second, for the analogies of form.

c) Treatment

This can be understood as a programme combining elementary processing with a view to transforming the stored information.

The elementary processes are of the logical type (union, intersection, negation, coming onto even more complex levels of classifications; seriation, implication, etc) or arithmetics which are derivatives of it (Piaget). The sequence of these processes represents a programme the aim of which is to reduce the quantity of afferent information.

One of the characteristics of the behaviour of organisms is that with the presence of the same arrangement of stimuli, several problem solving programmes are possible. It is therefore necessary to make a choice, taking into account both the cost of the treatment and the anticipated benefit. This decision making plays a primordial role; it allows in fact the modification of strategies as a function of the possible fluctuations in the environment and of the instant possibilities of the individual.

d) Execution

Once the decision has been made, the plan of action is transformed into verbal or non-verbal programmes. Two consequences result on one hand, a modification of the external environment, on the other, internal information, both of which constitute a new arrangement of related data to be dealt with. One can imagine that by virtue of this looping, more and more effective operations are are carried out at all levels and here perceptive intellectual and motor training are seen to be sustained.

2.12 - Functional model

To this discrete vision of the progression of operations which grossly reproduces the plan input → black box → output, one can contrast a one can contrast a wider approach covering, not the processes, but the more general characteristics which influence their execution.

a) Processing Capacity

This capacity represents the quantitative aspect; which for neither man nor machine is infinite. This

limitation is present at every level, whether it is concerned with sensory memory or with the number of proposals which it can deal with.

The processing capability is very weak in relation to the complexity of the afferent information; the latter must therefore be fragmented into sub-groups which, once treated, themselves constitute elements to be sequentially recombined. According to the past experience of subjects, certain data can be considered as pre-treated. Subjective complexity is therefore always weaker than objective complexity.

Two complementary properties allow this sequential progression, filtering and strategies.

b) Filtering

This will consist of separating from all the afferents the sub-groups considered useful by eliminating irrelevant information. This filtering is necessary at all levels.

- Directing the sense organs towards useful advantage, which will be put into the sensory memory
- Choice of distinctive features to be retained and others to be excluded
- Valuation of data stored in the long-term memory which will allow the identification and execution of processes.

c) Strategies

These are sub-programmes of elementary operations which one also finds at the perceptual level (visual exploration, search in the identification glossary), at the level of treatment (solution mode of logical problems) and of execution (gestual sequences). It seems that these strategies can be classified into two groups:

- One is of the analytical sequential type and corresponds to rational thought supported by language,
- The other is of the simultaneous constructive type and would be more connected to overall spatial comprehension.

d) Decision

This is made necessary by the multiplicity of possible strategies. At the global level, the existence of two modes of comprehension mentioned above implies either a choice or dynamics which alternate, with the eventual predominance of one over the other. Decisions intervene at all stages of mental activity; at the most elementary level, the absolute threshold of a sensation depends on a decision, the same goes for choices of the method of exploration and of relevant characteristics, and finally, to the problem solving mode and of acts to be carried out.

Two rational factors determine the choices: one is related to the distribution of information (subjective probabilities) and the other is related to the value which is given to information, its product represents the anticipated gain. At other times, the decision relates to more or less conscious stereotypes, conditioned by mental habits, socio-cultural or affective factors.

2.2 - Experimental Approach

Studies on attention principally treat two aspects of attention which partially cover the functional aspects considered in the preceding paragraph.

2.21 - The quantitative aspect covers the notion of processing capacity. As early as 1871, Jarvis remarked that in a very short time-space, it is possible to count objects if their number is less than 7. Various studies made in this field are fairly consistent: 6.9 letters for Glanville and Dallenbach (1929), 8 objects by Woodworth and Schlosberg (1954). In 1958, Miller, concluding that this capability limited the exercise of numerous processes at the levels of perception, mnemonics, absolute judgment, etc, made the hypothesis that the number 7 (plus or minus 2) fixed the possible limit of information processing by man. It is useful to note that this value concerns information treated as units. If, in effect, one can treat only 7 letters or 7 figures, it is possible to learn the same quantity of words or of significant numbers, representing a greater number of elements taken separately. In this case, redundant information is condensed into 1 only. Here one finds the difference between objective and subjective information, the latter being conditioned by the experience of regroupings already effected by the subject. It is definitely not the number of objects but the quantity of information they represent for the observer which constitutes the important variable.

Besides the notion of quantity of information which can be handled in one unique operation, one must take into account the duration required to treat it. Originally, limited to simple problems of reaction time (Donders, 1868), this research was based on information theory and since 1952 Hick showed that for a learned task, the function which related the number of signals to be treated to the response time was of a logarithmic form. In 1967 Welford compared the functioning of the human operator to that of a computer obeying a sequential programme where for every step requiring an interval of the order of 100 milliseconds, only a limited quantity can be treated: this is the single channel theory. Within the framework of this model, one understands the relation between data complexity and resolution time. The problem must be fragmented and each section treated separately, then, once condensed, recolated with the others. The separation may be more or less effective, the ideal being a partition; but this is possibly only if an effective selection of information occurs.

2.22 - Data selection

As early as 1904, Kulpe showed that during the tachystoscopic presentation of figures, the elements onto which the subjects' attention had been oriented were better discerned than the others.

Neisser, in 1962, distinguished two aspects: preattentive control and focal attention. The first is very early and would filter information from the moment of acquisition. On the other hand, attention would depend on later more integrated processes. The same distinction is made by Broadbent (1971) who compared selection based on the objective properties of stimuli (stimulus-set) to that which implements their significance (response-set).

Recently, Keren (1978) substituted a continuum for these dichotomies: the two aspects would act simultaneously and alone, their proportion would differ according to the situation. The structuralist model led to questions concerning the site of filtering. Was it pre-perceptive, mnemonic, conceptual, verbal? Interesting as these discussions may be, they are not directly related to our subject. Although Norman (1969) denied the usefulness of filter intervention, it seems that the concept is relevant. It appears in a publication by Broadbent (1958) in the form of a device acting by an all-or-nothing mode: the relevant information is retained, the rest blocked. As this model does not explain the awareness of unused information, Treisman (1960) proposed a more flexible model which brings in an attenuator; non-relevant information is no longer elimirated but weakened. This weakened information would then be taken into account as a function of the needs required to treat the information. Selfridge (1960) was able to show that the important characteristics of a stimulus one was trying to detect were essentially negative. One recognizes information more quickly by what it is not, than by what it is.

This hierarchical character of attention processes is confirmed by studies concerned with the characteristics of the stimuli which are most difficult to filter (Hines, 1978). These are essentially similarity to relevant stimuli, physical as well as semantic, and unexpected unreliable characteristics.

The first characteristic can be explained by the need to implement higher hierarchical levels because of the smaller number of negative characters, and the second corresponds to a phenomenon of alarm and disinhibition which will be dealt with at the end of this article.

A last point must be considered concerning filtering: its dynamic aspect; that is, the possibility of passing from one point of focalization to another. This mobility conditions all the strategy processes. The minimum duration of change is of the order of 80 milliseconds (Welford, 1967).

2.3 - Physiological Approach

We will pass rapidly over this point which to a great extent is developed elsewhere. Only information useful to further discussions will be retained. It was in 1949 that Magoun and Moruzzi described the important role of the reticular formation of the brain stem. This structure receives, in an undifferentiated manner, all the information which reaches the nervous system, and exerts an excitational action upon all cortical functions. In animals its destruction makes them incapable of integrating sensory input although these do reach the cortex; conversely, its excitation creates an arousal phenomenon in a sleeping animal. Its function is, therefore, that of a non-specific centre of diffuse attention. Later, in 1957, Hugelin and Bonvalet described a structure located in the thalamic region, the excitation of which results in the selective activation of cortical areas by surrounding them by an inhibitory area. This structure, hierarchically superior to the preceding one, corresponds to a more differentiated function. Soulairac (1978) added to these two aspects, which he called basic vigilance and focalized vigilance, a third aspect which he called effective vigilance whose anatomical support would be the rhinencephalic region responding to the primitive cortex. This anatomical approach had to be complemented by biochemical data. Basic vigilance would depend on adrenergic transmitters who anatomical distribution covers the reticular mesencephalic system, certain hypothalamic structures and the amygdaloid structures of the rhinencephalon. Focalised vigilance would bring into play the cholinergic system which combines the reticular thalamic formations and their projections in both directions to the cerebral cortex. Finally, affective vigilance seems to be dependent both on the cholinergic system and on the modulating effect of the serotoninergic mediators.

This brief summary allows us to recall the distinction between the global and focalized aspects and to emphasize the affective factors of vigilance as well as the longitudinal aspect of these different functions which are not localized in one place but act as interconnected systems. These different levels constitute the conditions of attention. In man, where cortical functions predominate, it is exercised by virtue of the implementation of more elaborated structures and notably the prefrontal area, which would condition strategies as a function of affective needs. Pribram showed the role which this could play as a detector of change.

3 - MEASURE OF ATTENTION

Two approaches are possible:

The first calls for direct observation of performance implying certain levels of attention. It may be a matter of carrying out a real task or more often standardized trials or tests. This psychometric approach can, in turn, be applied to attention as the characteristic stable aptitude of an individual, or to its fluctuations.

The second is indirect and principally concerns the physiological parameters which accompany attention.

3.1 - Measures of Performance

We will pay little attention to performance in real situations, owing to poor measurements- only estimations of speed and of mistakes or difficulties are indeed available.

a) Attention - Aptitude

The importance of attention in the rapid execution of tasks quickly led psychologists to construct psychometric tests intended to measure attention, often with the aim of selection or of professional orientation.

Attention is here viewed in its static aspect and considered as an aptitude. The model test is represented by blocking tests, the prototype of which is that of Pieron. It consists of detecting within a group of graphic signs those which correspond to a given model. The form of attention assessed here is focalization and more particularly resistance to distraction. The measurement of simple reaction time also constitutes a measure of the aptitude to be ready to respond to a stimulus. Other tests were quickly added to these simple ones, tests in which a choice had to be made between stimuli and responses. To remind ourselves we may quote choice reaction time, diffused attention tests. These tests were recently reviewed by Bremond (1978). These tests are concerned with the mobility of filtering processes and with the span of attention. Finally, one must remember that attention is the necessary condition for the execution of all

tasks, and therefore of all tests to the extent that familiarity does not make it an automatic response. Every test can thus be considered as a test of vigilance: in particular tests of immediate memory, those which implement new strategies to be discovered, and principally techniques which use non-verbal material. All of these tests are used by psychometricians for diagnosing mental deterioration which is a dimunition of efficiency connected to a pathological or an ageing process. It is already therefore a question of fluctuations of attention.

b) Attention - State

During studies on accident proneness, S Pacaud had already noticed that variability in reaction time was a better predictor than their mean value. In 1931 Bills also concluded that during measurements of reaction time, short periods (blocks) with abnormally long responses appeared, compensated by rapid reactions which masked the phenomena if only the average was calculated.

But it was not until the advent of studies on surveillance tasks during the Second World War (Ditchburn, 1943) and their organization by Mackworth (1950) that the problem of the development of attention led to a coherent series of research studies. They arise from the establishment of a loss of efficiency of Sonar and Radar operations during the course of prolonged wakefulness. These tasks are characterized by the detection of weak, rare, unpredictable signals. Mackworth called them vigilance tasks, a corruption of the physiological term. The tests aim to artificially reproduce such situations; the first one devised by Mackworth (clock test) consisted of a hand which jumped around a clock face, and the signal to be detected was a double length jump. The variables measured were latency, percentage of correct and erroneous detections. The combination of the latter two allowed, based on the decision theory (Sweets & Tanner, 1954), a determination of two new measurements: the coefficients of discrimination (d') which takes the ability to detect the signal into account, and the criterion (β) which interprets the cautious or risk-taking attitude of the subject in signal detection.

Among this group of tests we can also add those concerned with more easily detectable information which occurs more frequently, but is repeated for periods of about an hour. Tests of immediate memory of number identity are examples of these.

As opposed to these simple tasks, devices which simulate performance tasks with a high informational content have been made such as surveillance of numerous screens or counters, tracking or alignment in position or speed (Adams, 1959; Alluisi, 1967). The development of microprocessors has made the construction of simple, light devices without moving parts possible - signals being presented either in the form of numbers of symbols, or in the form of display (LED or CLD) or on-screen. For instance the use of such devices to judge a driver's level of attention (Attwood, D A, 1975) and to suspend driving in the presence of lapses in attention has been considered. We ourselves have adapted, on a print-out calculator (HP 97), a composite test (VIGIL 97) of attention coupling a self-adaptive number memory subtest to a number dissimilarity detection subtest. Correction is immediate, and results are given at the end of every four-minute period.

In 1965 Kalsbeek proposed a technique for measuring subjects' attention in real situations: the method of subsidiary tasks. This consists of adding a simple test to the normal execution of work, and measuring the change in test performances. For this end, one can use tests of detecting flashes occurring in peripheral vision, backward counting, time estimation, etc. These measurements give an idea of the quantity of residual attention available.

The use of measurements of fluctuations in attention implies a certain number of methodological precautions, notably when used during a real work situation. The application of a test constitutes in fact a new stimulus which in itself constitutes a source of arousal for the subject (Brown, 1977). The measurements obtained, therefore, give an estimation more of the attention induced by the test than that of its actual state.

Amongst performance measurements, one section should be reserved to subjective estimates of attention levels. Standardized observation scales exist, but they are especially oriented towards the "fatigue" phenomenon and self-scored questionnaires, such as that of Thayer which requires subjects to mark those adjectives which correspond to how they feel. Recently, Turner (1977) was unable to show a correlation between this scale and the objective performance tests.

3.2 - Psychophysiological Measurements

The parallel change of certain physiological parameters and attention allows them to be used as indicators, and this in two ways: one quantitative, the general level of vigilance, and the other qualitative, selective attention (Buser, 1976).

a) Quantitative Aspect

We well recognize the physiological characteristics of sleep (Kleitman, 1953). Four stages which correspond to deeper and deeper sleep are distinguishable, to which is added REM (Rapid Eye Movement) sleep. We are interested here only in the aspects which correspond to wakefulness. During this stage, cardiac frequency, muscle tone and central temperature are higher than during sleep, skin resistance is lower, but it is the electroencephalogram which best reflects the diffuse attention level of the subject.

We know that, with eyes closed, the record shows a rhythm of 8 to 12 Hertz with a minimum amplitude of 40 microvolts in the parieto-occipital region: this is the classical alpha rhythm. When attention becomes more intense, one sees the disappearance of this rhythm: this is alpha blocking. In hypervigilance states, one finds the same flat record in a continuous manner. The amount of alpha rhythm can thus be considered as a measure of lack of concentration. Originally estimated by the percentage of time occupied by alpha (index α), it can now be determined with the aid of more elaborate techniques which allow the calculation of the relative amplitudes of different frequencies.

On the basis of this information, it was possible to propose continuous vigilance control systems: on

the basis of the EEG of pilots, of grip strength of train drivers, of skin resistance of car drivers, etc.

The problem, however, is not so simple; in fact, this picture does not hold for all subjects, as was shown by Lacey (1958). Moreover, the circulatory system among others has its own regulation which, following a rise in pressure, can result in a paradoxical bradycardia. A waking EEG record can accompany a state of lack of attention, and conversely, we have seen effective radar operators showing electrical signs of sleep. All these facts call for the greatest caution, although these measurements are of interest in basic research.

b) Focalization of Attention

Most of the measurements concern cerebral evoked potentials which are the sequence of electrical events recorded from the scalp after the presentation of stimuli. The analysis technique has been available for about fifteen years; it consists of averaging the EEG by taking the stimulus as the origin for each one. Thus a curve with a certain number of characteristic peaks is obtained. One can roughly distinguish the early components located less than 150 milliseconds from the stimulus and the later components after 200 milliseconds. In 1963 Chapman showed that the amplitude of the late phases of evoked potentials increased when the attention was directed towards the stimulus and reciprocally, the same year, Garcia Austt concluded that they decreased when the subject was oriented towards other stimuli. Recent research (Schwartz, 1978) has confirmed this specificity of late phases, and, mainly, the positive wave located at 300 milliseconds in the focalization of attention. It would be sensitive principally to situations in which an uncertainty exists concerning the occurrence of stimuli and where the subject must decide on the usefulness of the information. Certain authors have showed that the early phases could also take focalization into account (Picton, 1974) and would be greater for expected than for unexpected signals. The evoked potentials can thus be considered as phenomena connected to selective attention; however, "they are more the result of the selection of a signal than a sign of a previous state conditioning this solution" (Posner, 1975). Furthermore, they are not only related to the selective attention, but they also change with the overall level of vigilance (Defayolle, 1971), this being the case for both the early and the late phase.

Besides these electroencephalographic aspects, other electrophysiological signs accompany the filtering process: thus, an increase in ocular movements during visual tasks relates to scanning which is itself conditioned by the selection of information. A cardiac parameter can also be revealing, as is the case of the sinus arrythmia described by Kalsbeek (1963). He showed that states of focalized attention are often accompanied not only by a tachycardia but also by an increase in the regularity of beats. One can also observe a decrease in respiratory frequency which may itself be the cause of the phenomenon.

4 - FACTORS INFLUENCING ATTENTION

The starting-point for all these research studies is the demonstration of a decrease in detection performance when they last for more than 45 minutes (Broadbent). This degradation was first of all considered in its quantitative aspect, and Mackworth, J F (1964) connected it to the time elapsed by a linear function of the square root of the latter. A detailed analysis, based on the detection model of Sweets and Tanner, shows that this deterioration is not connected to aptitude in detecting the signal (d') but to an increased carefulness in the decision-making (β) (Broadbent & Gregory, 1965).

Initially centred on simple surveillance tasks, research studies have been extended to other aspects:
- Repetitive motor tasks (Murrell, 1971)
- Tasks with a difficult mental load (Alluisi, 1967)
- Psychomotor tasks (Hauty, 1955).

In all cases the characteristics of the deterioration were identical with the exception of one constant. Attention during instruction would reach its maximum after 15 minutes and would decrease thereafter (Stuart & Rutherford, 1978). Detection errors would occur after 90 minutes in drivers of high-speed trains (Endo & Kogi, 1975).

A certain number of factors are likely to have an influence on this normal deterioration. We will classify them in three categories: those related to the characteristics of the tasks, those related to environmental conditions and finally factors which depend on the subjects.

4.1 - Characteristics of the Task

Differences related to the sensory modality were not observed: visual and auditory tasks are identically degraded (Cheney, 1968). The more a task is made up of weak intensity signals (Adam, 1956), short signals (Baker, 1963), the more rapidly it tends to deteriorate. The distribution of information also plays an important role. A weak frequency is accompanied by a greater degradation (Deese & Ormond, 1953) and by a slowing down of responses (Hartz, 1967). The important factor would be the duration separating the successive detections and not the signals themselves (Jenkins, 1958). Inversely, Taub and Osborne (1968) found that the degradation is more rapid when the total frequency of information becomes too high. This difference is only apparent; a certain optimum seems to exist to which corresponds a minimal degradation (Johnston & Coll., 1966). The anticipation of signals themselves also forms an element which favours the maintenance of performance (Buckner, 1961). Finally, the complexity of the task must be taken into consideration. The more the number of signal sources increases, the more susceptible it is to degradation (Bobey, 1963), although Gruber (1963) did show that the alternation of sensory modalities could have a favourable effect. Tasks implying a physical (pursuit) or mental activity tend to resist degradation better than passive tasks.

It seems that at the level of complexity, one finds a phenomenon analogous to that of the optimum which we mentioned above: tasks which are too simple or too complex are more susceptible when they are prolonged.

4.2 - Procedural Conditions

In this section factors not directly connected to the task and to the operator are grouped together: environmental conditions, psycho-social environment and chronological factors.

a) Environmental Factors

This is concerned with the influence of adverse factors on the execution of tasks involving a high level of attention. Two aspects have been especially studied: noise and temperature. The effects of noise are equivocal: numerous factors influence them. A high intensity (greater than 95 dB) tends to reduce performance, but absolute silence is equally unfavourable. The nature of the sound stimulus is also important: a constant noise has less effect than a noise with random characteristics (modulation in frequency or in intensity, presence of transients). The significance of the sound signal is also an important factor: we have, in decreasing order, speech, noise and music (Tarriere & Wisner, 1962). But these effects of noise can involve different effects according to the variation of other factors. Therefore simple tasks can be improved by adding sound stimuli, while the latter leads to the deterioration of a complex task. Music while you work helps to avoid the degradation in performance of repetitive, unstimulating work.

For temperature, one also sees an optimum of 26 degrees. An increase in external temperature to 36° or a decrease to 21° both lead to performance deficits (Mackworth, 1950). For Wilkinson (1964) the effects of heat depend on the type of task: it degrades complex tasks and helps those of passive surveillance. Heat increases error detection and cold slows down responses (Mackworth, 1969).

The effects of noise and of heat are susceptible to potentiation. It is thus that Papin (1973) was able to show that in a tracking task performances were worse at 34°C; on the other hand, although applied in isolation, noise did not result in degradation, its combination with heat brought about a greater deterioration. The same remarks could be made concerning atmospheric pressure: on either side of normal conditions performance is degraded. When considering the effects of environmental conditions, one must bear in mind that they act in two ways: on the one hand, they act on the general level of activation, and on the other hand, they constitute in themselves a stimulus which can compete with the relevant information.

b) Psycho-social Factors

From the very beginning of studies on surveillance tasks, authors have been aware of the significance of subjects' knowledge of their performance. This information in fact notably delays the time course of performance deficits in the couse of time (Mackworth, W N, 1950). A more detailed analysis has allowed the specification of the characteristics of this feed-back action.

Reward for a correct response and punishment for an incorrect one would have the same effect (Bevan, 1965); it is better to punish for an omission than for false signal detection (Smith, 1967). Incorrect information on results has, nevertheless, a beneficial effect, although to a lesser degree than for correct information (Mackworth, 1964); and verbal information is preferable to visual presentation (Hardesty, 1963). Finally, evaluative judgments are more effective than those which only take account of the quantitative aspect (Hardesty, 1964).

All these facts explain the importance of social reinforcements. The actual presence of the observer is not in fact necessary; Putz was able to show the same favourable effect whether the observer is located in the same room, seen through a window, or even on a television screen. Another aspect of social facilitation is shown by the smallest deterioration occurring while several operators are in the same room and can talk.

c) Chronological Factors

These allow us to effect change under the influence of operator characteristics. We will be brief, for this point has been presented elsewhere. We know the inauspicious influence of hours in the middle of the night, the existence of weekly and annual rhythms, not forgetting women's menstrual cycle: the postovulatory period is often characterized by problems of attention. The desynchronization of rhythms after travelling through time-zones have been the subject of numerous studies since long-distance flights have become common; they have shown a greater deterioration after west-east flights than for those in the opposite direction.

4.3 - Subject-Related Factors

There does not seem to be a correlation between the aptitude to carry out tasks requiring attention and the intellectual level. On the other hand, high performance levels in a task makes it more resistant to deterioration. This Klein and Coll. (1975) were able to show that the effects of time changes were less in subjects with better performances and those who were better trained. With Papin (1972), we showed a connection between the intellectual level of subjects and their resistance to detrimental effects of noise and of heat in a tracking task; here, intelligence probably acts at the level of learning capacity, the latter being in very short experiments.

As concerns personality variables, the British School of Eysenck looked for relations between intro - extroversion and attention. Introverts would be characterized by a high level of excitation of the central nervous system and would better resist the decrease in performance during surveillance tasks (Corcoran, 1965). Recently, Eysenck, H W (1976) showed that the best performances are related to an average level of introversion. This result was confirmed in depressed patients by Byrne (1976) who compared under-active psychotics to over-active neurotics. By estimating activation of the Shagass technique (sleep threshold under barbiturates), he found that average levels corresponded to the best detection rates. Other personality factors were concerned: Schlesinger (1964) compared subjects with a large attention span to those with a reduced field, and Witkin (1954) classified his subjects as a function of their ability to detach themselves from the irrelevant information which made up the background (as opposed to the relevant figure). Schlesinger is thus oriented towards the quantitative aspect and Witkin towards the selection of information.

State of the Subject:

We have previously seen the role of biological rhythms, their effects are most often combined with sleep deprivation: the latter is equally evident in difficulties in attention, more especially as the task is familiar and monotonous (Wilkinson, 1968). The deterioration related to the prolongation of the test is hence more marked. It is expressed by a more careful attitude for moderate deprivations, and then by an increase in false alarms when deprivation is severe (more than 3 nights). Knowledge of results and noise minimize the effects of sleep deprivation.

Physical fatigue also brings about a reduction in performance at attention tests (Defayolle, 1978). The same is true of illness: Alluisi, in 1969, observed a 25% deterioration in performance, during the course of an infectious illness, when tasks requiring prolonged attention were undertaken. We may note the effects of psychotropic drugs, a topic which will be covered during the course of the second day of this lecture series: hypnotics bring about a degradation of the attention whereas stimulants, the inverse, although they also have a negative effect when administered in high doses.

Motivation for the task constitutes one of the most important factors: knowledge of results is one means of maintaining it. Excess motivation or the presence of anxiety or of preoccupation have adverse effects.

Isolated effects of all these factors are liable to combine together, thus either potentiating or compensating for their adverse effects. Hence, motivation can compensate for detrimental effects of a repetitive task, of sleep deprivation, etc. On the other hand, noise has a more adverse effect on complex tasks performed with strong motivation. Chlorpromazine diminishes the negative effects of noise Hartley, 1977). Physical effort aids simple and impairs more complex tasks (Sjoberg, 1977).

5 - EXPLANATORY MODELS

The contrast which exists between the multiplicity of factors influencing attention and the relative simplicity of their effects leads one to propose explanatory theories. For some of these one single factor is suffucient to explain the observed facts. Three broad theories have been advanced:

- Mackworth (1950) based his theory on the model of Pavlovian conditions and attributed deterioration to the development of internal inhibition by non-reinforcement.
  McCormack (1962) adds the role of motivation to these inhibitory phenomena.
- Broadbent, in 1953, proposed the filter theory. The role of the filter is to select for later processing relevant stimuli by their intensity, biological significance and novel characteristic. It is the decrease of the latter during the course of the test which explains degradation of performance. In 1963 the same author gave an important role to decision processes.

- The last trend is founded on the physiological concept of activation which links the level of arousal to performance. We saw previously that different levels of attention were accompanied by modification of psychophysiological parameters, explaining the functioning of the non-specific reticular system. The theory of activation considers this parallelism as a causality, adopting on the psychological level the ideas of Cannon (1936) who attributed the function of preparation for fight or flight to the autonomic system. The different factors considered in the preceding paragraph generally involve autonomic phenomena; it was logical to consider their effects as a consequence of the activation which they induce.

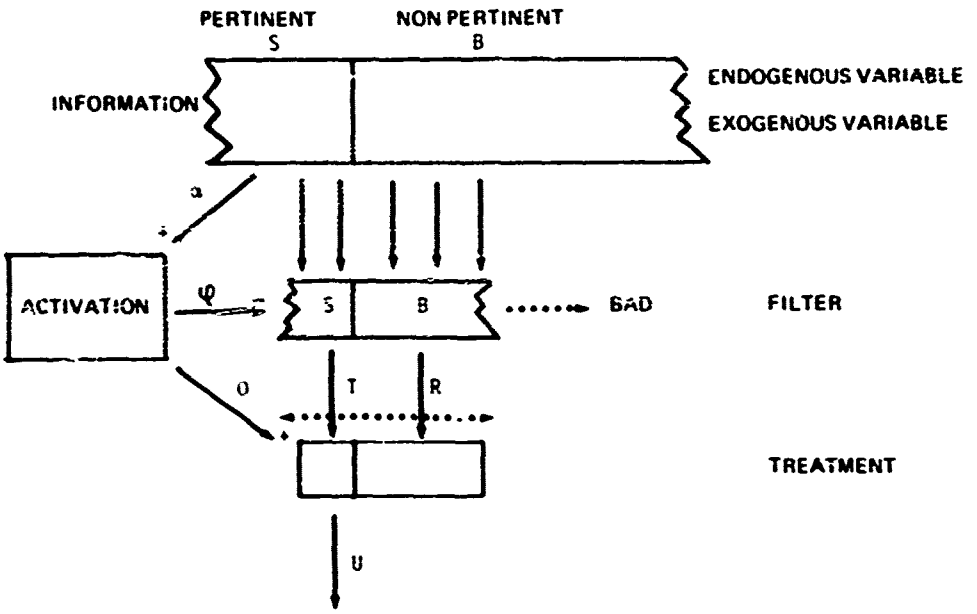
Experimental data often reveals that the connection between activation and performance is non-uniform but has the curved shape of an upside-down U. There would, therefore, exist an optimum point of activation such that on either side a decrease in effectiveness is observed (Malmo, 1962). This phenomenon had been described as early as 1908 by Yerkes and Dodson in connection with learning. We have already encountered it in relation to the effects of noise complexity, of psychotropes and of typology. The explanation of the ascending part of the curve seems simple; on the other hand, it is more difficult to understand how an increase of activation can induce a decrease in efficiency. Broadbent (1965) uses the decision model and connects activation to augmentation of risk-taking (B); the degradation would thus be due to an imprudent attitude which would increase false detections. Easterbrook (1959) attributes the phenomenon of degradation encountered during hyperactivation to an excess of focalization. McGrath (1963) proposes the combination of two factors: activation and filtering, an idea recently taken up and completed by Posner (1975) who distinguishes three components: alarm, selection and the conscious processes of choice strategy.

It is within this conceptual framework that we have proposed a model (cf Crocq, 1978) which calls for the intervention of two factors, the ability to process and filtering, each under the influence of the general level of activation. The information which the subject is able to treat at any instant can be separated into four sub-groups which conform to two criteria:

- its origin: it can be external, driven by sensory organs, or internal, and be constituted by all the images and representations which the subject can evoke
- its relevance to the task: pertinent external information (S) is that which corresponds to the modifications of the environment in relation with the task to be performed; orders, rules of treatment and expectation of gains or costs are equally relevant information. On the other hand, external data relative to the environment (noise, heat) and internal data constituted of irrelevant ruminations (worries, consciousness of hazards, etc) are non-pertinent information (B).

To order our ideas, external information corresponds to 10^7 bits distributed 87% and 9% respectively, to visual and auditory channels. This volume of data is considerably greater than man's overall capability of processing, which lies approximately at 15 bits. The solution to this disparity will consist of selecting information with the aid of a filter in such a way that only what is useful will be treated at any moment. The process could be outlined as follows. Faced with a signal which overloads the processing capability, the filter (F) positions itself in such a way as to set apart the section which is compatible with the possibilities of the treatment system (T), taking into account the internal information corresponding to the processing programme. The latter condenses the elements selected in order of superiority stored in the memory.

The filter is then re-employed in another part of the information. Each repositioning is defined by the exploration programme and by the results of the preceding treatment according to a Markovian-type process. A non-resolved problem or part of a problem can thus block the entire succession of operations unless the programme is changed, thus selecting a new one. We find here again the notion of vicarious process (Reuchlin, 1978).



The two factors T and F are dependent on the level of activation (A). The increase of the latter involves an increase in processing capacity and a decrease in the value of the filter. This last hypothesis is the inverse of that proposed by Easterbrook, the overactivated subject is not too focused, but on the contrary cannot ensure correct filtering. This point of view is in agreement with that of Naatanen (1975) who attributes performance degradation in overactivated subjects to "divergent demands", that is, to internal information not immediately relevant to the execution of the task. As for the level of activation (A), it is determined by the quantity of information to be treated, relevant or not, the physiological state of the subject and his motivation (M). The latter plays a very important role: it represents the affective vigilance (Soulairac, 1978). Bailey (1976) showed the relationwhich exists between boredom and arousal, and Murrell (1974) developed the notion of AUTOAROUSAL where internal information is used as waking generators.

The increasing function of A and therefore of T under the influence of the motive state and of the quantity of information to be treated represents a mechanism of adaptive self-regulation. The decrease in the selective value may seem paradoxical; actually, within the normal limits, it is also adaptive: too great a focalization at the moment when the problem has to be resolved reaches a certain complexity which results in the loss of information which could be relevant. It is only in extreme conditions that the phenomenon becomes worrying.

To represent the relations existing between S.B.M and A on the one hand, A and T.F on the other, we have chosen an exponential function. Besides its very general character in living systems, this equation has the advantage of taking into account the speed of development towards a maximum value.

The treatment capability T which corresponds to the treatable information in each time unit can be written:

$$T = T_{MAX} (1 - e^{-\theta A})$$

- T_{MAX}, which represents the maximum quantity treatable, is a parameter particular to the individual. It is one of the aspects of aptitude
- θ indicates the speed with which T increases when activation is improved: this is also a value particular to individuals.

The filtering value, or rather that of its reciprocal, is expressed by the quantity of non-pertinent information (B), non-filtered: we call it residual information (R).

$$R = B (1 - F_{MAX}) (1 - e^{-\phi A})$$

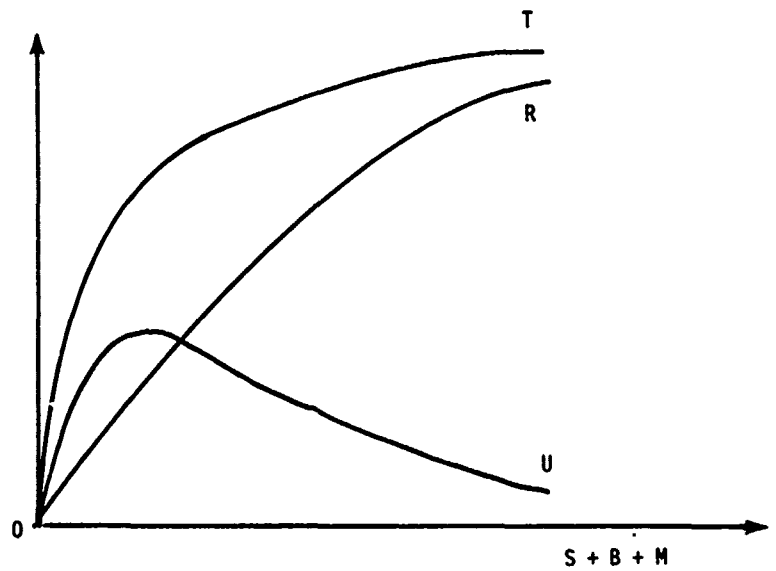
- F_{MAX}, varying from one to infinity, gives the maximum filtering value which can be anticipated for a given subject, and ϕ is the parameter which takes into account the deterioration of the filter as a function of the level of activation.

This level of activation A obeys the same type of function:

$$A = A_{MAX}(1 - e^{-\alpha(S + B + M)})$$

- A_{MAX} corresponds to the maximum activation the subject can proffer in his present state (sleep, drugged, fatigue), α is a parameter of reactivity to the increase in the quantity of information S, B and motivation M.

Confronted at every moment with a global quantity of information (S,B), presenting certain basic personal characteristics (T_{MAX} F_{MAX}) and certain personal characteristics of state (A_{MAX} M θ ϕ), the subject will be able to treat only one reduced part of it which corresponds to the difference existing between its capability T and the non-treated residual information R.



This difference which we shall call useful capability U = T - R, conditions the effectiveness of attention. The greater its value, the more information which can be dealt with. In the case of a task where the signals are discontinuous, they are added to the irrelevant basic noise and risk especially, if they are of short duration, of not being processed and therefore noticed.

The simulation of the complete equation will allow us to estimate the value of the model. We will then discuss the influence of the characteristics of relevant environmental information, personality variables and their joint effects.

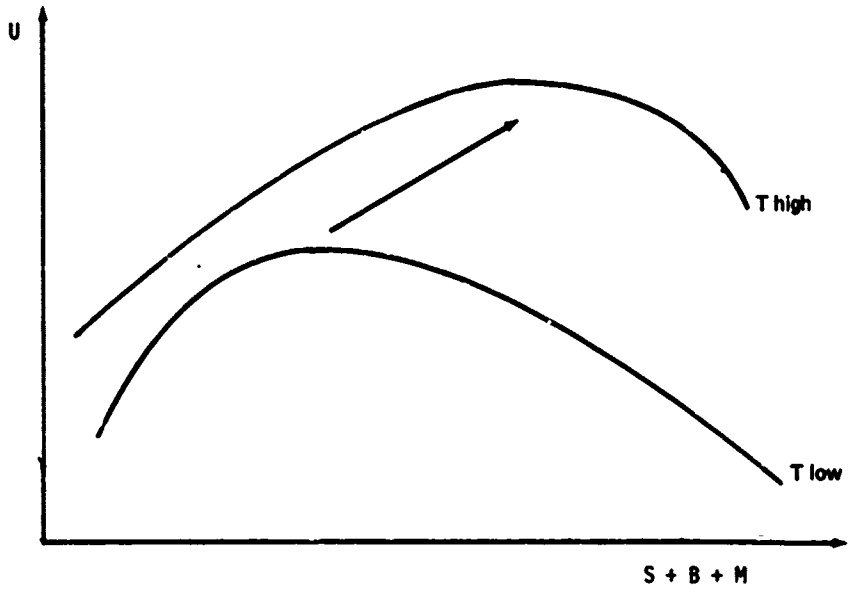
All that increases the information contained in S will be expressed by an increase in A: hence, complexity, the character of novelty and frequency.

Inversely, monotonous repetition, simplicity, all factors which develop with prolongation of the task will be expressed by a decrease of activation. The same goes for motivation and pertinent and non-pertinent stimuli, S, B and M having the same effect being mutually compensatory.

The resulting activation will be a function of the parameters A_{MAX} and α; a subject deprived of sleep will not be able to reach a level of wakefulness as high as that of a rested subject. The values of different parameters define the properties of the efficiency curve. For increasing values of activation, U tends towards an asymptotic value $T_{MAX} - B(1 - F_{MAX})$.

If this value is negative, the task cannot be performed, the related non-filtered noise being greater than the processing capability. For $\theta = \phi$, the curve is increasing with negative acceleration. For $\theta > \phi$, the curve reaches a maximum which corresponds to the highest level of activation. On either side of this point the performances are not as good. For a simple task this maximum will call for a higher level of motivation than for a complex task which could, in turn, deteriorate if this motivation is too intense. The "noise" which increases activation has a more complex effect because it must be filtered; there, too, we can observe that for weak levels of complexity of the task and weak motivation, it can exercise a favourable effect.

The parameter F_{MAX}, which corresponds to aptitude, also plays a very important role. The greater its value, the greater the effectiveness in the presence of non-pertinent stimuli, and the more the activation optimum is displaced towards elevated values. It would be one of operator reliability and could correspond to the introversion dimension of Eysenck.



This rapid overview of the properties of the model allows us to see that it takes into account a fairly large number of facts concerning the influence of the task, of the environment and of personality factors. It should not, however, be considered to possess an explanational value, but rather it should be considered as a useful descriptive means of pinpointing the important factors: quantity of information regarding Activation and Filtering.

We have not undertaken the problem of subject strategies which play an equally important role in effectiveness. We have seen that for a given situation numerous strategies may be available; their choice depends on the costs and gains relative to each one of them. Moray considers that a non unimportant part of the processing capability is taken by the programmes themselves. An optimum must therefore be found which reconciles economy of data to be processed and difficulty of the programme which allows it, the one and the other often varying in opposite directions.

CONCLUSION

Vigilance, considered as the state of availability to respond, and attention, considered as the capability to treat and filter information, appear to be intimately linked. Together they constitute the two aspects of the psychological and physiological duality of man.

In reality they cover three distinct processes: activation, processing capability and filtering proficiency. These three processes take into account the sometimes paradoxical effects of the improvement or the degradation of attention.

On the practical level, four types of solutions can be envisaged for avoiding the deterioration of these processes:

a) The ergonomic way consists of arranging the signals and the environment of the operator in order to bring him towards his activation optimum.

b) The psychotechnical way tries to find the most suitable subjects. We have seen the difficulty of defining an aptitude to attention. It would seem more interesting to orientate research towards the selective aspects centred on the filtering processes; it is possible that on this point physiological measurements might be employed.

c) The psychological way would consist of optimizing the motivation of subjects, as a function of the type of task. As a task requring little attention necessitates a greater level of motivation, one understands the usefulness of informing those carrying out such tasks of the importance of their actions the more so if these appear to be uninteresting.

d) Finally, the pharmacological way would call on chemical aids likely to act on the three important systems: catecholaminergic, serotonergic and cholinergic. These will be considered during the course of the next day.

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AROUSAL AND SLEEP DISTURBANCE:

BIOCHEMICAL CONSIDERATIONS

by

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PART I

BIOCHEMICAL INDICES OF STRESS: BIOCHEMICAL ASPECTS OF THE STRESS RESPONSE

INTRODUCTION

Perhaps the most characteristic feature of a person's response to stress is the release of certain hormones--the so-called stress hormones--which, in turn, affect virtually all body functions. Consequently, the search for a biochemical indicator which might aid in the detection and quantification of a stress response would logically begin with a biological substance which reflects either the quantity or the biologic activity of a stress hormone.

A second and equally important matter to settle prior to undertaking the search would be to determine what type of stress is to be detected or quantified. This, of course, is a most decisive issue to settle because of the very broad and widely differing views as to the usage, in a biomedical sense, of the term "stress." This differing of opinions about stress is not just among laymen--many scientists differ, sometimes quite vehemently, over the meaning of the word.

The concept of stress adopted for this review is a slight modification of the one that has guided our laboratory (USAFSAM/VM) in the study of factors confronting USAF flight personnel for the past three decades. The latter concept was initially conceived for use in flight-stress studies by Dr. Henry B. Hale, formerly of the USAF School of Aerospace Medicine but now retired. Dr. Hale is a knowledgeable endocrinologist and environmental physiologist, and a recognized authority in the field of stress physiology. He held that a force or stimulus, whether externally received or internally perceived, became a stress (or more appropriately, a stressor) if/when it was of sufficient intensity to elicit either one or both of two body responses; one is commonly referred to as Selye's Alarm Reaction and the other as Cannon's Fight or Flight Response. It is hardly appropriate to present to this audience a detailed description of these well-known physiologic responses. To lay a proper foundation for material to be presented here, however, some particularly relevant aspects of the two are given.

The two responses are similar to each other in several respects. For example, both are triggered by either physical, mental, or emotional stimuli, both are channeled through the hypothalamus, both involve the conversion of a nerve-borne message to a blood-borne type, and both involve the secretion of two or more hormones from the adrenal gland. The impulse received by the hypothalamus in the Alarm Reaction is converted to a blood message while still in that gland, after which the message travels to the nearby anterior pituitary with instructions to release one of its hormones which, in turn, travels in circulating blood to the adrenal cortex with the message to secrete certain (but not all) of its hormones. In contrast, the impulse received by the hypothalamus in the Fight or Flight Response remains an impulse while passing through the sympathetic nervous system (SNS) to the adrenal medulla, at which point the neuronal message is transformed into two blood messages--the catecholamine hormones epinephrine (E) and norepinephrine (NE).

According to the view adopted herein of a stressor, a stimulus need not have the intensity to activate either of the two physiologic responses mentioned above--to be stressful, it needs merely to stimulate the SNS. This view is supported by the current literature which shows that advantageous use has been made of the well-known fact that stimulation of the adrenergic neurones within the SNS causes the release of a neurotransmitter. The subsequent appearance of that substance in circulating blood is noteworthy in several respects. First, its concentration in blood has been shown to vary in direct proportion to the intensity of neuronal stimulation. Next, since the neurotransmitter is identical to one of the aforementioned adrenomedullary hormones (norepinephrine, or NE), its quantity in blood represents the combined input from two anatomic entities. The fact that NE in blood originates from two sites within the body does not negate its usefulness as a measure of stress. On the one hand, the inability to use it to quantify adrenomedullary function is inconsequential since the other hormone secreted by the adrenal medulla (epinephrine, or E) quite satisfactorily accomplishes that purpose. On the other hand, the blood NE level may be adjusted by statistical methods so as to provide a relatively specific measure of SNS function; that adjustment is based on using the blood E level to estimate the approximate contribution of the adrenal to the total concentration of NE in blood.

The advantage of including SNS stimulation alone as a physiologic response to stress is that it facilitates the quantification of stressors at substantially lower intensity levels than heretofore quantified. According to this concept, seemingly inconsequential stimuli are viewed as stressors. For example, the act of rising from a seated position is regarded as stressful since it causes a marked and highly significant increase in SNS function (reflected by a two-fold increase in blood NE). Moreover, physical or psychological events which are sufficient to set in motion the Alarm Reaction or the Fight or Flight Response result in more than a 100-fold increase in blood NE. Thus, this indicator of SNS function is sufficiently sensitive to quantify the less stressful situations, and yet it has the range to permit the quantification of the more stressful events. Indeed, it is perhaps too sensitive, when viewed by itself, to be a completely satisfactory indicator of stress. As a final clarifying comment regarding the quality of stress, this discussion is limited to acute stress. Chronic stress is a separate issue.

CATECORIES OF BIOCHEMICAL STRESS INDICES

It is clear from the introductory remarks that the assay of a stress hormone in blood (and/or urine) should facilitate the quantification of the biologic effectiveness of a stressor. While this is true, it

is also true that body constituents other than hormones can provide additional and, in some cases, better information regarding the impact of a stressor upon the body. As a matter of fact, several non-hormone indices were used long before technology made it possible to quantify hormones themselves.

Substances which have been used to detect or quantify stress in the past are categorized herein as follows: (1) hormones, (2) hormone precursors (involved in the biosynthesis of hormones), (3) hormone metabolites (involved in the metabolic degradation of hormones), (4) non-hormone metabolites (substances whose quantities are significantly altered by hormone action within a target tissue), and (5) enzymes of hormone formation/function. As a generalization, the use of hormone precursors as stress indices is based on the assay of tissues from the site of hormone synthesis, the hormones themselves are measured primarily in blood, the enzymes also in blood, and the hormone metabolites as well as the non-hormone metabolites are measured primarily in urine.

The remainder of this review will be devoted to the discussion of these categories of biochemical indices.

HORMONES

Corticotrophin-Releasing-Factor

Corticotrophin-releasing-factor (CRF) is the only stress hormone that is not currently regarded as a hormone; as reflected by its name, it is presently regarded as a factor. CRF is one of several biochemical materials secreted by the hypothalamus. Similar to several of the other hypothalamic hormones, CRF is conveyed to another endocrine gland where it stimulates the secretion of a second hormone which, in turn, travels to a third endocrine gland causing that gland to secrete certain of its hormones. Whereas the other hormones secreted by the hypothalamus were initially referred to as releasing factors, their designation was changed to hormone after their chemical structure had been determined. Thus, it is anticipated that the F designation of CRF will be changed to an H upon the elucidation of its structure.

In addition to CRF being the only one of the stress hormones which is not called a hormone, it unfortunately is also the only one for which an analytical method is lacking. Since CRF is known to be a peptide, perhaps a radio-immunoassay (RIA) will be forthcoming. The great sensitivity of that capability will likely be required to assay the extremely small quantities of CRF which are present in blood, at least in blood from the hypophyseal-portal system.

Adrenocorticotrophic Hormone

Another stress hormone is adrenocorticotrophic hormone, which is also called corticotrophin or, more simply, ACTH. ACTH is released from the anterior pituitary in response either to CRF or from a negative feedback mechanism controlled by the blood level of a hormone from the adrenal cortex. (See below.) There is evidence that, in addition to acting directly upon the anterior pituitary, this feedback system also acts indirectly upon that gland by regulating the release of CRF from the hypothalamus.

ACTH has been shown to be a peptide containing 36 amino acid residues of which the 24 on the amino-terminus of the molecule are required for activity. It has been synthesized. The bioassay method used in the '50s and '60s has now given way to RIA; analyses are primarily limited to blood samples. Inasmuch as metabolites of ACTH have not been identified, the use of ACTH as a measure of stress is based either on measuring its concentration in blood or another hormone whose concentration in blood is regulated by blood ACTH.

Glucocorticoids

Cortisol (hydrocortisone) and corticosterone are but two of several steroid hormones secreted by the adrenal cortex. Since they are the only ones secreted by ACTH stimulation, they are the only adrenocorticosteroids regarded as stress hormones; the other adrenocortical hormones include aldosterone (the hormone that regulates electrolyte and water balance) and several sex hormones (androgens and estrogens). Because of its principal influence on mineral metabolism, aldosterone is often referred to as a mineralocorticoid. On the other hand, cortisol and corticosterone exert their influence primarily on glucose metabolism and, therefore, are collectively referred to as glucocorticoids. These distinctions between cortical hormones are not mutually exclusive since glucocorticoids possess slight mineralocorticoid activity and vice versa.

Although the term glucocorticoid is frequently used herein, reference is primarily to cortisol since it is the chief glucocorticoid in man. Corticosterone is the principal glucocorticoid in the rat and a few other animals.

The quantity of cortisol stored in the adrenal cells is relatively small, but this is apparently of little consequence since its rate of synthesis is quite rapid and the entire quantity can be discharged within a very few seconds. Although cortisol is secreted in the free form, most of it becomes reversibly bound to certain plasma proteins upon entering the blood stream. About 95% of it is bound to an alpha-globulin called transcortin; the remainder is either bound to albumin or remains in the unbound (free) form. At high plasma cortisol levels, however, the binding sites on transcortin become saturated, and while there may be a slight increase in binding to albumin, the main portion of the increase remains unbound.

The level of cortisol in blood is subject to a distinct circadian rhythm (as is blood ACTH). As shown in Figure 1, the level is the lowest at about 2 a.m. and the highest at about 8 a.m. At first glance it might appear that the abrupt increase in early morning is due to the stress of arising. A closer examination of the pattern of change, however, shows that the increase is set in motion two or three hours before the hour of awakening; that swing upward apparently reflects the release of ACTH from the anterior pituitary via the aforementioned feedback mechanism (triggered by the low blood cortisol level). Although it scarcely needs mentioning, it is obvious from this rhythmicity of plasma cortisol that due consideration must be given to the time-of-day at which blood samples are drawn for stress appraisals.

Only free cortisol is biologically active and only free cortisol diffuses into the tissues. As it leaves the plasma to enter the tissues, more is released from the plasma proteins to replace it. Thus, the bound fraction of cortisol serves as a circulating reservoir which keeps a ready and steady supply of free cortisol available for uptake by the tissues.

It is of interest to compare the blood level of cortisol to those of the hormones involved in its secretion. Accordingly, its quantity secreted by the adrenal cortex is about 1000 times greater than its stimulus (ACTH), whose quantity secreted by the anterior pituitary is thought to be at least 1000 times greater than its stimulus (CRF) from the hypothalamus.

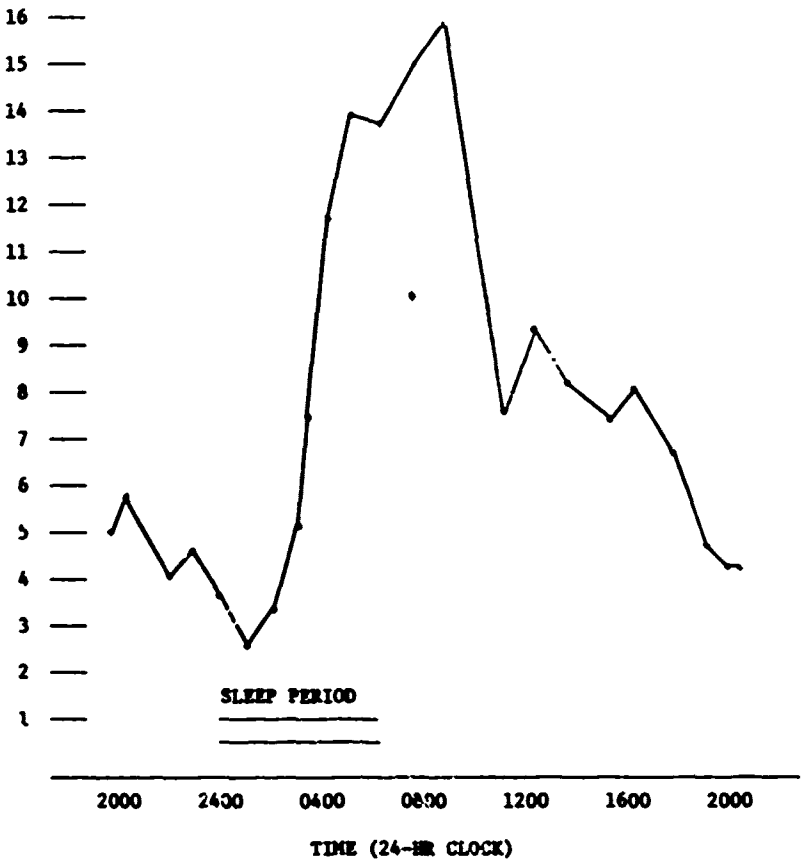


Figure 1. Diurnal variation in plasma cortisol (µg/100 ml)

Catecholamine Hormones

As mentioned earlier, E is secreted entirely by the adrenal medulla, whereas NE is released by that gland and from the SNS. The difference in the quantities of NE entering the blood stream from the two sites is clearly reflected by the relative concentration of NE and E in blood and urine versus that released from the adrenal gland. For example, E comprises about 80% of the two upon release from the medulla, but it makes up only about 20% of the two in blood and urine. This much greater proportion of NE in circulating blood clearly reveals that the quantity released at the adrenergic nerve terminals vastly exceeds the quantity released by the adrenal. It is pertinent to mention that the relationship between the amounts of E and NE secreted by the medulla is not fixed since the two catecholamines originate from different types of cells within that gland.

The transport of the catecholamine hormones from the adrenal to the various tissues differs from the glucocorticoids in that, owing presumably to their greater water solubility, it is unnecessary for them to be bound to plasma proteins while in transit. When functioning as a neurotransmitter, the transport of neuronal NE is not really an issue since it has a gap of only a few nanometers to cross in going from the pre-synaptic storage vesicles to the post-synaptic membrane of the receptor cells. Adrenal NE is properly termed a hormone since it exerts its function elsewhere in the body; however, since neuronal NE functions at its site of synthesis as well as elsewhere, it perhaps has been more appropriately termed a "local" hormone.

Material gathered for this review raises a rather serious question concerning the passage of neuronal NE from the adrenergic nerve endings into circulating blood. On the one hand, there is compelling evidence that very substantial quantities do, indeed, enter the blood stream. On the other hand, information contained in recently authored or revised textbooks indicate that after neuronal NE participates in nerve transmission, it is deactivated in two ways, i.e., a small portion undergoes enzymatic degradation and the remainder is "deactivated" merely by returning to the storage vesicles from which it had been previously discharged. Not only is there no mention of the portion of neuronal NE that passes into the blood stream, but quite to the contrary, it is stated that a portion of blood NE is actually taken up by the neuronal vesicles; thereby leading to the conclusion that, at any given time, NE contained in the storage vesicles is an admixture of freshly synthesized NE, NE which had been secreted from the same vesicles at an earlier time, and NE which had actually been synthesized in the adrenal. It is noteworthy that neither NE nor E is taken up by the medullary cells after being secreted.

Hormone Precursors

The next category of stress indices is comprised of substances involved in the formation of the stress hormones. As noted below, this review is limited to precursors of the glucocorticoids and catecholamines since little is known of the biosynthesis of ACTH and CRF. To provide insight into the formation of the hormones, this discussion includes a brief review of the various reactions and precursors involved in the synthesis of the stress hormones.

Biosynthesis of Glucocorticoids

The glucocorticoids are synthesized from acetate in the adrenal cortex through a pathway which includes cholesterol. The latter compound is usually regarded as the starting material, owing presumably to the fact that cholesterol in circulating blood is used for corticoid synthesis when adrenal stores are depleted. To show more clearly the rather slight structural changes involved in converting cholesterol to the cortical hormones, it is also customary to depict the ring structure which is common to all of the precursors in a highly simplified form. That ring structure (or nucleus), which is essentially that of cyclopentanoperhydrophenanthrene, is given in Figure 2 along with its condensed form. As shown by the structure on the right in the figure, simplification is accomplished by not showing the presence of the 17 carbon and 28 hydrogen atoms of the molecule.

The simplified structure in Figure 2 also shows the conventional numbering of carbon atoms and the lettering of the four rings. The structure does not show the location of the four additional carbon atoms present in the glucocorticoids and their precursors. Those atoms are situated as follows: C-18 and C-19 replace the single hydrogen atoms on C-13 and C-10, respectively, C-20 replaces one of the two hydrogen atoms on C-17, and C-21 is bonded to C-20. Whereas C-18 and C-19 remain as methyl groups (i.e., each containing three hydrogen atoms) throughout the synthesis process, C-20 and C-21 do not retain all of their hydrogen atoms.

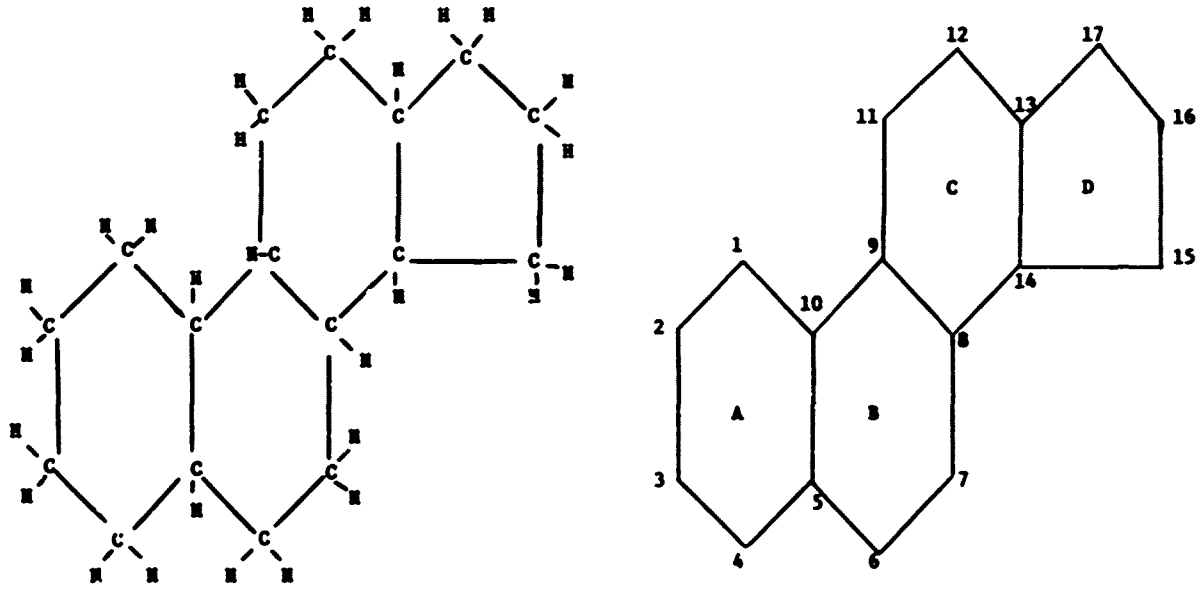


Figure 2. Cyclopentano-perhydro-phenanthrene (nucleus for adrenal cortical hormones, sex hormones, bile acids, sterols, and others)

With the foregoing comments as background, it is now appropriate to consider the individual steps leading to glucocorticoid formation. A schematic illustration of those steps is given in Figure 3. It is noted that the synthesis begins and ends in the mitochondria, but certain intermediate reactions take place in the cytoplasm. Although not mentioned above, cholesterol contains six additional carbon atoms connected in sequence with the first one (C-22) bonded to C-20 and the last two (C-26 and C-27) bonded to C-25 (thereby forming a branched chain of the carbon atoms).

As illustrated in Figure 3, cholesterol is first hydroxylated at C-20. This step, which is the first of several hydroxylating steps, is rate-limiting for the entire synthesis of the glucocorticoids. Hydroxylation is followed by the splitting off of the side chain at C-20 and the simultaneous replacement of the newly added hydroxy group by a keto group to form pregnenolone. This is the dividing point in the

synthesis of the two glucocorticoids. A major portion of pregnenolone is hydroxylated at c-17, which represents the only difference between the glucocorticoid precursors throughout the remainder of the synthesis. For example, the formation of progesterone involves a dehyirogenase to convert the hydroxy group at C-3 to a keto group, and an isomerase to switch the double bond from between C-5 and C-6 to between C-4 and C-5. These are the very same reactions involved in converting 17-hydroxypregnenolone to 17-hydroxyprogesterone.

Next, the two progesterones are converted to the corresponding deoxy compounds by hydroxylation at C-21. The naming of the latter two compounds is actually based on the absence of an oxygen atom which is not added until the next step. That step is catalyzed by the enzyme 11-beta-hydroxylase, and is the final one leading to the formation of the two hormones. It is noted that the only chemical difference between these two hormones is the hydroxy group at C-17 which, as mentioned in the above paragraph, is added by the only reaction in the cortisol sequence that is not in the corticosterone sequence. That small difference, however, is a most consequential one in several respects.

A substantial portion of corticosterone is converted to aldosterone; very little is present in human blood. It is also evident from Figure 3 that a portion of the three cortisol precursors is channeled off for the synthesis of estrogens and androgens. A small amount of cortisol is reversibly converted to cortisone, but, as detailed later, this takes place in the liver--not in the adrenal cortex.



Figure 3. Biosynthesis of glucocorticoids

Glucocorticoid Precursors Used as Stress Indices

Only one of the precursors shown in Figure 3 has been used to detect and quantify stress--that one is cholesterol. As far as can be ascertained, cholesterol was the very first of the stress indices. Its use has been limited to animal experimentation since the assessment is based on its depletion in the adrenal cortex. Another limitation or unfavorable circumstance which hindered its use in the early years was the method of analysis; it was time-consuming and quite laborious.

In addition to cholesterol depletion, it was subsequently found that the adrenal gland's rather high content of ascorbic acid was markedly depleted in moderately-to-severely stressed animals. Because the analytical method used for ascorbic acid analyses was much less objectionable than the cholesterol method, it rapidly became the method of choice in stress studies. Additionally, the adrenal ascorbic acid method served as the basis for Sayer's bioassay of blood ACTH.

Although it has never been determined exactly how or where ascorbic acid enters into glucocorticoid synthesis, its depletion generally parallels that of cholesterol. Ascorbic acid is included in this category of stress indices because of this seemingly close parallel with adrenal cholesterol.

As a point of interest, stress studies conducted by this laboratory in the early '50s utilized the adrenal ascorbic acid depletion assay for animal experimentation and the blood eosinophil count for appraisals involving humans. It is inappropriate to include the eosinophil count as a stress indicator here since it does not qualify as a biochemical per se. However, as detailed later, a biochemical contained within eosinophils (and lymphocytes) has been used as a measure of stress.

Biosynthesis of Catecholamine Hormones

The precursors and enzymatic reactions involved in the biosynthesis of E and NE are summarized in Figure 4. With respect to the ring structure appearing in the upper part of the figure, the one on the right is a simplified representation of the one on the left; both structures show the basis for referring to the two hormones as catecholamines. As shown, catechol is the trivial name given the chemical which is more correctly known as O-dihydroxybenzene. In addition to E and NE, it is apparent from other structures in the figure that dihydroxyphenylalanine (DOPA) and dopamine (DA) also have the molecular characteristics of a catecholamine.

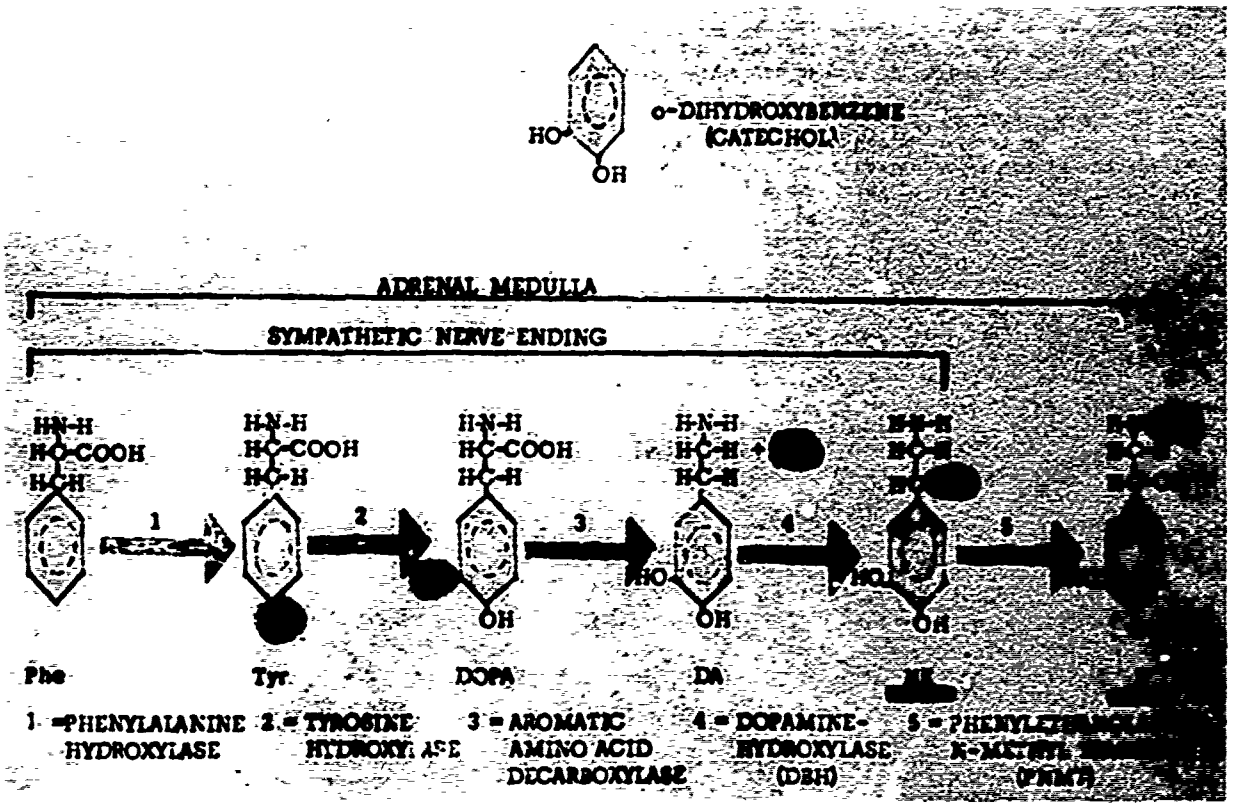


Figure 4. Biosynthesis of catecholamines

The pathway leading to the formation of NE is precisely the same in the adrenal medulla as it is at sympathetic nerve endings. However, the absence of the enzyme phenylethanolamine-N-methyl-transferase (PNMT) at the nerve terminals prevents the subsequent methylation of NE to form E. That enzyme is present only in the medulla. By noting this very important difference in the formation of E and NE, it is evident that in the customary viewing of these hormones as indices of sympatho-adrenomedullary function, E is regarded as a specific indicator of medullary function and NE as a less specific indicator of SNS function.

It is of interest to note that the prevalence of hydroxylation reactions in glucocorticoid synthesis mentioned earlier also characterizes catecholamine synthesis. For example, three of the four reactions leading to the formation of NE are hydroxylations; the only other reaction is the decarboxylation of DOPA to form DA. It is also noteworthy that the second hydroxylation reaction is rate-limiting; inhibition of the enzyme tyrosine hydroxylase by high blood levels of catecholamines identifies this step as the focal point in the negative feedback regulation of catecholamine synthesis.

ACTH's ability to optimize catecholamine synthesis in the adrenal medulla is presumably due to it increasing the secretion of cortisol which, in turn, speeds up the synthesis of E by optimizing the enzymatic activity of PNMT. It is noteworthy that the blood level of cortisol at the site of E formation is relatively high because most of the blood passing through the adrenal medulla comes directly from the adrenal cortex.

Catecholamine Precursors Used as Stress Indices

Evidence cannot be found in the literature which might suggest that any of the precursors shown in Figure 4 have been used to quantify stress. There are substantial quantities of all the precursors in blood, but their quantities in blood and tissues apparently have not been found to be significantly altered by stress.

ENZYMES OF HORMONE FORMATION/FUNCTION

In turning to the next category of stress indices, attention is directed to the enzyme shown in Figure 4 as catalyzing the conversion of DA to NE, i.e., dopamine-beta-hydroxylase (DBH). This enzyme is the only one whose activity in blood has been used to quantify stress. The various transaminases which are commonly used in clinical medicine are not included in this category because they seem to reflect much more than the stress response per se. In this connection, however, it is mentioned later that one of cortisol's action

on target tissues is the induction (increased synthesis) of several enzymes in the liver, among which are the transaminases.

With respect to DBH, a recent visitor pointed out that this enzyme is secreted into blood along with NE during sympathetic nerve discharge and remains in blood for much longer periods of time than NE (whose half-life was said to be quite short, averaging about two minutes). Despite the added fact that the assay of DBH was both easy and reliable, that clinician concluded that plasma NE levels reveal more about the SNS than plasma DBH levels.

NON-HORMONE METABOLITES

The next category of substances which have been used to quantify stress comprises those whose quantities are markedly altered (either raised or lowered) by hormone action in the various target tissues (end organs). This category is restricted to those substances which enter (or fail to enter) the blood stream from the affected tissues and which are not regarded as either precursors or metabolites of the stress hormones.

Carbohydrate Metabolites

The first sub-category under this heading is the group which reflects changes in carbohydrate metabolism. Since glucocorticoids were so named because most of their effects are on glucose metabolism, it is not surprising that the most widely recognized stress indicator in this group is glucose itself. In this case, the blood glucose is raised by E as well as by cortisol. The mechanism by which the two hormones increase the blood sugar level is different. For example, E increases glycogenolysis (the breakdown of glycogen) and decreases glycogenesis (glycogen synthesis), both actions serving to increase the blood glucose level. These effects are brought about by the activation of cyclic AMP which then converts the inactive form of the enzyme phosphorylase b to the active form. Cortisol also increases glycogen breakdown, but it does not decrease its synthesis; in fact, if anything, it increases it. The slight increase in glycogenesis produced by cortisol is brought about partly by increasing the conversion of pyruvate and lactate to glycogen and partly by increasing the conversion of amino acids to glucose (glycogen), which is more specifically called gluconeogenesis. Cortisol's stimulatory effect on glycogenolysis is attributed, at least in part, to its ability to optimize E's glycogenolytic action. It is worthy of note that the latter action of cortisol is not an isolated effect, for it has been shown to have an identical influence on many other phases of metabolism. When functioning in this manner, cortisol is said to be exerting a permissive action (or to be playing a permissive role) because it does not actually participate in a particular reaction, but it does permit those substances which do participate to function in an optimal fashion.

The only other carbohydrate metabolites that have been used to measure stress are lactate and pyruvate. Blood levels of the latter constituents are not as markedly elevated in stress as that of glucose, due presumably to their involvement in the aforementioned increase in glycogenesis.

Protein and Other Nitrogenous Metabolites

Another major influence exerted by the glucocorticoids which might be reflected by non-hormone metabolities is upon protein or nitrogen metabolism. Here, as in carbohydrate metabolism, cortisol's action is quite substantial. two diametrically opposing influences converge to bring about what has been termed the translocation of body proteins. One influence is reflected by the net loss of skeletal muscle mass (primarily protein), whereas the other involves the use of the liberated amino acids for the synthesis of other proteins. With respect to the loss of skeletal muscle protein, the term net loss is used because it has not been determined for certain whether the loss results from an inhibition of the anabolic phase of muscle protein metabolism with no change in the catabolic phase, or no change in the anabolic phase with an increase in the catabolic phase, or a combination of the two. Cortisol's stimulatory effect on protein synthesis is noteworthy in two respects: namely, the proteins are principally enzymes, and the enzymes are principally those involved in the aforementioned stress-sensitive mechanisms of glycogenolysis, glycolysis, and gluconeogenesis. There is no evidence that any of these increments in protein synthesis have been utilized to quantify the metabolic influence of cortisol (and of stress).

The quantities of the newly synthesized enzymes are substantially less than the quantity of protein lost from skeletal muscle. This imbalance is primarily—but not entirely—responsible for the negative nitrogen balance which is another well-established characteristic of the body's response to stress. The protein nitrogen from skeletal muscle not utilized for enzyme synthesis appears in the urine in two forms. One form is actually an unmodified form as certain of the amino acids are excreted at higher rates. (See below.) The other form in which protein nitrogen is lost is urea; urea is produced through the aforementioned gluconeogenesis process from amino acids by the action of several transaminases in conjunction with the various enzymes involved in the so-called urea cycle.

A rather small portion of the increase in amino acid excretion is attributable to the higher levels of amino acids in blood; a substantially greater portion of the increase results from a change in the renal handling of certain of the amino acids. In this regard, it was shown in a clinical study conducted more than a decade ago that cortisol lowers the threshold of five amino acids; those five are threonine, serine, glycine, alanine, and histidine. These findings prompted this laboratory to launch a feasibility study in 1974 to examine the usefulness of certain urinary amino acids as stress indices. That effort utilized a chromatographic method to quantify the individual amino acids and a colorimetric method to measure the amino acids collectively as amino-nitrogen. Two flight-stress appraisals have now been completed and a third one is nearing completion. The results are quite promising. It has been found, for example, that not only were the same five amino acids altered in the two appraisals, but, of even greater importance, the five were the very same five found to be cortisol sensitive in the clinical study. It is noteworthy that those five amino acids raised the sum of the individually measured amino acids to about the same extent as the increase found in the singly measured entity of amino-nitrogen. The latter finding is of immense practical value since it suggests that the measurement of urinary amino acids in future flight-stress appraisals can be made using the simpler and much less time-consuming assay of amino-nitrogen.

A small amount of amino acid data collected from one of this laboratory's flight studies is appended hereto. Among other things, the data reveal that urinary amino acid excretion may provide a more sensitive and precise measure of stress than the one which has enjoyed the greatest popularity in the past (i.e., the urinary 17-OHCS).

Another nitrogenous contributor to the negative nitrogen balance is creatine. It is well known that creatine occurs throughout the body but in highest amounts in skeletal muscle as a high-energy phosphate; very little is normally excreted as such, but is lost in the form of its anhydride, creatinine, in a rather constant amount. The stress-induced increase in creatine excretion has been attributed to its loss from skeletal muscle.

Losses of uric acid from the body also contribute to the stress-induced negative nitrogen balance. However, the particular body function which is responsible for the liberation or formation of this metabolite has apparently not been demonstrated. It is believed that at least a portion of the greater loss of uric acid comes either from lymphoid tissue or, as alluded to earlier, from the destruction of lymphocytes and eosinophils in circulating blood. Losses of that tissue and of those cells are known to occur in the stress response. A portion of the loss of lymphoid tissue is reflected by its content of the two purines, DNA and RNA; this is noteworthy since uric acid has long been recognized as the end product of purine metabolism in man.

Lipid Metabolites

Stress also affects fat metabolism, but usually to a less extent than protein and carbohydrate metabolism. The effects include an overall increase in the breakdown of lipids (lipolysis) and a decrease in their synthesis (lipogenesis), both actions contributing to the net increases seen in cholesterol and the free fatty acids of plasma. The glucocorticoids are thought to play primarily a permissive role in these changes, optimizing the lipolytic action of other hormones such as the catecholamines. In connection with the lipolytic action of the catecholamines, E is as effective as NE in increasing the blood levels of the free fatty acids. Although not mentioned earlier, the influence of E on blood glucose is much greater than that of NE.

The primary source of the increases in plasma fatty acids and cholesterol is apparently adipose tissue. It is worthy of note here that the aforementioned loss of cholesterol from the adrenal cortex goes entirely for the accelerated synthesis of the glucocorticoids, and thus does not contribute to the higher level of cholesterol in plasma; quite to the contrary, the increase in plasma cholesterol is an attenuation of an even greater increase--that attenuation caused by the replenishment of the depleted adrenal stores of that glucocorticoid precursor.

Mineral Metabolites

Substances contained in the final sub-category of non-hormone metabolites are not really metabolites--they are electrolytes. The two primarily involved in the stress reaction are sodium (Na) and potassium (K). In this respect, stress causes a greater retention of Na and a greater loss of K. The greater urinary output of K is attributed to the loss of intracellular fluid from the breakdown of skeletal tissue. The greater retention of Na, on the other hand, is attributed to the mineralocorticoid activity of the glucocorticoids.

In addition to expressing the outputs of Na and K separately, it is also meaningful to express the two as a ratio to one another. Theoretically, the ratio should have greater sensitivity than either of the two alone since it features a numerator changing in one direction and a denominator changing in the other direction. The customary usage is with Na as the numerator. It is of added importance to note here that an informal report is often required/desired by USAF operational commanders a short time after completion of the flight phase of a study. Such preliminary reports are generally based on urinary electrolytes since their analysis by flame photometry is quite simple and very rapid.

Non-hormone Metabolites as Stress Indices

In categorizing the non-hormone metabolites according to the biologic specimen required for stress appraisal, their initial sub-grouping remains essentially intact. For example, the fat and carbohydrate sub-groups emerge as one group (blood indices), whereas the nitrogenous and mineral sub-groups form another group (urine indices). Admittedly, stress-induced changes in virtually all of the constituents in this grouping of urine indices may also be detected in blood; however, without exception, the altered blood levels are usually neither as consistent nor as marked as the corresponding urine levels. Not all changes among these urinary indices are viewed as a mere amplification of the changes in blood. A notable exception is the level of Na in the two fluids. The altered renal handling of this electrolyte results in a lower level in urine and, if anything, a higher level in blood.

For the sake of completeness, one other group of non-hormone metabolites involved in the stress response is acknowledged; namely, those based on the analysis of certain target tissues. Despite the fact that changes in liver glycogen, peripheral fat, and skeletal muscle protein do occur, there is little evidence to support the use of those tissue substances as stress indices.

HORMONE METABOLITES

The final category of stress indices to be considered here is comprised of a goodly number of constituents as it includes the various metabolites of the glucocorticoids and catecholamines. In a manner analagous to the previous use of biosynthesis charts to discuss the hormone precursors, the corresponding metabolic charts are used as an aid in discussing the hormone metabolites.

Metabolic Degradation of Glucocorticoids

The metabolic degradation of the glucocorticoids is summarized in Figure 5. These reactions take place in the liver. It is noteworthy that only the metabolism of cortisol and cortisone are shown in the figure; as mentioned earlier, cortisone is reversibly formed from cortisol and is actually regarded as a metabolite of cortisol rather than as an independent secretion of the adrenal cortex.

As shown in Figure 5, the first degradative step is the breaking of the double bond between C-4 and C-5 with the simultaneous addition of a hydrogen atom onto each of those carbons. Next, the two dihydro derivatives are further reduced chemically to the tetrahydro form by conversion of the keto group at C-3 to a hydroxy group. In accord with the early designation of cortisone and cortisol as Kendall's Compound E and F, respectively, these tetrahydro derivatives are frequently referred to as THE and THF (the dihydro counterparts are designated DHE and DHF, respectively). At this point, the steroid metabolites are rendered water-soluble by being conjugated with glucuronic acid through the action of the enzyme glucuronyl transferase.

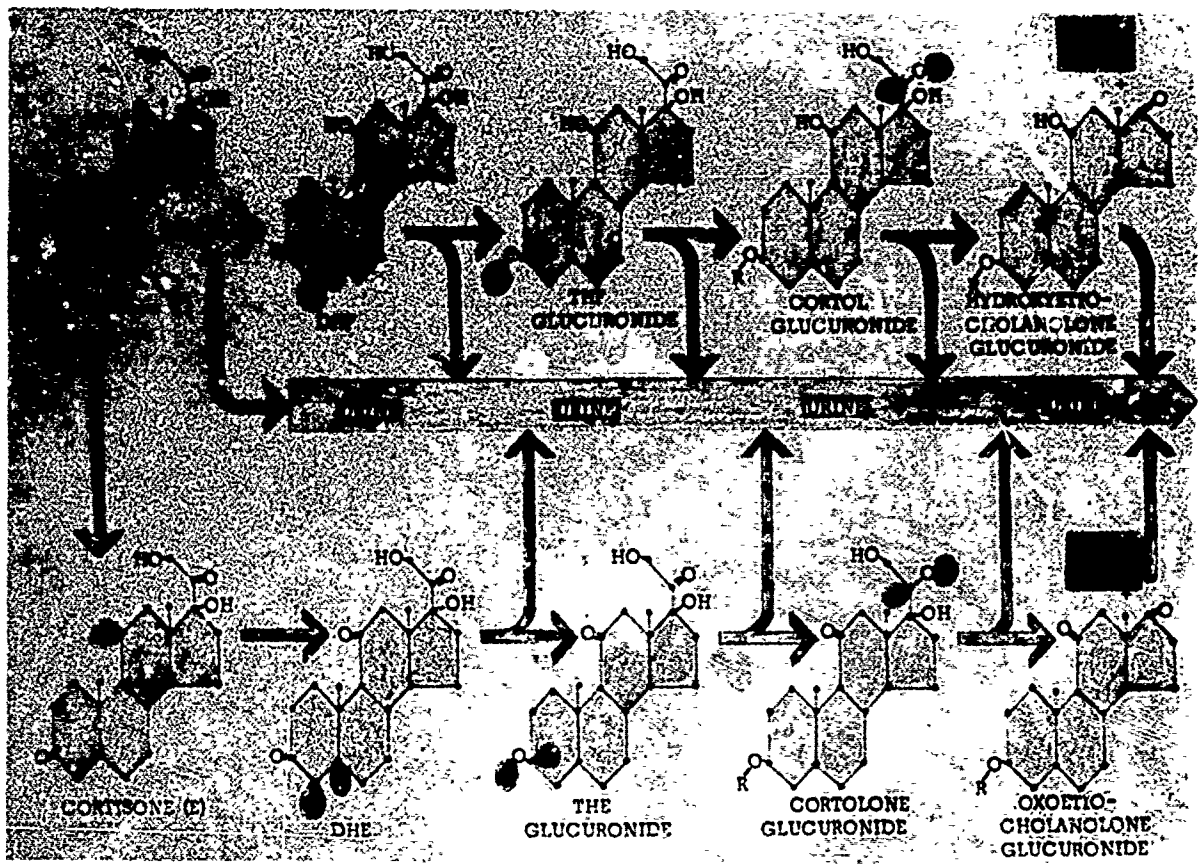


Figure 5. Metabolic degradation of glucocorticoids (cortisol)

A small amount of cortisol is excreted in the free form, but cortisone is not; instead it is converted either back to cortisol or to DHE. After their formation, the conjugates of THE and THF are partly excreted as such and partly converted, respectively, to the conjugates of cortolone and cortol. The latter steroids are oxidized to the corresponding etiocholanolones which, in their entirety, are excreted in urine. Whereas all of these metabolites are present in blood and urine, their quantities in circulating blood are normally too small to be quantified.

It is of interest to compare the reactions shown in Figure 5 with those involved in glucocorticoid synthesis (Figure 3). It was mentioned earlier that the synthesis of those hormones, as well as the catecholamine hormones, involve reactions which are predominantly hydroxylation in nature. In contrast, it is evident from Figure 5 that most of the degradative reactions involve a chemical reduction (hydrogenation). For example, in forming DHE and DHF, the reduction involves the addition of two hydrogen atoms and the simultaneous breaking of the double bond between C-4 and C-5. Chemical reductions also occur in the next two reactions, each involving the replacement of a keto group with a hydroxy group and each resulting in the net gain of two hydrogen atoms. The final step involves cleavage of the bond between C-17 and C-20 and the conversion of the hydroxy group at C-17 to a keto group.

Most of these metabolites of cortisol have been used in one way or another to quantify stress. Quantification is largely restricted to urine samples and, although the products can be differentially measured by gas-liquid chromatography, a far more popular procedure has been to measure them colorimetrically as a group (widely referred to as the 17-hydroxycorticosteroids or, more simply, 17-OHCS). All but two of the steroids depicted in Figure 5 have a hydroxy group at C-17. The other two have a keto group on that carbon; consequently, they can be measured along with metabolites of other hormones (including aldosterone and the sex hormones) as a group known collectively as the 17-ketosteroids (17-KS). Stress has little or no effect on this group of steroids.

Metabolic Degradation of Catecholamines

The pathways by which the catecholamine hormones are metabolized in man are summarized in Figure 6. As illustrated, E and NE are either methylated to form the corresponding methoxy derivative (metanephrine and normetanephrine, respectively) or oxidatively deaminated to form dihydroxymandelic acid (HMA). The methylation reaction is catalyzed by the enzyme catechol-O-methyl-transferase (COMT) and occurs rapidly, whereas the other reaction is catalyzed by monoamine oxidase (MAO) and is a much slower one. Both enzymes are present in most tissues, particularly in the liver and the intestines. Regardless which of the two reactions occur first, the catecholamines are degraded to the common metabolite vanillylmandelic acid (VMA).

In addition to contributing to the formation of VMA, metanephrine (MN) and normetanephrine (NMN) participate in two other reactions. In one reaction the two methoxy derivatives are converted to their corresponding conjugated form (as glucuronides and/or sulfates); in the other they are converted to a phenyl glycol by way of the aldehyde of VMA.

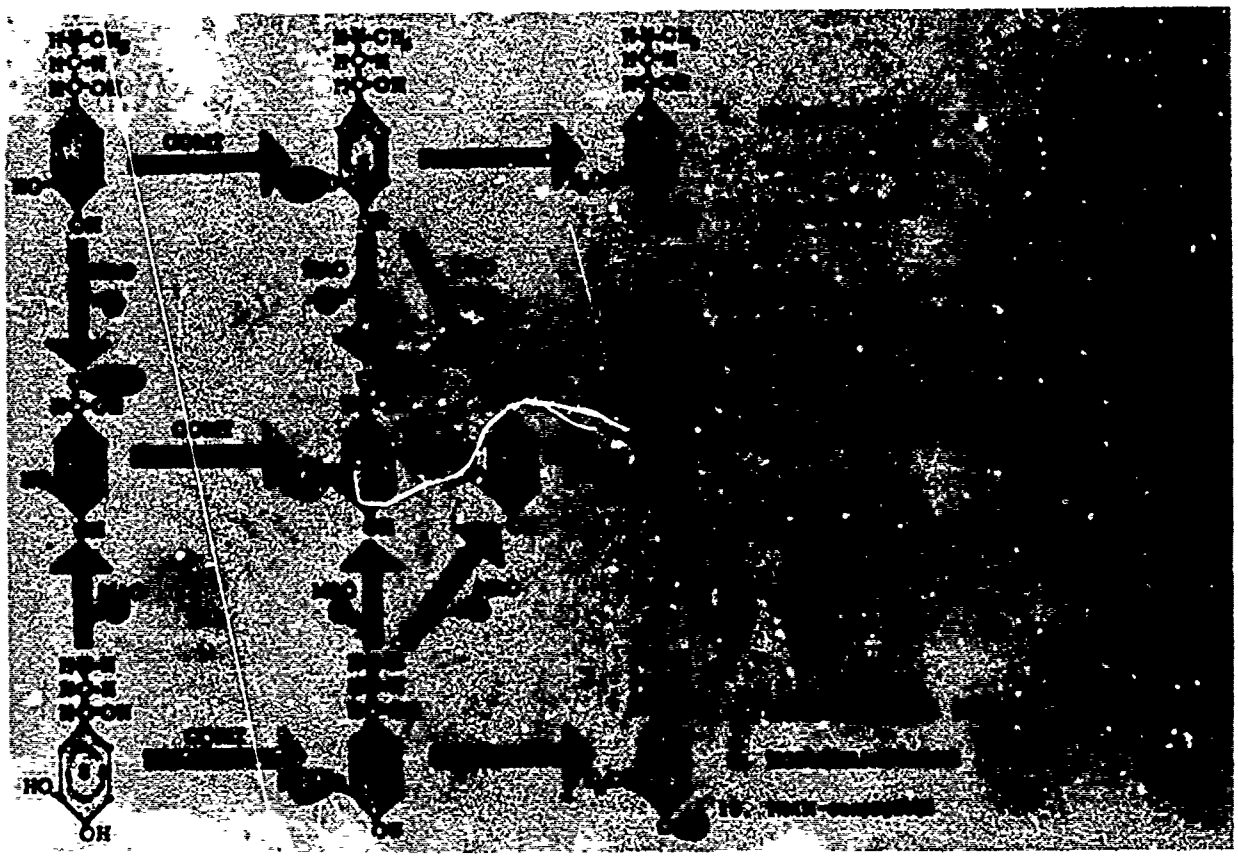


Figure 6. Metabolic degradation of catecholamine hormones

Of the catecholamine metabolites shown in Figure 6, VMA is not only the one excreted in the greatest amount, but its output greatly exceeds that of the free catecholamines themselves. For example, the normal 24-hour excretion of E and NE is about 6 and 30 ug, respectively, whereas the average daily output of VMA usually exceeds 700 ug.

The numbers shown in parentheses in Figure 6 are percentages and denote the relative amounts of these metabolites that appeared in urine after administration of a known amount of radio-tagged E. These data show that VMA is the major metabolite of E in man. It is noteworthy that only about 3% of the original E was excreted unchanged. A review of the literature did not reveal comparable data for isotopically administered NE.

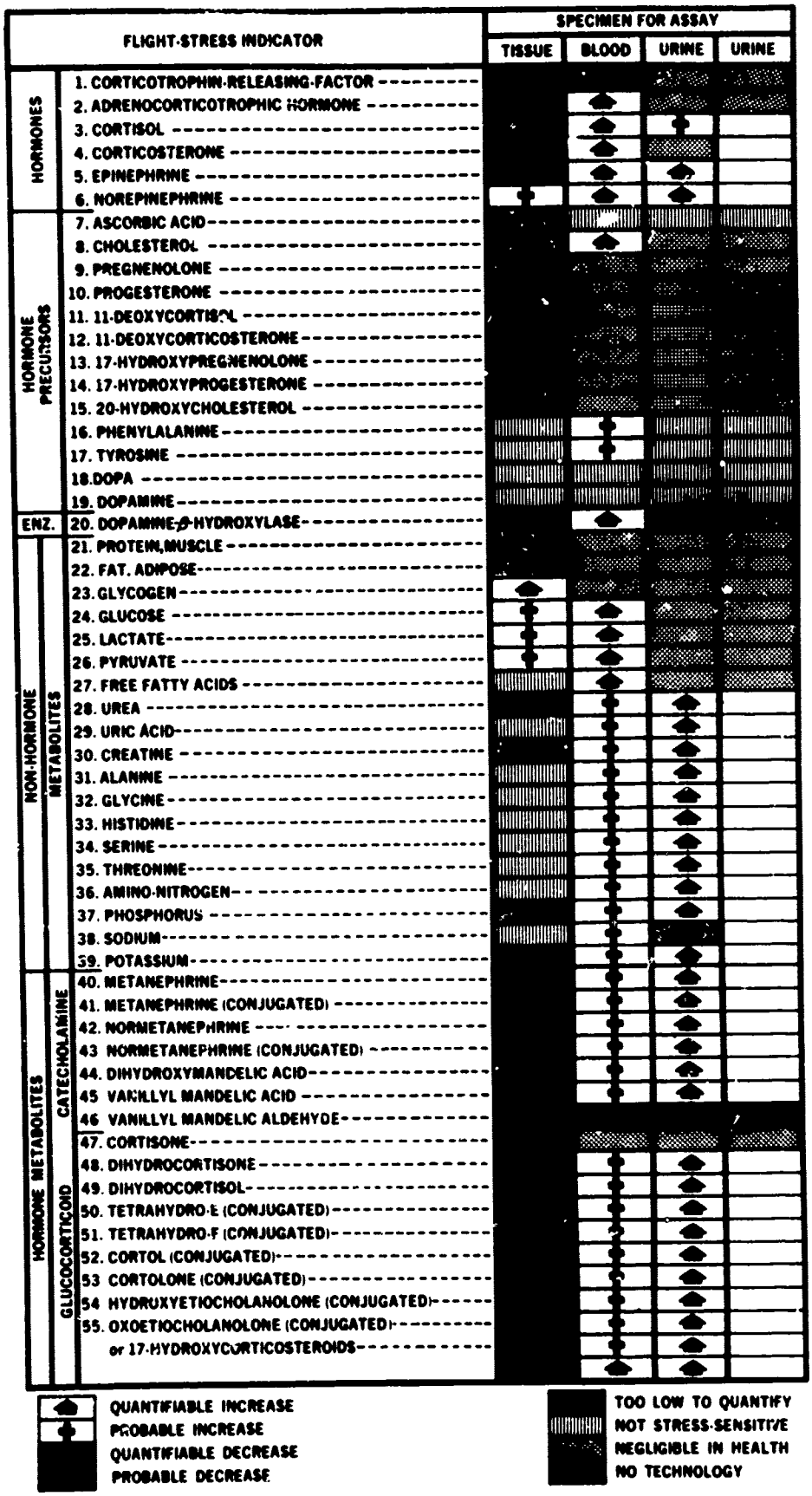
Catecholamine Metabolites as Stress Indices

With respect to their utility as stress indices, the metabolites of the catecholamine hormones have apparently not been used as successfully as have the glucocorticoid metabolites. A factor contributing to that lack of success is undoubtedly the marked influence which the diet has upon the excretion of those metabolites—particularly of VMA.

SUMMARY OF BIOCHEMICAL STRESS INDICES

As an appropriate conclusion, the body constituents listed in Table I provide a summary of the stress indices discussed up to this point. The placement of a symbol in a particular column indicates the type of specimen used for assay and the nature (direction and approximate magnitude) of the stress response. The

TABLE I. Summary of Biochemical Stress Indices



ASSAYS CURRENTLY PREVIOUSLY INCLUDED IN VN-STRESS BATTERY OF INDICES.

upward and downward pointing arrows indicate that the typical, uncomplicated response is a quantifiable increase and decrease, respectively; the plus and minus signs denote, respectively, an increase and decrease which may be small and perhaps insignificant.

Perhaps the most obvious feature is the preponderance of plus signs and upward-pointing arrows. Many of the arrows and pluses reflect increases in both the secretion and subsequent breakdown of the stress hormones; many others, however, reflect the hypercatabolic state to which most body functions are raised by the stress hormones.

Another point of interest is that about half of the constituents are characterized by significant increases in urinary output but by only borderline increases in blood concentration. This finding suggests that many of the hormone metabolites and nonhormone metabolites are discharged slowly and in small quantities from the various tissue sites so that increases in their quantities in circulating blood are scarcely detectable, but yet the cumulative increase in their quantities in urine is readily quantifiable.

It is unnecessary to deal individually with the various symbol assignments given in Table I because the basis for most has already been discussed. It is worthwhile, however, to acknowledge and clarify symbols assigned three of the indices. The slight increases indicated for blood levels of phenylalanine and tyrosine do not reflect stress-induced changes in catecholamine synthesis but in skeletal protein catabolism (as do the other five amino acids on the list). It is especially noteworthy that the qualitative makeup of steroids contributing to stress-induced increases in blood 17-OHCS and urine 17-OHCS is different; cortisol is the major 17-OHCS in blood but is perhaps the one of least importance in urine.

BATTERY OF URINARY STRESS INDICES

As a final point pertaining to information summarized in Table I, attention is directed to notations appearing under the column on the far right-hand side of the table. Indices which either have been or are currently used for stress appraisals conducted by personnel of this laboratory are identified by check marks; this grouping comprises what has frequently been termed the Hale battery of urinary stress indices--a token tribute (reference) to the pioneering efforts of Dr. H. B. Hale. Check marks accompanied by single and double asterisks identify those indices that were dropped from the battery either immediately after a preliminary feasibility study (creatine and VMA) or after subsequent application to a flight study (uric acid and phosphorus). As noted in the table, a study is currently underway to determine the feasibility of quantifying flight-stress by differentially measuring the individual 17-OHCS in urine.

QUESTIONS/ANSWERS ON USE OF THIS BATTERY OR URINARY STRESS INDICES

Perhaps the most frequent question asked is why base the stress appraisal on a specimen so problematical as urine? Why not base it on assays of the stress hormones in blood. The two most apparent and important answers to these questions are given here.

The first reason is a fairly obvious one--that being the requirement for blood-letting. In this connection, it was found from flight-stress appraisals conducted in the '50s that, due partly to operational restrictions and partly to subjective feelings against venipunctures, it was not always possible to obtain blood samples from the flight crews being evaluated. It was actually this difficulty that ultimately led to the search for stress indices in urine. The results of the final flight-stress appraisal based on blood hormones (plasma cortisol) were published in the late '50s. Since that time, all our flight-stress appraisals have utilized urinary measures.

The second reason is that, in at least one respect, it is even more advantageous to use urinary indices than blood indices. For example, stresses encountered during prolonged flights will likely be reflected by urine variables but not necessarily by blood variables. This would be particularly true to stresses occurring early in flight. The stress hormones have a relatively short half-life in circulating blood, ranging from about two minutes to slightly more than an hour.

A second series of questions is why include such a large number of urinary indices in the battery? Why not restrict the appraisal to assays of urinary hormones--particularly cortisol, E, and NE? What added information can be gained by measuring the urinary output of hormone metabolites and nonhormone metabolites? These are very pertinent questions, and some of the more acceptable answers are given here.

A good reason for not basing the appraisal on the urinary output of just the stress hormones is that their excretion is not only a very small portion of that which had contributed to their high level in blood, but their output is also very small compared to the output of their metabolites. It has long been known that free cortisol makes up less than 2% of the entire 17-OHCS fraction (in urine), the remainder being cortisol metabolites. Also, as mentioned earlier, only about 3% of administered E appears in urine as such, the remainder being metabolites of E. The same is presumably true for NE. Since the metabolites of these hormones are excreted in much greater quantities than the hormones themselves, they offer a more sensitive measure of hormone excretion.

At least two reasons can be given for including nonhormone metabolites in the stress battery. First, marked changes in their urinary output provide good information as to the impact of the stressor upon the target tissues from which they originate. Second, the stress-induced increases in the urinary output of many nonhormone metabolites are several times greater than the hormones that caused their formation or release. This is analagous to the comparison made earlier between the secretion of hormones from the hypothalamus, the anterior pituitary, and the adrenal cortex; expressed differently, picogram quantities of the hypothalamus hormone (CRF) causes the secretion of nanogram quantities of ACTH which, in turn, causes the secretion of microgram quantities of cortisol. Taking this comparison one step further, the microgram quantities of cortisol causes the excretion (not secretion) of milligram quantities of such substances as urea.

Another question concerns the quantitative base for expressing urinary data; what is the base and why was it chosen?

Although blood hormones are usually expressed as concentration (i.e., as a quantity per volume of blood), this is a virtually meaningless expression for urinary constituents since the water content of urine is perhaps the constituent which is subject to the widest variations.

The next possibility would be to express urinary data as excretion rates (i.e., as a quantity per unit of time), which is the one most widely used. This expression was initially selected for our flight-stress studies. However, it was subsequently found that many urine samples collected from flight personnel had to be discarded (without analysis) because essential time information covering the period of collection could not be ascertained. This difficulty occurred primarily in the collection of preflight specimens, resulting from the failure of the men to record the beginning time of that collection period (i.e., when the immediately preceding urination occurred). Difficulties of this nature were also experienced during prolonged flights in which the subjects collected their own urine samples periodically during flight but would not always record the collection time.

Instead of using excretion rates, the output of each urinary variable may also be expressed in terms of a urinary constituent which is least affected by altered physiologic function. The literature indicates that creatinine is the least influenced of the urinary constituents. Along with its advocates, the use of creatinine-based ratios also has its critics. In the case of our studies, comparisons have shown that urinary data expressed as creatinine-based ratios generally have smaller coefficients than the same output data expressed as excretion rates. This is a particularly welcomed finding in view of the rather wide fluctuations which characterize urinary excretion patterns.

Other valid questions concern the acquisition of contradictory data among the stress indices. Why do they occur and how can they be interpreted? There are no simple answers to these very important questions. However, a few factors which may aid in the interpretation of conflicting findings are given here.

First, one must give due consideration to the known or suspected stressors which are under study. Most of the indices discussed up to this point are involved in the stereotyped stress reaction which Selye calls the non-specific reactions--non-specific because any stressor having the intensity to trigger the Alarm Reaction will activate the stereotyped response. Distinctly separate from that response, each stressor usually produces a set of specific reactions in the body which is peculiar to that particular stressor. For example, exposures to heat and cold activate the Alarm Reaction and, thus, the non-specific reaction; however, sweating is one of the specific responses to heat just as shivering is to cold. Since the stereotyped reaction manifests itself throughout the body, it is a virtual certainty that many of its features are modified to a greater or lesser extent by components of the simultaneously occurring specific reactions.

In addition to viewing a stress response as an admixture of specific and non-specific reactions or as an interaction between two or more stressors, it is perhaps of equal importance to consider the interaction that results when an individual adapted (or acclimated, accustomed, etc.) to one stressor is acutely exposed to another stressor. This circumstance relates to such other broad areas in the field of Stress Physiology as Chronic Stress and Cross-adaptation. Moreover, it is inappropriate to discuss here how these factors might influence the "uncomplicated" stress response summarized in Table I.

Another factor to consider in explaining inconsistencies among stress data is the time interval between the stressful event and the collection of the urine sample for analysis. Data collected to date suggest that post-flight urine samples should not be collected until at least two hours after completion of a flight mission. Unfortunately, it is not always practical to keep flight crews around long enough to satisfy this requirement. The lag of two hours is not just for the passage of the various constituents from blood to urine; reactions resulting in the formation of many of the urinary indices continue long into the recovery period. For example, after cortisol has exerted its many influences throughout the body, it then passes into the liver where it is rather slowly degraded to its metabolites (the 17-OHCS). Urea formation is even slower since it depends on two stepwise and relatively slow reactions, those being the breakdown of muscle protein and the subsequent conversion in the liver of the liberated amino acids into urea.

Time-of-day, season-of-year, and the diet also have substantial effects on the output of most of the urinary constituents including those used as indices of stress.

PART II

ILLUSTRATIVE FLIGHT STUDY

Biochemical data obtained from a field study termed Operation Phantom Flame are interesting in several respects. First, the results were of a nature which, at least initially, were somewhat difficult to interpret. Next, the opportunity was taken in that study to determine the usefulness of certain urinary variables which had not been included in earlier flight stress appraisals but whose outputs had been shown in clinical studies to be sensitive to stress. Also, the results clearly reveal the importance and necessity of conducting appropriate baseline studies to identify and quantify the predisposition of experimental subjects to known or suspected environmental/psychological factors. These and other features of this study are discussed below.

To give a brief overview of the study, Operation Phantom Flame was undertaken to quantify the physiologic and performance effects of hot, low-level flight in the RF-4C. To accomplish this objective, the following factors capable of modifying cockpit temperature were examined: (1) crew position, i.e., rear-seater versus front-seater, (2) forenoon versus afternoon missions, (3) flights at predominantly high versus low altitudes, and (4) flights in the summertime versus wintertime. It was especially advantageous that the flight phase of this study was carried out at Shaw AFB SC as maximal outdoor temperatures in that locale were quite high in the summer, but were relatively mild--not cold--in the winter. All subjects were undergoing training in the RF-4C and all missions were of a reconnaissance nature, usually not exceeding 90 minutes. In addition to collecting urine from the aircrews before and after flight, urine was also collected from most of the men at approximately the same times of day on a nonflying day.

Before discussing the biochemical data, it is of interest to touch briefly on other findings of this study. For example, the impact of high cockpit temperature on mission accomplishment is clearly attested to by the combined findings that, percentagewise, more targets were missed and more missions were deemed unsuccessful in the summer than in the winter. Also, as might be expected, cockpit temperature was, on the average, more than 10°F higher during summer than winter flights, and sweat loss was accordingly much greater in the summer than in the winter--particularly during low-level flights in the afternoon. Inflight ECG data failed to reveal the occurrence of gross arrhythmias in either season, but did show heart rates to be 10-to-20 beats per min. higher during summertime flights. Although all conditions of flight significantly increased subjective fatigue, variations between seasons, time of day, level of flight, or crew position were not differentiated. Finally, sleep histories revealed that the men, perhaps by virtue of being F-4 trainees, got significantly less sleep the night before flights at low level than at high level. This evidence of anticipatory stress is strengthened by some of the biochemical data.

A summary of the biochemical data is presented in Table II. It is noted that the data are delineated only with respect to season and flight level; statistical analysis failed to identify time-of-day and crew position as influential factors. It is also noted that the last two urinary variables tabulated here are the ones alluded to earlier as being examined in this study for stress sensitivity. Both of these variables reflect free amino acid excretion; in the one case, the 20-odd amino acids were quantified individually and their quantities then summed, whereas in the other measure, they were quantified as a single entity. To touch briefly on why both measures were included in this study, one reason was to ascertain which, if any, of the amino acids contributed to the previously demonstrated stress-induced increase in urinary nitrogen. The reason for including the amino-nitrogen was primarily aimed at future flight-stress appraisals; namely, should the differential assay of the individual amino acids prove certain ones to be sensitive to stress, it was deemed important to ascertain whether or not that sensitivity might also be reflected by the single measure of amino-nitrogen, which requires much less time and instrumentation than the chromatographic method required for the assay of the individual amino acids.

With respect to the means appearing in Table II, attention is first called to the apparent failure to find statistically significant pre-to-postflight changes in the output of epinephrine, sodium, potassium, and the sodium:potassium ratio (Na/K). It is not unusual to find that these urinary indices do not uniformly agree as to the presence or absence of stress, and that is one of the reasons for including several measures in the stress battery. In contrast to that failure, rather clear cut changes were found in the excretion of the other urinary constituents, some of which were of a substantial magnitude and of statistical significance. It is especially noteworthy that the postflight changes were qualitatively identical and quantitatively similar.

The bar graphs presented in Figure 7 not only show the very close agreement between the two measures of amino acid excretion and between the five amino acids which clinical studies revealed were stress-sensitive, but they also show the quantitative relationship between the pre-to-postflight changes in the output of those urinary constituents to the six experimental test circumstances. As noted by the vertical scales, the bars show the direction and magnitude of those changes. The downward projection of an overwhelming majority of the bars indicates flight-induced decreases in excretion. It is also noted that the bars are arranged in an order of from 1 to 6, with 1 being deemed the least stressful test circumstance and 6 as the most stressful. This ranking of flight circumstances will be dealt with in greater detail later. Also, as this graphical presentation of data is shown here merely to demonstrate the close agreement between the two measures of amino acid excretion, there is no need to dwell further with this form of the data.

In turning attention back to the data in Table II, the finding of good agreement between the 17-OHCS, the amino acid, and the urea data are looked upon with favor as their outputs have previously been shown to be influenced by the blood cortisol level, which, in turn, reflects adrenocortical function. The finding of postflight decreases in their outputs, however, was not initially viewed with such favor since the hypoadrenocortical activity which they uniformly signified was exactly the opposite from what might have been deduced from certain physiologic measures made during flight, from mission performance assessments, and from subjective fatigue data obtained directly from the men themselves. To summarize briefly those other findings, low-level flights were more stressful than those at high level, and missions flown in the summer were categorically more stressful than those in the winter. Obviously, to

reconcile those assessments with the biochemical data, one would need to envision either the interplay of two diametrically opposing influences on the output of these urinary constituents, or of a single influence of an unusual nature.

TABLE II

Biochemical Stress Indices: Operation Phantom Flame

Urinary Variable	Season	Ground-Level Initial	Ground-Level Final	High-Level Before	High-Level After	Low-Level Before	Low-Level After
17-OHCS	Summer	440	380	429	397	451	386**
	Winter	312	347	385	324**	357	369
Urea	Summer	202	211	196	168	258	210**
	Winter	152	156	181	169	187	180
Sodium	Summer	9.44	11.42	10.46	11.54	11.16	8.38
	Winter	7.98	8.72	11.28	12.92	12.90	15.66
Potassium	Summer	4.46	5.16	4.38	4.48	4.52	3.56
	Winter	3.96	5.02	4.54	4.36	4.90	4.66
Na/K	Summer	2.37	2.31	2.56	2.62	2.81	2.56
	Winter	2.32	1.94	2.71	3.14	3.08	3.73
Epinephrine	Summer	0.75	1.21	1.19	1.23	1.38	1.42
	Winter	0.85	0.76	0.86	1.01	0.95	1.00
Amino Acid (sum)	Summer	3.92	3.36**	3.99	2.90***	4.58	3.19***
	Winter	3.46	3.32	4.19	3.71**	4.33	3.50**
Amino Nitrogen	Summer	5.04	4.67	4.80	3.89**	5.27	3.70***
	Winter	3.86	3.86	4.49	4.31	5.13	4.47

* p 0.05
** p 0.01
***p 0.001

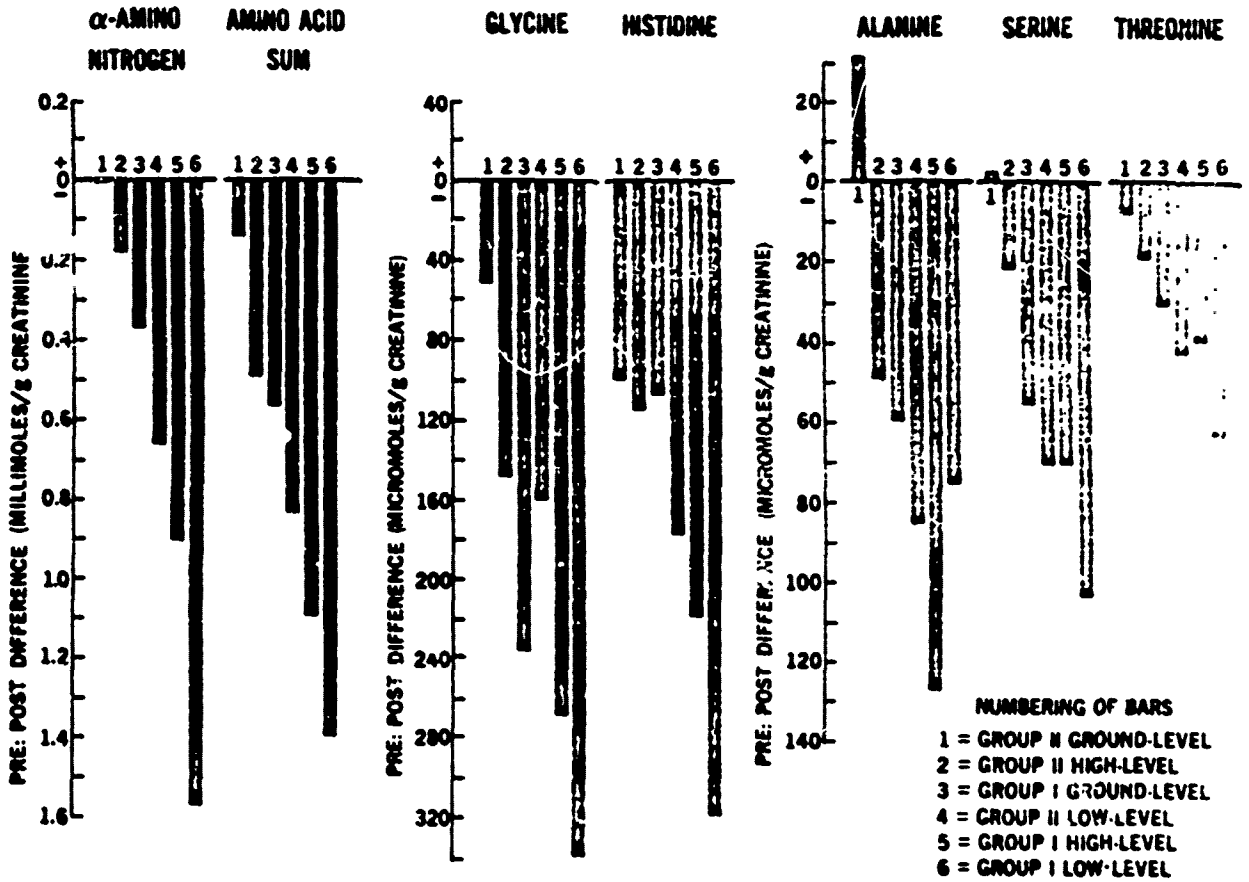


Figure 7. Variations in amino acid excretion as a function of flight stress and season.

While either or both of those explanations may account for the apparent disparity, there is at least one other explanation which is both attractive and logical. Namely, it is conceivable that the men may have been predisposed by the encounter of one or more stressors shortly before flight. When viewed in this light, the postflight decreases would not be seen as an unusual response to stress, but as the normal recovery from stress. Moreover, the magnitude of those decreases would reflect the relative extent to which the men had recovered from that preflight stress.

The finding in each season that excretion data from the second sample collected on flight days (postflight) were quantitatively similar to data from the second sample on nonflying days is, in itself, indicative that the men were about as stressfree after flight as when they had merely remained in the air conditioned laboratory. Another hint that the men were predisposed by at least one preflight stressor is seen by comparing seasonal differences in ground-level data, particularly the amino acid sums (Table II). In that example, the finding of a significant drop in amino acid excretion in the second sample collected in the summer but not in the winter strongly points to an influence other than circadian rhythmicity. To reconcile those seasonal differences, one might view the men examined on the nonflying "temperate" days of winter as being essentially free of stress, and view those examined on nonflying days in the heat of summer as manifesting signs of heat stress upon first reporting to the laboratory for collection of the initial urine, but, by waiting in that air conditioned facility for approximately four hours to give their second sample, they would have had sufficient time for recovery from that heat exposure.

The likelihood that the F-4 trainees were predisposed by at least one preflight stressor led to a reevaluation of the Phantom Flame data--this time limited only to preflight and initial ground-level data. As shown in Table III, six sets of data were involved in that further evaluation. For the analysis, it was necessary to identify the set which reflected the most stressfree circumstance, and then compare that set with the other five sets. As mentioned in the preceding paragraph, the men examined at ground-level in the winter were regarded as being the most stressfree. Accordingly, the notations of significance shown in Table III identify those means which differ significantly from the corresponding winter (Phase II) ground-level mean. The results of this analysis offer strong and compelling support for the view that the men examined in this study were, indeed, exposed to preflight stressors. In every instance (Table III), the winter ground-level mean is substantially and, in most cases, significantly less than the other means. Moreover, it seems more than coincidental that all data from urine collected before low-level flight in the summer are not only the furtherest removed from baseline levels, but that the significance of those differences is, without exception, at the highest statistical level. Since the men manifesting those highest preflight values would appear to be stressed to the greatest degree, it is only reasonable to assume that their subsequent recovery from that stress would be characterized by the greatest drop in excretion rates. The postflight data in Table II clearly and strongly support the latter assumption.

TABLE III. "Baseline" Data: Operation Phantom Flame

Urinary Variable	Season	Ground Level	High Level	Low Level
17-OHCS	Summer	440**	429**	451***
	Winter	312	385	357
Urea	Summer	202*	196*	258***
	Winter	152	181*	187*
Amino Acid (Sum)	Summer	3.92	3.99	4.58**
	Winter	3.46	4.19**	4.33**
Amino Nitrogen	Summer	5.03*	4.80*	5.27***
	Winter	3.86	4.49*	5.13*

* p 0.05
** p 0.01
*** p 0.001

While it is clear that the men examined in the summertime were stressed before flight, it does not necessarily follow that the stressor was climatic heat alone. In this connection, it was mentioned above that the intensity of preflight stress tended to be the greatest for the men in the summer who knew they were about to take off on missions at predominantly lower altitudes; although not shown in Tables II or III, that tendency was found to be of statistical significance for many of the urinary constituents. Yet another and even more obvious demonstration that climatic heat was not the only preflight stressor is given by the winter data in Table III. Without exception, the urinary constituents were excreted in much greater quantities before all flights than on nonflying days. Furthermore, of those preflight elevations, only those of 17-OHCS failed to show statistical significance. Since climatic heat would seemingly be of little or no consequence in the wintertime, it seems apparent that those preflight elevations were caused by a stressor other than heat. The possibility that the stress may have been caused by temperatures at the other end of the scale was ruled out for several reasons; namely, (1) the ambient temperatures were not all that low, (2) the men could more effectively shield themselves from cold, and (3) cold could not, of course, be the second preflight stressor shown to be present in the summer data.

A stressor which could fully explain the preflight elevations in the winter and at least partially explain those in the summer is anticipatory stress. There is ample reason to believe that the men may have been a bit apprehensive since they were undergoing training in an aircraft with which they were not too familiar. Also, as mentioned earlier, sleep histories obtained from those men indicated that some of them may have been predisposed by anticipatory stress. In comparing the relative effectiveness of

the sleep data and urinary data to identify, at least qualitatively, the presence of anticipatory stress, there is only one major difference between what the two signify. Specifically, the urinary data suggest that the men experienced that psychologic stress prior to flight at both levels in both seasons; in contrast, the sleep data indicate that the men were predisposed by anticipatory stress in both seasons, but only before flight at the lower altitudes.

As a final point concerning the data in Table III, it is enlightening first to compare the magnitude of the differences between those six data sets for each of the four urinary variables, and then to derive a stress index from those differences which might provide a quantitative estimate of the intensity of the two stressors--both singly and in combination. Accordingly, the data presented in Table IV show the % difference between the "stressfree" baseline mean (winter ground-level) and the mean for each of the other five experimental circumstances for each of the urinary variables. This presentation of the data obviously lends itself more readily to comparing differences between the experimental variables and between the urinary variables than that used in Table III. For example, whereas it is difficult to compare the mg differences in steroid excretion with the mmole differences in urea excretion (Table III), the relative values in Table IV indicate that the two urinary variables were affected to a comparable extent by the six test conditions. The only real difference between the two is the intensity of stress indicated for the circumstance which was identified earlier as being the most stressful of the six, i.e., preceding low-level flight in the summer.

TABLE IV

"Baseline" Data (% Change): Operation Phantom Flame

Urinary Variable	Season	Ground Level	High Level	Low Level
17-CMCS	Summer	41	38	45
	Winter	0	23	14
Urea	Summer	33	29	70
	Winter	0	19	23
Amino Acid (Sum)	Summer	14	25	32
	Winter	0	21	25
Amino Nitrogen	Summer	31	24	36
	Winter	0	16	33
Mean of Above	Summer	30	26	46
	Winter	0	20	24

Another and perhaps greater advantage of expressing the data in relative rather than absolute units is that an overall estimate of the stress intensity produced by each of the six test conditions can be obtained merely by computing the average of the intensities found for the four urinary variables. Those average percentages are given in the lower part of Table IV and constitute the aforementioned stress index. Based on the use of that index, the following observations are made concerning the relative strength of the principal stressors which were undoubtedly encountered before flight by the Phantom Flame aircrews: (1) when heat stress is not accompanied by anticipatory stress, as at ground-level in the summer, its intensity is rather mild but still significant, (2) when anticipatory stress is not accompanied by heat stress, its intensity is about the same as heat stress alone, and apparently is not influenced by prior knowledge as to the altitude at which the upcoming mission is to be flown, and (3) when both stressors are present, then the degree of anticipatory stress is influenced by the altitude of the subsequent mission.

To summarize briefly the information gained from Operation Phantom Flame which should be of interest and concern to operational commanders and aircrews, the following tentative conclusions are drawn:

(1) Of greatest importance, the high cockpit temperatures which occur during low-level flight in a hot environment did not elicit in the crewmen those biochemical changes which typify the normal physiologic response to stress.

(2) The men did manifest signs of heat stress, but those signs occurred before flight and on nonflying days.

(3) The men also showed signs of a relatively mild degree of anticipatory stress.

(4) The only physiologic response reflected by the urinary stress indices was the recovery during flight from exposure to preflight stressors.

In addition to the foregoing conclusions, there are several other bits and information gained from Operation Phantom Flame which would be of interest and value to flight surgeons and others in the biomedical community. One feature is the rather high sensitivity which certain of the urinary amino acids were found to have toward flight stress. The finding that those stress-sensitive amino acids were primarily limited to threonine, serine, glycine, alanine, and histidine is of particular importance in view of the fact that a clinical study reported the urinary output of those amino acids closely paralleled plasma cortisol. With respect to their sensitivity as stress indices, Phantom Flame revealed that, in most instances, the stress-induced changes in the output of those amino acids (and of the amino acid sum) were generally more consistent, of greater magnitude, and of greater statistical significance than changes

in 17-OHCS. This, too, is an especially noteworthy finding in view of the fact that the output of those corticosteroids has long been viewed as the most sensitive and specific urinary measure of stress.

Another significant feature of this study is the close agreement found between the two measures of amino acid excretion. While the differential quantification of the individual amino acids served a very useful purpose in linking the results of this study to that earlier clinical study, such detailed information would not require reaffirmation in every flight stress appraisal in the future--especially since the gathering of that information would be very time-consuming and quite costly. Thus, thanks entirely to this information gained from Phantom Flame, amino acid excretion in all future USAFSAM stress evaluations will be measured by the rather simple and inexpensive assay of amino-nitrogen.

As a final bit of useful information gained from this study, the data clearly show the need for adequately controlling or at least identifying experimental variables which impact upon the particular experimental circumstance being investigated. It may seem inappropriate to emphasize here the importance of such a fundamental issue, but even a cursory examination of the literature reveals that due attention is frequently not given this important issue. Even in the realm of stress studies, it is not difficult to find one which, in attempting to assess the influence of a given experimental variable on a particular body function, limits the period of observation to shortly before and immediately after exposure to that experimental variable. Had such an experimental design been used in Phantom Flame, the results would have been interpreted in a far different manner. For example, since the sole objective of Phantom Flame was to ascertain the physiologic and performance effects of low-level flight in a warm climate on F-4 aircrews, the experimental protocol might have specified simply the collection of urine before and after flight during the summertime. Moreover, even if it was deemed necessary to collect urine from the same men at the same times on a nonflying day, the results still would have been interpreted in a different and inappropriate fashion. Thus, it is apparent that in order to study the effects of flying on a hot day, it is essential to collect data on flying and nonflying days in the winter as well as in the summer.

PART III

HISTORICAL REVIEW OF STUDIES FROM OUR LABORATORY

In the material which follows, we trace the development of a standard biochemical battery in our laboratory, starting in 1958. The standard battery today consists of: (1) epinephrine; (2) norepinephrine; (3) 17-hydroxycorticosteroid; (4) sodium; (5) potassium; (6) urea, and the ratio of sodium to potassium. All of the above are expressed as a ratio against creatinine (in the denominator) The use of creatinine in our battery is based on the premise that creatinine is excreted at a steady rate and therefore compensates for variation in sample collection time.

Quantification of the stress and fatigue experienced by USAF personnel participating in real-world operations and simulated, laboratory exercises have been a major effort of this laboratory for the past 2 decades. The battery of urinary substances has been studied to attempt assessment of the physiologic cost in such varied operations as aircrews flying long-range cargo missions, fighter pilots flying high sortie rates daily for 1-2 weeks, and 48-hour-alert duty tours in missile crewmen. Urinalysis was selected as a means of assessing physiologic cost because urine samples are relatively easy and quick to collect from a large number of people in field situations (in aircraft, on flight lines), urine collection does not impair operational performance and safety, and urine collection is a noninvasive procedure and, therefore, not stressful in itself and acceptable to those being studied. Measures of individual crewman performance have been seldom available in field studies, although a few laboratory studies have attempted to relate changes in urinary concentrations to changes in mental and motor performance.

The general procedure utilized in these studies has been to collect urine samples, but not total volume, at 4-hour intervals a few days before, during, and after the mission, test, or event of interest. Usually the samples are collected only during working hours. The before or premission data serve to describe normal baseline concentrations and within-day patterns. The concentrations occurring during and after the mission are compared to the baseline data to determine the extent of physiologic stress or cost and the amount of time for return or recovery to baseline values. Baseline and recovery phases are usually each of 3-4 days duration, depending on the availability of the crews under study. Often, it is not possible to collect urine samples during all three phases. As in most field work, there can be considerable missing data.

The urine sample collection bottles (100-250 ml) each contain 6 ml of dilute HCl acid (1.6 normal) which serves as a preservative. The urines are frozen (using freezers or dry ice in shipping containers) as soon as possible and shipped to this laboratory for analyses. Frequently the samples can only be refrigerated when collected and it may be 12 hours before they are frozen. The importance of immediate freezing of the samples is an issue under study once again in our laboratory.

During baseline and recovery phases, the crewmen under study are often off duty. Requiring them to report several times a day to a urine collection point to provide a sample can be annoying, undermine cooperative participation, and even violate USAF crew rest regulations. Therefore, urine samples are often collected by the participant at home during baseline and recovery phases. This procedure requires voluntary use of a home refrigerator or a door-to-door pickup scheme. The procedures described above are cumbersome, at times, in field or inflight studies, so we are now seeking alternatives.

In the remainder of this part of the paper, we are modifying the format somewhat. Abstracts of papers will be found on the left and "operational applications" will be found on the right. Most of the papers presented here have Henry B. Hale as senior author, so the citation will consist only of the title and the journal in which the paper was published. Many others joined with him in studies. Their contributions are acknowledged with co-authorship. As indicated earlier, Dr. Hale is a pioneer in the application of endocrine physiology to USAF operational problems. In particular, his unique contribution was the development of a standard battery and its use in a host of studies.

PLASMA CORTICOSTEROID LEVELS IN AIRCREWMEN AFTER LONG FLIGHTS

Journal of Clinical Endocrinology and Metabolism XVIII (12):1440-1443, Dec 58

ABSTRACT

The fluorescence method of Sweat for the determination of hydrocortisone and a corticosterone-like fraction in blood was utilized in an attempt to evaluate flying fatigue in a group of 44 aircrewmen participating in flying activities in military aircraft. Mean preflight values for each of the two steroid fractions agreed with those reported by Sweat for normal male subjects, but significant increases in both fractions were noted after flights of nine to twelve hours' duration. This change was not of the nature of a diurnal variation.

OPERATIONAL APPLICATIONS

1. Steroid activity indicates the conversion of protein and fats to carbohydrates in order to provide energy for work. This study shows the B-52 crews prior to a mission had plasma corticosteroid levels like those of unstressed nonflyers and a 50% increase after training missions lasting nine to 12 hours. Therefore, the job of flying imposes demands (at least an increased workload) to which the body responds by drawing on energy reserves. The increase is not high nor physiologically compromising but is opposite the normal diurnal trend.

2. All crewmembers showed responses of similar magnitude, indicating no special crew-position factor in these bomber training missions.

3. Instructor pilots yielded the same effects as other crewmembers.

EFFECTS OF PILOTING SUPERSONIC AIRCRAFT ON PLASMA CORTICOSTEROIDS AND BICARBONATE

Journal of Applied Physiology 14(4):629-631, July 1959

ABSTRACT

While flying high-speed military aircraft, pilots frequently hyperventilate to a degree sufficient to induce marked alkalosis. Psychogenic factors are thought to be responsible for the hyperventilation. Comparison was made of pre- and post-flight plasma bicarbonate (determined titrimetrically) and corticosteroid levels (Sweat's technique) for 20 instructor pilots and 47 student pilots flying F-100 aircraft for 50 minutes. No differentiation of students and instructors was possible on the basis of either pre- or post-flight values; therefore, the data for the two groups were combined. The plasma bicarbonate value following the flight was 1.1 ± .24 mEq/l. (mean ± S.E.) lower than before the flight. Free 17-hydroxycorticosteroone was increased 5.8 ± .70 µm/100 ml, while conjugated 17-hydroxycorticosterone increased 5.7 ± .75. The free corticosterone-like fraction increased 3.1 ± .34 µg/100 ml, while the conjugated corticosterone-like fraction increased 3.2 ± .35. Each of these changes was significantly different from zero ($P < .001$). No statistically significant correlation was found between the fall in bicarbonate and any of the increases in steroid fractions.

OPERATIONAL APPLICATIONS

1. Hyperventilation (rapid breathing) is a common response to threat. Most (70%) of the fighter pilots in this study hyperventilated. However, the resulting acid-base change in blood was not significantly correlated with increased steroid activity which reflects one aspect of the mobilization of energy to respond to the demands of flying. This finding therefore eliminates a common behavioral response (hyperventilation) to stress as a contributor to a more fundamental stress mechanism (steroid activity), and reinforces the value of steroid determinations made routinely in the USAFSAM biochemical battery.

2. The steroid responses (a 50% increase) of instructors and "students" were not significantly different, in contrast to the finding of a crew-position effect (A/C's most stressed) in a C-5 crew study performed subsequently. It should be noted, however, that the nature of the mission profile and the flying job are quite different in fighters versus transports.

STRESS RESPONSES OF PILOTS FLYING 6-HOUR OVERWATER MISSIONS IN F-100 AND F-104 AIRCRAFT

Aerospace Medicine 34:15-18, 1963

ABSTRACT

Postflight urine and blood samples for pilots flying 6-hour overwater missions in F-100 and F-104 aircraft were employed in an attempt to appraise flying stresses. Comparison was made with a third group of pilots on an off-duty day. Urinary determinations included epinephrine, norepinephrine, corticosteroids (17-OHCS), sodium, potassium, inorganic phosphate, urea, uric acid, and creatinine. Blood determinations included free and conjugated hydrocortisone and corticosterone-like fractions. Flying raised corticosteroid levels in plasma but not in urine. Levels for the F-100 group were higher than for the F-104. Urinary epinephrine and norepinephrine values for the flying groups were significantly above those for the control, values for the F-104 exceeding those for the F-100. Differences in flying groups appear to relate to aircraft characteristics, weather conditions, and flying experience. Both flying groups showed high urinary excretion of urea and uric acid, but only in the F-104 group was sodium and potassium excretion elevated. Flying induced no variation in urinary phosphate. Singly and collectively, these determinations are basic to future studies on flight stress.

OPERATIONAL APPLICATIONS

1. Flying a fighter on a 6-hour deployment mission is a strong stress and the body responds by activating stress mechanisms (3-5 fold increase) which help the flyer meet the challenge.

2. The degree of physiologic activation is related to the intensity of the challenge. In this study, a more demanding aircraft (F-100), experience level, an earlier departure (F-104), inflight refuelings (F-104), and enroute weather (F-104) were identified as probable factors causing greater physiologic activity.

3. For the first time in this series of papers, the concept of a physiologic "cost" of flying was presented; this concept has been an important element for evaluating findings in our studies.

4. In contrast to the previous paper, presumed hyperventilation might be implicated as a possible cause for some of the physiologic activity.

ENDOCRINE AND METABOLIC EFFECTS OF SHORT-DURATION HYPEROXIA

Aerospace Medicine 35:449-451, 1964

ABSTRACT

This investigation was concerned with the effects of breathing 100% oxygen (by mask) at 1 atmosphere ambient pressure for 4 hours on sympathoadrenal, adrenocortical, and metabolic function in healthy human subjects. Control determinations were made on the same subjects on a separate occasion, the subjects then breathing room air (by mask). Sympathoadrenal activity was appraised by means of urinary

OPERATIONAL APPLICATIONS

This study demonstrates that many factors contribute to physiologic activity in flyers; in this case, breathing 100% oxygen resulted in some changes opposite to those found in fighter pilots and mask discomfort resulted in changes like those considered to be a "flight effect." A biomedical team needs to "tune in on" many factors when it attempts to assay flight stress.

ABSTRACT (continued)

epinephrine and norepinephrine determinations; adrenocortical activity was appraised by means of plasma cortisol and urinary 17-hydroxycorticosteroid determinations; and metabolic appraisal was made by means of urinary creatinine, urea, uric acid, phosphate, potassium, and sodium. Evidence of hyperoxia-induced adrenocortical and sympathoadrenal depression was found--plasma cortisol concentration, as well as catecholamine excretion, falling below the control levels. Urine volume also was relatively low, as were urinary sodium and phosphate values. Mask discomfort was shown to be an obscuring factor, since it acted oppositely to hyperoxia in many respects.

FLYING STRESS IN RELATION TO FLYING PROFICIENCY

Aerospace Medicine 36:112-116, 1965

ABSTRACT

Postflight urinary determinations were employed for the purpose of evaluating flight stress in 10 pilots who were practicing bombing/strafing maneuvers. Tests were conducted in daytime and at night. Control data were obtained on nonflying days. Urinary determinations included norepinephrine, epinephrine, 17-hydroxycorticosteroids, creatinine, urea, uric acid, phosphate, potassium, and sodium. By the use of this battery of determinations it was possible to appraise flight-sensitivity in sympathoadrenal, adrenocortical, and metabolic activities. The results give good leads for further research and suggest that flying proficiency is high when endocrine-metabolic displacement (physiologic cost) is low. These observations also indicate that stress reactions to flight conform to the General Adaptation Syndrome pattern.

OPERATIONAL APPLICATIONS

F-100 fighter pilots flying 2-hour bombing/strafing training missions gave the following physiologic stress effects:

a. these pilots were generally minimally responsive to the stresses of training flights, suggesting that a concomitant of piloting experience is physiologic adaptation (tolerance for training flight stress).

b. the stress response was greater for daytime missions where their performance was being scored.

c. those pilots performing more poorly had a greater stress response.

In general, it appears that training missions are not as stressful as operational missions.

ENDOCRINE AND METABOLIC CHANGES DURING A 12-HOUR SIMULATED FLIGHT

Aerospace Medicine 36:717-719, 1965

ABSTRACT

Forty-eight young men were studied by means of serial urinary determinations while working in flight simulators for 12 hours. The "flights" began at 0700 and ended at 1900. Postflight values obtained at 2100 were compared with control values obtained at 2100 on the day before the test. Creatinine excretion did not show statistically significant variation with time. All other urinary constituents were expressed as ratios with creatinine. Simulated flight induced statistically significant elevations in urine volume, urea, uric acid, phosphorus, sodium, the Na/K ratio, 17-hydroxycorticosteroids, epinephrine, and norepinephrine. The NE/E ratio fell significantly

OPERATIONAL APPLICATIONS

Inexperienced nonpilots flying a simulated mission showed substantially greater stress responses than experienced pilots flying real missions. It is clear that physiologic adaptation is a characteristic of experienced pilots despite the "real world" stresses they face.

PHYSIOLOGICAL EFFECTS OF AN 18-HOUR FLIGHT IN F-4C AIRCRAFT

Aerospace Medicine 37:1095-1098, 1966

ABSTRACT

Physiological assessment was performed by means of postflight urinalysis for 8 pilots who flew F-4C aircraft for 18 hours. Flight effects were neither numerous nor of large magnitude, nor were the pilots unduly fatigued. The flight-induced, physiological changes included: (1) increased 17-hydroxycorticosteroid excretion, which implies adrenocortical stimulation, and (2) decreased excretion of uric acid, potassium,

OPERATIONAL APPLICATIONS

1. The factors of flight duration, degree of flying difficulty, and amount of flying experience interact to determine the nature of physiologic changes considered to underlie fatigue.

2. Though generally at normal levels, pilots respond to preflight preparations and anticipation of the mission with some enhanced physiologic activity (twice normal).

ABSTRACT (continued)

and urine, which suggests metabolic depression.

(Note: Edward F. Kramer was senior author.)

OPERATIONAL APPLICATIONS (continued)

3. Enhanced steroid activity and some metabolic depression occurred in the later part of this 18-hour F-4C mission but at best the study revealed only low grade fatigue and low grade physiologic effects.

4. There were greater physiologic changes in the less experienced flyers; variations in flight difficulty did not result in variations in physiologic activity.

VALIDITY OF THE HUMAN 17-HYDROXYCORTICOSTEROID/CREATININE RATIO

Aerospace Medicine 38:1095-1098, 1967

ABSTRACT

Short-term and long-term trends for urinary creatinine excretion rate, 17-hydroxycorticosteroid (17-OHCS) excretion rate, and the 17-OHCS/creatinine ratio were investigated, utilizing data obtained from 11 healthy men during forenoon and afternoon periods on 5 consecutive days in each of 4 consecutive weeks. Creatinine excretion rate did not show significant forenoon-afternoon variation, but there was forenoon-afternoon variation ($P < .01$) for both 17-OHCS excretion rate and the 17-OHCS/creatinine ratio, each declining as time proceeded. Using creatinine as the base for 17-OHCS did not cause distortion; instead, there was a statistical gain, as the variance was then lessened. Significant week-to-week variation was detected only in afternoon data, and it was limited to creatinine excretion rate ($P < .001$) and 17-OHCS excretion rate ($P < .01$), both declining progressively over the 4-week test period. Since the 17-OHCS/creatinine ratio did not show week-to-week variation, it was concluded that creatinine acted as a correction factor, eliminating the long-term variation in 17-OHCS.

OPERATIONAL APPLICATIONS

No direct application. This paper is included for the use of the reader in evaluating the use of the creatinine based ratios.

ENDOCRINE-METABOLIC EFFECTS OF UNUSUALLY LONG OR FREQUENT FLYING MISSIONS IN C-130E OR C-135B AIRCRAFT

Aerospace Medicine 39:561-570, 1968

ABSTRACT

Flight-stress appraisal was made by means of a battery of urinary determinations (epinephrine, norepinephrine, 17-OHCS, urea, uric acid, phosphorus, magnesium, sodium, and potassium) for flyers who participated in (a) 20-hour missions in C-130E aircraft (flights from New Zealand to Antarctica, and back), (b) 6-day missions in C-135B aircraft (over-frequent transoceanic and transcontinental flying). The adrenal medulla (judging by urinary epinephrine consistently showed flight-sensitivity but other endocrine-metabolic functions varied in ways indicative of adaptation. With flight circumstances standardized (particularly with respect to time of day), flight effects tended to be reproducible. With crew rest limited to 2 days, recovery from flight-stress tended to be incomplete. Sleep-deprivation and crew position were shown to be factors which modify flight-stress reactions. Eastbound and westbound earth-circling missions did not induce different degrees of flight-stress, as judged by these endocrine-metabolic indices.

OPERATIONAL APPLICATIONS

1. Repeated transport missions result in greater physiologic "cost" for crewmembers than for mechanics and laboratory staff, but the physiologic effects are generally few in number and low in magnitude.

2. There is substantial evidence that transport flyers have achieved some physiologic adaptation to transport mission stresses.

3. Stresses secondary to the mission per se act to enhance physiologic change (displacement from "normal"). Sleep deprivation and crew position produced such enhancement in this study. Pilots were the most stressed crewmembers.

4. There is evidence that some physiologic changes show a slow postmission reversal and that complete recovery was not achieved in two days of postmission rest in these missions; there was also evidence of overcorrection ("rebound") across a 10-day postmission period.

5. Delayed departures increased the physiologic effects of flight stress. Late afternoon and night departures had a similar effect.

6. Time-zone transition did not increase the physiologic effects of flight stress in the multi-day mission.

7. Crews showed an early adaptation to the stresses of a 7-week committed period of repeated missions.

URINARY CREATININE-BASED RATIOS IN RELATION TO SEASON

Aerospace Medicine 39:1048-1051, 1968

ABSTRACT

A group of 12 healthy men was studied over an entire year for the purpose of establishing seasonal baselines for each of a number of urinary variables which are currently being used for assessing flight stress, reasoning that seasonal changes, if any, might predispose toward flight stress or obscure flight effects. One overnight urine specimen per man per week was analyzed for norepinephrine, epinephrine, 17-hydroxycorticosteroids, phosphorus, potassium, sodium, uric acid, urea, and creatinine. As is done in flight-stress studies, creatinine was used as the base to which the other urinary constitutents were referred. The seasonal trends for the sodium/potassium and the norepinephrine/epinephrine ratios were investigated also. On the basis of either monthly or seasonal mean values, the creatinine-based ratios all showed long-term cyclic shifting, as did the two special ratios; however, there was no common pattern of changes. The minimal values for the individual creatinine-based ratios came in various months, as did the maximum values. Flight-stress studies must take into full account such background shifting.

OPERATIONAL APPLICATIONS

No direct application. This paper is included for the use of the reader evaluating the findings of studies from our laboratory. It should be noted that two of our major studies spanned a range of months sufficient to let seasonal variations contribute to the effects to some extent.

ANTICIPATORY STRESS AND FLIGHT STRESS IN F-102 PILOTS

Aerospace Medicine 40:385-388, 1969

ABSTRACT

Pilots of F-102 aircraft were studied during a period of preparation for an unaccustomed flying mission as well as during the actual mission, using a battery of urinary determinations (norepinephrine, epinephrine, 17-hydroxycorticosteroids), urea, phosphorus, magnesium, potassium, sodium, and creatinine). There were four different test circumstances: (a) pretraining briefings dealing with overwater flying and inflight refueling, (b) the first refueling training flight, (c) the first leg of the actual mission (California to Hawaii), and (d) the second leg of the mission (Hawaii to Guam). In each circumstance there was evidence of endocrine-metabolic hyperactivity, which suggests nonspecific stress, but only during the training flight was there an increase in 17-OHCS excretion and hypophosphaturia (the latter condition suggesting hyperventilation, a known specific response to flight). Flight effects during the second leg of the transoceanic flight were less numerous than during the first leg, which suggests that an adaptive change occurred.

OPERATIONAL APPLICATIONS

Fighter pilots facing a demanding new task gave physiologic changes prior to flying as great as those occurring during flying the new mission (inflight refueling); adaptation to this new kind of exercise occurred during the second half of the transpacific deployment.

(Note: George T. Demos was senior author on this paper.)

AEROMEDICAL ASPECTS OF THE FIRST NONSTOP TRANSATLANTIC HELICOPTER FLIGHT: III. ENDOCRINE-METABOLIC EFFECTS

Aerospace Medicine 40:718-723, 1969

ABSTRACT

Endocrine-metabolic appraisal was made by means of urinalysis for all participants (2 crews of 5 men each) in the first nonstop, transatlantic helicopter flight. Serial urine specimens were analyzed for epinephrine, norepinephrine, 17-hydrocorticosteroids (17-OHCS), urea, creatinine, phosphorus, magnesium, potassium, and sodium. Nonspecific stress was evident, as flight caused a 143% gain in epinephrine, a 25% gain in urea, and a 51% reduction in the norepinephrine/epinephrine ratio. It also modified the circadian trends for 17-OHCS and phosphorus. The

OPERATIONAL APPLICATIONS

1. This high-demand, high-hazard mission yielded levels of physiologic activity ranging from moderate to strong, in contrast to C-135 transport missions and F-4C 18-hour missions which yielded levels which were mild to moderate.

2. A specific near-disaster (stallout on the first inflight refueling) resulted in maximum physiologic change for the aircraft commander of that helicopter.

3. Sleep disturbance (reduced quantity and quality, atypical schedule) during the mission increased the

ABSTRACT (continued)

interindividual endocrine-metabolic variability was high.

OPERATIONAL APPLICATIONS

level of physiologic activity, best demonstrated by a strong response from the on-board flight surgeon who slept little.

EXCRETION PATTERNS OF AIR TRAFFIC CONTROLLERS

Aerospace Medicine 42:127-138, 1971

ABSTRACT

Twenty air traffic controllers at O'Hare Airport, Chicago IL, were studied daily during two 5-day work periods. During one of these periods they worked from 1500 to 2300 (evening shift); in the other period they worked from 2400 to 0800 (morning shift). Traffic density (workload) was maximal during the early part of the evening shift, and it was minimal during the early part of the morning shift. Stress appraisal was made by means of urinalysis, using a battery of determinations which included epinephrine, norepinephrine, 17-hydroxycorticosteroids, urea, inorganic phosphate, potassium, and sodium. Control data were obtained from seven members of the biomedical observer team which conducted the study. Urine specimens were collected at the middle and near the end of each work period and also at the end of each postwork period of sleep. Direct relationship to workload was indicated for epinephrine, norepinephrine, urea, potassium, and sodium. Urinary catecholamines provided evidence of sympathoadrenomedullary hyperactivity during each work shift, with full reversal in the "postevening" recovery period and incomplete reversal in the "post-morning" recovery period. Adrenocortical hyperactivity was evident only during the morning shift, and it was late in onset. Relatively high urea output characterized tower work, suggesting high protein catabolism. It persisted to some extent into the postevening recovery period, but not into the post-morning recovery period. Inorganic phosphate indicated stress in the evening work-postwork period, but not in the morning. Potassium and sodium elevations appeared during the evening and morning work-postwork periods. The Na/K ratio became elevated late in the evening work period, but not in the morning work period. In many respects the stress of O'Hare tower work exceeded the stress induced by long or difficult flying operations, a 10-hour test in a flight-simulator (inexperienced subjects), or prolonged decompression.

OPERATIONAL APPLICATIONS

Though this study involves air traffic controllers (O'Hare tower) instead of flyers, it contains findings pertinent to our aircrew studies. The findings are as follows.

1. Physiologic changes were greater on the graveyard shift than on the early evening shift, even though workload was heavier in the latter period.

2. A heavy workload prior to a specific duty period induces physiologic displacement from normal which persists into the duty period.

3. Recovery from large physiologic changes (in this case, early morning duty) starts later and requires longer than from small or moderate physiologic changes.

4. Working at night does not always by itself induce significant changes in the level or cyclic characteristics of physiologic activity. There are other factors to be considered in evaluating this factor.

5. Subjects showed some adaptation to altered work schedules during the 5 days on the changed schedule.

6. Anyone (not just flyers) will respond to heavy workload and concomitant stresses (e.g., schedule changes) by deviations from normal physiologic states. These tower controllers were, in some respects, more stressed than transport flyers under those conditions where the missions proceed in a "routine" fashion.

NEUROENDOCRINE AND METABOLIC RESPONSES TO INTERMITTENT NIGHT SHIFT WORK

Aerospace Medicine 42:156-162, 1971

ABSTRACT

Six men were studied nightly during three cycles of unaccustomer alternating shift work, with each cycle including five days on a morning shift (2400 to 0800) and five days on an afternoon-evening shift (1500 to 2300). Neuroendocrine and metabolic functions were appraised by means of determinations of urinary epinephrine, norepinephrine, 17-hydroxycorticosteroids (17-OHCS), urea, potassium, sodium, and inorganic phosphate. Evidence was obtained of work-associated neuroendocrine and metabolic hyperactivity (nonspecific stress) which was most distinct during the first week of morning work. Relatively high values of urinary epinephrine and 17-OHCS were found during morning periods in the weeks in which there was no morning work, indicating that the

OPERATIONAL APPLICATIONS

1. Work at even a sedentary job induces some physiologic changes.

2. Work during the graveyard shift increases this physiologic activity.

3. Alternating shifts, even when a schedule is maintained for 5 days, further increases this activity.

4. There was some adaptation to the alternating shift stress, but it was not complete, particularly when combined with the graveyard shift stress.

ABSTRACT (continued)

rotating shift schedule itself, not just the night work, acted as a stressor. An adaptive change was evident, since there was a lessening of the physiologic disturbance with each return to morning duty, as judged by urinary epinephrine, norepinephrine, 17-OHCS, and urea. Full adaptation was not attained, for the work-associated changes in potassium and inorganic phosphate reappeared with each return to morning duty, and there were no reductions in the magnitudes of either of these responses. The potassium and phosphate responses to morning work were both biphasic. Morning work consistently induced elevations in urinary potassium, and there were compensatory reductions in urinary potassium in the postwork (sleep) periods. Morning work consistently caused relative hypophosphaturia, and as an after-effect there was always relative hyperphosphaturia.

This historical development carries us up into the early '70s. The monumental contributions to the flight stress problem by Dr. Hale are evident. In the remainder of Part III, we will continue the review of the literature in a more conventional fashion, drawing on multiple source (including Hale). But, before we proceed, two tables (V and VI) are provided to summarize the papers just reviewed. The summary is the sole responsibility of the senior author (Hartman).

TABLE V

Summary of Hale Studies (by "aircraft" type)

Study	General Stress	General Response	Other Factors	Specific Response
B-52	9-12 hour training mission; no unusual stress	Mild	Crew position and/or instructor vs experienced students	No differences
F-100	1-hour training flight	Mild	Hyperventilation (spontaneous) instructor vs experienced students	No steroid effect No differences
F-100/F-104	6-hour overwater mission; many stressors	Strong	Aircraft demands Weather Departure time Airflight refueling	All contribute to total stress effect
Hyperoxia (lab)	100% O_2	Slight depression	Mask discomfort	Moderate (like flying)
F-100	2-hour bombing/strafing mission	Minimal	Being scored performing poorly	Mild Mild to moderate
Drug study	12-hour simulated flight; nonflyer subjects	Moderate to strong	No others	
F-4C	18-hour mission (stimulant in latter parts of mission)	Mild and mixed (some depression, some activation)	Anticipatory stress inexperience	Mild to moderate Moderate
C-130/C-135B a. 1-day missions 20-hour duty C-130 (Antarctic supply)	Long duty day	Moderate	Crew position time course of recovery (2 days vs 10 days) 15-hour delay (2 crewmen)	Pilots, FE's most stressed 2 days = little recovery
b. 6-day missions "Embassy runs" C-135B	round-the-world with intervals of crew rest	Mild	Time zone stress (east vs west)	No difference
c. 7-week missions "exercise" C-135B	Repetitive transport missions	Mild	Time course of recovery (1 week) from chronic stress (7 week exposure)	Some overcorrection (rebound) and incomplete recovery on some measures, but good evidence of adaptation

Study	General Stress	General Response	Other Factors	Specific Response
			Sleep deprivation	Progressively longer, with strong response for those flying during normal sleep periods
			Comparison to mechanics at work	"Cost" of flying slightly higher than the "cost" of other kinds of work
F-102	Transoceanic deployment with inflight refueling; 5.5 and 8 hour legs	Mild to moderate	Anticipation Refueling training flights leg 1 vs leg 2	Mild to moderate Moderate Stress response lower on leg 2
Helicopter	Transatlantic 30-hour mission with refueling	Moderate to strong depending on crew position	Crew position Specific near-disaster sleep pattern disruption (departure 0100)	Moderate (A/C and FE most) Strong Moderate
FAA Tower controllers	Tower workload (8 hours)	Mild	Working graveyard shift	Moderate
			Recovery compounded by graveyard shift	Incomplete
FAA medical test personnel	Observing and recording data	Mild	Night shift work Altered work/rest schedules	Mild to moderate
			Adaptation to work schedule	Some, over 5 weeks
			Recovery from night work	Incomplete on succeeding day
			Individual differences*	Large

*emphasizes need for a large number of subjects or for repeated studies on smaller numbers.

TABLE VI

Summary of Hale Studies (by selected stressors)

	Degree of Response		
	Mild	Moderate	Strong
Work			
workload	These interact to produce responses anywhere from mild to strong		
duration			
altered schedules		x	
sleep disturbance		x	
The man			
crew position	x		x
inexperienced		x	
performing poorly		x	
nonflyers in the laboratory			x
become adapted		x	
time course of recovery	x	x	
The machine			
hard to fly?		x	
inflight refueling		x	
inflight rest facilities		x	
The mission			
training	x		
training; being scored		x	
operational		x	
instructor/student (I/S)		x (no I/S diff.)	
departure time	x	x	
near-disaster			x
highly hazardous, unique			x
frequent repetition		x	
anticipatory stress		x	
time zone transition	x x		
The environment			
insults		x (additive)	
weather		x	
life support deficit		x	
Some undefined combination of several of the above		x	x

Hale, et al. (1) conducted an extensive study of the stress of flying transport missions. The study included double crew missions (continuous flying for 50+ hours, sleep on board the aircraft) and single crew staged missions (discontinuous flying with a typical 12 to 16-hour duty day, sleep on the ground at enroute stations) over essentially the same routes. This paper contains an unusually succinct statement of method and the rationale for the choice of biochemical variables in our standard battery, as follows:

Urine specimens were collected from the crew members at approximately 4-hour intervals (except when prevented by sleep) during flight and postflight periods. For the purpose of assessing anticipatory stress, the first urine collection in each mission covered the 2 hours that preceded departure and the first 2 hours of flight. This overlap into the flight period makes allowance for a lag that urinary stress indices generally show, since urinary changes tend to be about 2 hours behind the physiologic events they reflect.

The physiologic aspects under study all show circadian periodicity under ordinary circumstances; therefore, the urine collections had to be standardized with respect to time of day. To accomplish this synchronization, the different missions were all started in the period of 0800-1000. The physiologic data are most meaningful when viewed in relation to the time zone to which the crew members were physiologically entrained, namely, Eastern Standard Time. The urinary stress indices were expected to show either entrainment per se or entrainment plus stress. To reveal each stress effect, the entrainment effect was to be extracted mathematically by the use of control (baseline) data obtained from unstressed persons.

The stress indices were as follows: norepinephrine, epinephrine, 17-hydroxycorticosteroids (17-OHCS), potassium, sodium, the sodium/potassium ratio (Na/K), and urea. Stressors have stimulatory influence on the regulatory systems of the body as well as on fundamental metabolic activities, particularly the energy-releasing (catabolic) processes. Urinary norepinephrine and epinephrine determinations enabled indirect assessment of activity levels in the sympathetic nervous system and the adrenal medulla, respectively. One phase of adrenocortical activity was quantified by means of urinary 17-OHCS determinations. Urinary potassium and sodium determinations enabled limited appraisal of mineral metabolism, and the Na/K ratio served to indicate whether or not there is a weak or strong regulation of the distribution and/or excretion of these two ions. Urinary urea, a by-product of protein catabolism, provided rough quantification of protein breakdown rates. Urinary creatinine, an index of lean body mass, was used as an adjusting factor, not a stress index. By expressing the individual hormones and metabolites as creatinine-based ratios, the influences of the factors of body size and age are minimized. Moreover, precise timing of urine collections is unnecessary.

The Hale battery is properly described as an endocrine-metabolic battery, tapping two stress-responsive systems. The deviations, averaged across 6 missions and all crew members, are described as follows:

Using only the data that represent the part of the day in which wakefulness is the normal physiologic state, meaningful flight-postflight variation was detected for all of the physiologic variables. Most of the flight values (means for the 9 selected times in the flight period), when expressed as percent deviation from the respective post-flight values, tended to clump around one level. Specifically, the epinephrine and 17-OHCS deviations were +59 and +55, respectively; the sodium and Na/K deviations amounted to +56 and +61, respectively; the norepinephrine deviation was +45; and the urea deviation was +27.

Data for nocturnal variation was consistent with the changes just described, except that relative 17-OHCS excretion rates rose from +4% to +63% for flight day 1 and from +18% to +102% for flight day 2, indicating flight during periods for normal sleep at home station represent a more stressful condition than corresponding daytime periods. Hale, et al. also report that epinephrine excretion rates are higher for aircraft commanders than for other crew members and that elevated excretion rates are readily reversed during post-mission rest but require up to 5 days to stabilize at pre-mission levels.

In staged missions (sleep at en route stations), there was a gradually increasing upward drift of excretion rates, not as pronounced when generically similar missions are flown in 7 vs 5 days. This probably results from greater opportunity to rest and recover. Furthermore, the augmented excretion seen in staged missions is perhaps half of that seen in double-crew, continuous missions (where on-board sleep is poor), further emphasizing the importance of sleep and rest.

Hale, et al., use % deviation and average % deviation in several of the presentations of data. Discussion of this approach is of methodological interest. They state:

Physiologists have long used "percent deviation" from a baseline (control) level for the purpose of crudely quantifying specific physiologic responses to adverse factors acting singly or in combination. Some distortion may result from conversion to percentage, so for ordinary purposes it is better to express the deviations in absolute terms. For the present purpose, the use of percentage was merely expedient, enabling us to combine the results for a number of interrelated physiologic functions. Flight surgeons are thus provided with a single measure of stress. The "mean deviation" for the component stress responses is not necessarily a precise measure of the aggregate physiologic response. The subordinate responses appear to be weighted differentially when expressed in percentage terms, so the derived value for the group of responses may be reasonably correct or even be a somewhat conservative measure. Currently, investigators tend to use single stress measures (for example, urinary epinephrine), but this may over-estimate the stress, for this is a low-threshold response. In the present effort, for example, epinephrine responses were at times not accompanied by 17-OHCS responses, which means that the stressor had not triggered an important high-threshold response.

In a follow-on study of double crew operations in the C-5, Hale, et al. (2), duplicated procedures from the study just cited. Nominal mission duration for the 4 missions was 70+ hours. Numerous procedural difficulties hampered the statistical analysis, and were only partially resolved by treating each mission as "an experiment." Catecholamine (E and NE) and 17-OHCS values were somewhat higher than in the C-141 study just described, leading the authors to state that:

Crew performance in the C-5 flights (and the C-141 flights), however, did not show decrement. This is not unexpected where the task demands are operationally meaningful and the subjects have a very high level of skill. The relatively high values for catecholamines and 17-hydroxycorticosteroids may therefore be interpreted as reflections of compensatory responses which contributed to the maintenance of psychomotor performance. This interpretation is in accord with a current concept of the neurophysiology of alertness, which holds that the reticular activating system, when responding to environmental stimuli, activates the sympatho-adrenomedullary and adrenocortical systems, and these systems in turn feed back in positive manner to the reticular activating system. The role of the catecholamines and corticosteroids is even more clearly demonstrated by studies where performance decrement occurs (less meaningful task demands, lower skill levels).

In general, the results for C-5 paralleled the C-141 findings. Physiologic entrainment remained the primary driver of physiologic activity and the primary determinant of physiologic responsiveness to the complex of stressors in the flight environment. Flight factors had a modifying influence, affecting the amplitude of the cycles, as well as average level, and occasionally causing phase shifts. The data on 17-OHCS particularly illustrated these effects, showing progressive reduction in cycle amplitude, with the descending portion of the cycle showing a shift to the right relative to the baseline curves but nevertheless demonstrating overall maintenance of the basic cycle.

These results are the clearest statement of the kinds of effects this laboratory observes in its biochemical studies of operational flight stress.

Hartman, et al. (3), conducted a study of stress and fatigue in FB-111 crews. Fifteen dedicated missions of 8 hours duration were flown as part of the initial operational evaluation. The standard urinalysis for this laboratory was performed on post-mission samples obtained from 2 crews (4 men). The means (N = 4) were:

Measure:	E, µg*	NE, µg*	17-OHCS, mg*	Urea, mg	K, mEq	N, mEq
Quantity:	1.52	5.09	691	1689	4.65	12.5
(*quantity per 100 mg creatinine)						
% Change:	+90	+40	+136	+56	+51	+54
(% change compared to separate set of pilots on non-flying day)						

Epinephrine, 17-OHCS, urea, and potassium all showed elevations which were statistically significant. These relatively high values indicate physiologic stress of a moderately high degree.

It is appropriate to note, with regard to the previous sentence, that in our laboratory we view stress effects qualitatively in 3 categories:

a. Mild = up to 50% increase in excretion rate

b. Moderate = 50 to 100%

c. High = over 100%

In rare occasions we have seen a fourth category:

d. Severe = over 200%

Storm, et al. (4), conducted a study of stress and fatigue in nonstop, transoceanic tactical deployment. F-4D's deployed from New Mexico to Germany engaged in training exercises for one month and redeployed back to New Mexico. Both the deployment and redeployment phases were studied. Of particular significance were the factors of a full day of work prior to the transoceanic flight, the requirement for 6 inflight refuelings, and the transition through 8 time zones. Ten pilots and 10 weapons systems officers participated in the study. Two periods for baseline (non-flying days) were acquired for comparison purposes. The endocrine-metabolic measures showed the expected elevated excretion rates but only in the mild-to-moderate range (25 to 75% increase). Several changes were statistically significant but the pattern was not systematic. This was consistent with subjective reports, in which the crew members reported that the flights were not particularly stressful. Redeployment was somewhat less stressful than deployment. Time zone transition did not appear to be a problem. On deployment arrival time was 1600 local, allowing the crews to debrief, go to quarters, get a good night of sleep, and arise behaviorally in step with the social environment. On redeployment, departure was at 1000 and was preceded by a full night of sleep, with arrival back at home base at 1600, again an arrival time which facilitated getting back in synchrony with the social environment.

In a study reported by Storm (5), we have an opportunity to examine a different class of inflight work, the acquisition and analysis of surveillance information. Mission crew (as contrasted to flight crews) in an RC-135 were studied, with a variety of measures being obtained, including our biochemical battery. The 17-OHCS data were not analyzed because of some procedural problems. Biochemical changes were small. Neither E nor NE were statistically different from baseline values, K was significantly lower on mission days compared to baseline, the Na/K ratio and urea were statistically different, and Na approached a significantly elevated excretion rate. At times, amplitude was reduced, an effect we discussed earlier. It should be noted that baseline days were working days, so the comparisons were working while flying vs working on the ground. Overall the data showed that mission crews experienced only mild stress, so the biochemical findings were consistent with the other measures. This is an important point--biochemical effects do not lead to "alarmist" findings, in our experience. It also emphasizes the importance of a multi-dimensional assessment of the stress of flying.

Bollinger and Carwell (6) present results of particular interest because their study included a combination of a specific stressor (heat) and the generalized stress of flying tactical aircraft. Pilots and weapons systems officers were studied flying low-level and high-level missions in the summer (August) and the winter (January). Each cell in this 2 x 2 design contained from 26 to 46 aircrewmen. Mean cockpit temperatures were 36.1°C for winter flights and 45.6°C for summer flights depending on crew position. Biochemical data for urea, epinephrine, the ratio Na/K, and 17-OHCS were reported. The biochemical findings were mixed, though epinephrine showed a significantly high excretion rate for low-level summer flights. (E was lowest for high-level winter flights.) These findings were supported by target acquisition scores. The findings were confounded, according to the authors because crewmen spent a substantial portion of the work day in air-conditioned work areas, and because the efficiency of the aircraft air-conditioning system differed for front vs rear cockpit. The study illustrates some problems encountered when a generalized stressor (flying) interacts with a specific stressor (heat).

We shall turn now to a provocative study from outside our laboratory, with somewhat different findings. Frankenconi, et al. (7), report on a study of two groups of highly trained teams operating a ground-based fire direction center in accordance with a simulated combat scenario, under two conditions of sleep deprivation and two expectations of the duration of the "exercise." A urinary biochemical battery reasonably like ours was part of the measurement array. Team I showed elevations in 17-OHCS and total catecholamines when informed that they might have to continue the exercise for a considerably longer period than originally briefed. Team II had depressed 17-OHCS and total catecholamines midway through the exercise (42 h). These authors state that:

(1) "Generally similar effects are noted for sympathico-adrenomedullary and adrenocortical activity"

(2) Biochemical "results are affected by situational uncertainty as well as apparent cumulative fatigue"

(3) Other workers have "concluded that sleep deprivation without physiological or psychological stress did not elicit increments in plasma or urinary indices"

(4) "Subjective fatigue may be associated with a repressive effect on adrenocortical activity"

(5) That "the normal excretory pattern of urinary catecholamines is labile and can be altered by a variety of influences."

We feel that the main lesson here is that biochemical effects can be modified in a number of ways by complex combination of psychological and physiological stressors.

Two review articles are germane to this publication. In the first, Crump (8) reviews stress studies in air traffic control personnel. After distinguishing between "stress" (objective demands made upon an individual) and "strain" (subjective responses to these demands), he goes on to state:

"It is generally agreed that the strain which results from the stresses on the controller is dependent upon the less-easily definable concepts of personality, skills, and aptitude, and intervening variables such as age, experience, and morale. Strain can be manifested in a number of different ways and to varying degrees; probably the most common symptom is fatigue."

He then goes on to discuss other, more chronic, health-related manifestations. With regard to shift work, he takes the position that this aspect of air traffic control work, by itself, has little effect on biochemical/physiological variables, adding that where affects are seen "other factors must account for any measured stress. The most obvious source of stress must, therefore, be workload. There are a number of other factors which may affect physiological stress manifestation. For instance, the effects of cognitive appraisal of stress have been found to affect physiological response. Similarly, stress itself may act as a source of arousal when a controller is experiencing fatigue."

Crump then goes on to discuss two other stressors as factors in ATC work:

"Time is a vital determinant of ATC stress. One consequence of time stress is that as workload increases the controller tends to employ more procedures which are less costly in time, together with a relaxation of certain self-imposed qualitative criteria. The use and effectiveness of such coping techniques or regulating strategies varies between individual controllers and may depend on such factors as age, skill, and experience . . ."

"Another factor related to time is the number of decisions to be made, which becomes a source of stress when a controller's decision-making capacity is stretched to the maximum. Therefore, while routine or overlearnt tasks may be performed adequately, the capacity to deal with extraordinary situations may be reduced or even, sometimes, blocked when the controller is suffering from fatigue, overload, preoccupation, or the effects of age."

"While this type of ergonomic approach may improve our understanding of the causes of stress, it is only related to the controller as part of a system rather than as an individual. As a result, there tends to be a concentration on task elements such as memory and decision-making to the exclusion of other important variables, for example, personality, interpersonal interactions and factors outside work such as domestic and financial problems, all of which may impinge on the controller's performance."

The final point of interest to the readers of this paper goes as follows:

"Evidence from the physiological studies indicates that shift work and workload stress differ between centres but are no greater when compared to normal populations. The psychological work on anxiety and mood largely substantiate these findings. However, these results do not agree with some investigations into the longer-term effects of ATC work . . ."

The second review article, by Miller (9), deals specifically with 17-OHCS findings in military flyers. This extensive review includes 40 selected references, including some from our laboratory reviewed previously in this paper. Miller offers the following summary:

"Increased adrenal corticosteroid secretion occurs in response to flight factors such as danger, duration of exposure, degree of responsibility, and amount of adaptation (experience level). Changes in plasma, urinary and parotid fluid 17-OHCS concentrations have been shown to be an excellent index for the evaluation of stress . . . the story of response to stress of combat in aviators is only beginning to be written."

PART IV

SUMMARY

It is appropriate to conclude on this optimistic note. This has been a wide-ranging paper. We started with the underlying biochemistry and the elicidation of mechanisms, as well as the rationale for selecting some measures in preference to others. We provided an illustrative study, which also gives the reader a glimpse of the utility of amino acid assays in stress research. We reviewed over a dozen studies from this laboratory, displaying not only the historical trend, but also the multiplicity of operational factors which have been evaluated. Finally, we looked at a few more recent studies, more behaviorally oriented, and two reviews.

The behavioral side of this kind of research will be examined in a second paper. Suffice to say, for the time being, that there is reasonable congruence between behavior and biochemistry provided the examination of such a relationship is sufficiently global. Certainly there is comfort to be found in at least one aspect--when behavioral measures indicate no more than mild stress, the biochemical measures agree. We can even go further--when we use global, qualitative terms for the stress of a particular occupation, like "mild," "moderate," "severe," there is considerable support and agreement between the two approaches.

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BIOLOGICAL RHYTHMS OF MAN LIVING IN ISOLATION FROM TIME CUES

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INTRODUCTION

In 1729 de Mairan (1) first reported to the French Royal Academy of Sciences in Paris, that a biological organism (a "sensitive plant") would continue to have a 24 hour rhythm of activity when light-dark entraining stimuli were absent. De Candolle (2), in 1832 first described a free-running rhythm in the same species of plant with a progressive phase advance of 1.5 to 2 hours per day. Subsequent studies have demonstrataed that organisms not entrained by 24 hour "zeitgebers" (time cues), develop daily cycles with periods greater or less than 24 hours (3). Extensive research in animals utilizing a rest-activity measurement has demonstrated that these "free-running" period lengths are species-specific and genetically influenced. When an animal is maintained in constant conditions the new cycle length can be remarkably constant for months to several years (4-7). In 1962, Aschoff and Wever (8) did their studies on three men and three women living for 3 to 19 days in a "deep cellar" in Munich, and first demonstrated that normal man would also maintain a "circadian" activity-rest cycle which would "free-run" with a non-24 hour period when isolated from all time cues. Many subsequent studies have repeatedly confirmed those observations in man (9-12), and have extended the measurements to include body temperature, urinary electrolytest and certain hormonal metabolic products (13-17). In almost all instances of several hundred such studies now performed (18-24) including cave and controlled laboratory environments, the period length of such activity-rest rhythms have been greater than 24 hours typically occurring at approximately 25 hours. Important conclusions have been arrived at such as the change of phase angle relationship between body temperature and rest time (17,25), the ability of different variables to develop independent cycle lengths during free-running (26,27), and the concept of multiple oscillators normally synchronized with each other but which can become desynchronized under free-running conditions(28,29). The importance of "social" entraining rather than light-dark cues for man has been emphasized (30), and in some subjects the ability to develop and sustain very long rest-activity periods, (between 30 and 50 hours in length) has been recognized (19,18,31,13,11).

It has been assumed that the "rest" segment is a sleep period in these studies determined either by "lights out," absence of activity, or "bed-rest" time. Except for the cave studies of Jouvet et al (19), and the short "isolation" studies of Webb et al (22-24), systematic studies of the temporal complexity of polygraphically defined sleep stages have not been reported. Analysis of the previously reported detailed sequential durations of the "rest" (selected lights out) time indicates that a significant day to day variability is present in almost all subjects, suggesting that interval sleep stage amounts and timing may be related to such variability. The previous assumption that "rest" is sleep cannot be made. These events alter biological rhythm cyclic properties and will influence other correlative measured periodic events such as body temperature and hormonal cycles. All previous reported studies have maintained subjects in time-free environments totally isolated from direct human contacts during the duration of their stay. We considered it important to study subjects in temporal isolation but with human social communication. This has the major advantage of allowing us to make certain biological measurements and psychological observations not possible with the previous constraints. Finally, all previous studies of hormonal cycles in temporal isolation studies have only used urinary measurements of derived metabolic products (8,13). In a series of recent studies, (32-36), we had developed methods of obtaining frequent plasma samples, and demonstrated that important relationships exist between hormonal blood concentrations, sleep and sleep stages.

We have carried out detailed and prolonged measurements of sleep-waking function in human subjects for time periods ranging from 25 to 105 calendar days. We measured polygraphic sleep-stage characteristics, minute by minute body temperatures and frequent (approximately 20 minutes) blood sampling for cortisol and growth hormone in normal adult men living in an environment free of all time cues, under entrained, free-running and re-entrained conditions. The results described are part of a comprehensive multi-variable study of the chronophysiology of man living in a time free environment with a non-schedule daily pattern of living.

A special environment was established where the individual subjects lived for many weeks. A three room apartment (study, bedroom and bathroom) was arranged without windows, the walls sound attenuated and a double door entrance, temporal isolation facility (ITF). A closed circuit TV system and voice intercom monitored the subject's activities.

Ten male subjects were individually studied. The first group (3 subjects, FRØ1, 2 and 3) was studied for 15 calendar days and the second group (6 subjects, FRØ4, 5, 6, 7, 9, 10) for 25 calendar days and a single subject (PRØ1) for an extended stay of 105 calendar days (Table 1). No subject had significant psychopathology, medical illnesss, nor were any on drugs. Each subject kept a written daily diary of sleep times for at least 2 weeks and maintained a regular scheduled sleep-wake schedule in accord with their usual habits. After entry in the TIF, an entrained condition of 3 or 4 scheduled 24 hour sleep-wake periods preceded the non-scheduled "free-running" portion of the study. The entrained clock times was determined by the subject's recorded habitual lights off-lights on time at home. The subject was told that his sleep time would be scheduled for certain portions of the study but was not advised of the clock times nor the duration. Following the entrained portion, each subject was told that he could choose to go to sleep and awaken at any time he wishes. He was not allowed to "nap." A decision to go to sleep, therefore, represented the sleep period for that biologic "day." Food was available to the subject on demand as breakfast, lunch, dinner and a "snack." The subject could request any meal type at any time. A set of buttons were available which when pushed was coded on a paper punch tape and indicated the behavior the subject was about to initiate and the elapsed time (to the nearest minute) from the beginning of the study. These behaviors included meal and type, sleep time, awake time, urinate, take shower, defecate, blood sample and exercise. The paper punch tape structured the entire time series of each study.

The subject was totally isolated from contact with all non-laboratory persons but communicated by intercom and direct discussion with selected laboratory staff. The supervising staff members were scheduled on a random basis as to time of day and duration of work-shift to prevent the subject from obtaining a time cue.

The following measurements were made for each subject. (1) Polygraph-Sleep Recording - The interval between the subject's decision to sleep and lights-out with full electrode application was less than 15 minutes. All polygraphic records were scored by standard methods (37).

(2) Rectal Temperature - A rectal thermistor probe was maintained by each subject throughout the entire study except for brief daily periods of defecation. The temperature was automatically recorded every minute on the punch paper tape and a print-out.

(3) Plasma Cortisol and Growth Hormones - A catheter with 3 holes at the tip instead of the usual one, was inserted into an arm vein of nine subjects at the start. At approximately 20 minutes, sampling of blood was obtained. This venous catheter was changed at 2-5 day intervals using alternating arm veins without interrupting the sampling. Subject PRØ1 did not have blood samples obtained. Plasma cortisol assays were performed using the competitive protein binding technique (38). The samples were assayed in duplicate using 25ul aliquot for each assay. HGH was assayed in duplicate from each plasma sample by radioimmunoassay using 20ul of plasma for each assay.

(4) Polygraphic Data Scoring - All scored data was transferred to a computer compatible format and analyzed for total sleep, lights out, and all sleep stages for each lights out-sleep period. The pattern of sleep stage sequences was virualized by a special display program. A quantitative determination was made for a set time perod of the percent of each sleep stage and waking. The result of that analysis was also displayed utilizing a computer plotting technique.

(5) Special Mathematical Techniques and Computer Algorithms - In addition to the usual statistical method of analysis and computer plotting and display routines, several mathematical techniques were created to assist in the analysis of the data. These include a) estimate of period length using a minimum variance fit, b) wave form eduction and c) averaged time locked response.

ACTIVITY-REST CYCLE AND SLEEP STAGE RESULTS

Each of the 10 subjects developed a free-running sleep-wake cycle following the entrained baseline condition. In each case the mean period length was longer than 24 hours (Table 1). The subject population was divided into two types (excluding the tenth subject (PRØ1)). In Type A, (6 subjects - FRØ1, 2, 5, 6, 7, 9) the period lengths during FR averaged between 24.4 and 26.2 hours, whereas Type B (3 subjects - FRØ3, 4, 10) had consistently long periods greater than 37 hours. The lights-out period for the type B subjects ranged from 8 to 20 hours, with an average of 14 hours. Linear regression analysis through mid-sleep times demonstrated a very stable period length, (r^2 0.99 for each). Short sleep periods recurred at a regular phase of the circadian cycle with a period slightly

longer than 24 hours. The long sleep periods began at a phase angle approximately 180 degrees shifted from that of the short sleep periods. Variation in sleep lengths were related to the phase of the ongoing circadian oscillation at which the sleep period occurs. When prior wakefulness lasted more than 1440 minutes, there was a clear increase of sleep length with episodes lasting 600 to 1200 minutes.

Subject PRØ1 lived under "free-running" conditions for 80 calendar days and demonstrated several important features. He maintained a regular free-running period length of approximately 25 hours for the first 30 activity-rest cycles. He then developed an activity-rest cycle pattern consisting of alternating long cycles (36 hours) with a series of shorter cycles (approximately 25 hours). This alternating pattern persisted until it was interrupted by a special light-dark entrainment protocol on calendar day 84. The sleep time continued on an approximately 25 hour period length in spite of the interruption by very long non-circadian periods. These approximately 25 hour self-selected sleep-wake times were therefore entrained to an internal periodic process, which can be considered an "internal zeitgeber." The long sleep periods (600 minutes) occurred at a phase angle approximately 180 degrees shifted from the short sleep periods but in parallel with the same period-length mid-sleep regression line. Analysis of the relationship between length of sleep period and length of prior wakefulness demonstrated that for only 7 out of 16 waking periods lasting greater than 20 hours, did the subsequent sleep period exceed 12 hours in length. However, as was the case for the other subjects, no long sleep period was preceded by a wake period less than 20 hours in length.

There was a rapid phase delay of lights-out and sleep onset of at least 6 hours within 48 hours of the onset of the free-running condition for 8 of the 9 subjects. The ninth subject (FRØ7) delayed his sleep onset by 5 hours on the third biologic day. In addition, all 6 subjects in Group A had a characteristic "scalloped" appearance of the timing of lights-out with a variable cycle of 3-4 days. This could not be explained as a "transient" process related to the onset of FR since it clearly continued throughout the FR condition in four subjects (FRØ2,5,7,9).

The lights-out period in general corresponded with the sleep period for each subject and for each night. However, it was found that at times, there was a short delay from lights-out to sleep onset. The two older subjects (ages 50, 51) (FRØ9 and FR10) consistently interrupted their sleep periods by awakening for short periods during the subjective night as well as remain awake in the dark for periods up to one hour after awakening and prior to signaling "lights on." These waking interruptions were also present during the entrained segment as well. These findings emphasize the importance of defining sleep stages polygraphically when measurements of biological rhythm variables are made.

There was considerable variability in the mean total sleep time (TST) during FR with two subjects averaging 13.8 and 12.8 hours (FRØ3, FRØ4). In spite of this variability in total sleep time per sleep period during FR, the ratio of sleep time to period length only varied between .24 and .35 across subjects with an average of .29. This compared with .30 during the entrained condition. When the entrained ratio was compared to the FR ratio for each subject, it was noted that two subjects with high entrained ratios (long sleepers) (.31 and.32) increased the value to .35 and .34 respectively during free-running, whereas four subjects with the lowest entrained ratios (.27, .28, .29 and .29) (short sleepers) all decreased the ratio to .25,.25,.24 and .25 respectively during FR. The 3 other subjects with intermediary entrained values had little change during FR.

The sleep stage characteristics for all subjects were compared as a function of sequential experimental nights during the three experimental conditions (Entrained, Free-Running and Re-Entrained). The values of REM % of TST were remarkably constant throughout and did not differ significantly as a function of experimental conditions. The stages 3+4% of TST did increase to a small extent from the entrained (27.8%) to the FR (29.8%) condition, especially during the last 6 FR sleep periods. A small average increment occurred during the five re-entrainment nights (32.2%) for 5 subjects.

An interesting result was obtained when comparisons were made for REM% of TST, by subject and by experimental condition. There was considerable variability in REM sleep across subjects (range 15 to 30%), during the entrained period. However, the intra-subject variability was very small as a function of experimental conditions. This was not the case for stages 3+4 since both the inter and intra-subject variability was similar in all 3 experimental conditions. These results indicate that each subject maintained an individual control of REM% of sleep time which was independent of the entrained or free-running state. This does not apear to be the case for stages 3 and 4 sleep.

Three subjects (FRØ, 4 and 10) consistently had long sleep periods associated with long sleep-wake cycle lengths. There were a total of 26 sleep perids lasting 12 hours or longer. These long sleep periods differed from the short sleep periods. The timing of the onset of these long sleep periods occurred at a different phase of the subjects circadian temperature rhythm (130 degrees to 270

degrees, 0 degrees = mid-trough) than the onset of the short sleep periods (270 degrees to 120 degrees). In addition, during the long sleep episodes, sustained stages 3 and 4 sleep would characteristically occur between 12 and 18 hours after sleep onset. However, the first 4 hours of the long sleep periods did not differ significantly in regard to the characteristic timing and amount of Stages 3 and 4 sleep seen under entrained conditions. Thus despite normal amounts of 3-4 sleep present at the onset of these long sleep periods, stage 3-4 would reappear after 12 to 16 hours of sustained sleep. Although occasional awake episodes interrupted these long sleep times, (especially for subject FR10) they were not sufficiently long to explain the reoccurrence of stages 3 and 4.

Another characteristic difference between the long and short sleep periods was the timing and amount of REM sleep within the first 3 hours after sleep onset. All of the sleep periods which had a very small REM latency (20 minutes) were short sleep periods during the FR conditions. The mean REM latency (sleep onset to onset of first REM period) clearly decreased for 9 of the 10 subjects (FRØ9 was the exception) comparing entrained to the free-running condition. A partial recovery took place during the re-entrainment conditions. In addition, the mean total minutes of REM sleep in the first 3 hours of sleep increased for 8 of the 9 subjects (subject FRØ9 excepted) between entrainment and free-running). However, during re-entrainment these values did not return to baseline. The timing and amount of REM sleep during the first 3 hours after sleep onset in PRØl was determined during the free running condition when he had the alternating long and short sleep-wake cycles. All the nights with a short REM latency (10 minutes) and the nights with more than 30 minutes of REM sleep in the first 3 hours except one occurred within 90 degrees of the nadir (0 degrees) of the circadian temperature rhythm. In addition, for 12 REM onsets which occurred within 10 minutes of sleep onset, 11 occurred within 60 degrees of a specific phase (mid-trough) of the circadian temperature rhythm.

An analysis was made of REM-Non-REM sleep cycling during the different experimental conditions. The latency in minutes from sleep onset to first mid-REM period, first mid-REM to second mid-REM, etc. was determined. It was found that except for a shortened latency from sleep onet to the mid-first REM period during free-running there were no differences in cycle lengths as a function of experimental condition. There was a consistent decrease in cycle length for the fourth and fifth cycle for each condition. The sleep cycle length remained stable ($\bar{x}$ 85 minutes) for up to 11 cycles during the long sleep periods (10 hours). Thus there is no evidence that sleep stage cycle length is altered by the increased sleep-wake period length during free-running conditions. In addition, previous ported results (39) of a stable but slightly reduced cycle length when sleep is extended, are confirmed by these data for those long sleep periods which extend from 10 to 20 hours.

BODY TEMPERATURE RHYTHM

The mean core (rectal) temperature for all subjects as a group was essentially the same in all three conditions. However, for each subject in Group A there was an increase in the mean temperature during FR whereas there was a decrease for each subject in Group B. During re-entrainment, the mean value of most subjects had returned to that of the entrained section.

During the entrained condition, the rectal temperature curve (values obtained every minute) demonstrated the well described sharp fall (1-2 degrees F) following sleep onset (17,15,40). A small decrease in temperature typically occurred at approximately 3 hours before sleep onset with a sharp elevation of temperature at the end of the sleep period. During "Free-Running" for all subjects in Group A a change in both phase and shape of the curve occurred (25). The temperature began to decrease 6 to 8 hours prior to sleep onset. At the time of choosing sleep the body temperature was close to the lowest value of the circadian rhythm. An additional small fall of temperature (0.5 degrees F) took place just after sleep onset during FR. During re-entrainment, the curve was similar to that found in the entrained condition, although it had not fully established the original shape. In two subjects with long sleep periods a wave shape pattern was educed during the FR condition at the same period length as the sleep-wake cycle (39.1h (FRØ3) and 37.6h (FRØ4)) and one at a period length near 25 hours (24.6 (FRØ3) and 24.7 (FRØ4)). The curves at the long period lengths, resembled those in the entrained conditions (normalized to 360 degrees), both in shape and phase relationship to the average sleep time. These results suggest that the approximately 40 hour component in the temperature rhythm was a "response" to sleep onset in the sleep-wake cycle rather than an independent self-sustained rhythm. In each of these cases (FRØ3, Ø4, 10) as mentioned above there was also an approximately 25 hour component in the circadian temperature rhythm. The amplitude was small (approx. 1 degree F) compared to the entrained condition (approx. 2.0 degrees F) and compared to subjects FR with a sleep-wake cycle of approximately 25 hours (1.5 to 2.0 degrees F).

Subjects PRØl had a small drop of overall mean temperature in the entrained compared with the Free-Running Condition (98.42 degrees to 98.17 degrees F). He had a circadian temperature period

length of 25.0 hours during the first 30 free-running days which shortened to 24.55 during the next 50 days.

PLASMA CORTISOL PATTERNS

We have been successful in obtaining plasma samples at 20 minute intervals for each of 9 subjects during the experimental conditions (FRØ1 - FR10; total samples obtained, 15,000).

During the entrained condition all subjects demonstrated the normal episodic pattern of secretion during each 24 hour period. The typical pattern was evident with very low values just prior to and during the first 3 hours of sleep, followed by a series of secretory episodes during the latter half of the night. An intermittent, episodic secretory pattern was present during the waking day (32,33). The educed wave form for the entrained condition also demonstrated this circadian pattern of hormonal activity. During the free-running condition, a clear phase advance and change of wave shape of the circadian cortisol curve was evident for subjects FRØ5, FRØ6, FRØ7. The nadir of the curve was now occurring 100 to 150 degrees in advance of that during entrainment with respect to sleep onset. In addition, the average rate of rise of cortisol after the low point was much more gradual, nevertheless reaching the highest value at approximately the same time, namely the end of the sleep period.

It is important to emphasize that the process of wave form eduction produces an overall mean curve at a defined period length and therefore will "smooth out" specific point related events. Examination of the cortisol time series itself revealed that on many "free-running" days, especially with a progressive phase delay, cortisol would be secreted just before sleep onet and then would stop being secreted for several hours just after sleep onset.

The duration of this inhibition was 1-3 hours at the beginning of sleep and did not continue throughout sleep. Sleep onet was therefore used as a "zero" point about which a time locked response cortisol curve was obtained in several subjects. All demonstrated a clear pattern of cortisol inhibition following sleep onset. Therefore during the free-running condition a phase advance of cortisol occurred in relation to the sleep period, the overall wave shape was changed and a specific sleep related inhibition of cortisol secretion was apparent. During the re-entrainment condition, a similar pattern was evident since the phase relationship between the cortisol rhythm and sleep had not yet returned to normal. Therefore the subject was going to sleep when the concentration of the hormone was high. Evidence that this sleep related inhibition may well be operative even in subjects habitually living on a 24 hour routine may be deduced from the data obtained during the transition from the entrained to the free-running condition on those nights when a phase delay of sleep onset on a single night exceeded 2-3 hours. On those occasions, the hormone was released just before sleep and then immediately inhibited after sleep onset.

It thus appears that the episodic pattern of cortisol secretion is influenced both by an endogenous rhythmic component, not directly related to the behavioral sleep-wake cycle and a specific sleep (or lights out in bed) related component. Whether other daily behavioral events such as sleep onset, lights on, out of bed, meal time, etc. are also determinants of the episodic pattern will require further detailed analysis of the extensive data we have obtained in these studies.

GROWTH HORMONE PATTERNS

HGH was found to be secreted in an episodic normal manner in all subjects with the typical pattern of brief episodes of secretion (1-2 hours) followed by long inter-episode intervals (6-12 hours) with no HGH detectable (41). The hormonal concentration was less than the overall average (1 ng/ml) 80% of the time. A striking highly consistent relationship between sleep onset and an episode of HGH secretion was found for all 3 experimental conditions for all subjects (43,44,34). A clear secretory episode followed sleep onet approx. 90% of the time. Thus far no independent rhythm of HGH could be detected but further analysis for an ultradian, or specific behavioral related event will be searched for.

SUMMARY AND CONCLUSIONS:

We confirm previous studies that biological rhythms of human beings free-run at period lengths greater than 24 hours, typically at approximately 25 hours, but with individual variability. After a variable time of free-running, many normal humans will spontaneously develop "long" biologic days (35 hours) and often these will alternate with "short" days, (approximately 25 hours).

During free-running, although the sleep to total time ratio remains remarkably constant (approx. .30), short sleep periods (10 hours) occur at a specific phase angle of an internal circadian rhythm

(e.g./body temperature) whereas long sleep periods (12 hours) take place approximately 180 degrees out of phase with the short sleep periods, but maintain the same period length. Sleep stage organization changes during "free-running" such that REM sleep advances to an earlier time during sleep, with a shortened REM latency (occurring at times less than 10 minutes after sleep onset) and increased amounts during the first 3 hours of sleep. The total REM amount and percent for the entire sleep period however remains constant. The timing and amount of REM sleep following sleep onset also occurred preferentially at a specific phase of the circadian temperature cycle, strongly supporting the concept that certain sleep processes in the brain are endogenous biological rhythms. The stage 3-4 sleep distribution remains essentially the same during the three experimental conditions. During the long sleep periods (12 hours), stages 3 and 4 recur following 14 to 16 hours of sleep indicating that these stages are not dependent on length of prior waking but may be related to length of prior elapsed time.

The Core (rectal) temperature develops an approximate 25 hour rhythm in humans during free-running, but the wave-shape changes such that a phase advance (6-8 hours) of the falling phase develops in relation to the onset of sleep. The subject usually then selects sleep when the circadian temperature approaches its lowest value of the day. In addition, at the time of sleep onset (lights out and in bed) there is an additional drop of body temperature. This is especially noted when sleep onset occurs when the immediately preceding core temperature is high (e.g./for the long sleep periods).

Measurements of plasma cortisol throughout each study demonstrated two components of the circadian cortisol curve during free-running. One component had a phase advance (6-8 hours) relative to sleep onset whereas a second component clearly followed sleep onset. This second component appeared to be a sharp inhibition of cortisol secretion during the first 2-3 hours of sleep interrupting a rising phase of the hormonal curve. Growth hormone secretion, on the other hand, was intimately related to the first 2 hours after sleep onset. A sharp episode of hormonal secretion occurred just after sleep onset for almost all sleep periods. No other independent circadian rhythm of GH has been detected thus far.

These and previous reported studies emphasize the lawfulness of biological rhythm functions in man and demonstrate the importance of the methodology using temporal isolation and the analysis of "free-running" rhythms to unravel these chronobiological processes.

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SLEEP DISTURBANCE AND PERFORMANCE

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SUMMARY

While the type of sleep obtained does not appear to be an important factor in performance, the time of day the sleep is obtained and when the performance occurs are very important. Time-of-day effects may be a more crucial factor in performance than the preceding sleep patterns. While the effect of total sleep loss becomes pronounced after 48 to 60 hours, consistent performance decrement following reduced sleep or fragmented sleep has not been found. Feelings of fatigue, however, are a consistent finding in all sleep-loss studies. A significant relation between sleep quality (good vs. poor sleep) and performance is not easily found. The deleterious effect of hypersomnia, especially that due to narcolepsy, has been documented.

INTRODUCTION

While it was a relatively simple task to talk yesterday about sleep disturbances, detailing the consequence of disturbed sleep on performance is more difficult. Although it is a well-accepted conclusion that a good night's sleep is crucial if one is to be "at his/her best" the next day, consistent quantitative data detailing the detrimental effects of disturbed sleep are not readily available. Insomniacs feel that even a single night of disturbed sleep will impair their functioning the following day.[1] Significant performance impairment has been reported following acute sleep reduction in normal subjects,[2,3] but others have reported no performance impairment during gradual sleep reduction.[4] While it is difficult to present clear and consistent effects on performance, fatigue is a concept that appeared in sleep-disturbance studies from all areas. When referring to the consequences of total sleep loss, a sleep deficit, or to fragmented sleep schedules, fatigue is a unifying, though over-simplified, concept. Fatigue is an inevitable consequence of sleep loss. It is what caused our subjects to discontinue their gradual sleep reduction, as their total sleep time approached 4 to 5 hours. Fatigue is the complaint after a jet flight across several time zones, it is what shift workers complain about, and "always being tired" is a common complaint of the insomniac. The complaint of fatigue may be the first indicator of disturbed sleep and it usually precedes performance decrement.

Fatigue as a Concept

Klein, Brüner, Ruff, and Weggman,[5] in their discussion of the importance of fatigue, emphasized that terms like "workload" and "stress" should not be used as synonyms for fatigue. For them, stress is a part of a workload, and workload is a cause of fatigue; hence, fatigue is a consequence of stress and workload. Klein and his associates have emphasized the interactions of the various stressors, the difficulty of obtaining an absolute measure of fatigue, and the problem of establishing the relative weights to assign to the various factors contributing to fatigue. As Klein *et al.* so aptly commented, the unraveling of cumulative fatigue into its component parts is extremely complex.

When considering the effects of sleep disturbances, factors other than performance should be taken into account and examined in some detail. Recent studies have revealed that performance degradation following sleep loss might remain small, not because sleep deficit has only a minor influence on task performance but because task performance is kept at a high level by greater compensatory efforts. As shown in the various studies by Hale and his associates,[6-10] sleep-deprived subjects mobilize and expend a considerable amount of biochemical, physiological, and behavioral resources to maintain their presleep-loss level of performance. "Physiological cost," not performance decrement, is viewed by Hale and his associates as an operationally more meaningful measure of sleep-deficit effect. Naitoh,[11] in a review of sleep-deprivation effects, also stressed the importance of other than performance measures in the study of sleep deprivation. Expressed in terms of an analogy offered by Teichner,[12] task performance would be similar to rectal temperature with respect to its relative constancy, in that rectal temperature does not show a large change even under exposure to an ambient temperature of 100°F. This is not because body temperature is insensitive to high ambient temperature, but because of its being placed under the control of other body-temperature-controlling activities, such as an increased sweat rate, a raised skin temperature, and an increased peripheral blood flow. As the relative constancy of body-core temperature is achieved by compensatory physiological activities, so is the relatively high level of task performance achieved by compensatory expenditure of biochemical, physiological, and behavioral resources. More attention, therefore, must be given to the physiological cost of sleep deficit. Levi[13] has recently suggested that repeated exposures to sleep loss and stress effects might ultimately result in the disease of stress. While "costs" imply that the physiological changes as a result of sleep deficits are detrimental and may contribute to the "disease of stress," there are little data to indicate that the changes reported by Hale and his associates, or those from the extensive studies of Levi and his colleagues, have long-term detrimental effects.

Circadian Influences

In the evaluation of performance, the circadian influence must be taken into account. Other participants in this lecture series will be discussing the biological rhythms, so I will only briefly note the importance in controlling for time of day in performance studies. A recent report from our laboratory detailed the circadian variation in performance, subjective sleepiness, sleep, and oral temperature during an altered sleep-wake schedule.[14] Thirty-eight male students, aged 18 to 22, participated in the study. Following one baseline sleep night, 8 subjects underwent a 60-minute sleep/160-minute wake schedule for 40 hours. Ten subjects pedaled a stationary bicycle (Ex group) and 20 subjects rested in bed (Bdr group) during the same 1-hour interval that the nap subjects were allowed to sleep. Neither of these latter two groups was allowed to sleep during the 40-hour period. There were ten 1-hour treatment sessions during the 40 hours: at 0817, 1149, 1528, 1851, 2243, 0209, 0546, 0942, 1348, and 1656 (times based on mean of all subjects). The Stanford Sleepiness Scale immediately preceded and followed each session, followed by the Wilkinson Auditory Vigilance Test (40 minutes) and the Wilkinson Addition Test[15] (40 minutes). Oral temperature readings were taken approximately midway between sessions.

All sleep recordings were scored according to the Rechtschaffen and Kales Manual.[16] A more detailed description of the experimental design and the recording techniques has been presented elsewhere.[17-18] We were not surprised to find that the total sleep time (TST) was greater when the nap fell when body temperature was low, that the subject reported feeling sleepier at this time, and that there were more errors of omission on an auditory vigilance task (Figure 1). We also found, as illustrated in Figure 1, that the longer naps (TST) were followed by poorer performance. The 15-minute nap at 1851 was followed by few vigilance errors and lower ratings of sleepiness. This pattern of poor performance and sleepiness was also found for the group of subjects who pedaled a bicycle for the hour our nap subjects slept, and for the third group who lay in bed and "rested" but were not allowed sleep for the same hour. For the sake of simplicity, the times of day given in Figure 1 represent the <u>starting time</u> of each treatment session. Since oral temperature (OT), auditory vigilance task (AEO), and Stanford Sleepiness Scale (SSS2) were taken <u>following</u> each treatment session, the actual times of day these measures were taken lie about midway between the time given. Thus these measures in all three groups, despite the differences in the sleep-wake schedule and amount of sleep loss, maintained the same relationship.

To determine if the consistent relation among the three variables was due solely to the diurnal rhythm common to them or to effects independent of the circadian cycle, the correlation between any two variables was calculated with the circadian effect removed. It was possible to do this by combining the three groups and obtaining the between-subjects correlation <u>within each epoch</u>; thus, the effect of time of day was held constant. This approach is exemplified in a study by Rutenfranz, Aschoff, and Mann.[19] For example, the OT reading at epoch 1 (0817) was correlated with the SSS2 rating for epoch 1 across the 38 subjects, scores for epoch 2 were correlated, and so on through epoch 10. Thus, a total of 30 correlations were calculated; 10 each for OT and AEO, OT and SSS2, and SSS2 and AEO. Because there were 30 correlations performed, the multistage Bonferroni procedure[20] was used. This is a conservative test which takes into account the number of statistical tests performed. The critical value of r at the 0.05 level was 0.495 with the Bonferroni procedure, and 0.313 without the correction. The results of the between-subjects analysis holding time of day constant, thus removing the circadian effect, are presented in Table 1. Only 2 of the 30 correlations were significant without the correction for multiple tests; none of the correlations were significant with the correction.

Our results indicate that there is no direct causal effect among temperature, performance, and sleepiness independent of the circadian rhythm. The results of the analysis holding time of day constant showed that knowledge of the level of one variable at a particular time of day provides little or no information as to the absolute value of any other variable at that time. Thus, one could not predict a sleepiness rating or number of errors from knowledge of the OT at a particular time of day. Changes in OT across time, however, would indicate whether performance and sleepiness are increasing or decreasing, as shown by the significant correlations among the variables across different times of day. Thus, the synchronous variation in these variables was due

TABLE 1. Correlations of oral temperature, sleepiness, and performance holding time of day constant.

Measure	E1 (0817)	E2 (1149)	E3 (1528)	E4 (1851)	E5 (2243)	E6 (0209)	E7 (0546)	E8 (0942)	E9 (1348)	E10 (1656)
OT, AEO	0.04	-0.12	-0.01	-0.19	-0.26	-0.04	-0.22	-0.01	-0.20	-0.28
OT, SSS2	-0.18	0.12	-0.13	-0.01	-0.35[a]	0.06	0.17	-0.11	0.18	0.10
SSS2, AEO	0.27	0.26	0.21	0.28	0.34[a]	0.12	0.28	0.21	0.29	0.24

[a]Significant at the 0.05 level without correction for multiple tests (none of the correlations were significant with the correction) (from Moses *et al.*[14]).

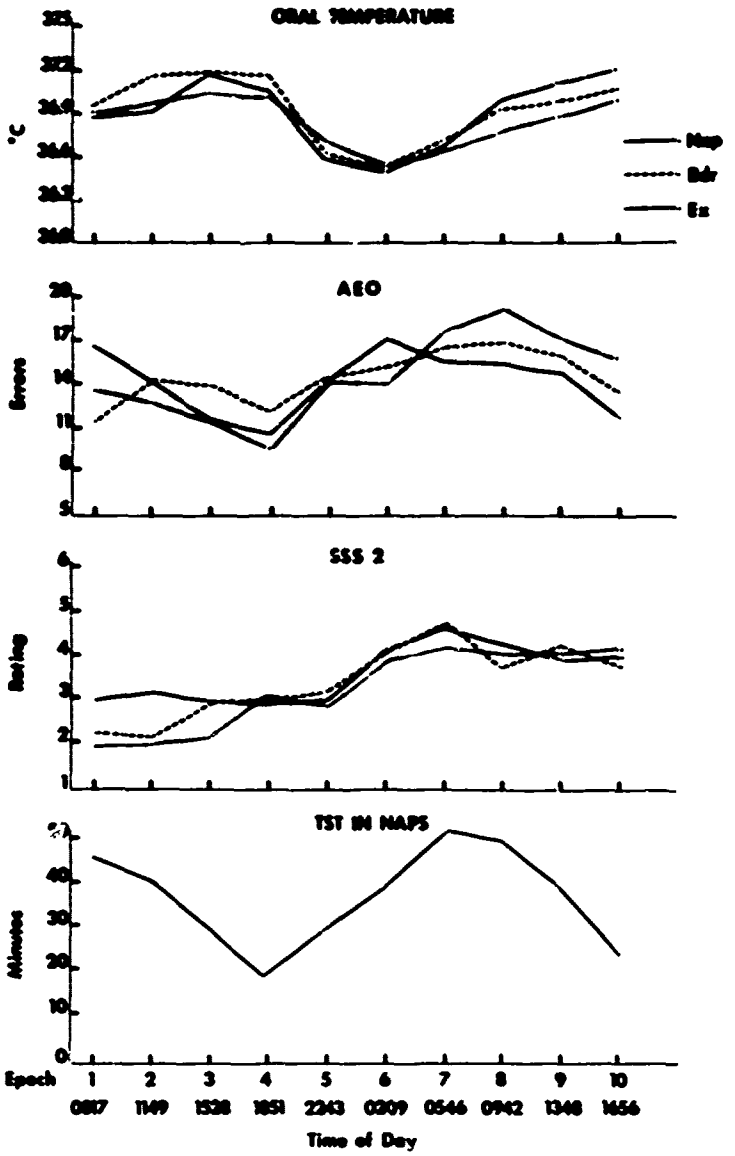


Fig. 1. Distribution of oral temperature, performance, self-rated sleepiness, and sleep time in naps during 40 hours (from Moses *et al.*[14]).

primarily to their common link with time of day. These results support the findings of Rutenfranz *et al.*,[19] who found significant correlations in temperature and reaction time across times of day, but no correlation between the two variables between subjects when time of day was held constant.

Rutenfranz *et al.*[19] took their analyses a step further by also performing within-subject correlations holding time of day constant (the afore-discussed study lacked sufficient data for this type of analysis). Rutenfranz *et al.* found no significant correlations between temperature and reaction time when time of day was held constant, providing further evidence that temperature and performance were not causally related.

The results support the studies cited previously in demonstrating that relatively short-term alterations in the sleep-wake cycle and/or sleep loss do not disrupt rhythmicity in oral temperature, performance, or sleepiness. Further, the interrelationship of these measures in the present study was similar in the three groups, despite the wide differences in the subjects' activities during the 40-hour period.

From the analysis of the Nap group alone, it would appear that sleep itself increased sleepiness and was detrimental to performance, since naps on which the most sleep occurred were followed by the highest sleepiness ratings and the poorest performance. The Ex and Bdr groups, however, also reported highest sleepiness and had the worst performance at the same time of day as the Nap subjects, indicating that the circadian variation in these measures was primarily responsible for what appeared to be a detrimental effect of sleep. These results are in contrast to a study by Carskadon and Dement,[21] who reported that slow wave sleep (SWS) in naps was associated with increased sleepiness ratings and rapid eye movement (REM) sleep with decreased sleepiness.

The strikingly similar CT curves in the three groups further demonstrate the pervasiveness of the 24-hour rhythm, despite the differences in experimental treatment. Thus, sleep and specific sleep stages had little, if any, effect on performance and sleepiness; the primary source of variance in the relation of TST and sleep stages, oral temperature, performance, and sleepiness was the circadian rhythm.

Rutenfranz *et al.*[19] and Moses *et al.*[14] controlled for circadian influence by holding time of day constant in their statistical analysis. In an effort to control for the circadian influence, Klein and his associates[22] have used the "normal night minimum of activation point" as a reference level. Performance, psychological, and behavior data from various times of day and during various phases of the study are referenced to this "standard" baseline reference point.

Sleep-stage Deprivation

In my lecture yesterday, I indicated I was not going to discuss stages of sleep because there had been no convincing body of data that indicated that the amount of any stage of sleep, be it REM, stage 2, 3 or 4, had any effect on waking behavior. To support this statement, I briefly mention our work on sleep-stage deprivation.

In Experiment 1, performance measures on addition, memory, and vigilance tasks, measures of affect and mood, and indices of autonomic and central nervous system activity were obtained from 16 Navy enlisted men, ages 17 to 21. After 4 baseline days, 12 subjects were totally sleep-deprived for 2 nights. Total sleep deprivation was followed by either (1) uninterrupted recovery sleep for 5 nights (the control group, N = 4); (2) 2 nights of REM deprivation and then 3 nights of uninterrupted recovery sleep (this REM-deprived group was allowed all NREM sleep, N = 4); or (3) 2 nights of SWS deprivation and then 3 nights of uninterrupted sleep (this slow-wave deprived group was allowed all stages of sleep but stage 4, N = 4). The remaining 4 subjects were allowed approximately 8 hours of uninterrupted sleep every night during the 2-week period.

Stage 4 deprived subjects were aroused when the EEG indicated SWS. At the first appearance of a stage 1 EEG pattern with rapid eye movements, subjects to be deprived of stage REM were aroused. The remaining 4 subjects were allowed approximately 8 hours of uninterrupted sleep every night during the 2-week period. Both uninterrupted and interrupted recovery sleep were limited to the period between 2200 and 0600. A rebound effect for both REM and SWS was present for the appropriate groups on the first night of uninterrupted sleep, indicating that the selective sleep-stage deprivation was effective.

Performance on a Continuous Counting task, the Wilkinson Addition Test, Auditory Vigilance, X Cross-out Test, Williams Immediate Word-recall Test, and a serial addition test (plus 7) deteriorated significantly during total sleep loss. Fewer signals were detected on the vigilance task, fewer additions were attempted, fewer words were scanned on the cross-out test, and fewer words were recalled on the memory test. Accuracy in all tasks tended to decrease as sleep loss increased.

All subjects improved after the first night of recovery sleep, but there was no significant difference in the amount of recovery for the three kinds of recovery sleep. The illustration of performance on the Continuous Counting task presented in Figure 2 is representative of the results for all the tasks. Similar results were obtained on mood scales. After 2 nights without sleep, our subjects, not unexpectedly, were more fatigued, depressed, and hostile, and less energetic, happy, and friendly. As with the performance tasks, the return to the predeprivation psychological states was the same for all subjects regardless of the type of recovery sleep.[23] Our measures of autonomic and central nervous system activity also showed no significant differences between the REM and stage 4 deprived groups.

The results from our first stage-deprivation study offered no support for the belief that stage REM or stage 4 had unique recuperative value. Following sleep loss, the amount rather than the type of sleep appears to be the most important factor.

Still not ready to abandon the idea that deprivation of stage REM or stage 4 would have deleterious effects, in our next study we hypothesized that perhaps deprivation of either of these two stages of sleep would lessen a person's ability to tolerate the stress of total sleep loss and perhaps other stressors. Although we were now cautious enough not to predict overtly which stage deprivation would be more debilitating, we still covertly expected the subjects deprived of stage 4 to show the most decrement following total sleep loss.

Fourteen Navy enlisted men, ages 18 to 21, participated in this study. After 3 nights of baseline sleep, 7 subjects were deprived of REM sleep and 7 were deprived of stage 4 sleep for 3 nights. Both groups were then deprived of total sleep for 1 night and then allowed 2 nights of recovery sleep. Sleep-stage deprivation was produced by arousing the subjects, as in the first experiment.

The physiological and performance measures obtained in Experiment 1 were recorded again, but other tests were added to obtain measures of both long-term and short-term memory, measures of reading speed and comprehension, and additional ratings of affect for feelings of happiness, anger, fear, depression, and arousal. A Rorschach measure of conceptual consistency, conformity, and looseness was also included.[24]

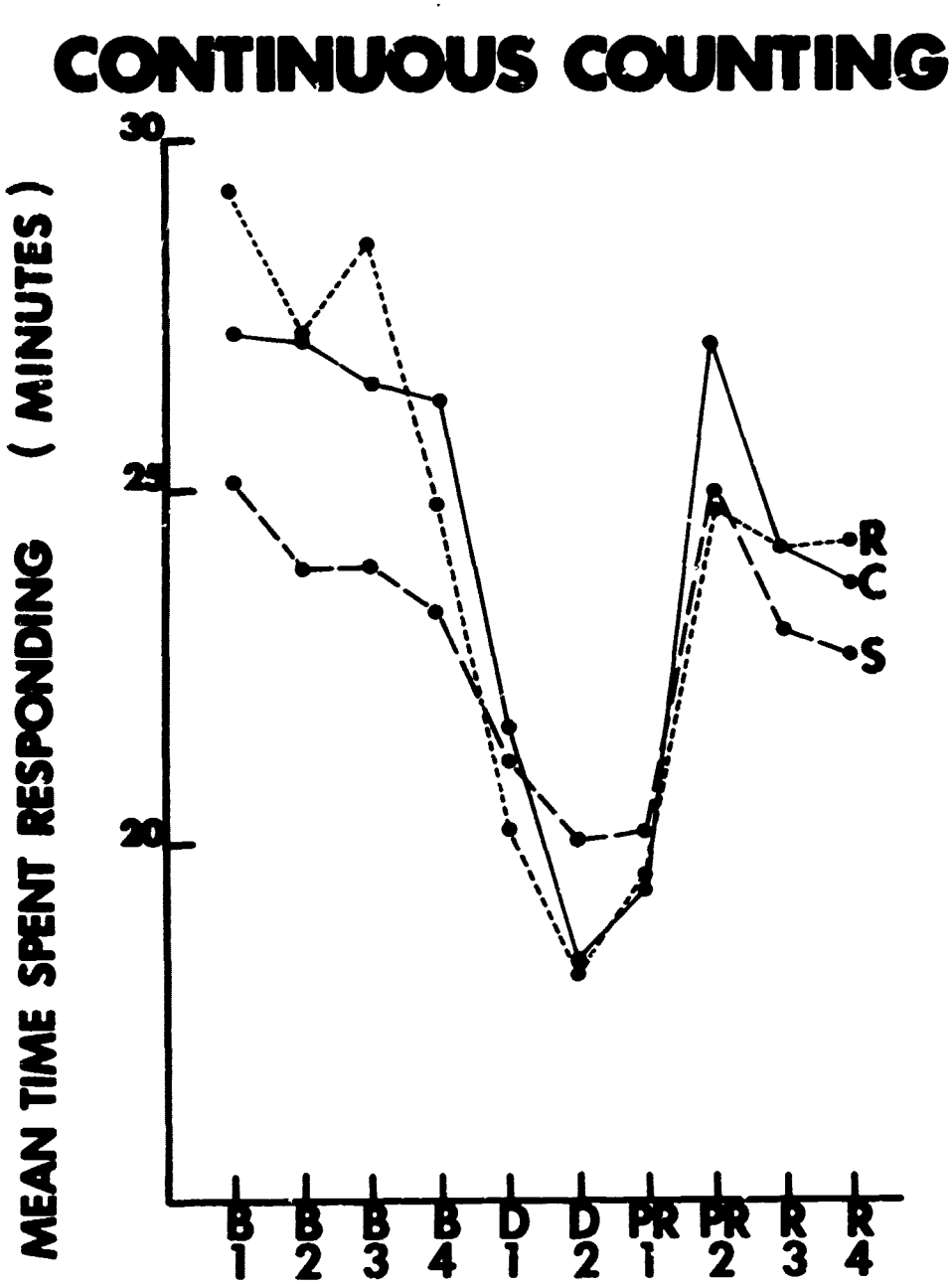


Fig. 2. Performance on a Continuous Counting task during baseline (B), following total sleep loss (D), and following partial (PR) and total recovery (R) sleep. The S group was deprived of stage 4, R group was deprived of REM, and C group was allowed all sleep during PR_1 and PR_2 nights.

Three nights of REM and stage 4 deprivation produced minimal changes in our subjects, and what changes were present were similar for both groups. Following the night of total sleep loss, the expected decrement in the tests was evident and, again, the decrement was the same for both groups. Prior deprivation of stage REM or of stage 4 did not potentiate the effect of total sleep loss. While we know people cannot function effectively without sleep, they perform quite well without ever entering into, or receiving only limited amounts of, all stages of sleep.

With this general introduction, I would like to now discuss what we know about the effects of the various types of sleep disturbances I discussed yesterday.

Externally Caused Sleep Disturbances

Although there is always an internal factor that interacts with external causes, I assume you will all agree that disturbed sleep due to noise, temperature, or variations in work-rest schedules should not result in the diagnosis of a sleep disorder and fall into the medical area. The complaint of inadequate sleep may be similar to that heard in medical offices but, as I noted yesterday, perhaps the supervisor or shop steward would be the first person whom the disturbed sleeper should see.

Noise. If noise has an effect on sleep, it is to cause awakenings or shifts to lighter stages of sleep. There is a general belief, and I imagine supported by the personal experiences of most of you, that frequent sleep arousals due to noise would result in measurable behavioral effects during the following day. This commonly held belief, however, has been hard to document. Kramer, Roth, Trindar, and Cohen[25] exposed 6 males, ages 20 to 70, to 9 consecutive nights of either continuous, impulse, or a combination of the two noise types, with inconclusive results as to an effect on any of six performance tasks. Herbert and Wilkinson,[26] to investigate the effects of sleeping in a noisy environment, studied 10 subjects who slept for 5 nights each. On one of the 5 nights, pairs of randomized clicks at one of four intensities, 65, 75, 80 and 90 dBA, were presented through a speaker at the foot of the bed. On performance tests, which lasted all day, Herbert and Wilkinson found that the effects on performance on days following noise-disturbed sleep were relatively small and confined to the early part of the day. This early-morning effect, they felt, was due to lower motivation and perhaps a time-of-day effect. During sleep, the noise produced an increase in stage 1 and in time awake.

In the longest exposure period studied, Johnson, Townsend, Naitoh, and Muzet[27] studied 20 Navy enlisted subjects, mean age 20.7, during a 30-day, 24-hour exposure to a 660 msec click, 3.5 Khz, at 80, 85, and 90 dB SPL, for 10 days each. The clicks were separated by 22 seconds. The noise-exposure period was preceded by 15 baseline days and followed by 10 recovery days. During the 30-day exposure period, no performance decrement was found on a series of mental and motor performance tests.[28] The subjects reported subjective sleep-onset problems at 85, 90 dB SPL; however, the objective EEG measures showed no significant changes in sleep quality, *i.e.*, sleep latency, amount of stage 1, number of awakenings, number of stage changes, or in the sleep cycle (REM-NREM) stability. There are thus no convincing data to indicate that the brief disturbances of sleep caused by most noises result in large performance decrements.

Temperature. Although there are no studies on the effects on performance of disturbed sleep due to temperature extremes, based upon the above studies of noise, I would doubt that performance on most tasks would be affected.

Changes in work-rest schedules. Although changes in usual sleep times bring about complaints of disturbed sleep, as noted earlier, the effects of the disturbed sleep *per se* on performance cannot be separated from the circadian effects. As with sleep, other bodily rhythms will be altered and performance may be required at varying times over the 24-hour period. Colquhoun[29,30] has summarized the diurnal variations in human performance, and, as already noted, other speakers will focus on biological rhythms.

Sleep disturbances imposed by work or duty schedules can result in total sleep loss or in reduced sleep. The latter can be due to shortened single sleep periods or due to brief sleep periods scattered over the 24-hour period. The latter is often referred to as fragmented sleep. Johnson and Naitoh,[31] in an extensive review of the operational consequences of sleep deprivation and sleep deficit, detailed the effects of total sleep loss and partial sleep loss on performance, as well as mood, biochemical, physiological, and neurological changes. In our summary, we concluded that, within the 36 to 48 hour range of total sleep loss most likely to be experienced by aircraft personnel, no consistent or uniform performance decrement had been found in operational studies. Results from laboratory studies indicated that performance decrement depended upon several factors.

(1) Duration of task: The longer the task, the more sensitive it is to sleep loss.

(2) Knowledge of results: Immediate feedback to the subject as to quality of performance minimizes the effects of total sleep loss.

(3) Difficulty of task: Performance on difficult and complex tasks are more sensitive to sleep loss.

(4) Task pacing: Self-paced tasks resist sleep-loss effects much better than work-paced tasks. Tests with speed as a factor are more affected by sleep loss than tasks which stress accuracy.

(5) Proficiency in task performance: Newly acquired skills are more affected by loss of total sleep than those skills which have become automatic.

(6) Memory requirement: Tasks which require a short-term memory chain will be affected by sleep loss.

In summary, the long, work-paced, complex tasks with high attention and vigilance requirements and which do not provide information on how well the subject is performing can be expected to show high sensitivity to total sleep loss.

Non-task factors that influence the effects of sleep loss are:

(1) High interest: High interest and involvement in task mitigates sleep loss.

(2) Time of day: Sleep loss tends to enhance circadian effects.

(3) Physical exercise: Physical exercise just prior to task performance helped reduce decrement.

(4) Drugs: Amphetamines can reduce sleep-loss effects, but their chronic use can cause sleep problems and other possible difficulties.

The most common explanation of the performance decrement following total sleep loss is the lapse or microsleep hypothesis put forth by Williams, Lubin, and Goodnow.[32] Kjellberg,[33-35] after reviewing the inconsistent findings from sleep-loss studies, concluded: "The variable results reported during the eighty years of SD [sleep deprivation] research has definitely shown that SD does not lead to a state of the organism which can be described by enumerating a number of physiological, behavioral, and phenomenological effects. The futility of a search for the effects of SD in itself on any of these levels has been repeatedly demonstrated. It is evident that, in this respect, depriving an organism of sleep cannot be treated as analogous to depriving it of a vital substance like e.g., water.

"However, SD does seem to influence the individual's response to certain situational features in a predictable way. In particular, the situational factors which tend to lead to a lowered arousal level seem to get an accentuated effect after SD. One consequence of this accelerated dearousal after SD is that *Ss* fall asleep faster which may take the form of longer periods of sleep or of lapses depending upon the situational demands. The lowered arousal, however, also manifests itself in *Ss'* subjective state and as a deterioration of the capacity for sustained selective attention" (p.151).

I have no quarrel with Kjellberg's conclusions.

Partial Sleep Loss or Reduced Sleep

Relative to total sleep loss, there are fewer studies on partial sleep loss, but partial sleep loss is the most likely sleep disturbance to be experienced. The occurrence of fragmented sleep and partial sleep loss in aircrews was clearly documented in our NATO AGARDograph.[31]

Partial sleep loss is both easy and difficult to define. Decreasing TST by going to bed later or getting up earlier results in a sleep deficit. Partial sleep loss may occur if one sleeps 2 hours, gets up, and then sleeps for 3 hours, gets up, etc.; the fragmented sleep may not equal his/her usual TST. Also, does this fragmented sleep, even when equal to usual TST, have the same recuperative value as uninterrupted sleep? The data are inconclusive. Simply stated, partial sleep loss occurs when there is a reduction of the usual amounts of sleep obtained in 24 hours.

But is a person who sleeps only 4 hours in 24 necessarily suffering from partial sleep loss? Is there a fixed amount of sleep that must be obtained if a sleep debt is to be avoided? The answers appear to be "no." There are wide individual differences as to amounts of sleep required. Two men who slept only about 3 hours in each 24 hours reported no sleep-loss complaints.[36] A more extreme example is the report of a 60-year-old lady who slept on the average of 1 hour each night with no daytime naps and was reported to be alert, competent, with no need or desire for more sleep.[37]

Stuss and Broughton[38] recently reported on 6 additional short sleepers who slept less than 4 hours in 24. Sleep patterns and results on performance tests were studied in one 1.5-hour sleeper. A performance battery (calculations, vigilance, sensory motor) was administered after baseline, extended, and abbreviated sleep following laboratory adaptation. Stuss and Broughton concluded that the impaired performance found on most tests following extended sleep (50% extension of baseline) indicated that this less than 2-hour sleeper was obtaining his optimum sleep requirement.

Sleep reduction. While the health and performance of natural short sleepers are of interest to sleep researchers, our interest here is on those with shortened sleep. Those who abruptly shorten their sleep for whatever reason generally return to their usual sleep schedules when allowed to do so. In acute sleep-reduction studies, the data have shown no marked changes in performance, whether this was in subjects allowed only 3 hours for 8 consecutive days,[39] 4.5 hours for 60 days,[40] or when sleep was restricted to about 5 hours per day for 3 months.[41] The latter study involved 12 young German Naval Cadets on a training cruise.

In a study of gradual sleep reduction, Friedmann *et al.*[4] found no performance decrement on a battery of cognitive and motor tasks as sleep was reduced from 7.5-8.0 hours to 5.0-4.5 hours in 6 subjects, and from 6.5 to 5.0 hours in 2 subjects. In contrast to the acute sleep-reduction studies, the TST of the 6 8-hour sleepers was still reduced 1.0 to 1.5 hours a year later. The 2 6.5-hour sleepers returned to 6.5 hours TST when the sleep-reduction period ended.

Although there were no consistent performance decrements in the laboratory or in their graduate studies or work, these subjects began to complain of discomfort between 6.5 and 6.0 hours of sleep. There were complaints of feeling more sleepy, feeling the need for more sleep, and having less vigor and more fatigue (see Figures 3 & 4).

In their interviews, all 8 subjects reported difficulty in getting up in the morning as sleep was reduced below 6 hours. This difficulty increased as restriction proceeded to the lowest, 4.5-hour, level. Subjects elected to stop sleep reduction because they were "just too tired" and "just wanted to sleep." Specific reasons included overwhelming fatigue and falling asleep while in class, playing cards, visiting friends, and difficulty in remaining vigilant while driving.

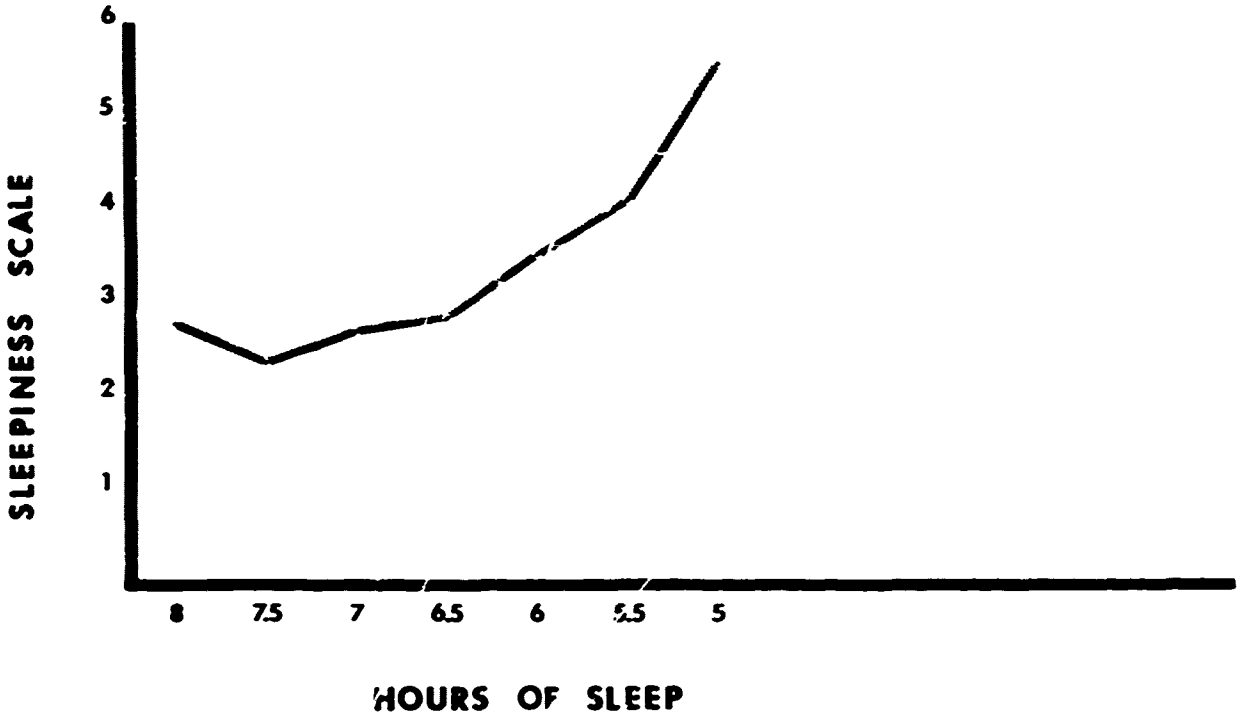


Fig. 3. Average ratings on Stanford Sleepiness Scale during gradual sleep reduction.

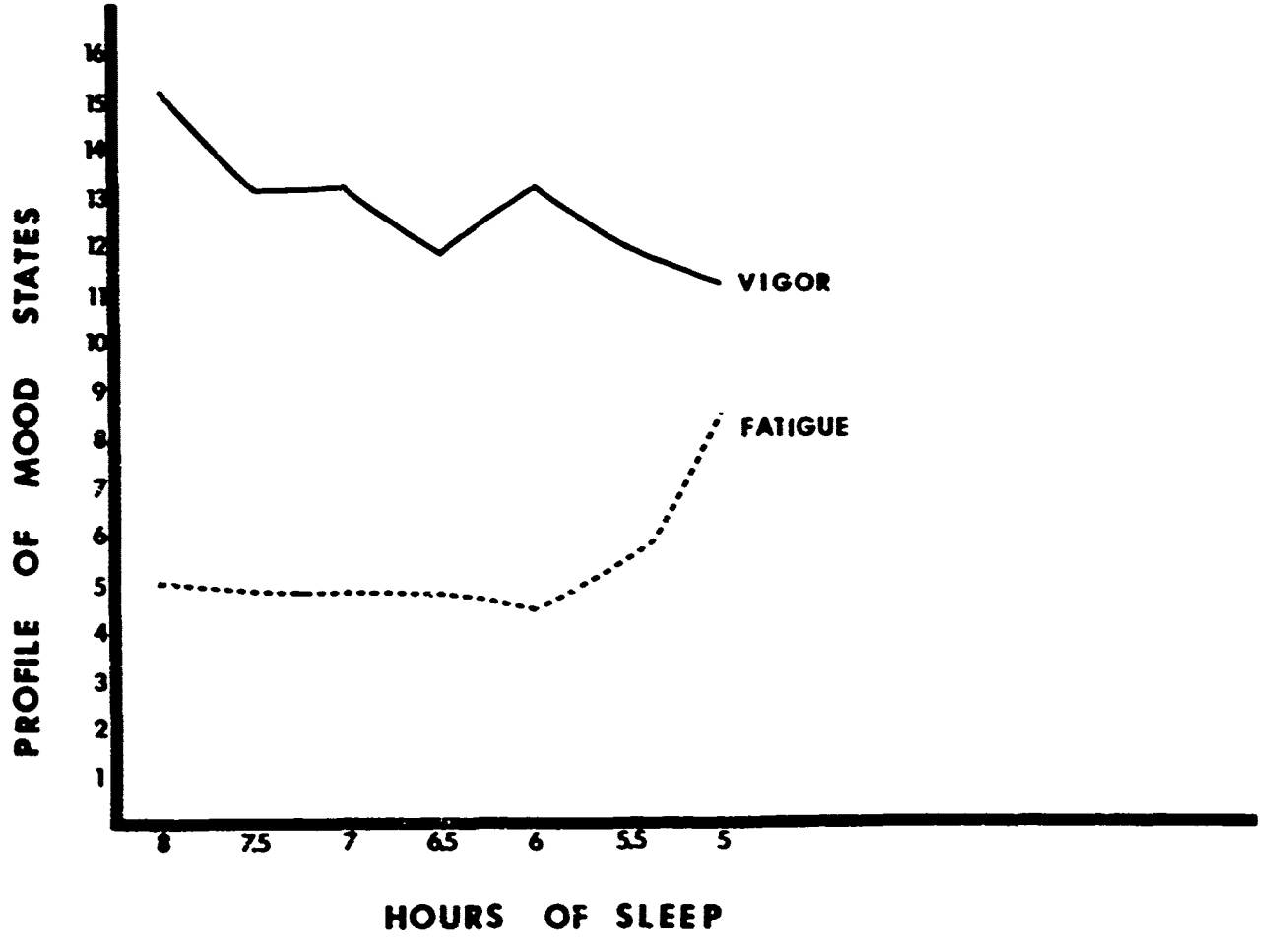


Fig. 4. Average ratings on vigor and fatigue scales during gradual sleep reduction.

There was some change in personal efficiency noted by most subjects, but this change did not appear on any of the objective tests or in their school or job performance. As one subject put it when at his lowest sleep level: "I am noticeably less efficient, less energetic; e.g., I can't seem to study as long as I used to, I get discouraged more easily, slightly depressed about overcoming difficulties, very much like I feel when I am sick with a cold" (p.248).

Fragmented sleep. It is felt by many sleep researchers in the area of biological rhythms that the fragmentation of sleep and the desynchrony of the physiological rhythms have a greater impact on behavior. Following changes in both sleep times and sleep-wakefulness cycles, disruption of the circadian cycle was felt to be a more important determiner of performance and of subjective mood changes than the shortened hours of sleep.[41] One of the few studies of sleep during combat conditions documented the effect of fragmented sleep. Sleep of carrier pilots was recorded while on duty stations off Vietnam.[42] While TST of the 27 aviators was found to be similar to 28 nonflying personnel, the aviators' sleep-wakefulness cycle was significantly different. The aviators had a far more variable intersleep interval than nonaviators. The more variable a pilot's intersleep interval, the more likely he was to make a landing error.

Laboratory studies of scheduled nap sleep, however, have found little performance decrement. In an extreme variation of the sleep-wake schedule, Carskadon and Dement[43] placed 5 subjects on a 90-minute day; 30 minutes of sleep, 60 minutes awake, for 5 days. Subjective self-reports of sleepiness and mood revealed initial discomfort on the 90-minute schedule. However, the sleepiness and mood of the subjects tended to show improvement during the experimental period, approaching baseline levels by the 4th or 5th experimental day. Daily 24-hour fluctuations were present on both measures.

In our laboratory, we compared the effects of naps, exercise, and bedrest to sustained performance over a 40-hour period.[18] In this study, noted in my introductory discussion of the influence of circadian rhythms, young male naval volunteers were denied normal nocturnal sleep and maintained on a 60-minute treatment/160-minute testing schedule during 40 consecutive hours. Ten subjects bicycled, 20 subjects were allowed to rest in bed but not sleep, and 10 subjects napped. Eight measures of addition, auditory vigilance, mood, and oral temperature were obtained. The Bedrest group showed significant impairment on all eight measures and, thus, gave no support to the forced-rest theory of sleep function. The Exercise group was worse than the Nap and Bedrest groups for all measures. In spite of fragmented, reduced sleep (about 3.7 hours per 24 hours), the Nap group showed no impairment on six of the measures. The results suggest that exercise increases the impairment due to sleep loss, and naps reduce or remove this impairment. Bedrest is not a substitute for sleep.

In summary, while performance decrements do not appear to be a major problem, sleep disruption and sleep deficits appear to raise the "cost" of maintaining pre-deficit levels of performance. This cost is sometimes reflected in increased physiological stress-related responses, but, most often, it is reflected in the increased effort to overcome feelings of fatigue. Subjective feelings of fatigue are the major findings whether sleep reduction occurs in the laboratory or in an operational setting.

Sleep Disorders and Performance

As one turns from the sleep laboratory and from the field of ergonomics to patients seen in the sleep clinic, one finds few controlled studies on the effects of disturbed sleep on performance. Yet, the anxiety over "not getting a good night's sleep" is clearly reflected in the high consumption of both prescribed and over-the-counter sleep medication.[44,45] As undoubtedly will be highlighted in the presentation by Commander Nicholson, we know more about the effects of the drugs used to treat the poor sleep than of the poor sleep *per se*. The devastating effects of excessive daytime sleepiness due to narcolepsy or sleep apnea have been repeatedly documented in patients with this complaint.

Short and long sleepers. In a study of natural long and short sleepers, Webb and Friel found no significant relation between length of sleep and academic performance.[46] Likewise, Johns, Dudley, and Masterton,[47] in a study of 104 fourth-year medical students, found no significant relation between TST and grades. Johns *et al.*, however, did find that poorer academic performance was significantly related to later times of waking up in the morning, particularly on weekends, and to subjectively poorer quality of sleep. Difficulty in getting to sleep and awakening during sleep, signs of poor sleep present in about 10% of their students, were not related to academic performance.

Good and poor sleepers. Because of the oft repeated concerns of insomniacs over the effects of their poor sleep on performance, the goal of one of our recent studies was to examine whether the relatively short and "unrefreshing" sleep of poor sleepers impairs their functioning. In a questionnaire survey of 1,033 Naval Hospital corpsmen and 303 college students, sleep habits were related to academic performance in both samples and to sick calls in the naval sample. The questionnaire contained 36 items related to sleep habits, including one that asked, "Overall, what kind of sleeper are you? Very good, good, average, poor, or very poor." Five percent of the college students said they were "poor sleepers"; none reported "very poor" sleep. Eight percent of the naval subjects described their sleep as "poor" and 1.2% said their sleep was "very poor." Since most of you do not work in medical settings, it is these types of poor sleepers rather than the chronic and complaining insomniac that you will most likely encounter. With that in mind, it might be of interest to contrast these non-complaining

and untreated poor sleepers with those who state they were good sleepers. I will later report on a sample of 12 poor sleepers and 12 good sleepers studied in our Naval Hospital laboratory. These poor sleepers most often complained of inability to fall asleep, and the most frequent cause was "thoughts keep racing through my mind." They had been poor sleepers for 6 months to several years, most had not sought medical help, and none were taking any sleep medication when studied. If there were such a classification, these poor sleepers could be classified as "healthy" insomniacs.

Due to the nature of our study, the sailors were examined in four segments over a 2-year period, and the college students were in my class on "Sleeping and Dreaming" over a 2-year period. For statistical analysis, we treated our navy sample as four groups and our college sample as two groups. This subgrouping allowed us to test the reliability of our analysis over the six samples. Only some of our results will be presented here.

First, in this sample of nontreated poor sleepers, what were the correlates of good versus poor sleep? In Table 2 are the items from the sleep questionnaire that were significantly related to subjective quality of sleep over all four navy samples and for at least one of the two college samples. The navy sample generally showed more consistent results over the four subgroups than did the college subjects. The mean ages of the two groups were not significantly different, but there were more females in the college sample. Although the women did significantly report that they went to bed earlier and got up earlier than men and reported more nightmares, they did not differ significantly from men in TST, sleep latency, or quality of sleep ratings.

The sleep profile of the poor sleepers followed expected patterns; longer reported sleep latencies on most nights, feeling less rested in the morning, having a more irregular sleep schedule, and being more easily aroused by noise. The navy sample of poor sleepers more frequently reported nightmares. Poor sleepers also had higher scores on all the Profile of Mood States (POMS) scales; *i.e.*, for feelings of tension, confusion, depression, anxiety, fatigue, and less vigor, but only those for tension, confusion, fatigue, and vigor were significant.

Was quality of sleep or any of the items that contributed to the poor sleep profile related to academic performance? The answer is "no." None of the sleep items or POMS scores correlated significantly with final class average for the sailors or for final examination score for the college students. The poor sleepers in the Navy had no more sick-call visits than did the good sleepers.

Laboratory-studied good versus poor sleepers. The above results were from questionnaire data and it can be argued, from previous studies, that subjective reports of sleep quality will differ from objective sleep laboratory data. As part of a study on the EEG, sleep, mood, and performance effects of flurazepam, 30 mg, 12 good sleepers and 12 poor sleepers were intensively studied. To be accepted into the study, the poor sleepers had to have a laboratory sleep latency of greater than 30 minutes on 2 consecutive nights, and, for the good sleepers, sleep latencies of less than 30 minutes were required. The average EEG sleep latency for the poor sleepers was 58 ± 26.1 minutes and, for the good sleepers, 11.1 ± 3.6 minutes. Thirty-six poor sleepers were screened to obtain 12 who qualified. Both groups received placebos for the first 7 nights after screening. Then 6 of the poor sleepers continued to receive placebos for 10 additional nights while 6 poor sleepers were given 30 mg flurazepam 15 minutes before bedtime. This period of the study was double-blind. Three placebo follow-up nights were recorded 2 to 3 weeks post-drug. Total bedtime was 7.5 hours for all subjects.

The subjective responses on the sleep questionnaires for those who qualified in the laboratory as good or poor sleepers were similar to those obtained for the total sample (Table 3). The poor sleepers showed the same pattern as the total sample on the POMS (Figure 5).

In the laboratory, the poor sleepers had a higher pre-sleep heart rate and higher oral temperature. There were no morning differences on these two measures. After sleep onset, the two groups did not differ on any sleep measure and there were no significant differences in the dB levels of a tone required to awaken the two groups from stages 2, 4, or REM sleep. As with the total sample, these good and poor sleepers did not differ as to final class averages, number of sick calls, and in performance on the Wilkinson 4-Choice Reaction Time Test, the Digit Symbol Substitution Test (DSST), or on a short-term memory test, the Digit Span Test.

The EEG-screened poor sleepers thus exhibited the sleep patterns and complaints of many insomniacs, yet there were no differences in their academic performance or on laboratory performance tests. Undoubtedly, some severe insomniacs treated in sleep clinics would exhibit impaired waking behavior; however, the above data indicate, as with the partial sleep-deficit studies, that the insomniac's concern over the effect of reduced sleep may be exaggerated. Again, as with partial sleep deficit, the major demonstrable changes were in mood and subjective feelings of fatigue.

Effects of flurazepam. Dr. Nicholson will review the effects of hypnotics in his lecture, but, since there are few studies that measure drug effects before, during, and after as long a period as 10 consecutive drug nights, I would like to briefly present our findings.[48]

The three performance and mood tests were administered in the morning, approximately 30 minutes after awakening, on 3 placebo baseline mornings, 4 drug mornings, and on 1

TABLE 2. Correlation of Sleep Questionnaire items with subjective quality of sleep.

Question	Navy Sample				College Sample		
	Group I	Group II	Group III	Group IV	1977 Group	1978 Group	Mean % Variance
How long does it usually take you to fall asleep after lights-out? (min)	.43	.50	.41	.49	.51	.53	23
Do you ever have trouble falling asleep? (1 = never; 4 = always)	.62	.59	.59	.60	.64	.65	38
If you do have trouble falling asleep, how often does this happen? (1 = once/year; 6 = 5 or more times/week)	.58	.61	.60	.56	.51	.62	34
If you do have trouble falling asleep, how long does it take you to get to sleep? (1 = less than 15 min; 6 = more than 60 min)	.44	.38	.27	.43	.37	.43	15
If you have trouble falling asleep, what is it that keeps you awake? (Answer: Thoughts running through my mind)	.24	.24	.28	.35	.18	.15	6
How many times during your usual sleep period do you wake up by yourself and then go back to sleep? (1 = never; 6 = 9 times or more)	.36	.36	.34	.23	.18	.39	10
On how many days per week does this happen? (1 = 1 or 2 days/week; 3 = 5 or more days/wk)	.31	.37	.20	.30	.12	.34	8
When you wake up during your usual sleep period, how long does it usually take to go back to sleep? (1 = 10 min or less; 5 = more than an hour)	.34	.35	.25	.19	.28	.46	10
Do you ever wake up too early and find you cannot go back to sleep? (1 = never; 4 = always)	.32	.33	.23	.33	.28	.39	10
On how many days per week does this happen? (1 = 1 or 2 days/wk; 3 = 5 or more days/wk)	.37	.32	.23	.31	.30	.42	11
Do you have disturbing dreams or nightmares? (1 = never; 4 = always)	.34	.36	.40	.34	.13	.20	10
On workdays, do you go to bed and get up at fixed, regular times? (1 = always; 4 = never)	.16	.21	.30	.08	.27	.17	4
Do you usually feel well-rested after you wake up and first get out of bed? (1 = always; 4 = never)	.37	.44	.47	.45	.14	.28	14
How do you usually feel for the first two or three hours after you wake up from your normal sleep period on workdays? (1 = alert, wide awake; 7 = almost asleep)	.32	.34	.21	.45	.31	.31	11
How do you usually feel for the first two or three hours after you wake up from your normal sleep period on days-off? (1 = alert, wide awake; 7 = almost asleep)	.27	.21	.17	.33	.25	.26	6
Which of the following applies to you? (1 = I never have great difficulty getting out of bed; 4 = I always have great difficulty getting out of bed)	.25	.31	.30	.27	.06	.14	6
Are you easily awakened by noises? (1 = never; 4 = always)	.18	.33	.27	.20	.23	.41	8

TABLE 3. EEG-screened good and poor sleeper responses to subject selection-criteria questions.

Selection-Criteria Questions	Good Sleepers		Poor Sleepers	
	Mean	SD	Mean	SD
1. How long does it take you to fall asleep (min)?	8.0	(3.6)	91.3[c]	(35.3)
2. Do you have trouble falling asleep (1 = never; 4 = always)?	1.3	(0.5)	3.4[c]	(0.8)
3. How often do you have trouble falling asleep (1 = once/year; 6 = 5 or more times/week)?	1.5	(1.1)	5.5[c]	(0.7)
4. How many times per night do you wake up?	1.2	(0.4)	1.8[a]	(0.9)
5. How many nights per week do you wake up?	0.2	(0.6)	1.6[c]	(1.2)
6. How long does it take to fall back asleep after nocturnal arousals (min)?	6.0	(5.0)	17.0[b]	(11.0)
7. Do you wake up and cannot fall back asleep (1 = never; 4 = always)?	1.2	(0.4)	1.9[a]	(1.0)
8. How many days per week does this happen?	0.1	(0.3)	1.0[c]	(0.9)
9. Are you easily awakened by noise (1 = never; 4 = always)?	1.7	(1.0)	2.6[a]	(1.2)
10. How long do you usually sleep (hr)?	7.0	(0.8)	5.5[c]	(0.5)
11. Do you feel well-rested in the morning (1 = always; 4 = never)?	2.4	(0.9)	3.5[c]	(0.5)
12. How do you feel 2-3 hr after you wake up (1 = alert; 7 = almost asleep)?	2.2	(1.0)	4.4[c]	(1.4)
13. Do you have difficulty getting out of bed (1 = never; 4 = always)?	1.6	(0.5)	3.0[c]	(1.0)

[a] $p < 0.025$
[b] $p < 0.005$
[c] $p < 0.001$

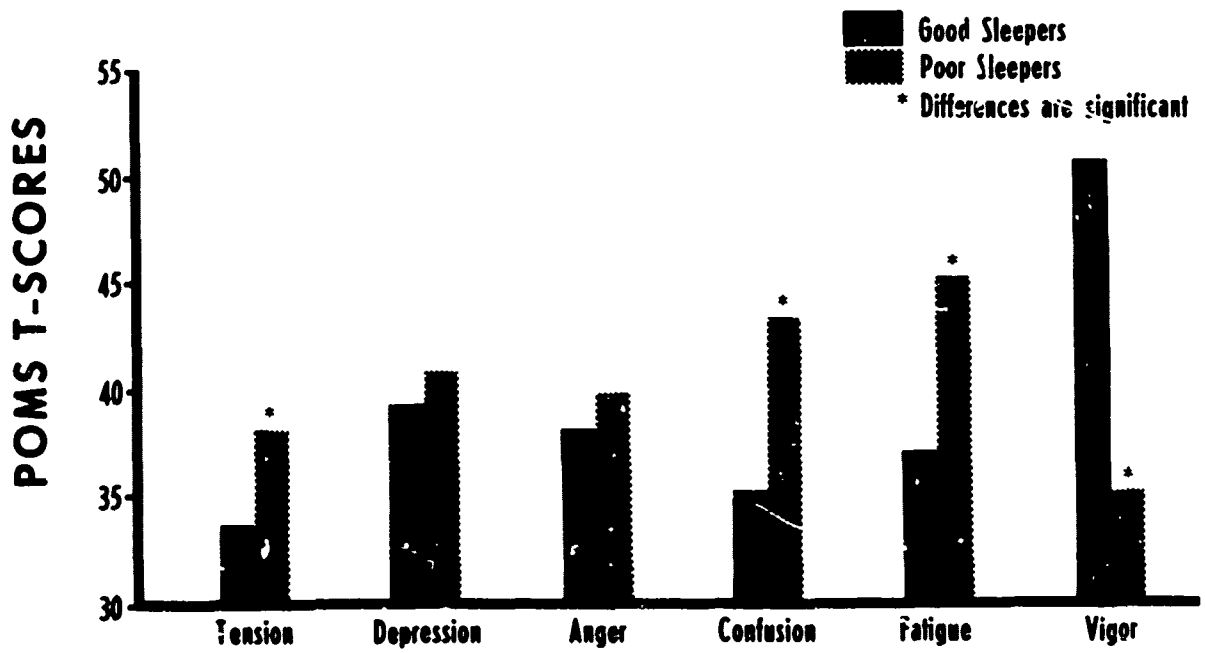


Fig. 5. Comparison of good and poor sleepers on the Profile of Mood States. Asterisks (*) indicate significant difference ($p < 0.05$) between two groups.

follow-up morning. When compared to the placebo group, flurazepam significantly impaired performance on the 4-Choice Reaction Time task and the DSST but not on the short-term memory task (Figures 6, 7 & 8). Performance impairment on the DSST showed a drug-tolerance effect across the 10-day drug period (Figure 7), while performance impairment on the reaction time task showed no tolerance effect (Figure 6). Flurazepam had no significant effect on mood (POMS) or feelings of sleepiness in the morning or at bedtime despite subjective ratings of a "more restful" and "better sleep" and EEG evidence of shortened sleep latencies.

Hypersomnias. Perhaps because it does not take extensive laboratory studies to determine that sleepy or sleeping subjects perform poorly, there are no studies detailing the performance of hypersomniacs, but the impact of narcolepsy on the life of the patient is often dramatic and extends into all aspects of life. Broughton and Ghanem,[69] in a questionnaire study of 43 (24 female, 19 male) narcoleptics with cataplexy and 43 normal controls, found that narcolepsy is a severe, debilitating, and chronic condition. "It frequently leads to very disturbing visual problems, memory difficulties, an extremely bad driving record, recurrent household and smoking accidents, poor productivity, blocking of promotion, decreased earning capacity and even job dismissal, personality changes including a striking tendency to depression even to suicidal levels, hallucinations and paranoia, difficulties and embarrassment in both education and recreation, loss of libido and (for males) impotence, miscellaneous disturbances of balance, bizarre dysesthesias, terrifying dreams, headaches, and the danger of loss of life through accident or drowning" (p.217).

The above is a composite picture of deficits and the effect of narcolepsy is not as totally devastating for every patient. However, 48% complained of defocusing or visual problems; memory problems affect about one-half of the persons with narcolepsy-cataplexy;

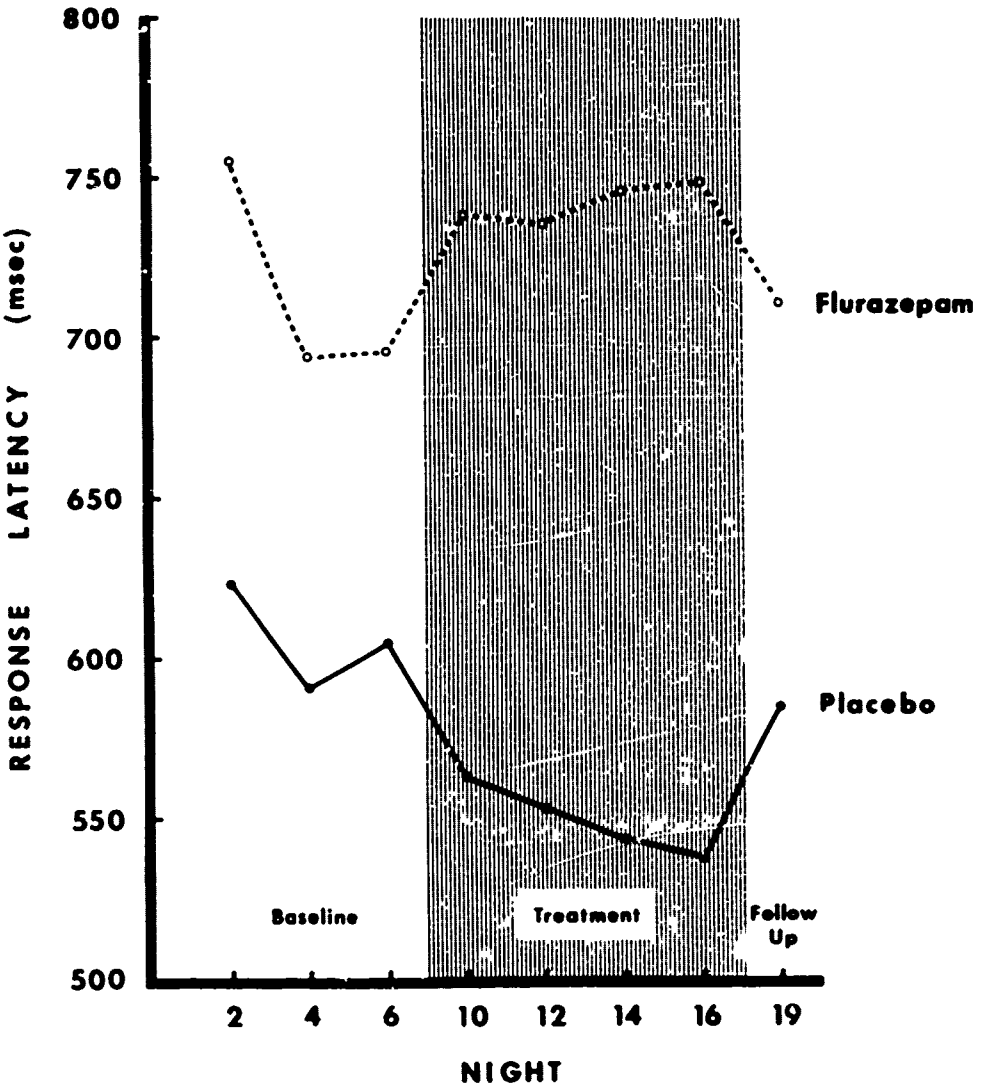


Fig. 6. Mean response latencies (of correct responses) on the 4-Choice Reaction Time Test. The flurazepam and placebo groups' performances differed significantly in the mornings following nights 14 and 16 of the drug-administration period (shaded area) (from Church & Johnson[69]).

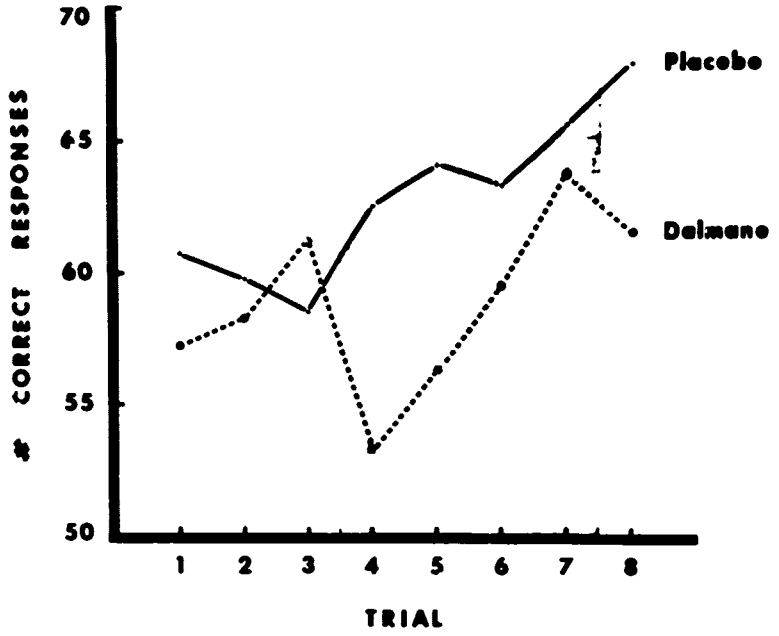


Fig. 7. Mean number of correct responses on the DSST. The flurazepam and placebo groups' performances differed significantly in the mornings following nights 10 and 12 of the drug-administration period (shaded area) (from Church & Johnson[48]).

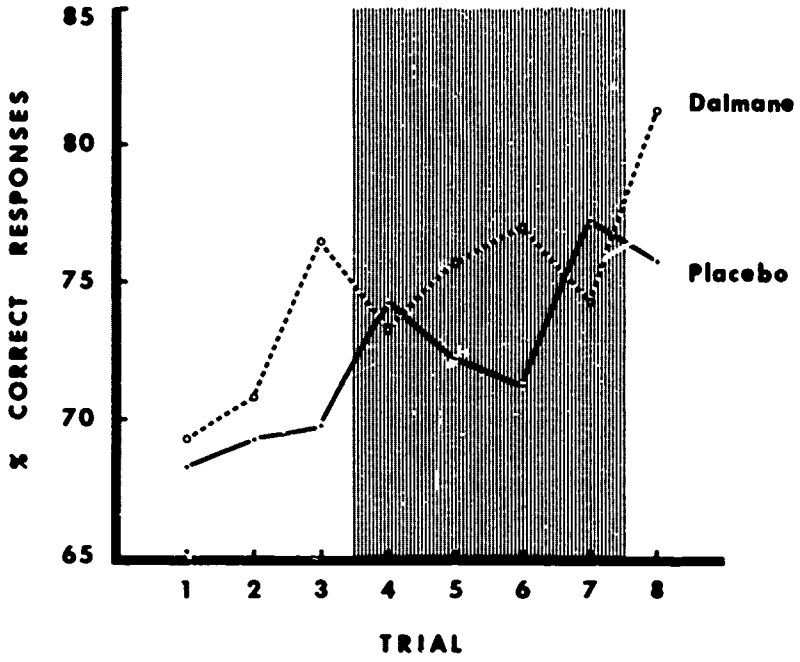


Fig. 8. Mean percent correct responses on the Digit Span memory test. The flurazepam and placebo groups' relative performances did not differ significantly during the drug-administration period (shaded area) (from Church & Johnson[48]).

39% said that narcoleptic attacks had led to a car accident; and 51.2% said their narcoleptic symptoms had led to an industrial accident. Sixty-two percent said that narcolepsy had reduced their job performance.

Since many narcoleptics report they feel refreshed after their sleep attack, Billiard[50] examined whether the type of sleep obtained during their nap was related to the recuperative value of the nap. As many narcoleptics have sleep-onset REM, the study of naps of narcoleptics offered an opportunity to compare REM-NREM sleep. The results from an extensive 2-day study of 18 narcoleptics and 5 normal controls led to inconclusive results. The length of the nap appeared to be more important than the type of

sleep obtained, when ratings of sleepiness, mood, and performance on an addition and serial alternation test were evaluated. The narcoleptic generally performed poorer than control subjects on the performance measures, due to "variations in alertness."

Sleep apnea. Anecdotal accounts of impaired performance due to excessive daytime sleepiness of sleep apneic patients also have been reported. In a recent article, Block, Boysen, Wynne, and Hunt[51] have reported that sleep apnea, hypopnea, and oxygen desaturation could occur in normal subjects. These symptoms, as does the sleep apneic with hypersomnia, occur mostly in males and the incidence increases with age and with obesity. Thus, periodic breathing can occur in normal subjects without clinical importance. While the "normal" sleep apneic patients report few episodes of less than 10-seconds duration, the patients with complaints of excessive daytime sleepiness may have over 100 episodes each night which last from 15 to 45 seconds. The frequency and duration of apneic episodes undoubtedly account for the impaired waking performance of the chronic sleep apneic patient.

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TOLERANCE DU TRAVAIL POSTE: UNE APPROCHE CHRONOBIOLOGIQUE

par

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RESUME

Le but des recherches fut d'éprouver les hypothèses concernant une relation possible entre l'amplitude A du rythme circadien de la température orale et (a) la vitesse de l'ajustement lors d'un changement de poste, d'une part et (b) la tolérance du travail posté, d'autre part.

L'étude I intéressait 25 opérateurs de raffineries de pétrole. Une corrélation négative ($r = -0.63$; $P < 0.01$) a été trouvée entre le A moyen et le déplacement de l'acrophase $\Delta\Phi$ résultant du premier poste de travail nocturne: plus A est grand, plus $\Delta\Phi$ est petit. Ce fait est en faveur de l'hypothèse proposée par J.Aschoff.

L'étude II comportait 23 travailleurs de l'industrie métallurgique et 25 travailleurs de l'industrie chimique ayant vis-à-vis du travail posté une tolérance excellente ou mauvaise. Cette tolérance fut évaluée à partir de trois critères cliniques classiques: les troubles digestifs, la fatigue persistante et les perturbations du sommeil. L'amplitude A du rythme circadien de la température orale est plus grande chez les sujets qui tolèrent le travail posté que chez les sujets devenus intolérants. Ce fait est en faveur de l'hypothèse proposée par P.Andlauer.

L'étude n° III, comportant 29 opérateurs d'une raffinerie de pétrole, a été programmée et organisée de manière à pouvoir éprouver les deux hypothèses, étudier leur complémentarité et prendre en considération des groupes de sujets différant par leur âge. Une excellente tolérance du travail posté, après de nombreuses années, semble être associée à une large amplitude du rythme circadien thermique et un ajustement lent durant les postes de nuit ($\Delta\Phi$ petit).

INTRODUCTION

Un rythme circadien peut être caractérisé par son acrophase Φ (emplacement du sommet dans l'échelle des 24 heures de la fonction sinusoïdale qui donne la meilleure approximation de toutes les mesures expérimentales), son amplitude A (la moitié de la variabilité totale, c'est-à-dire la différence entre le sommet et le creux) et son mésor M (la moyenne ajustée du rythme) (Halberg, Reinberg[1]; Halberg et al.[2]).

Un changement de phase ($\Delta\Psi$) des synchroniseurs socio-écologiques est suivi par un déplacement de l'acrophase ($\Delta\Phi$) qui se produit dans la même direction que $\Delta\Psi$. Des exemples pratiques de $\Delta\Psi$ chez l'Homme sont.

(a) les vols transméridiens à travers 5 fuseaux horaires ($\Delta\Psi > 5$ heures).

(b) le travail posté avec $\Delta\Psi \simeq 8$ heures qui comporte des changements abrupts entre l'activité-diurne/le sommeil-nocturne et l'activité-nocturne/le sommeil-diurne ou l'inverse.

Un ensemble d'études précédentes (Halberg, Reinberg[1,3], Reinberg[4], Aschoff et al.[5]) ont montré que l'espace de temps nécessaire pour s'ajuster de "l'ancienne" synchronisation à la "nouvelle", après un $\Delta\Psi$, varie: (a) d'une variable à l'autre chez le même sujet (par exemple le Φ de la température corporelle s'ajuste plus rapidement, que le Φ des 17-OHCS urinaires), (b) varie suivant la direction du $\Delta\Psi$ (par exemple après un $\Delta\Psi$ équivalent à un vol de Paris à New York retard de phase les acrophases s'ajustent plus rapidement qu'après un $\Delta\Psi$ équivalent à un vol de New York à Paris avance de phase), (c) varie d'un sujet à un autre pour une variable donnée.

Avec P.Andlauer, N.Vieux, J.Ghata et d'autres collègues, nous avons utilisé ces connaissances chronophysiologiques et une méthodologie chronobiologique pour essayer d'atteindre une meilleure compréhension de la tolérance individuelle au travail posté[6,7,8].

A partir de faits cliniques, il apparaît que dans une population d'adultes sains, seul un nombre limité de sujets (dont le pourcentage n'est pas encore quantifié) est capable de tolérer le travail posté. (Åkerstedt[10], Landier et Vieux[11], Andlauer et al.[12]). De nombreux travailleurs, même après plusieurs mois de travail posté, souffrent de fatigue, de perturbation du sommeil, entre autres symptômes. Ces symptômes cliniques d'intolérance peuvent apparaître après plusieurs années (ou même après une ou deux décades) de travail posté pour certains travailleurs (par exemple, lorsqu'ils atteignent la quarantaine ou la cinquantaine). Cependant, quelques sujets sont capables de faire un travail posté durant toute leur vie active sans aucun problème médical et sans altération de la santé. Malheureusement, il n'est pas possible aujourd'hui de prédire si un sujet est ou n'est pas capable de tolérer facilement le travail posté pendant de nombreuses années. Seule l'expérience sur le tas, dans une situation réelle, permet d'évaluer cette capacité individuelle.

Puisque le nombre de personnes intéressées par le travail posté est grand (presque un million de travailleurs en France) et puisqu'il est important (aussi bien pour l'employeur que pour l'employé) de connaître cette tolérance individuelle au travail posté, il est d'un intérêt pratique d'évaluer, à partir d'expériences chronobiologiques, les indicateurs possibles d'une bonne tolérance à long terme du travail comportant des changements de poste. L'amplitude du rythme circadien de la température (entre autres variables) a été considérée comme un indicateur potentiel par référence à deux hypothèses complémentaires.

La première fut proposée par Aschoff[13] : l'amplitude circadienne de certaines variables telles que la température orale est un index chronobiologique permettant d'apprécier la capacité individuelle à déplacer la phase des rythmes circadiens. En d'autres mots, un rapide ajustement de l'acrophase Φ à un changement de synchronisation $\Delta\Psi$ est-il associé à une petite amplitude circadienne?

La seconde hypothèse a été proposée par Andlauer[14] : la bonne tolérance au travail posté est-elle liée à une grande amplitude du rythme circadien de la température orale?

Les valeurs expérimentales collectées au cours d'experiences antérieures chez les travailleurs postés d'une raffinerie (Reinberg et al.[15,16]) ont été complétées et réanalysées pour voir si oui ou non $\underline{A}$ et $\Delta\Phi$ (résultant de $\Delta\Psi$) sont corrélées pour des variables telles que la température orale, la spirométrie de pointe, les 17-OHCS urinaires, etc. (Etude I).

La relation possible entre l'amplitude circadienne du rythme de la température orale et la tolérance du travail posté a été suspectée à partir de l'inspection de valeurs brutes de 25 sujets. L'observation était en fait une proposition d'Andlauer pour des recherches complémentaires. Ces dernières ont été faites[8]. Elles comportent des travailleurs postés d'industrie différentes (étude II).

Le schéma expérimental de l'étude III a été fait pour éprouver les hypothèses que l'amplitude du rythme circadien (celui de la température par exemple) est lié à la vitesse de l'ajustement et/ou à la tolérance du travail posté. En éprouvant ces hypothèses, le problème de leur compatibilité (et même celui de leur complémentarité) a été pris en considération[9]. D'un point de vue pratique, la complémentarité signifierait qu'un sujet tolérant (capable de résister au travail posté) a une grande amplitude de son rythme circadien de la température et s'ajuste lentement après un changement de poste. Le sujet non tolérant (qui souffre de divers troubles médicaux, révélant une certaine fragilité) aurait une relativement faible amplitude de son rythme circadien de la température et un ajustement rapide après un changement de poste ($\Delta\Psi$). En outre, un sujet qui a pu tolérer le travail posté de façon excellente pendant des années, peut voir apparaitre de grandes difficultés quand il atteint la quarantaine ou la cinquantaine. Ainsi, des paramètres caractérisant les rythmes circadiens tels que $\underline{A}$, Φ et $\underline{\Delta\Phi}$ ont été estimés à partir de séries temporelles individuelles, cependant que l'âge des sujets et la tolérance au travail posté étaient pris en considération pour constituer les groupes de l'étude III.

UNE GRANDE AMPLITUDE CIRCADIENNE EST-ELLE LIEE A UN AJUSTEMENT LENT DES RYTHMES CIRCADIENS DE TRAVAILLEURS POSTES? (Etude I[6,7])

Sujets:

Des séries temporelles (auto-mesures et dosages cliniques d'échantillons urinaires) ont été obtenues de travailleurs postés de sexe masculin de deux raffineries de pétrole situées respectivement à Reichstett et à Petit-Couronne en France. L'ancienneté du travail posté variait de un à seize ans. L'étude de Reichstett comportait 20 travailleurs de 25 à 48 ans, la rotation des postes avait lieu toutes les semaines; l'études de Petit-Couronne comportait 5 travailleurs postés âgés de 21 à 28 ans et la rotation des postes avait lieu tous les 3 ou 4 jours (rotation rapide).

Méthodes:

Des auto-mesures de la température orale, de la force musculaire et de la spirométrie de pointe ont été faites toutes les 4 heures (excepté pendant le sommeil) aux mêmes heurs, le jour n° 1 (entre autres) de chaque poste de travail. Les

échantillons d'urine ont été collectés de 4 heures en 4 heures pour le dosage des 17-OHCS, du potassium, du sodium etc. La durée de l'étude a été de 6 à 8 semaines.

La méthode du cosinor singulier[2] a été utilisée pour quantifier l'amplitude $\underline{A}$, l'acrophase $\underline{\Phi}$ et le rythme de chaque sujet pour chaque variable au cours des différents quarts

Pour chacune de ces variables et chacun des 25 sujets, nous avons étudié

(1) l'amplitude moyenne $\underline{A}$ calculée à partir de la série longitudinale complète (ce faisant, toutes les variations de ce paramètre sont prises en considération),

(2) la magnitude (ou la vitesse) du déplacement de l'acrophase $\underline{\Delta\Phi}$ $\underline{\Delta\Phi}$ est la différence (en heures) entre l'acrophase $\underline{\Phi}$ des jours de contrôle (travail et activité-diurne/repos-nocturne) et le $\underline{\Phi}$ correspondant au premier travail de nuit (le premier cycle de 24 heures qui suit le premier travail-de-nuit/repos-et-sommeil-diurne). Les $\underline{\Delta\Phi}$ estimés correspondent à un retard de phase $\underline{\Delta\Psi}$ d'environ 7, 5 heures

Le coefficient de corrélation a été calculé entre $\underline{A}$ et $\underline{\Delta\Phi}$ de chaque variable et aussi entre les $\underline{\Delta\Phi}$ de différentes variables.

Résultats

La figure 1 montre une corrélation négative obtenue entre $\underline{A}$ et $\underline{\Delta\Phi}$ de la température orale ($r = 0,63$, $P < 0,01$), plus l'amplitude est petite, plus le $\underline{\Delta\Phi}$ est grand

Le tableau 1 montre des corrélations négatives statistiquement significatives entre $\underline{A}$ et $\underline{\Delta\Phi}$ pour la spirométrie de pointe et pour l'excrétion urinaire des 17-OHCS. Cependant, la corrélation entre $\underline{A}$ et $\underline{\Delta\Phi}$ pour la force musculaire et l'excrétion urinaire de K^+ et de Na^+ ne sont pas statistiquement significatives

Il était intéressant d'examiner dans quelles mesures les amplitudes des différentes variables sont corrélées. Il apparaît que le $\underline{A}$ de la température orale est corrélé avec le $\underline{A}$ de la spirométrie de pointe ($r = 0,48$, $P < 0,05$) mais n'est pas corrélé avec le $\underline{A}$ de l'excrétion urinaire des 17-OHCS ($r = 0,07$, $P > 0,005$)

Une corrélation positive entre l'âge des sujets et le $\underline{A}$ de leur rythme circadien a été trouvée pour une seule variable la spirométrie de pointe. Plus les sujets sont âgés, plus l'amplitude est grande ($r = 0,57$, $P < 0,01$)

TABLEAU 1

CORRELATION ENTRE L'AMPLITUDE $\underline{A}$ du RYTHME CIRCADIEN ET LE DEPLACEMENT $\underline{\Delta\Phi}$ DE L'ACROPHASE APRES LE 1er QUART DE NUIT POUR 6 VARIABLES PHSIOLOGIQUES

VARIABLES	r	P
Température orale	-0,63	< 0,01
Spirométrie de pointe	-0,53	< 0,01
Force musculaire	-0,20	< 0,05
17-OHCS urinaires	-0,60	< 0,01
Potassium urinaire	-0,15	> 0,05
Sodium urinaire	-0,18	< 0,05

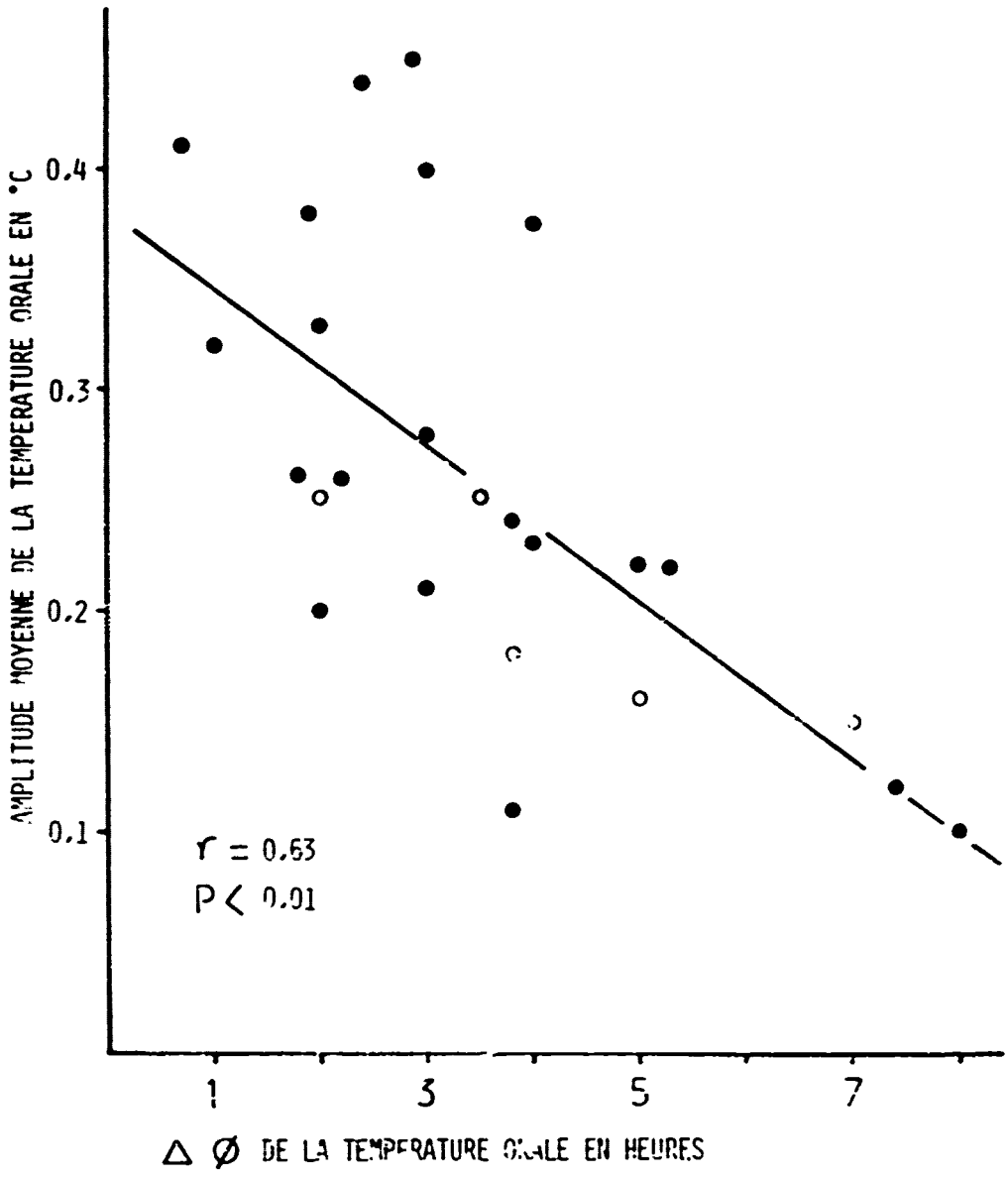


Fig.1 Correlation entre l'amplitude moyenne A (en Celsius) et le déplacement ΔØ de l'acrophase Ø (en heures) du rythme circadien de la température orale

ΔØ correspond à la différence des localisations de Ø sur l'échelle des 24 heures entre les jours à activité diurne et le premier quart de nuit (travail de 21 à 05 ou 06 h et sommeil de jour)

- . 20 travailleurs postés étudiés à Reichstett.
- . 5 travailleurs postés étudiés à Petit-Couronne

UNE GRANDE AMPLITUDE DU RYTHME CIRCADIEN DE LA TEMPERATURE ORALE EST-ELLE LIEE A UNE BONNE TOLERANCE CLINIQUE DU TRAVAIL POSTE (Etude II: 8).

Sujets

48 travailleurs postés ont été volontaires pour cette étude. 23 d'entre eux travaillaient pour la métallurgie (Steel Industry SI) près de Saint-Etienne, en France, les 25 autres travaillaient dans l'industrie chimique (CI) près de Grenoble, en France. Les distributions des âges des sujets étaient presque similaires en ce qui concerne les groupes (type d'industrie) et les sous-groupes (tolérance au travail posté). Cependant, un grand nombre de sujets non tolérants avaient une ancienneté de travailleur posté d'au moins 10 ans. Cette distribution inégale n'est pas surprenante si l'on prend en considération que l'intolérance du travail posté augmente avec l'âge des sujets[10,11] Les métallurgistes avaient des quarts de 7 jours (rotation hebdomadaire). Les travailleurs de l'industrie chimique étaient soumis à un système de rotation rapide: la durée des postes étant de deux jours.

Critères de la tolérance du travail posté

Cette tolérance clinique a été appréciée par les critères classiques en considérant à la fois l'existence et l'intensité de trois types de troubles associés au travail posté. Ils peuvent être classés en: troubles digestifs, neurologiques et/ou perturbations du sommeil. Les troubles digestifs sont le plus souvent: la dyspepsie, la gastrite, la colite et l'ulcère. Les problèmes neurologiques sont principalement une irritabilité inhabituelle et une fatigue persistante. Cette dernière diffère de la fatigue physiologique consécutive à des efforts physiques ou mentaux, qui disparaît après un espace de temps de repos adéquat. Finalement, les altérations du sommeil (par exemple: mauvaise qualité subjective: insomnies, sommeil interrompu par des éveils fréquents etc.) font l'objet de plaintes de la part des postés intolérants. Deux ou trois types de troubles peuvent être présent simultanément chez un sujet donné. Insistons sur le fait qu'un sujet posté, depuis de nombreuses années, est capable de reconnaître des modifications à la fois dans sa capacité de faire son travail et dans sa forme physique après un sommeil de nuit, pendant les jours de repos. Ainsi, l'intolérance du travail posté est appréciée à la fois en fonction de la propre expérience du sujet et des observations cliniques.

Méthodes

Des thermomètres médicaux contrôlés, ayant une précision d'1/20ème de Celsius, ont été utilisés pour les mesures de la température orale. Ces dernières ont été faites pendant un espace de temps de 4 semaines, le dernier (2ème ou 7ème) jour de chaque poste, à deux heures d'intervalles et heures fixes.

Les méthodes conventionnelles et celles du cosinor ont été utilisées pour les analyses statistiques.

Résultats

Pour chaque sujet, la différence entre le maximum et le minimum (Max-min Dif.) ont été réunies par groupes et sous-groupes pour l'analyse statistique. Le tableau 2 indique une variation statistiquement significative ($P < 0,005$) de la Max-min Dif. entre les sujets qui tolèrent et ceux qui ne tolèrent pas le travail posté. Cela est vrai pour les postés des deux industries considérées (SI et CI).

Des rythmes circadiens statistiquement significatifs (avec $\underline{A}$ différent de zéro avec $P < 0,005$) sont détectés dans les sous-groupes des sujets tolérants et non tolérants des deux industries (méthode du cosinor). Les valeurs de Mésor ne diffèrent pas de façon statistiquement significative d'un groupe à l'autre entre les personnes qui tolèrent et celles qui ne tolèrent pas le travail posté. Les localisations de l'acrophase dans l'échelle des 24 heures sont très proches dans toutes les séries temporelles considérées (aux environs de 16.00). Seule l'amplitude laisse apparaître, dans chaque cas, des différences statistiquement significatives. Une amplitude circadienne petite est associée à une mauvaise tolérance du travail posté cependant qu'une excellente tolérance est associée à une valeur de $\underline{A}$ relativement grande (tableau 3).

Il était intéressant de voir si ce phénomène se vérifiait non seulement pour le groupe mais aussi pour les individus en ce qui concerne la tolérance et le $\underline{A}$ circadien. Le test du χ^2 a été utilisé pour analyser la distribution des sujets étudiés en fonction de leur tolérance au travail posté et de la Max-min. Dif. de la température orale. La différence de distribution n'est pas statistiquement significative pour les sous-groupes de SI elle est significative pour les sous-groupes de l'industrie chimique. (9 des 11 sujets qui tolèrent le travail posté ont une Max-min Dif. $> 0,94$ C [valeur moyenne générale], cependant que 9 sur 14 des sujets qui ne tolèrent pas le travail posté ont une Max-min Dif. $< 0,94$ C avec $\chi^2 = 5,31$ et $P < 0,025$). Pour l'ensemble des valeurs des deux industries et des deux sous-groupes, 16 sur 20 des sujets qui tolèrent bien le travail posté ont une Max-min Dif. $> 1,07$ C [moyenne de l'ensemble des valeurs], cependant que 18 des 28 sujets qui ne tolèrent pas le travail posté ont une Max-min-Dif. $< 1,07$ C, $\chi^2 = 9,22$, $P < 0,005$

TABLEAU 2

ANALYSE "MACROSCOPIQUE" DES VALEURS BRUTES. DIFFERENCE ENTRE LES MAXIMA ET LES MINIMA CIRCADIENS (MAX-MIN. DIF.) DE LA TEMPERATURE ORALE DE TRAVAILLEURS POSTES. MAX-MIN.DIF. EN CELSIUS

Groupe (rotation tous les)		Max-Min. Dif. en °C Tolérance du travail posté Excellente	Mauvaise	p .
Sidérurgie	$\bar{X}$	1.42	1.06	
SI	± 1ES	± 0.13	± 0.09	<0.005
(7 jours)	n	9	14	
Chimie	$\bar{X}$	1.16	0.77	
CI	± 1 ES	± 0.06	± 0.08	<0.005
(2 jours)	n	11	14	

Une différence statistiquement significative apparaît entre les sujets qui tolèrent et ceux qui ne tolèrent pas le travail posté, pour les deux industries. La Max-min.Dif. des sujets non tolérants est plus petit (P < 0,012) pour le groupe CI par rapport au groupe SI. (pas de différence chez les sujets tolérants). Cette différence inter-groupe pourrait résulter de variations liées à l'environnement et/ou aux conditions expérimentales : rythmes circannuels; activité physique; exposition à la chaleur; type de rotation etc.

TEMPERATURE ORALE, AMPLITUDE DU RYTHME CIRCADIEN, TOLERANCE AU TRAVAIL POSTE ET AGE DES SUJETS (Etude III: 9).

Sujets:

Des opérateurs d'une raffinerie de pétrole ont été volontaires pour cette étude. Quatre groupes de travailleurs postés ont été formés.

Groupe I: 6 opérateurs jeunes, sans aucun trouble: âge moyen 25, 3 ans (de 21 à 35 ans). Leur ancienneté dans le travail posté est en moyenne de 2, 3 ans (de 1 à 4 ans).

Groupe II: 10 opérateurs anciens sans aucun trouble. Age moyen de 50 ans (de 44 à 57 ans). Ancienneté moyenne du travail posté 25, 1 ans (de15 à 32 ans).

Groupe III: 6 opérateurs anciens souffrant de troubles mineurs. (fatigue après le quart de nuit et médiocre qualité du sommeil.) L'âge moyen est de 50, 2 ans (de 46 à 56 ans). L'ancienneté moyenne est de 26 ans (de 22 à 31 ans).

Groupe IV: 7 opérateurs anciens souffrant de troubles majeurs (fatigue persistante même pendant le repos; profonde détérioration du sommeil; utilisation de somnifères pour dormir) et dès lors devant abandonner le travail posté peu après l'étude. L'âge moyen était de 47, 4 ans (de 30 à 56 ans). L'ancienneté moyenne est de 22, 9 ans (de 9 à 29 ans). Les opérateurs anciens ont contribué de façon pertinente à décider dans quel groupe (II, III ou IV) ils devaient être placés. Les employés constituant le groupe III considérèrent eux-mêmes qu'ils pouvaient poursuivre leur activité de travailleurs postés; cependant, que ceux constituant le groupe IV demandèrent ou agréèrent de passer en travail de jour. Le salaire des postés n'est pas diminué quand ils recommencent une activité diurne régulière; ainsi la proposition de passer du travail posté au travail de jour est faite sans poser de problèmes financiers pour le travailleur.

Les opérateurs changeaient de poste tous les 3 ou 4 jours (rotation rapide).

Methodes:

La température orale fut mesurée toutes les 4 heures à heures fixes, 5 fois par 24 heures (pas de mesure pendant le sommeil). Des thermomètres médicaux, à grande échelle, ayant une précision de 1/20ème de Celsius et recontrôlés ont été utilisés.

Pour chacun des 29 sujets, il a été possible d'obtenir des séries temporelles longitudinales (pendant 3 semaines, avec environ 100 mesures) pour quantifier les rythmes circadiens de la température. Comme pour les études I et II plusieurs méthodes statistiques ont été utilisées pour analyser les valeurs expérimentales.

TABLEAU 3

RYTHMES CIRCADIENS DE LA TEMPERATURE ORALE DE SUJETS TOLERANT LE TRAVAIL POSTE DE FAÇON EXCELLENTE OU MAUVAISE. RESUME PAR LE COSINOR SINGULIER

Groupe (rotation tous les :)	Tolérance du travail posté (Nb de sujets)	Détection du rythme P	Mésor M Moyenne ajustée des 24 h M ± 1 ES en Celsius	Amplitude A en Celsius (95% limites de confiance)	Acrophase Ø en hr. min. Ø réf. : minuit = 00.00 (95% limites de confiance)
Sidérurgie SI (7 jours)	Excellente(9)	0,005	36,66±0.17	0,49(0.41 à 0.56)	16.41(16.07 à 17.15)
	Mauvaise(14)	·0,005	36,62±0.10	0,32(0.26 à 0.38)	15.34(14.55 à 16.13)
Chimie CI (2 jours)	Excellente(11)	·0,005	36,85±0.08	0,35(0.30 à 0.40)	15.52(15.19 à 16.26)
	Mauvaise(14)	·0,005	36,86±0.06	0,25(0.21 à 0.29)	16.24(15.44 à 17.05)
SI + CI	Excellente(20)	·0,005	36,77±0.06	0,40(0.36 a 0.44)	16.21(15.57 à 16.45)
	Mauvaise(28)	·0,05	36,76±0.04	0,27(0.24 a 0.31)	16.02(15.33 à 16.32)

- Dans tous les groupes A diffère de zéro avec P · 0,005.
- Mésor M. Pas de différence entre les sujets qui tolèrent et ceux qui ne tolèrent pas le travail posté. Pas de différence entre SI et CI.
- Amplitude A. A (moitié de la variabilité totale) est plus grande lorsque la tolérance est excellente.
- Acrophase Ø : pas de différence entre groupes et sous-groupes.

Résultats:

L'amplitude de la température peut être appréciée grossièrement par la différence entre les maxima et les minima circadiens (Max-min. Dif.) La Max-min. Dif. est de 0,80°C ± 0,04 (une ES) pour le groupe I, 0,76 ± 0,03 pour le groupe II; 0,70 ± 0,05 pour le groupe III et seulement 0,48 ± 0,04 pour le groupe IV. La différence de la Max-min. Dif. entre le groupe IV et respectivement les groupes I et II est statistiquement significative ($P < 0,0005$). Les résultats obtenus par la méthode du cosinor sont résumés dans le tableau 4. Un rythme circadien statistiquement significatif est détecté pour chacun des 4 groupes ($\underline{A}$ diffère de zéro avec $P < 0,005$). Le mésor $\underline{M}$ ne diffère pas entre les groupes et se situe aux environs de 36,5°C. Les acrophases $\underline{\varphi}$ du rythme circadien de la température sont proches les unes des autres. Le $\underline{\varphi}$ du groupe II est aux environs de 15.51 (de 15.21 à 16.27) pour 95% de limite de confiance, cependant que le $\underline{\varphi}$ du groupe IV est 17.11 (de 16.07 à 18.14).

Les valeurs de l'amplitude sont similaires pour les groupes I, II et III; elles sont réduites pour le groupe IV. Cette diminution est statistiquement significative. $\underline{A}$ = 0,35°C (de 0.30 à 0.40 pour 95% de limite de confiance) pour le groupe II. $\underline{A}$ = 0,23°C (de 0.17 à 0.29) pour le groupe IV. Ainsi, l'analyse par le cosinor montre également que les sujets qui tolèrent ou ne tolèrent pas le travail posté, diffèrent seulement par l'amplitude de leurs rythmes circadiens thermiques.

$\underline{A}$ et $\underline{\varphi}$ ont été quantifiés pour chaque série temporelle individuelle. Les déplacements de l'acrophase $\underline{\Delta\varphi}$ résultant du poste du nuit (travail débutant à 21.00 et se terminant le lendemain matin à 05.00) peut être estimé par la différence entre le $\underline{\varphi}$ mesuré lors du poste de nuit et le $\underline{\varphi}$ correspondant au travail de jour des autres postes. Ainsi, l'amplitude individuelle moyenne $\underline{A}$ et le déplacement de l'acrophase $\underline{\Delta\varphi}$ ont été utilisées pour éprouver à nouveau l'hypothèse suivant laquelle plus $\underline{A}$ est grand, plus $\underline{\Delta\varphi}$ est petit.

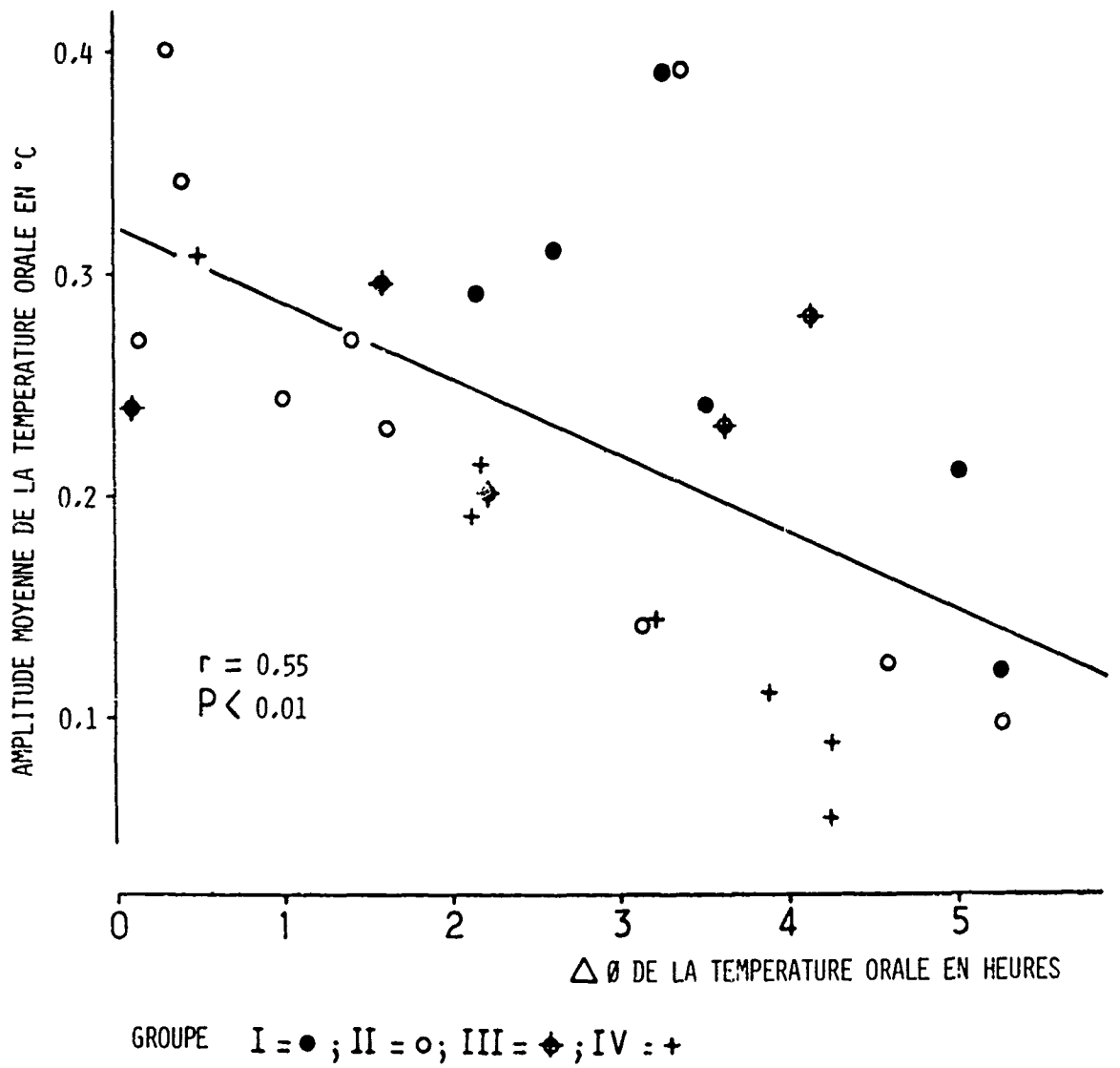


Fig.2 Correlation entre l'amplitude moyenne individuelle A (en Celsius) et le déplacement de l'acrophase $\Delta\varphi$ (en heures) du rythme circadien de la temperature orale.

Représentation graphique pour les valeurs confondes des 4 groupes considérés

TABLEAU 4

RYTHMES CIRCADIENS DE LA TEMPERATURE ORALE DE SUJETS
TOLERANT LE TRAVAIL POSTE DE FACON EXCELLENTE, PASSABLE OU MAUVAISE.
RESUME PAR LE COSINOR SINGULIER

Groupe (âge moyen : ans)	Tolérance du travail posté (Nb de sujets)	Détection du rythme P	Mésor M Moyenne ajustée des 24 heures M ± 1 SE en Celsius	Amplitude A en Celsius (95% limites de confiance)	Acrophase Ø en hr. min. Ø réf. = minuit = 00.00 (95% limites de confiance)
I (25,3)	Excellente (6)	·0,005	36,53±0,08	0,37(0,29 à 0,45)	15.49(14.38 à 17.00)
II (50,0)	Excellente (10)	·0,005	36.51±0,07	0,35(0,30 à 0,40)	15.54(15.21 à 16.27)
III (50,2)	Passable (6)	·0,005	36,53±0,11	0,30(0,24 à 0,36)	16.57(15.41 à 19.05)
IV (47,4)	Mauvaise (7)	·0,005	36,52±0,12	0,23(0,17 à 0,29)	17.11(16.07 à 18.14)

- Dans chaque groupe A diffère de zéro avec P · 0,005.
- Mésor M : pas de différence entre les groupes.
- L'amplitude A est plus grande pour les groupes I et II (tolérance excellente) que pour le groupe IV (mauvaise tolérance).
- Acrophase Ø : pas de différence d'un groupe à un autre.

Une corrélation négative statistiquement significative est observée entre $\underline{A}$ et $\underline{\Delta\Phi}$ ($r = -0,55$, $P < 0,01$; figure 2).

La valeur moyenne de A calculée pour 29 sujets est de 0,23°C. Par rapport à cette moyenne, une difference de distribution statistiquement significative peut être observée entre les groupes. Par exemple, chez 7 sujets sur 10 du groupe II, $A > 0,23$°C; cependant que 1 sujet sur 7 du groupe IV, $\underline{A} > 0,23$°C. ($\chi^2 = 5,16$ avec $P < 0,025$).

RESULTATS DE L'EXPERIMENTATION ANIMALE

Les résultats obtenus par Yunis et collaborateurs[19,20], ont dans une certaine mesure, des aspects intéressants qui peuvent être comparés avec les résultats des études I, II et III. Les paramètres du rythme circadien de la température rectale ($\underline{A}$ et $\underline{\Phi}$) de différentes souches de Souris (principalement CBA et NZB) ont été quantifiés avant, durant et après manipulation du synchroniseur lumière/obscurité (LD) en relation avec le vieillissement des animaux. A partir des résultats présentés dans ces deux papiers, nous avons pu déduire que. 1) les souris de la souche CBA sont résistantes aux maladies auto-immunes; elles s'ajustent lentement après un $\underline{\Delta\Psi}$ résultant d'une manipulation du cycle LD et ont une relativement petite diminution de l'amplitude du rythme circadien de la température en fonction de vieillissement. 2) les souris de la souche NZB développent une anémie hémolytique auto-immune, des anticorps antinucléaires et des lésions rénales avant l'âge de un an, elles s'ajustent rapidement après la même manipulation $\underline{\Delta\Psi}$ du cycle LD et montrent une réduction relativement importante de l'amplitude circadienne avec le vieillissement. En outre, les résultats obtenus par Yunis et collaborateurs suggèrent que la vitesse d'ajustement $\underline{\Delta\Phi}$ et l'amplitude $\underline{A}$ du rythme de la température, aussi bien que les variations de $\underline{A}$ et des $\underline{\Delta\Phi}$ avec l'âge ont une origine génétique.

Commentaires:

Les résultats obtenus par ces trois études sont en bon accord. D'une part, ils montrent une corrélation entre les $\underline{A}$ et $\underline{\Delta\Phi}$ circadiens tels que: plus $\underline{A}$ est grand, plus $\underline{\Delta\Phi}$ est petit. D'autre part, les sujets étudiés par Andlauer et collaborateurs[8] et Reinberg et collaborateurs[9] comprenant des postes jeunes et anciens des industries chimiques, métallurgiques et pétrolières (avec des différences dans les horaires des postes et la vitesse des rotations) montrent qu'une excellente tolérance du travail posté est associée à une amplitude relativement grande du rythme circadien de la température orale.

Les deux hypothèses (une relation entre $\underline{A}$ et $\underline{\Delta\Phi}$ et une relation entre $\underline{A}$ et la tolérance du travail posté) ont été éprouvées pour les même groupes de sujets, lors de l'étude III.

Pour une meilleure compréhension des relations entre l'amplitude du rythme circadien thermique et la tolérance du travail posté, la possibilité du rôle joué par le vieillissement (et/ou l'ancienneté du travail posté) doit être pris en considération. Dans les expériences rapportées, nous avons à faire à des sujets de différents âges et de différentes tolérances plutôt qu'à un effet du vieillissement. Le modèle animal de Yunis et collaborateurs[19,20] suggère une origine génétique à la diminution de l'amplitude du rythme circadien de la température liée à l'âge.

Evidemment, d'autres expériences sont necessaires pour éprouver l'hypothèse suivant laquelle les sujets ayant un $\underline{A}$ relativement petit (ou un A devenu petit du fait du vieillissement?) sont prédisposés à devenir intolérants au travail posté. Cependant, la possibilité qu'une faible amplitude observée resulte (plus ou moins?) d'une mauvaise tolérance du travail posté ne peut pas être exclue.

PERSPECTIVES PRATIQUES

Si la tolérance à long terme du travail posté est associée à l'existence d'une grande amplitude du rythme circadien thermique et à celle d'un ajustement lent, il semble préférable de choisir un système de rotation des équipes de postés qui ne permet pas au sujet de s'ajuster à la "nouvelle" synchronisation. Plus explicitement, une rotation rapide (avec un changement de quart tous les 2 à 4 jours) semble être un meilleur choix que la rotation hebdomadaire classique. Cet argument en faveur d'un système de rotation rapide est lié à la solution du problème de la tolérance à long terme du travail posté.

Cependant on doit garder présent à l'esprit que, dans des études antérieures,[6-9] les travailleurs postés étudiés s'ajustaient rapidement, en tant que groupe. Cette capacité pourrait être liée à l'âge. Les travailleurs en question étaient relativement jeunes au moment de l'étude (en moyenne 34, 5 et 24, 4 ans) et il semble que l'ajustement est plus rapide chez les jeunes que chez les anciens postés. En outre, l'échantillon des sujets étudiés était moins homogène que prévu en ce qui concerne la tolérance à long terme du travail posté. Certes, nous avions à faire à des operateurs sélectionnés sur la base d'une bonne tolérance au travail posté. Mais l'appréciation de la tolérance, dans ce travail, portait sur une observation de moins de 10 ans, dans 23 les 26 cas étudiés. L'intolérance au travail posté peut se révéler plus tard, comme ce fut le cas des sujets du groupe IV de l'étude III résumé dans ce papier. Si l'on considère que l'ajustement rapide d'un sujet jeune est un avantage immédiat (ce qui reste à vérifier) cette rapidité de l'ajustement ne peut pas servir à prévoir si cette tolérance au travail posté persistera ou non pendant 20 ans et plus. Néanmoins, l'amplitude du rythme circadien de la température apparaît comme un bon candidat pour un index chronobiologique de la tolérance à long terme du travail posté. Il évident que d'autres études sont nécessaires pour étendre les applications pratiques de ces résultats

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TOLERANCE TO SHIFT WORK : A CHRONOBIOLOGIC APPROACH

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SUMMARY

The aim of these studies was to test the hypotheses of possible relationships between the amplitude A of the circadian rhythm of oral temperature and (a) on the one hand, speed of adjustment during shift work, and (b) on the other hand, tolerance to shift work.

Study I involved 25 oil refinery operators. A negative correlation ($r = -0.63$; $P < 0.01$) was found between the mean A and the acrophase shift $\Delta\phi$ resulting from the first night-shift : the larger the A, the smaller the $\Delta\phi$. This fact supports the hypothesis of J. Aschoff.

Study II involved 23 steel industry workers and 25 chemical industry workers with either good or poor tolerance to shift work. Tolerance was evaluated conventionnally according to 3 types of complaints : digestive troubles, persistant fatigue, sleep alterations. Circadian A of oral temperature is larger in subjects who tolerate to shift work than in intolerant subjects. This supports P. Andlauer's hypothesis.

The study III involved 29 oil refinery operators and was designed so retest both hypotheses, their complementarity and to take different age groups into account. Good tolerance to shift work, over many years, appears to be associated with a large circadian amplitude and a slow adjustment during night-shifts (small $\Delta\phi$).

INTRODUCTION

A circadian rhythm may be characterized by its acrophase ϕ (crest time, along the 24 h scale of the best fitting cosine function approximating all data), its amplitude A (1/2 of the total variability that is crest minus trough difference) and its mesor M (rhythm adjusted mean) (Halberg, Reinberg : 1; Halberg et al : 2).

A phase-shift ($\Delta\tau$) of socio-ecological synchronizers is followed by an acrophase-shift ($\Delta\phi$) which is in the same direction and the same magnitude as $\Delta\tau$. Practical examples of $\Delta\tau$ of men are :

(a) transmeridian flights across at least 5 time zones ($\Delta\tau > 5$ h).

(b) Shift-work, with $\Delta\tau = 8$ h which involves abrupt changes from either day-work/night-sleep to night-work/day-sleep or vice versa.

A set of previous studies (Halberg, Reinberg : 1, 3; Reinberg : 4; Aschoff et al : 5) have shown that the time needed to adjust from the "old" synchronization to the "new" one after a $\Delta\tau$ varies :

(a) from variable to variable in the same subject (e.g. as a rule the bodycore temperature ϕ adjusts faster than the urinary 17-OHCS ϕ);

(b) with direction of $\Delta\tau$ (e.g. after $\Delta\tau$ equivalent to a flight from Paris to New York (phase delay) ϕs adjust faster than after a $\Delta\tau$ equivalent to a flight from New York to Paris (phase advance);

(c) from subject to subject for a given variable.

With P. Andlauer, N. Vieux, J. Ghata and other colleagues we have used this chronophysiological background (as well as a chronobiological methodology) to try better understand individual tolerance to shift work (6, 7, 8).

From clinical evidence it appears that in a population of healthy human adults only a limited number of subjects (not yet quantified) are able to sustain shift work (Åkerstedt : 10; Landier and Vieux : 11; Andlauer et al : 12). Many workers, even after several months of shift work, suffer from fatigue and sleep disturbance as well as other sympstoms. Clinical symptoms of intolerance may be seen after several years (or even 1 or 2 decades) of shift work by some workers (when they reach forty to fifty years of age). However, some subjects are able to shift work during all their active life span without medical problems or complaints. Unfortunately, at the present time it is not possible to predetermine whether or not a subject can tolerate shift work easily for many years. Only by on the job experience is it possible to evaluate one's capability.

Since the number of persons involved in shift work and transmeridian flights is large (almost one million workers in France) and since it is of interest (both to the employer and employee) to know the individuals' potential to keep to shift work it is of practical concern to evaluate data from chronobiological experiments for possible indicators which may predict successful long-term adherence to shift work schedules. The circadian rhythm amplitude of the body core temperature (among other variables) was considered as candidate for such an indicator with regard to two complementary hypotheses.

The first one was proposed by Aschoff (13) : the circadian amplitude of certain variables such as the oral temperature, is a chronobiological index indicative of one's ability to phase shift circadian rhythms. In other words, is a rapid adjustment of ϕs to a phase shift, $\Delta\nu$, associated with small circadian amplitudes?

The second hypothesis was proposed by Andlauer (14) : is a good clinical tolerance to shift work related to a large amplitude of the oral temperature circadian rhythm?

Data gathered from previous studies on oil refinery shift workers (Reinberg et al: 15-18) have been complemented and re-analyzed to test whether or not As and $\Delta\phi$s (resulting from $\Delta\nu$s) are correlated for variables such as oral temperature, peak expiratory flow, urinary 17-OHCS, etc. (Study I).

The possible relationship between the circadian amplitude of oral temperature rhythms and tolerance to shift work was suspected only from the inspection of raw data of 25 subjects. The statement was actually a proposal from Andlauer for further studies. These latter have been carried out (8). They involved shift workers from two different industries (Study II).

The experimental protocol of Study III was designed to test the hypotheses that the circadian rhythm amplitude, e.g. of oral temperature, is related to either the speed of adjustment and/or the tolerance to shift work. In testing these hypothesis, the problem of their compatibility (and even that of their complementarity) has been taken into account (9). From a practical point of view, the complementarity would mean that the tolerant subject (resistant to shift work) has a large circadian amplitude of temperature and adjusts slowly after a shift. The non-tolerant subject (with medical complaints revealing a certain fragility) would show a small circadian amplitude of temperature rhythm and a rapid adjustment after a shift ($\Delta\nu$). Moreover, a subject with an excellent history of tolerance to shift work for many years may exhibit great difficulties upon reaching his fifties or even his forties. Thus rhythm parameters such as A, ϕ and $\pm\phi$ were estimated from individual time series, while subjects'age and tolerance to shift work were taken into consideration to form the groups of the Study III.

IS A LARGE CIRCADIAN AMPLITUDE RELATED TO A SLOW PHASE-SHIFT IN CIRCADIAN RHYTHMS OF SHIFT WORKERS? (STUDY I : 6, 7).

Subjects :

Time series (measurements and chemical determinations in urine samples) were obtained from male shift workers in 2 oil refineries : Reichstett and Petit-Couronne - France. The subjects had been on shift work (shift work duration) from 1 to 16 years. The data analyses involved : (a) Reichstett study : 20 shift workers, aged from 25 to 48, whose shift length was 7 days (weekly rotation); (b) Le Petit-Couronne study : 5 shift workers, aged from 21 to 28, whose shift length was 3-4 days (rapid rotation).

Methods :

Self-measurements of oral temperature, grip strength and peak expiratory flow were performed every 4 h (except during sleep) at the same clock time on day n° 1 (among others) of each shift ($\Delta\nu$). Total urine voidings (for determination of urinary 17-OHCS, K^+, Na^+, etc.) were collected simultaneously. The data gathering covered a 6 to 8 week span.

The single cosinor method (2) was used to quantify the amplitude A , the acrophase ϕ of the rhythm of each subject for each variable on the different shifts.

For each variable and each of the 25 subjects, we derived :

(1) the mean amplitude A, computed from all available time series (in so doing, the total variance of this parameter was taken into consideration);

(2) the magnitude (or the speed) of the acrophase shift $\Delta\phi$. $\pm\phi$ is the difference(in hours) between ϕ on control days (diurnal-work and activity/nocturnal-rest) and ϕ on the first night shift day (the 24 h span following the first session of night-work/diurnal-rest and sleep). The estimated $\pm\phi$s correspond to a phase delay $\pm$ - 7.5 h.

Correlation coefficients were calculated between A and $\pm\phi$ for each variable, and also between the $\Delta\phi$s of different variables.

Results :

Figure 1 shows the negative correlation obtained between A and $\pm\phi$ for oral temperature ($r = -0.63$; $P < 0.01$); the lower the amplitude, the greater the $\pm\phi$.

Table 1 shows similar significant negative correlation between A and $\pm\phi$ of the peak expiratory flow (PEF) and the urinary excretion of 17-OHCS. However, the correlations for A and $\Delta\phi$ of grip strength, and the urinary excretion of K^+ and Na^+ were not statistically significant.

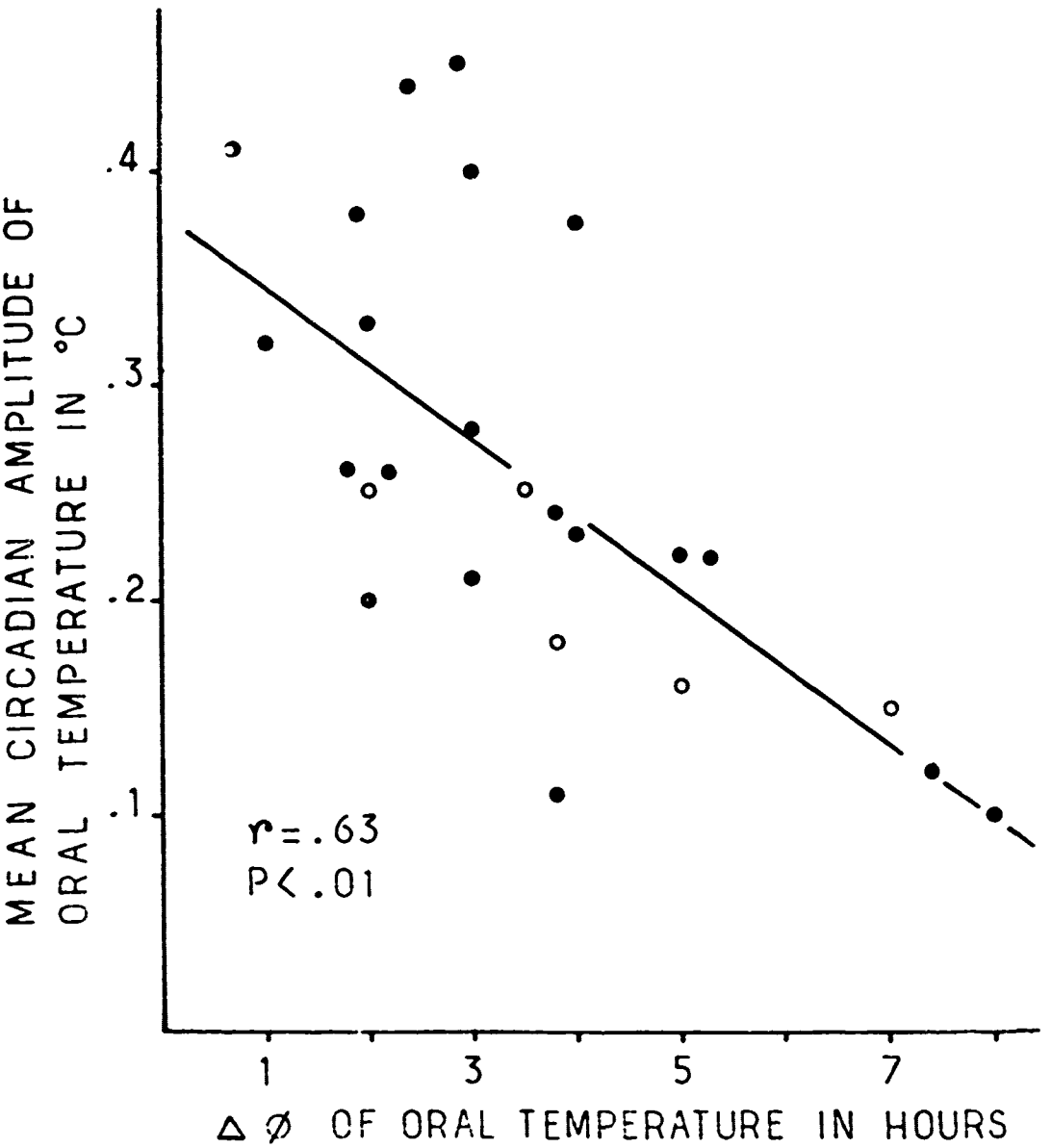


Figure 1 . Correlation between individual mean amplitude A (in Celsius) and acrophase shift ΔØ (in hours) of the oral temperature circadian rhythm.

Ø corresponds to the difference of Ø locations on the 24 h scale between control days and the first night-shift (night-work from 21.00 to 05.00 or 06.00 associated with day sleep).

● : 20 shift workers; Rechstett study.
o : 5 shift workers; Petit-Couronne study.

TABLE 1

CORRELATION BETWEEN THE CIRCADIAN RHYTHM AMPLITUDE A AND THE ACROPHASE SHIFT $\Delta\phi$ AFTER THE FIRST NIGHT SHIFT, FOR 6 VARIABLES

Variables	r	P
Oral temperature	- 0.63	<0.01
Peak Expiratory Flow	- 0.53	<0.01
Grip strength	- 0.20	>0.05
Urinary 17-OHCS	- 0.60	<0.01
Urinary potassium	- 0.15	>0.05
Urinary sodium	- 0.18	>0.05

It was of interest to examine whether or not the amplitudes of different variables were correlated. It appeared that the oral temperature A was correlated with the peak expiratory flow A ($r = 0.48$; $P < 0.05$) but not with the A of urinary 17-OHCS ($r = 0.07$; $P > 0.05$).

A (positive) correlation between subjects age and their circadian rhythm A was found for only one variable : the peak expiratory flow. The older the subject, the larger the circadian A ($r = 0.57$; $P < 0.01$).

IS A LARGE CIRCADIAN RHYTHM AMPLITUDE (ORAL TEMPERATURE) RELATED TO A GOOD CLINICAL TOLERANCE TO SHIFT WORK? (STUDY II : 8).

Subjects :

Forty-eight shift workers volunteered for the study. Twenty-three were employed as shift workers for a Steel Industry (SI) near the city of Saint-Etienne-France; the other 25 were employed as shift workers for a Chemical Industry (CI) near the city of Grenoble -France. Age distribution was quite similar within groups (industry) and subgroups (tolerance to shift work). However, a larger number of non-tolerant subjects had been employed as shift workers for at least 10 years. This unequal distribution was not surprizing, since intolerance to shift work occurs with aging (10, 11).

Steel workers had a seven-day shift (weekly rotation). Chemical workers worked a rapid rotation system, the shift-duration being two days (rapid rotation).

Criteria of the tolerance to shift work :

Clinical tolerance was appreciated conventionally by considering both the existence and the intensity of 3 types of shift work-associated problems. These can be classified as either digestive, neurologic and/or sleep disturbances. With respect to digestive troubles, common complaints were : dyspepsia, gastritis, colitis and peptic ulcer. Neurologic problems were mainly unusual irritability and a persistant fatigue . The latter differed from physiologic fatigue resulting from physical and/or mental efforts since it disappeared after an adequate rest time. Finally, sleep alterations e.g., poor subjective quality of sleep, insomnia, sleep disrupted by frequent awakening, etc. were reported by intolerant workers. Two or three types of disturbances may be present simultaneously in a given subject. It must be emphasised that a subject shift-working for many years is able to recognize changes in both his capacity to carry out work and in

his physical vigor after nocturnal sleep when off duty. Thus, the intolerance to shift work is judged from both the subject's experience and clinical observations.

Methods :

Normal large-scaled and calibrated clinical thermometers (1/20 Celsius precision) were used for oral temperature measurements. Data were collected during a 4-week span on the last (either the 2d or 7th) days of each of the shift, at 2 h intervals and fixed clock hours.

Both conventional (means and t test; group distribution and χ^2 test etc.) and cosinor (2) methods were used for statistical analyses.

Results :

The individual difference between the maximum and the minimum (Max-min.Dif.) were pooled for group and subgroup statistical analyses. Table 2 indicates a statistically significant differences ($P < 0.005$) in the Max-min. Dif. between subjects tolerating and not tolerating shift work. This is true for shift workers of both SI and CI.

TABLE 2

MACROSCOPIC EXAMINATION OF INDIVIDUAL RAW DATA.
DIFFERENCE BETWEEN CIRCADIAN MAXIMA AND MINIMA (MAX-MIN.DIF.) IN ORAL TEMPERATURE OF SHIFT-WORKERS.
MAX-MIN. DIF. IN CELSIUS

Group (Shift-duration)		Max-Min Dif. in °C		P
		Tolerance to shift work Good	Poor	
Steel Industry SI (7 days)	$\bar{X}$ ± IES $\bar{n}$	1.42 ± 0.13 T3	1.06 ± 0.09 T4	<0.005
Chemical Industry CI (2 days)	$\bar{X}$ ± IES $\bar{n}$	1.16 ± 0.06 T1	0.77 ± 0.08 T4	<0.005

A statistically significant difference in (Max-min. Dif.) between subjects who were tolerant and intolerant to shift work was found in all groups.
The Max-min. Dif. of intolerant subjects was smaller (P < 0.012) in CI than in SI (no group difference in tolerant subjects). The group differences could be related to differences of some factors and/or experimental conditions such as circannual changes, physical activities, exposures to heat, type of rotation.

Statistically significant circadian rhythms (with A differing from zero with $P < 0.005$) were detected in both tolerant and intolerant subgroups of subjects working in steel and chemical industries (cosinor method). Mesor values were not statistically different from group to group or between tolerant and intolerant persons. $\underline{\phi}$ locations are very closed (around 16.00) in the considered time series. In each case only the amplitude showed a statistically significant difference. A small circadian A is associated with poor shift work tolerance, while good tolerance to shift work is associated with a relatively large A. (Table 3).

TABLE 3

CIRCADIAN RHYTHM IN ORAL TEMPERATURE OF SUBJECTS WITH AN GOOD OR A POOR TOLERANCE TO SHIFT-WORK
SINGLE COSINOR SUMMARY

Group (Shift duration)	Tolerance to shift-work (No of subjects)	Rhythm detection P	Mesor M 24 h rhythm adjusted mean M ± 1 SE in Celsius	Amplitude A in Celsius (95% confidence limits)	Acrophase φ in hr. min. φ ref. : midnight = 00.00 (95% confidence limits)
Steel Industry SI (7 days)	Good (9)	< 0.005	36.66±0.17	0.49(0.41 to 0.56)	16.41(16.07 to 17.15)
	Poor (14)	< 0.005	36.62±0.10	0.32(0.26 to 0.38)	15.34(14.55 to 16.13)
Chemical Industry CI (2 days)	Good (11)	< 0.005	36.85±0.08	0.35(0.30 to 0.40)	15.52(15.19 to 16.26)
	Poor (14)	< 0.005	36.86±0.06	0.25(0.21 to 0.29)	16.24(15.44 to 17.05)
SI + CI	Good (20)	< 0.005	36.77±0.06	0.40(0.36 to 0.44)	16.21(15.57 to 16.45)
	Poor (28)	< 0.05	36.76±0.04	0.27(0.24 to 0.31)	16.02(15.33 to 16.32)

- In all groups, A differs from zero with P < 0.005.
- Mesor M : no difference between subjects who were tolerant or intolerant to shift-work; no difference between SI and CI (P > 0.05).
- Amplitude A 1/2 of the total variability is larger in tolerant than in intolerant subjects.
- Acrophase φ no difference between groups.

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It was of interest to examine not only group differences but also the data from individual workers with regard to tolerance and circadian A. The χ^2 test was used to analyse the distribution of the studied employees according to their tolerance to shift work and the Max-min. Dif. in the oral temperature rhythm. The difference in distribution was not statistically significant for the subgroups of SI, while it was significant for the subgroups of the studied workers of CI (9 out 11 subjects who tolerate shift work have a Max-min. Dif. > 0.94°C [overall mean value]; while, 9 out 14 subjects who did not tolerate shift work had a Max-min. Dif. < 0.94°C with $\chi^2 = 5.31$ and $P < 0.025$). In pooled data (across industries) of both subgroup, 16 out 20 subjects who tolerated shift work well had a Max-min. Dif. greater than 1.07°C [overall mean value]; while 18 out of 28 subjects who did not tolerate shift work had a Max-min. Dif. less than 1.07°C ($\chi^2 = 9.22$; $P < 0.005$).

ORAL TEMPERATURE, CIRCADIAN RHYTHM AMPLITUDE, TOLERANCE TO SHIFT WORK, SUBJECTS'AGE (STUDY III : 9).

Subjects :

Oil refinery operators volunteered for this study. Four groups of shift workers were formed.

- Group I : 6 young operators with no previous complaints. Mean age = 25.3 years (range from 21 to 35 years). They had been shift-working for 2.3 years (range 1 to 4 years).
- Group II : 10 senior operators with no history of shift work difficulty. Mean age = 50 years (range from 44 to 47 years). Mean shift work duration = 25.1 (range 15 to 32 years).
- Group III : 6 senior operators with minor complaints such as feeling tired after the night-shift and poor quality of sleep. Mean age = 50.2 years (range 46 to 56 years). Mean shift work duration = 26 years (range 22 to 31 years).
- Group IV : 7 senior operators with major complaints (persistant fatigue during rest; large subjective deterioration of sleep; use of sleeping pills) and who therefore were to be discharged from shift work at the time of the study. Meanage = 47.4 years (range 30 to 56 years). Mean shift work duration = 22.9 years (range 9 to 29 years).

Senior operators contributed pertinently in the decision into which group (II, III or IV) they were to be placed. Employees constituting group III considered themselves capable of continuing shift work; while those constituting group IV requested or agreed to be discharged. The salary of the shift worker was not reduced when resuming regular day work; thus, the proposal for changing from a shift work to day work schedule was done without financial considerations.

Operators were shifting every 3-4 days (rapid rotation).

Methods :

Oral temperature was measured, four-hourly at fixed clock hours, five times/24 h (not during sleep). Large clinical mercury thermometers (1/20 Celsius precision) were used.

For each of the 29 individuals it was possible to obtain a longitudinal time series (a 3 week duration with ~ 100 data) to quantify the oral temperature circadian rhythms. As for studies I and II several statistical methods were used to analyse the data, including cosinor.

Results :

The temperature amplitude can be appreciated roughly by the difference between circadian maximum and minimum (Max-min. Dif). The Max-min. Dif. is 0.80°C ± 0.04 (1 SE) for group I; 0.76 ± 0.03 for group II; 0.70 ± 0.05 for group III and only 0.48 ± 0.04 for group IV. The difference in the Max-min. Dif. between group IV with respect to group I and II is statistically significant ($P < 0.0005$).

Results obtained with the cosinor method are summarized in table 4. A statistically significant circadian rhythm was detected in all of the 4 groups (A differs from zero with $P < 0.005$). The mesor M did not differ between groups and was around 36.5°C. The circadian temperature ϕ were close to each other. The ϕ of group II is located around 15.51 (95% confidence limits being 15.21 to 16.27); while, the ϕ of group IV is 17.11 (16.07 to 18.14).

Amplitude values are similar for group I, II and III; they are reduced for group IV, this reduction is statistically significant. A = 0.35°C (95% confidence limits being 0.30 to 0.40) in group II. A = 0.23°C (from 0.17 to 0.29) in group IV. Thus, cosinor analysis also shows that the only difference between subjects who are tolerant and intolerant to shift work is in their temperature circadian A.

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TABLE I

CIRCADIAN RHYTHM IN ORAL TEMPERATURE OF SUBJECTS WITH AN GOOD, ADEQUATE OR POOR TOLERANCE TO SHIFT-WORK
SINGLE COSINOR SUMMARY

Group (mean age in years)	Tolerance to Shift-work (no of subjects)	Rhythm detection P	Mesor M 24 h rhythm adjusted mean M ± 1 SE in Celsius	Amplitude A in Celsius --------95% confidence limits)	Acrophase Ø in hr. min. Ø ref.:midnight = 00.00 ----------
I (25.3)	Good (6)	< 0.005	36.53±0.08	0.37(0.29 to 0.45)	15.49(14.38 to 17.00)
II (50.0)	Good (10)	< 0.005	36.51±0.07	0.35(0.30 to 0.40)	15.54(15.21 to 16.27)
III (50.2)	Adequate (6)	< 0.005	36.53±0.11	0.30(0.24 to 0.36)	16.57(15.41 to 19.05)
IV (47.4)	Poor (7)	< 0.005	36.52±0.12	0.23(0.17 to 0.29)	17.11(16.07 to 18.14)

- *In any groups A differs from zero with P < 0.005.*
- *Mesor M : no difference between groups.*
- *The amplitude A : 1/2 of total variability) is larger in groups I and II (good tolerance) than in group IV (poor tolerance to shift-work).*
- *Acrophase Ø : no difference between groups.*

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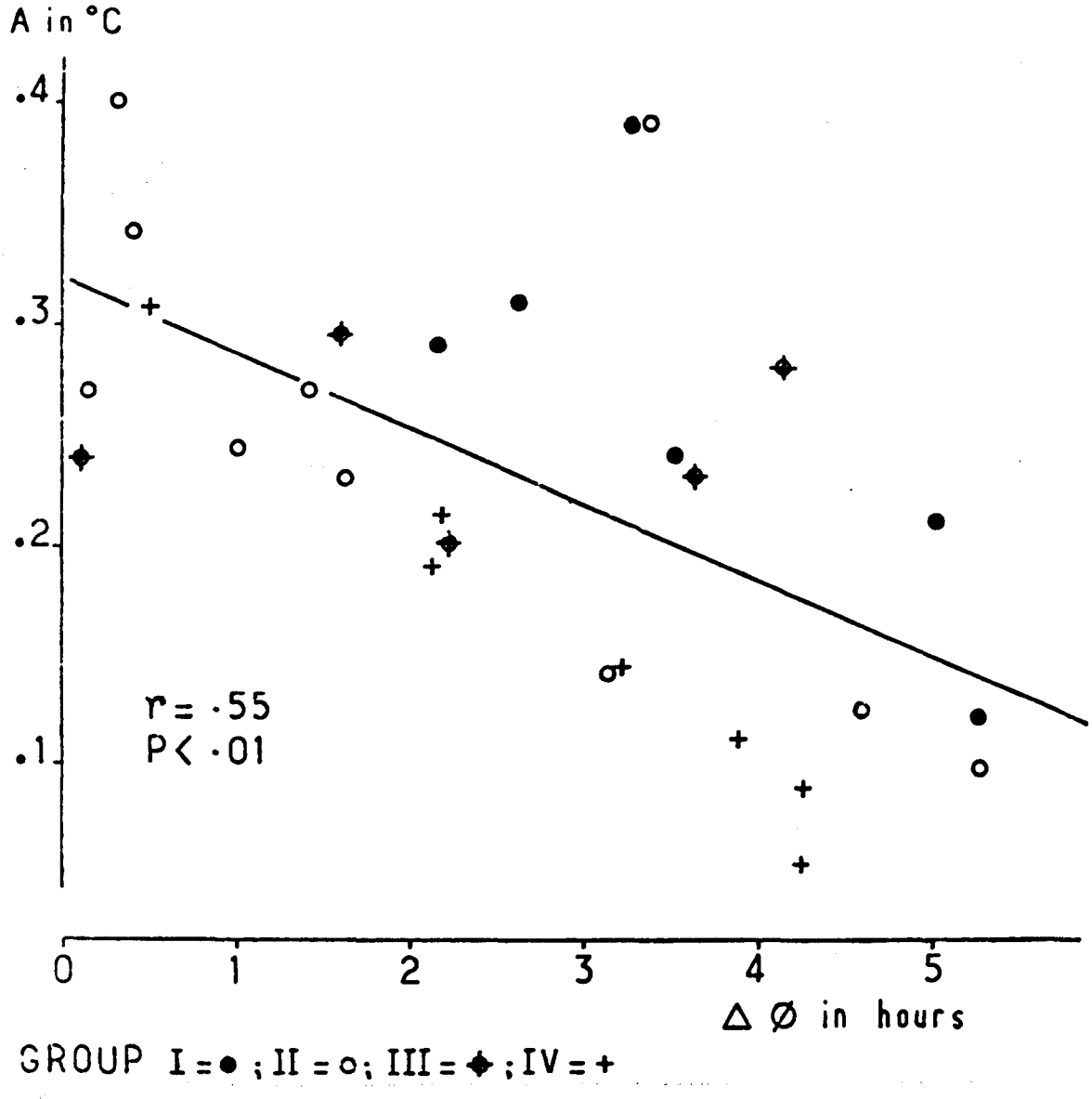


Figure 2. Correlation between mean individual amplitude A (in celsius) and acrophase shift ΔØ (in hours) of the oral temperature circadian rhythm.

Pooled data of the 4 groups considered in the study.

As and Øs were quantified in individual time series. The acrophase shift $\Delta\bar{\emptyset}$ resulting from the night shift (work starting at 21.00 ending at 05.00) could be estimated by the difference between Ø corresponding to night work and the $\bar{\emptyset}$ corresponding to work on other shifts. Thus, the individual mean amplitude $\bar{A}$, and acrophase shift $\Delta\bar{\emptyset}$, were used to retest the hypothesis that the larger the $\bar{A}$, the smaller the $\Delta\bar{\emptyset}$.

A statistically significant negative correlation was observed between $\bar{A}$ and $\Delta\bar{\emptyset}$ ($r = -0.55$; $P < 0.01$; figure 2).

The mean $\bar{A}$ value calculated from the 29 subjects is 0.23°C. With regard to this mean statistically significant difference in distribution were observed between groups. For example, in 7 subjects out of 10 in group II : $\bar{A} > 0.23$°C; while in 1 subjects out of 7 in group IV : $\bar{A} > 0.23$°C ($\chi^2 = 5.16$ with $P < 0.025$).

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RESULTS OF ANIMAL EXPERIMENTS

The results obtained by Yunis et al (19, 20) have some interesting aspects when compared with results of studies I, II and III. Circadian rectal temperature parameters (A and Ø) of different strains of mice (mainly CBA and NZB) were quantified before, during and after manipulations of the light-dark (LD) synchronizer in relation to aging of animals. Based upon the results presented in both of these papers we deduced that : (1) mice of strain CBA were autoimmune resistant; they adjusted slowly after a $\Delta\Psi$ resulting from a LD cycle manipulation and had a relatively small decrease in circadian A of the temperature rhythm with aging; (2) mice of strain NZB developed autoimmune hemolitic anemia, antinuclear antibodies and kidney lesions before one year of age; they adjusted rapidly after the same $\Delta\Psi$ of the LD cycle and showed a relatively large reduction in the circadian A with aging. In addition, results obtained by Yunis et al suggested that the speed of adjustment $\Delta\emptyset$ and the amplitude A of the temperature rhythm, as well as changes in A and $\Delta\emptyset$ with aging were of genetic origin.

COMMENTS

Results obtained from these three studies are in good agreement. On the one hand, they show a correlation between the circadian A and $\Delta\emptyset$, the greater the A, the smaller the $\Delta\emptyset$. On the other hand, results from subjects investigated by Andlauer et al (8) and by Reinberg et al (9) involving young and senior workers of chemical, steel and oil industries (with differences in both shift - schedule and shift-duration) show that good tolerance to shift-work is associated with a relatively large amplitude in the circadian rhythm of oral temperature.

Both of these hypotheses (a relationship between A and $\Delta\emptyset$ and a relationship between A and tolerance to shift work) were tested in the same groups of subjects with the study III.

In order to understand the relationship between the temperature circadian A and the tolerance to shift-work the possible role played by aging (and/or the number of years of shift-work) must be taken into account. In these experiments we are dealing with subjects of different ages and tolerance rather than with the effect of aging. The animal model of Yunis et al (19, 20) suggest that the aging-related reduction of the circadian temperature A could be genetically dependant.

Nevertheless, other experiments are necessary to test the hypothesis whether human subjects with a relatively small A (or a small A resulting from aging?) may become intolerant to shift work. However, the possibility that an observed small A results from a poor tolerance to shift work cannot be excluded.

PRACTICAL PERSPECTIVES

If the long term tolerance to shift work is associated with a large circadian A and a slow adjustment of the temperature rhythm, shift schedule which do not allow subjects to adjust to a "new" synchronization seem to be preferable. More precisely, a rapid rotation (with shifts every 2 to 4 days) seems to be a better choice thant the conventional weekly rotation. The argument in favor of a rapid rotation system relates to solving the problem of the long-term tolerance to shift work.

However, it should be kept in mind that in previous studies (6-9) the investigated shift workers adjusted rapidly, as group mean. This ability may be related to age. The employees were rather young at the time of the study (34.5 and 24.4 years of age as respective means) and it seems that the adjustment is faster in young than in senior shift workers. In addition the samplesof subjects were less homogenous than expected with respect to long-term tolerance to shift-work. We were indeed dealing with operators selected on the basis of (a good) tolerance to shift work -- tolerance in this case being less than 10 years of this type of occupation in 23 cases out of 26. Intolerance to shift-work may be revealed later as it is the case for subjects of group IV in the present study III. In considering the findings the rapid adjustment of a young subject seems to be an immediate advantage (if any), but it is of no help in predicting whether or not tolerance to shift work will persist for 20 years or more. Nonetheless, the circadian temperature rhythm amplitude appears to be a good candidate for a chronobiologic index of the long-term tolerance to shift work. Obviously, other studies are needed to extend the practical application of these findings.

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CIRCADIAN RHYTHMS IN AIR OPERATIONS

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SUMMARY

After a brief introduction into the principles of environmental and biological timing systems, the phenomenology of post-transmeridian de- and resynchronization of circadian rhythms is presented, its control and modification through external and internal factors described, and the consequences for human efficiency and health discussed. There are conclusions drawn as to possible relief measures, and formulas and models reviewed which try to define the physiological processes and predict work loads occurring in transmeridian flight operations. Finally, the incorporation of circadian rhythm's aspects into Rest/Duty Regulations is described.

INTRODUCTION

Where air transport operations do not involve geographical displacement along the latitudes but, only, call on human efficiency during sustained activity around the clock they must deal with the general principles of circadian rhythmicity and its implications for physical and mental performance; this aspect has been reviewed earlier during this lecture series. Where air transport operations occur as transmeridian flights they, in addition, bring along specific consequences for the human organism which were called "Desynchronosis" (143), "Transmeridian Dyschronism" (57) or "Jet Lag Syndrome". It is this phenomenon which will be discussed here. For a better understanding of the mechanisms implicated, at first, a brief description may be given of the physical and biological principles involved.

The Temporal Structure of the Environment

The globe is divided from pole to pole into 360 meridians. Due to earth rotation daylight travels within 4 minutes from one meridian to the next. The geographical time difference, thus, comes up to 1 hour per 15 meridians. This corresponds to one time zone and results in a total of 24 time zones around the globe (Figure 1).

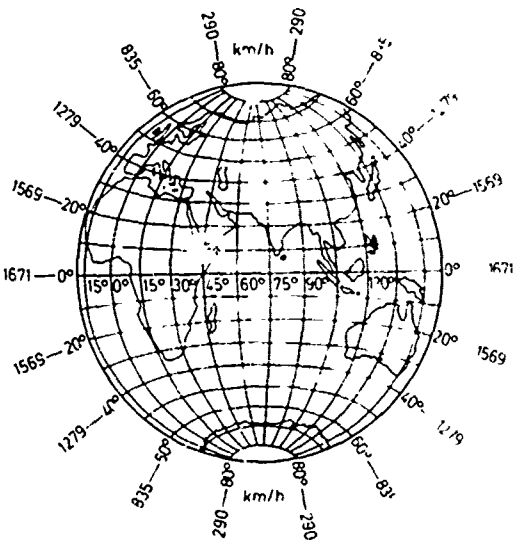


Figure 1: Globe with meridians and speed of daylight.

When 15 meridians are crossed the time of day changes: During east-bound travel the day shortens, that is, the clock must be set ahead for as many hours as time zones have been crossed; during west-bound travel, correspondingly, the clock has to be set back.

Biological Circadian Rhythms

The temporal structure of the environment in 24-hour periods corresponds to the periodic oscillation of physiological functions and behaviour which has been defined as circadian rhythm.

Often, different rhythmic functions exhibit diverse curves with respect to the temporal position of minima and maxima as well as to the amplitudes. Under constant conditions, i. e. during isolation from the temporal environment, biological rhythms oscillate with spontaneous period lengths deviating from 24 hours (7, 14), and different functional systems, like body temperature and activity, sway with divergent frequencies, a phenomenon which was called "internal desynchronization".

Persistence of rhythms under constant conditions and the phenomenon of internal desynchronization give rise to the hypothesis that biological circadian rhythms are endogenous in origin, selfsustained and controlled by more than one "internal clock" (16, 162). Several models have been developed to describe the circadian timing system (7, 159, 162) of which the non-hierarchical multi-oscillatory model (105) explains the presently known facts best (Figure 2).

Interrelationship between Environmental and Biological Timing Systems

The fact that under normal conditions biological rhythms concordantly show periods corresponding exactly with the length of one day, has been explained with the influence of environmental synchronizers or Zeitgebers. For plants and animals these are, in particular,

the cyclic variations of light and temperature directly related to earth rotation. For man, knowledge of the clock-hour and daytime-related social activities (11), like meal timing (53, 58, 64, 127), work and rest scheduling and, in particular, sleep-begin and sleep-end (151), seem to be of greater importance as temporal reference than the natural light-dark cycle. In addition, electromagnetic fields in the 10 Hz range may act as synchronizers in the living organism (158).

It is the inability of the endogenous rhythms to adapt rapidly to a sudden shift of external synchronizers which causes a transitory desynchronization or dysrhythmia of body and environment.

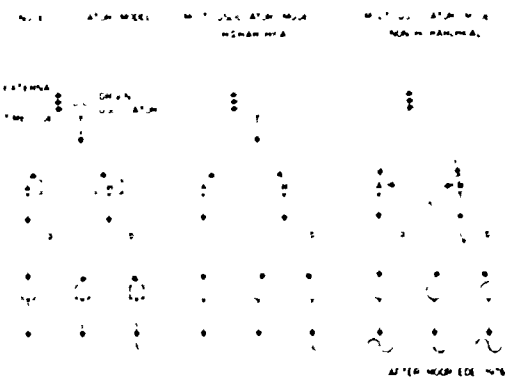


Figure 2: Oscillator models.

POST-TRANSMERIDIAN DESYNCHRONIZATION

After transmeridian flights, in a certain percentage of individuals well-being is subjectively impaired. Impairment becomes mainly manifest in vegetative functions which, like hunger, wakefulness and sleepiness, and evacuation of intestines, are daytime dependent: due to the persistence of biological rhythms, in relation to the environment, they appear at unusual and unconvenient hours. Apart from subjective symptoms, even if they are not evident, objectively post-transmeridian desynchronization is demonstrable in numerous psycho-physiological variables. Strughold (142) seems to be the first who published a scientific paper on this subject.

Rhythms of Physiological Variables

Postflight desynchronization of human physiological rhythms has been described during the last 20 years in a series of investigations, mainly, for body temperature, cardiovascular and metabolic variables, and hormone and electrolyte excretion (29, 33, 35, 37, 41, 45, 50, 52, 54, 57, 58, 63, 65, 66, 67, 86, 91, 92, 102, 125, 126, 134, 137, 138, 153, 157).

From our own research (on various groups of 8 young males transported on the transatlantic route), examples of postflight rhythm changes are presented for 17-OHCS excretion (153) in Figure 3, and for heart rate response to submaximal exercise on a bicycle ergometer (157) in Figure 4; they exhibit some features typical for desynchronization (though not all

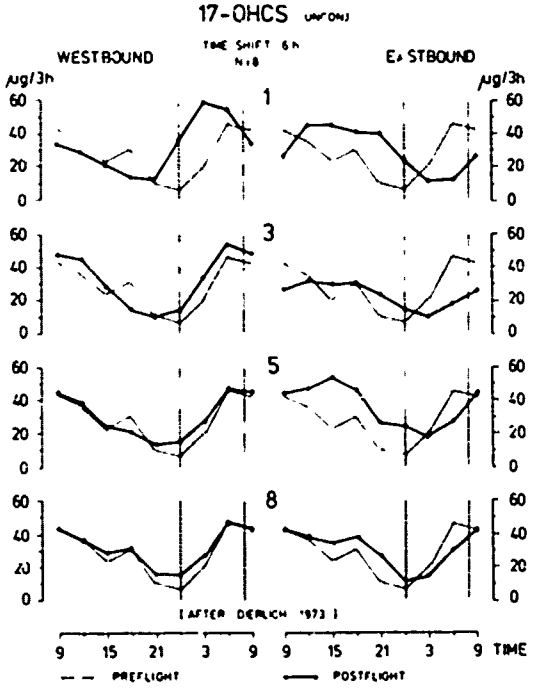


Figure 3: Urinary 17-OHCS excretion after transmeridian flights.

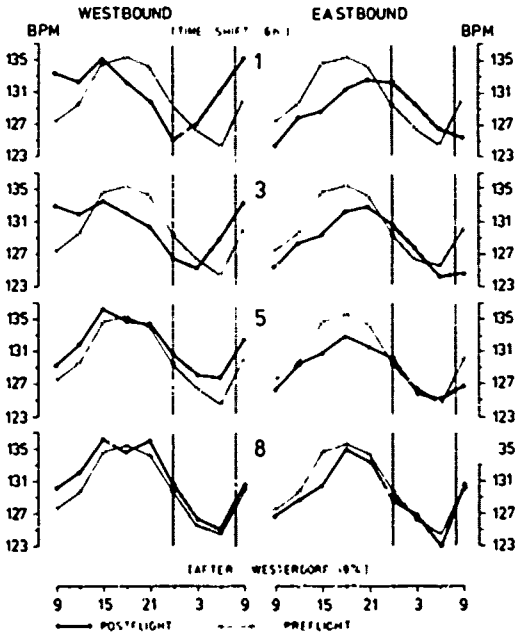


Figure 4: Heart rate response to submaximal exercise after transmeridian flights.

of them, necessarily, specific and appearing simultaneously):

- a displacement of the curve to the left after west-bound transportation, a displacement to the right following the east-bound flight (shift of rhythm into the normal position occurring gradually);
- an alteration in the range of oscillation (sometimes, resulting in disappearence of rhythm);
- a change in the 24-hour mean;
- lower functional values (than preflight) at certain daytimes, higher values at other hours of the circadian cycle, the positions of higher and lower postflight values depending on flight direction.

Through continuous pre-, in-, and postflight measurements (83) it is possible to demonstrate some additional modifications of circadian rhythm (Figure 5):

- speed differences in shift of maximum and minimum (134, 153);
- alterations of the "form-factor", the ratio of the length of the inclining section to the length of the declining section of the circadian curve (160).

Both changes are dependent on flight direction: The maximum shifts earlier and farther, and the form-factor becomes higher after west-bound transportation; both is reversed when travel was east-bound.

Continuous measurements allow, also, to show that circadian rhythm of body temperature, immediately after an 8-hour flight across 6 time zones, is still entrained to preflight environmental periodicities, and shift commences, only, with onset of the first sleep period in the new time zone (Figure 5). This finding suggests that faster means of long-range transportation, like supersonic flight, through return on the same day allows to avoid shifts of biological rhythms; otherwise the degree or "jet lag" will not change, since it is maximal with subsonic speed of flight already. On the other hand, it was shown before, that speed of travel not resulting in more than 30 min time shift per day, for instance by ship, permits complete adjustment of body temperature rhythm already during the journey (134).

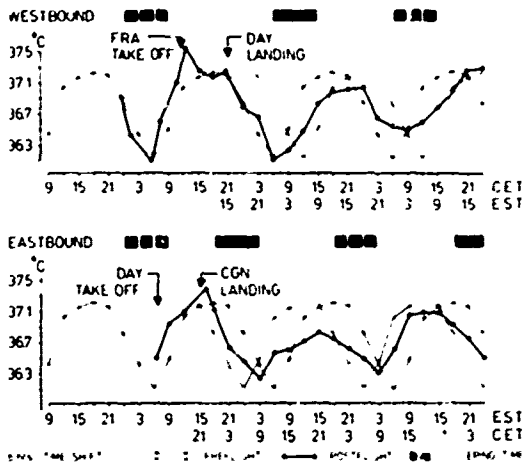


Figure 5: Continuous measurement of body temperature.(Preflight rhythm is hypothetically shifted into the postflight position expected after completion of resynchronization.)

Finally, it should be mentioned that control investigations have shown displacement of biological rhythm (phase shifting), indeed, to be the specific consequence of a disturbance in the temooral relationship of body and environment; while other changes of the form of a 24-hour rhythm including those of amplitude and 24-hour mean may, also, result from other forms of human activity like strenuous flights in north-south direction or vice versa, for instance (51, 52, 68, 138).

Rhythms of Mental Performance

In principle, mental performance rhythms, desynchronize in a similar way as just described for physiological parameters (75, 76, 81, 86, 154). In fact, some task variables like psychomotor performance respond to a rapid phase-shifting of the environmental Zeitgebers in close analogy to the rhythm of body temperature (Figure 6). The changes typical for a post-transmeridian desynchronization are again: Displacement of rhythm, modification of amplitude and 24-hour mean, and lower functional values at certain hours, higher values at other daytimes (Figure 7). For instance, on the first day after crossing of 6 time zones performance degradation becomes obvious in the later afternoon and early night after a west-bound flight, and in the morning and afternoon when travelling had been in the opposite direction. On the average, impairment at the "typical" hours reached maxima of -8 % and -10 % of the corresponding preflight level when computed for west-bound or east-bound transportation, respectively (Figure 8). It was often demonstrable for up to 5 cycles; but statistical significance, usually, was lacking by the 3.postflight day. In view of the fact that through a high motivation and extra effort, circadian cycling of mental performance may be overcome (see pertinent section in the paper on Human Performance Rhythms) we must conclude that the above mentioned periods of the circadian cycle are those times where it will be much more difficult, at least, to obtain the preflight performance level.

As an indication of total performance efficiency, the 24-hour mean is of particular operational significance. We were able to prove a postflight degradation of performance for several task variables; however, it was small, and statistical significance was reached only after east-bound transportation (Figure 9). Halberg et al. (57, 60) also demonstrated deterioration of performance, only, following east-bound flights, while Hauty and Adams (66,67).

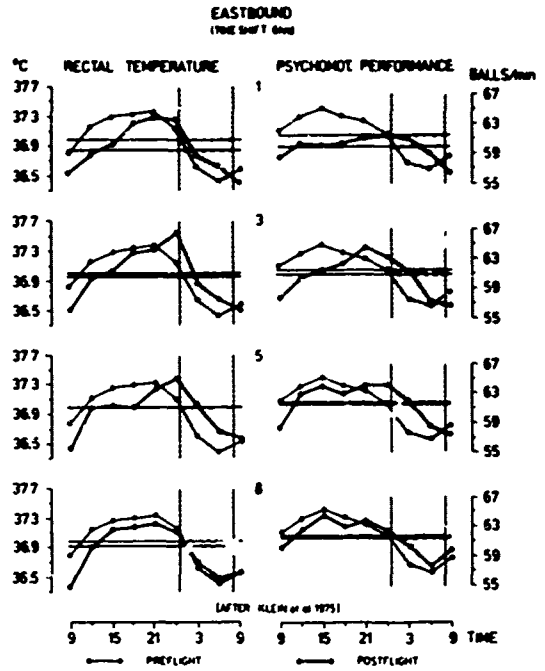


Figure 6: Body temperature and psychomotor performance rhythms following an east-bound flight. (24-hour mean is indicated through horizontal lines.)

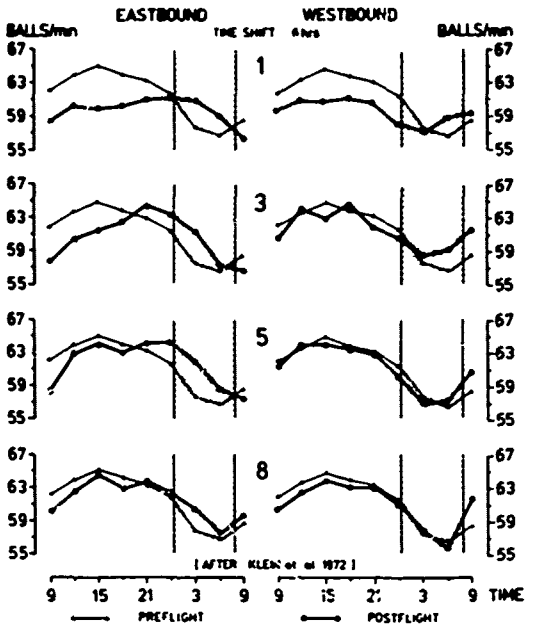


Figure 7: Psychomotor performance after transmeridian flights.

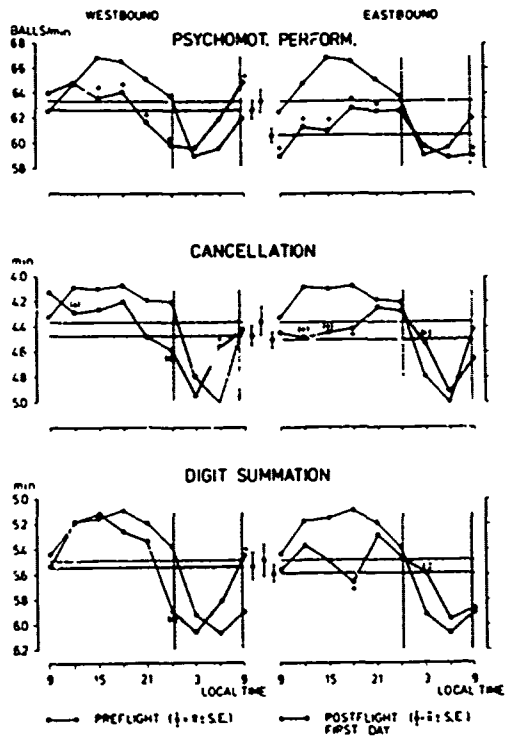


Figure 8: Three performance tests after transmeridian flights. (Time difference: 6 hours.)
(*) 0.1 > p > 0.05;
* 0.05 > p > 0.01.

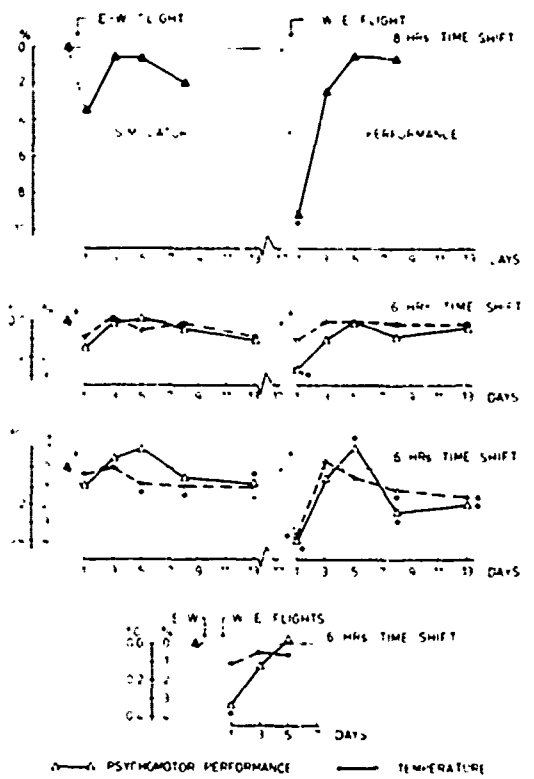


Figure 9: 24-hour means of temperature and performance rhythms after transmeridian flights. (For further explanation, see figure 8.)

found a remarkable impairment, only, after west-bound travel which, however, was related with a time in transition of 23.5 hours as against 15.5 hours after east-bound transportation.

To what degree disruption of rhythm, or other causes, like flight stress and fatigue, contribute to the deterioration of the overall level of mental performance is not easy to decide. The decrease of performance in airline personnel (123, 124) and in animals (130) following simulated time zone flights indicate just as much a direct effect of internally disturbed time structure, as the finding of Taub and Berger (145) who demonstrated a performance degradation after shifts of sleep periods without changes of prior sleep length or any specific alteration in the electrophysiological patterns of sleep. On the other hand desynchronization (displacement) of performance rhythms in man (136) and resistance rhythms in animals (109) without alteration of the 24-hour mean indicate that a change in the overall level of rhythm is not a compulsory aftermath of rhythm disruption.

Rhythms of Physical Performance

During international sportive competitions athletes' subjective complaints about sleep loss and fatigue, and observations of impaired performance after transmeridian flights have been related to the "jet lag" syndrome (133, 165). Unfortunately, postflight measurements round the clock of physical performance variables are almost lacking, completely. We know, only, of the evaluation of "grip strength" (125), and of our own assessment of heart rate responses to submaximal exercise loads (Figure 4) which could be taken as an indirect measure of aerobic performance capacity.

Indeed, did exercise heart rate reveal desynchronization; but in view of the somewhat complex circadian relationship between heart rate, oxygen uptake and exercise capacity (84) it seems difficult to predict, from the data available, as to what degree and in what way performance efficiency might be impaired. From the fact, that (similar as for mental performance) physical efficiency during the night is lower than during the day one could speculate that (in dependence on flight direction) a decrement or an increment of physical performance variables might be expected at similar times as observed for instance for psychomotor performance.

Basing on the heart rate response (Figure 4) we would assume that it might be more difficult to produce preflight performance between 1500 hours and 0300 hours after a west-bound flight across 6 time zones, and between 0700 hours and 1900 hours following an eastward flight. A prediction as to the order of magnitude of these changes, as to their duration and as to the response of the overall level of performance (24-hour mean) is, however, far beyond any reasonable speculation.

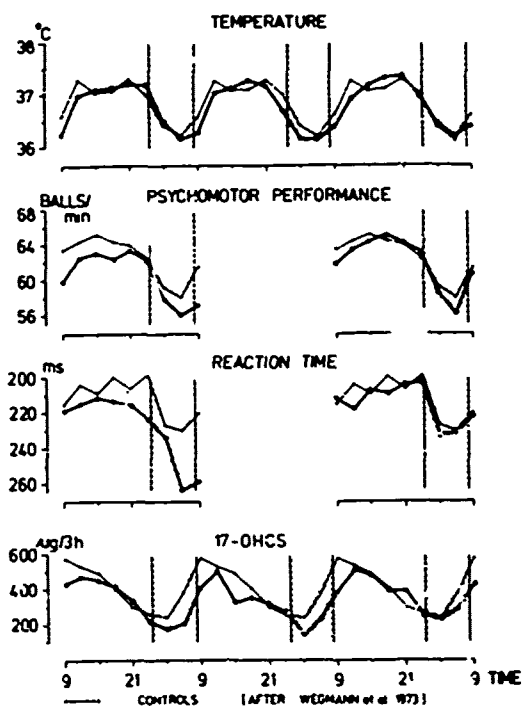


Figure 10: Circadian rhythms before and after a rapid transmeridian round trip Frankfurt-Chicago-Frankfurt.
(Time difference: 6 hours, layover time: 24 hours.)

Desynchronization in Consequence of a Rapid Transmeridian Round Trip

Often aircrew duty is such, that an outgoing transmeridian flight, after a short sojourn in the new time zone, is shortly followed by a return flight to the home base. With respect to desynchronization of circadian rhythm such flights have been investigated, only, rarely; in addition, different variables have been followed, which makes conclusions difficult. In one study, the layover in the new time zone was 2 hours, only; as a result there was a reduction of the amplitude of the rhythm of urinary electrolyte excretion on the first day after the return to the homebase, but no further changes for instance of phase angle (50). This seems not surprising in view of the finding mentioned above, that, only, with the first sleep period in the new time zone shift of biological rhythms commences.

This prerequisite was certainly fulfilled in an early study on 8 subjects who on a round-trip between Paris and Alaska stayed 20 hours in Anchorage before returning to France. According to the authors, the experimental variations of 17-OHCS and potassium-excretion in urine immediately became concordant with the reference circadian curves on return to Paris (92); however, for analyzation mathematical models, apparently, have not been applied. Also, Buck (25), measuring psychomotor performance on pilots (over 2 - 3 min once immediately before and after transmeridian flights), concluded that "subjects remained adapted to

local time at the home base", if layover time in the new time zone was only 24 hours. Contradictionary, in a study performed by our own group (63, 91, 137, 155) circadian rhythms of 17-OHCS, body temperature and psychomotor performance in comparison to pre-flight positions, showed a significant phase shift in the magnitude of 1.5 to 2.0 hours on return to the home base which, on the 3rd day was reduced to about 1 hour (Figure 10). Curves of catecholamines and reaction time were not displaced. A significant reduction of the 24-hour mean was evaluated for all variables except noradrenalin; also the amplitudes were significantly altered in some rhythms (63, 91, 137, 138).

Layover times abroad were 2 - 3 days in a Japanese investigation on a round trip between Tokyo and San Francisco. Under this condition circadian rhythms were disturbed while on route; normalization after returning to the home base took between 1 day for 17-OHCS and 17-KS, and 4 - 5 days for heart rate and body temperature. The authors concluded that a short-stay flight pattern, because of shorter resynchronization times, minimizes the ill effects of time zone flights. Similar conclusions have been drawn for rapid rotating shift work (55, 88).

Response of Sleep-Wake-Cycle

The sleep-wake-cycle is part of the circadian timing complex, it, therefore, participates in the desynchronization of body and environment. Normally, the desire to sleep coincides with the environmental phenomenon "night" which is not just darkness but more so the social related period of relative inactivity. After transmeridian flights the elementary disposition to be active or not, with relation to the environmental cycle, exist at unusual and inappropriate daytimes. This is the reason that sleep disturbance is one of the major, subjective complaints of transmeridian air travellers. Difficulty in falling asleep, repeated spontaneous awakening during the night, and abbreviation of sleep by early morning wakening are symptoms which have been substantiated by sleep charts and diaries.

Sleep duration and sleep pattern. The view has been expressed that the most common cause of fatigue amongst pilots, generally, is not getting enough sleep. In view of this statement the small number of research on this subject presently existing is surprising. Even, though results are not consistent, they suggest that the problem may be a real one.

From an inquiry on 312 crew members of an European airline (93) it became obvious that during flights on the transatlantic route, 55 % subjectively experienced a shorter than normal sleep. Individual differences seemed considerable. Around one fourth reported to sleep normal from the first night on, between 40 to 45 % had this feeling only during the second night, and sleep disturbance lasted even longer in 25 to 35 % of those questioned. Twenty percent admitted to use hypnotics when on flights,as against 5 % during duty free periods at home; in stewardesses this figure was highest with 44 %. A somewhat similar result, with respect to the use of hypnotics by flight crews, was obtained in a recent study through personal interview technique on 358 crew members (69): Only 54 % declared never to use hypnotics on the line, whereas at home this figure was 87 %; of those admitting use of sleeping medication, 21 % did so "rarely", the same percentage "sometimes", and 4 % "frequently". In the same study similar figures were given for alcohol as an aid to sleep with the difference that 11 % took alcohol "rarely", but 11 %, also, "frequently". Of particular interest were the answers with respect to the custom of the methods of use of hypnotics: Though 6 to 8 hours before duty were the more frequent figure, use of up to 4 hours before duty was admitted; in 86 % Nitrazepam (Mogadan) was taken.

In view of the long lasting residual effects of most hypnotics, including Nitrazepam, on human performance (74, 112), the practice of an uncontrolled consumption is precarious. In two studies, there have been some drugs identified which seem relatively harmless with respect to side effects on performance; in one case (112) it was Diazepam (10 mg) and Methaqualon hydrochloride (400 mg), in the other (62) Flurazepam (30 mg). However,recently polyneuropathy has been reported as effect of Methaqualone, so that it, probably must be eliminated, again, from those hypnotics which could be recommended for use by aircrews, if (a) requested by an individual because of serious sleep peroblems while on routes with irregular sleep patterns, and (b) the potential user is instructed to observe the following rules (62):

- try the drug in a low dose several nights before using it on a regular trip;
- not use the drug during layover time if "hangover" is significant during the trial use;
- not use the drug if the layover time is less than 12 hours.

Preston and coworkers, in the early 70s, studied sleep with the use of sleep logs and of subjective assessments of fatigue (121, 122, 124). The results obtained in aircrews operating on world-wide schedules may be summarized as follows.

In comparison to normal pattern and duration, sleep on route

- was disrupted and broken into many periods;
- was well below the individual normal amount at home, average differences per 24 hours occasionally being as high as 2.5 to 3.0 hours;
- resulted in a cumulative sleep loss; this was i.e. during a 15 day-flight operation in the magnitude of almost 30 hours at the maximum and 10 hours at the minimum, the older crew members experiencing the greater sleep deficit (Figure 11).

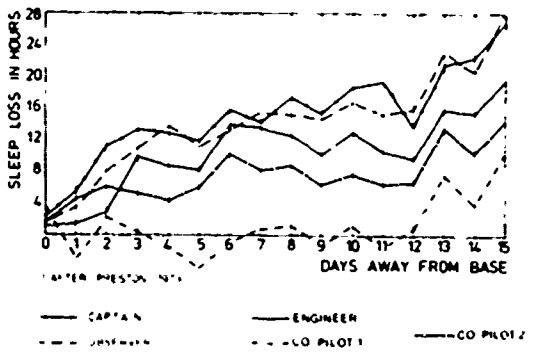


Figure 11: Cumulative sleep loss during a world-wide flight schedule.

(See ref. 80, 164 for the interaction between sleep loss, circadian rhythm and performance.)

Air cabin crews, mainly investigated on transatlantic routes, showed a consistent loss of five to six hours per night flight, or of about one hour per day on route; loss of sleep in this study seemed mainly associated with the number of night flights at local time, but hardly with time zone changes (124).

Also, in a longitudinal study over 3 months on 23 crew members operating in patterns of 3 and 5 days on the Tokyo-Moscow (Western Europe) route, a sleep loss of 6 to 10 hours on night flights was recorded, amounting to 1.5 to 2.5 hours per day on route (17). It was concluded that several days were necessary for recovery. From sleep deprivation studies it is generally believed, however, that one night of somewhat extended sleep of about 13 hours makes the symptoms, usually, disappear in most individuals (131).

The average sleep loss evaluated in these studies are comparable with those quoted for night or rotating shift workers: 0.5 - 2.0 hours per day; however, if naps were taken into account the sleep deficit seemed to be reduced (134). The situation seems to be similar in the aerospace environment.

Nicholson (110, 111) following the sleep patterns of aircrews operating world-wide routes, established that sleep disturbance arising from irregular duty periods and through adaptation to time zone change, rather than sleep deprivation is the main problem. He concluded that there was no overall sleep loss as long as the total sleep over each 3 days period preceding any duty period was similar to that observed under normal conditions. Short periods of sleep (naps) were observed both, during rest periods and during duty, when the workload was not demanding. The occurrence of inflight sleep of cockpit crew members was meanwhile confirmed through micro-sleep EEG patterns during the over-night parts of flights with the aeroplane on autopilot (28).

According to Nicholson "naps appeared to play an important part in maintaining the necessary balance of sleep and activity". Deducting his conclusions from observations on a few individuals, only, he admitted that "personal modification of the natural need to sleep plays an important part in the overall strategy of sleep planning and, therefore, in minimizing tiredness during duty". Indeed, in some of the other sleep studies mentioned above, the individual difference not only to be able to sleep on route during rest periods was high, but also the ability to take sleep while on duty (17, 69, 122). Moreover, we are left with the decision whether naps on duty should, deliberately, be incorporated into the system.

Sleep structure. According to differences in the electrical activity of the brain (EEG), the eyes (EOG) and the muscles (EMG), sleep has been divided into stages: stage 1 to stage 4 (orthodox) sleep and REM (Rapid Eye Movement, or paradoxical) sleep. The stages do not emerge in a random order but are distributed across the total sleep period in a characteristic manner: Stage 3 and stage 4 sleep (high amplitude slow-wave sleep) predominates in the early part, while REM sleep does so in the latter; there are 2 to 3 periods of stage 4 and 4 to 5 periods of REM sleep. Also, sleep stage percentage is reproducible in different nights, though it varies slightly from individual to individual, and changes with age; so does sleep length (150).

It has been speculated that sleep as part of a basic rest-activity cycle, in addition to the intrasleep characteristics, might have daytime related circadian aspects. This hypothesis was supported through an obviously circadian distribution of sleep stages: if sleep was interjected into different time periods of the circadian cycle, the proportion of stage 3 and stage 4 sleep decreased from a maximum in the early hours of the night to a minimum between 0400 and 0800 o'clock in the morning, only to increase then again during the day; REM sleep took about a specular course (44, 150). Later it was established, however, by autocorrelation analysis that there was no consistent circadian influence on the duration of REM intervals but rather the REM cycle is a sleep-dependent rhythm hardly related to the time of day of sleep (106, 107).

Sleep displacement into different segments of the 24-hour cycle modifies prior wakefulness, sleep onset times and length of sleep; these factors, again, are known to affect the structure of sleep. This may be the reason that the results from transmeridian studies (42, 44, 81, 90, 104, 149), like those from shift workers or sleep inversion in the laboratory (36, 47, 90, 145, 150, 152, 156) are not very consistent. (An example from own investigations is presented in Figure 12.)

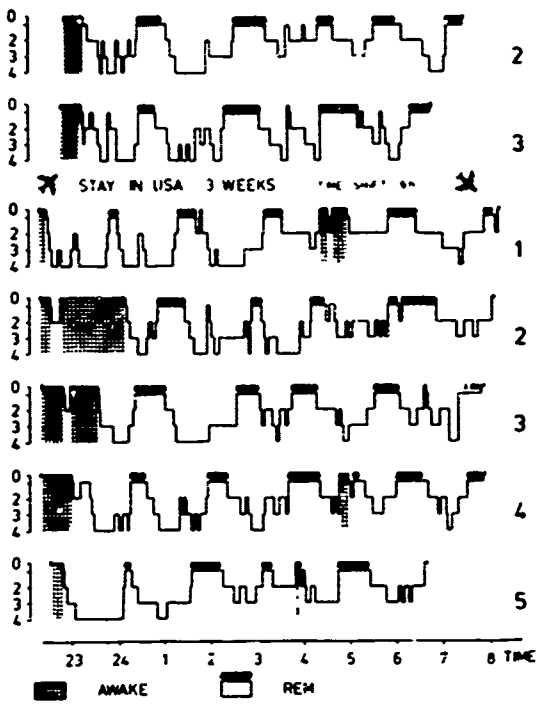


Figure 12: Sleep structure after an east-bound flight (60 years old woman).

The attempt to compile the findings reads as follows:

- delay to sleep is often shortened if prior wakefulness was long and stressful; it was more consistently observed during the first postflight night and after eastward time shift, later, sleep latency may be prolonged;
- ..wakenings and transitions between sleep stages occur more often; the increase in awake time may cause a reduction in total sleep time, in particular, if time in bed is limited by programmed work-rest schedules;
- delay to the first REM period is often reduced, REM sleep occurs ealier;
- duration of REM sleep may be reduced, this was reported after delay and advance shifts (west-bound and east-bound transportation); but also, an increase of REM sleep was recorded after advance shifts;
- duration of stage 3 and stage 4 sleep occasionally was increased; this, again, was demonstrated more consistently for east-bound transportation, and for the first postflight period which is particularly affected by the stress and fatigue of flying;
- sleep structure seems to adapt fast to shifts of the environmental time cues; in general, it normalizes within a few days.

POST-TRANSMERIDIAN RE-ENTRAINMENT

Synchronization of circadian rhythms in man occurs to a high degree under the influence of social time cues. During night and shift work, environmental and social synchronizers diverge; this seems to be one reason, why night- and shiftworkers often are in a continuous state of circadian desynchronization. Transmeridian flights favour re-entrainment of biological rhythms since all components of the temporal environment are shifted at once. Nevertheless, does it take days to weeks before the biological timing system is completely re-adjusted. The rate of resynchronization is affected by flight direction, is divergent between physiological rhythms, depends on the characteristics of time cues, and may be different between individuals.

Circadian Asymmetry

In an early study (77) on 75 aircrew members flying transatlantic shuttle, subjective estimations of load as well as objectively measured changes in psycho-physiological variables were more pronounced after east-bound flights than after flights in west-bound direction. A higher number of flight lags contributed to the results in the expected manner but did not affect the outcome with respect to flight direction. However, since west-bound flights, always, were outgoing and day flights, eastward flights, always,homegoing and night flights, and in addition, layover times nad been 30 hours, only, the results could hardly be conciusively associated with the direction of time shift.

Later, it became obvious that retardation and acceleration of the "internal clocks" occur with different speed: Nearly all flight experiments indicated a faster shift of rhythms after east to west flights in comparison with west to east flights (54, 56, 60, 65, 66, 67, 76, 93, 125, 135, 153). Through several experiments in which German and U.S.A. residents served as subjects, and flights in both directions occurred during daytime, we then, excluded time of day of flight and homegoing/outgoing as main contributing factors for circadian asymmetry (Figure 13).

Also, the hypothesis was supported by experimental results (154) that a variation within the length of the wake period, as caused by different flight schedules, does not affect the course of de- and resynchronization as long as a sleep period of normal length precedes the following duty period (Figure 14): It was insignificant for the response of the 24-hour mean and for resynchronization of phase angles whether the transmeridian transportation required a period of 33 hours of wakefulness followed by 9 hours of sleep (east-bound night flight), or whether subjects had to stay awake for only 17.5 hours, and then slept for 7.5 hours before they were tested (east-bound day flight).

In our results resynchronization on a total average was faster by about 50 % following the west-bound flight: In 17 assessments of various psycho-physiological variables,

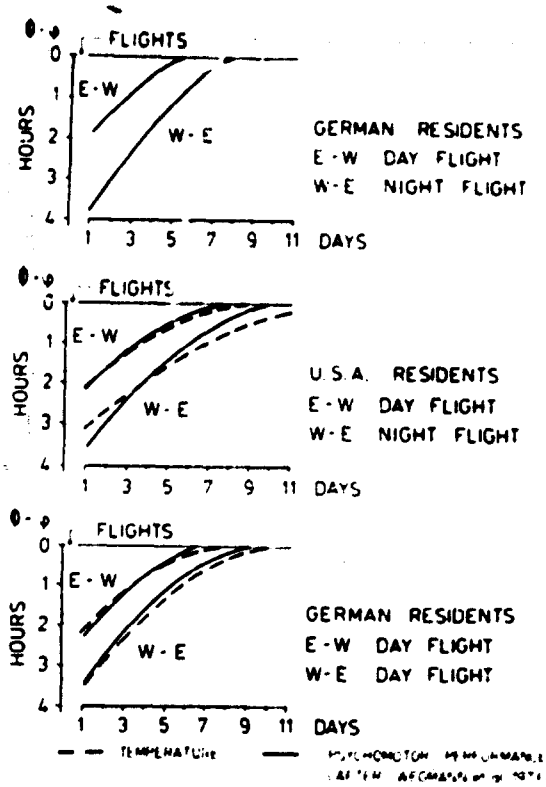


Figure 13: Resynchronization of phase angles in 3 different groups of subjects showing circadian asymmetry to be independent from relative flight direction and time of day of flight. (Time difference: 6 hours. ¢ - ψ: Phase angle difference between environment synchronizers represented through local time, ϕ, and the biological rhythms, ψ; "0" indicates a relationship between the two, identical with that before the flight.)

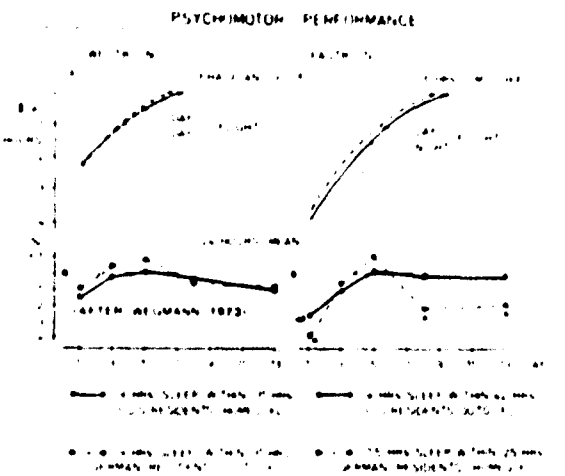


Figure 14: Independence of resynchronization from relative flight direction and length of preceding wake period. (For further explanation: see figures 8 and 13.)

including heart rate, body temperature, catecholamines, 17-OHCS, and various mental performance tasks (each one evaluated from 8 subjects on flights in both directions), re-entrainment occurred with a rate of 88 min/day and 56 min/day as consequence of west-bound and east-bound transportation respectively.

It was shown earlier that the direction of the circadian asymmetry varies with the species and with the natural length of the circadian period: In birds (15) and in man, if the period length was shorter than 24-hours (8, 160), resynchronization was faster after an advance shift of time cues corresponding to an eastward transportation; in species with period lengths usually longer than 24-hours (including man) the opposite was true (43). However, for man there are remarkable exceptions: in some isolation experiments, re-entrainment after advance shift of artificial Zeitgeber, with 80 min/day was faster than after delay shift with 57 min/day (10), even, if the circadian period was longer than 24 hours (160). As possible reasons for the difference to flight experiments, knowledge of the purpose of the study and strength of time cues have been discussed (12).

Antidromic Phase Response and Re-entrainment by Partition

Usually biological rhythms re-entrain by shift in the same direction as the environmental Zeitgebers. However, several cases have become known in which the opposite was true: a so-called "antidromic" phase response (61, 78). Often this process is accompanied by a splitting of rhythms of different psycho-physiological functions, a "re-entrainment by partition" (10). This phenomenon, meanwhile, was observed during a 12-hours delay shift of sleep time in a hospital (94), as consequence of a 6-hours advance shift in an isolation unit (163) and after a 9-hours advance shift following transmeridian flights (Figure 15): 8 subjects resynchronized body temperature, psychomotor performance and 17-OHCS rhythm after a west-bound flight by a delay shift; after eastward transportation all subjects re-entrained rhythm of performance and 17-OHCS by an advance shift. But, only, 4 subjects did so with body temperature, while the other 4 subjects delay-shifted the temperature rhythm in spite of the fact that this meant a shift across 15 hours instead of 9 hours.

Aschoff (9) has pointed to the fact that the probability of partition occurring seems to be greater after advance-shifts (east-bound flights) than after delay-shifts (west-bound flights), and seems to increase with the extent of shift or the number of time zones crossed. We have speculatively related the preference of man for delay shifting with his easier adaptation to this direction (96). But free-running cycling due to weakness of Zeitgeber has also been discussed as possible reason (43).

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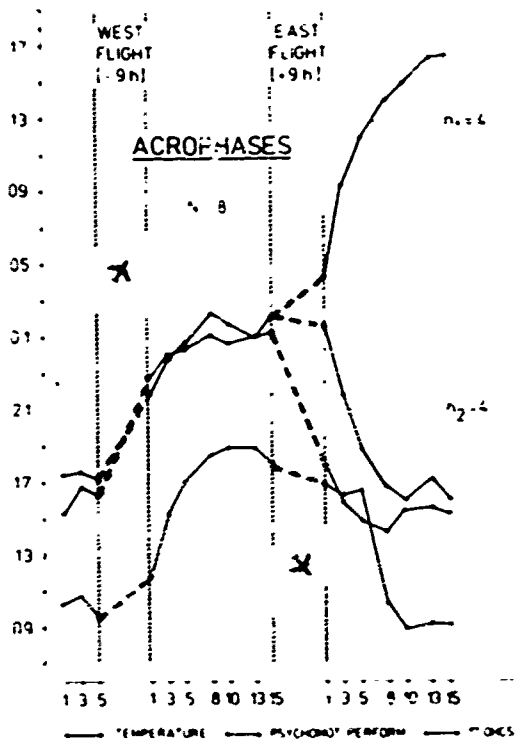


Figure 15: "Resynchronization by partition" in one group of subjects after an east-bound flight.

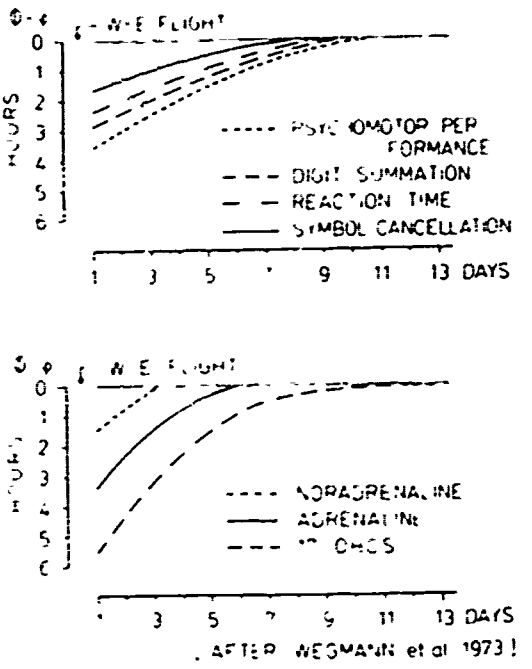


Figure 16: Difference in rate of resynchronization of rhythms after a transmeridian flight: internal dissociation. (For further explanation, see figure 13.)

Internal Dissociation

Different circadian rhythms resynchronize with divergent speeds; this is true for physiological functions, as well as for mental task variables (Figure 16). If the average figures, given above for delay and advance resynchronization, are broken up for different circadian rhythms, divergent shift rates result (Table 1).

In other studies on man, also divergencies of speed of resynchronization for different functional rhythms have been observed which, in general, well agree with those demonstrated by us; from these studies, in addition to the classification shown in the table, blood pressure as well as urinary sodium, calcium and chloride excretion must be rated as fast adapting, while urinary potassium and serotonine are slow (56, 64, 93, 96, 102, 128, 141, 161).

FUNCTION	WESTBOUND	EASTBOUND
CATECHOLAMINES (URINARY)	135	90
ADRENALINE	90	60
NOR-ADRENALINE	180	120
MENTAL PERFORMANCE	93	57
PSYCHOMOTOR PERF.	52	38
REACTION TIME (VIGILANCE)	150	76
HEART RATE	90	60
BODY TEMPERATURE	60	39
17-OHCS (URINARY)	47	32
ALL	88	56

Table 1: Shift rates after transmeridian flights in minutes per day.

However, the figures listed in table 1 do not yet reflect the fact that re-entrainment very often occurred in a non-linear way (75, 82), being faster immediately after shift of time cues, and slower later on. In addition, the extent of daily shift was in relation to the number of time zones crossed i.e. it was the higher, the larger the phase angles difference between the environmental and biological timing systems. (For a more extensive discussion, see reference No. 5, and the section "Formulas and Models" later in this paper).

It is not clear, yet, what causes internal dissociation. It has been postulated earlier that higher nervous processes adapt faster than vegetative ones to an abnormal temporal routine (48): however, we know, now, that this is not generally the case. For mental performance rhythms, also, the complexity of the task seems to be of importance (66, 67, 75). In addition there may be a "specifity" in task variables which affects the speed of resynchronization: It has been demonstrated (17) that a higher memory loaden task adapted faster to night work conditions simulated in a laboratory and to time shift following transmeridian flights.

Otherwise, in our results, it was observed that those rhythms were more persistent, i.e. adapted slower, which under control conditions had shown the higher statistical significance for the circadian oscillation; in particular, that was true for temperature, 17-OHCS, and psychomotor performance. On the other hand, the variation of the fast entraining noradrenalin, rarely, ever reached the level of statistical significance. In another study (4) noradrenalin allowed, only, a poor fit to a sinus curve, so that one gets the impression the endogenous circadian component of this hormone is weak or lacking, at all, and variation might reflect, merely, responses to changes of the environment. This could, well, be the case in other abrupt adapting rhythms, also.

Characteristics of Time Cues

Strength of time cues. For animals a negative correlation between the strength of Zeitgeber (light intensity or range of temperature cycling) and the time needed for re-entrainment of rhythms has been established (12, 43, 73). For man a similar relation seems to exist between social time cues and speed of resynchronization (Figure 17): In a group of passengers who were kept in the relative isolation of hotel rooms, time for 95 % completion of resynchronization of psychomotor performance rhythms was about 50 % longer, on average, than in passengers who were allowed to leave the accommodations for outdoor activities every second day (19, 79, 80). Since both groups were aware of preceding time shift and local time the higher degree of social contact, related to the divergent activities, should be the reason for the differences in shift rates.

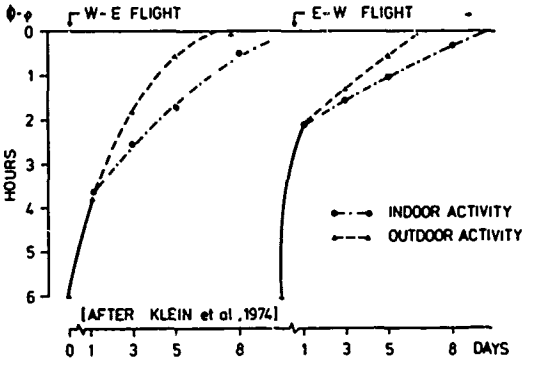


Figure 17: Difference in rate of resynchronization of performance rhythm depending on mode of activity. (Time difference: 6 hours.)

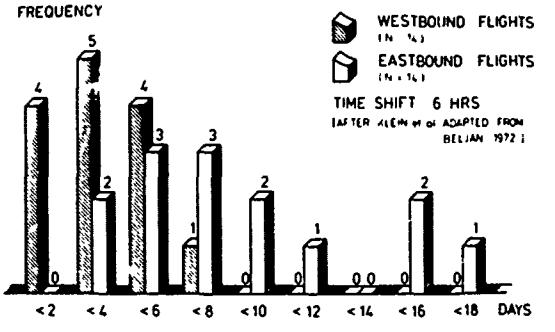


Figure 18: Frequency distribution of the resynchronization time of psychomotor performance rhythm.

Food and drugs as rhythm controlling agents. Earlier endeavours to hasten post-transmeridian resynchronization by a corticosteroid-like substance (30, 95) or by a tranquilizer (140) have failed, so far. On the other hand, timing of food intake, is among the social Zeitgebers which have been shown to control circadian variables. In animals, controlled access to food could be made either to oppose or to augment effects of synchronization by lighting regimen (58). In addition, composition of food was found to have Zeitgeber characteristic (38, 39, 99, 117). On these results "a diet plan for shift workers and transmeridian travellers" was developed (37) which is based upon (a) the chronobiotic (= synchronizing) action of tea (theophylline) and coffee (caffeine); (b) the operation of food as a Zeitgeber in a feeding program with a prolonged starvation phase (presumably acting through glycogen depletion); and (c) the tendency of a high protein meal to favour synthesis of catecholamines, and of a meal high in carbohydrates to favour the synthesis of serotonine. (According to normal circadian variation, the first should be high during the active phase, the second during the inactive phase of the circadian cycle). Through preflight alternation of "feast" days (large meals) and "fast" days (light meals) in combination with food timing synchronized with that at the flight destination, and programmed intake of coffee or tea, an acceleration of phase shift of biological rhythm is attempted. On base of subjective results trials with humans are supposed to be highly successful (37). Objective measurements taken from humans living under the diet plan have apparently not been obtained, yet.

Individual Differences

It was predicted from differences in subjective sensitivity that 25 % to 30 % of the transmeridian travellers have no or only minor difficulties in adjusting to the sudden displacement of external time cues; about the same percentage was estimated not to adjust at all (100, 143). A figure of 20 % was also given for the latter group from experiences with shiftworker (24, 148), however, this figure is considered somewhat conservative since it is based or fficially recognized transferees.

Using resynchronization of psychomotor performance rhythms as an indicator of the ease or difficulty of time zone adjustment we have demonstrated (78) individual differences for 14 subjects of one age group, objectively (Figure 18): Resynchronization times for the west-bound direction distributed in a range between 1.7 and 6.0 days, corresponding to a rate of shift between 210 min/day and 60 min/day; travel in the opposite direction resulted

in an accumulation of resynchronization times in the range between 2.9 to 11.3 days; this corresponded to a rate of shift of 125 min/day to 31 min/day. Finally, there were 3 individuals out of 14 who required between 14.3 days and 17.9 days to advance shift their psychomotor performance rhythm across 6 hours. With an average rate of shift of 22 min/day resynchronization for psychomotor performance is so unusually long that one could consider them to be examples for the individuals who "adapt only with considerable difficulty". Their number (22 %) matches well with the figures mentioned above for the group with a high subjective sensititivity; however, it is remarkable that they become evident, only, in connection with east-bound transportation.

Meanwhile, there have been some factors identified which may be responsible for individual differences in speed of resynchronization.

Characteristics of rhythms. It has been demonstrated that the individual resistance to displace body temperature rhythm, in response to a shift of time cues in an isolation unit, is proportional to the amplitude of rhythm before shift; the negative correlation between the amplitude and the duration of re-entrainment was higher for the advance than for the delay shift (163). This relationship has been confirmed, recently, for shift workers after delay shifts, it was significant for oral temperature, urinary 17-OHCS and peak expiratory flow (129).

Also the standard deviation (SD) of temperature rhythm, computed from measurements on 12 consecutive cycles, was used for a stability (low SD)/lability (high SD) characterization of circadian variation (32). Through the negative correlation between SD and the personality factor "introversion" there was a relationship established between stability and lower rate of shift, and lability and higher shift rate.

Personality. "Morning" and "Evening" types of individuals, and in a similar manner "Introverts" and "Extraverts", have been related with early and late peaking in circadian rhythms (like body temperature, catecholamines, and mental performance and behaviour), and with shorter and longer periods of cycles, respectively, while isolated from time cues (3, 20, 21, 31, 46, 87, 97, 113, 114, 115).

These relationships encouraged the hypothesis that ease of shift of body rhythm might depend on personality factors. It was supported through subjective ratings in industrial shiftworkers that extraverts (with longer circadian periods) adapt faster for about 50 % to a delay shift than to an advance shift (116). This, again, is in agreement with the more recent finding that evening types, as compared to morning types, do not experience sleep deficiency and tend to increase duration of sleep easier, when sleep onset is shifted to later hours (23); on the other hand, they sustain sleep latencies longer than in morning types if sleep onset is advanced. In the same study, a better ad ability to delay shifts was demonstrated for subjects with a lower ratio of pulse and respiration frequency. (For the significance of this quotient see ref. 71, 72). Also, it was predicted from investigations on industrial workers that morning types better cope with the early day shift while evening types easier adapt to permanent night shift (118).

Meanwhile, Colquhoun and Folkard (32) found (a) that the differences in temperature rhythms between introverts and extraverts was much more pronounced in the subgroup "neurotic" subjects, while in the subgroup "stable" subjects it actually did not exist, and (b) that in re-analyzed figures from a previous transmeridian flight study the resynchronization rate between the groups was decreasing in the following order: neurotic extraverts, stable extraverts, stable introverts and neurotic introverts.

Introverts and highly "neurotic" people have, also, been identified as those who quit shift work after a shorter time (108). The assumption that this might be so, because of greater difficulties in adjusting to the abnormal temporal routine is backed by the finding that "neuroticism" is related to a higher degree with internal desynchronization of different circadian systems if subjects are isolated from external time cues; the same was true for older people (161).

Age. It appears, that older people subjectively have greater difficulties to adapt to changes in the temporal relationship of body and environment (24). This could partly be caused by the susceptibility to sleep disturbances, obviously, increasing with age (150 ; see, also, Figure 11). But age-related differences have, also, been verified, objectively. In animals, aging caused a decrease in amplitude and a slower adjustment of temperature rhythm following a change in lighting routines (58). In man, also, higher age retarded phase shift of temperature rhythm in shiftworkers (128) and of urinary potassium cycling in response to a simulated delay shift of time cues (140). Wever (161), in his study mentioned above, did not only demonstrate a higher rate of internal desynchronization of older people in a time cue free environment but also, speculatively, established a "threshold age" of about 40 years from which on the tendency to a "decoupling" of rhythms might significantly increase. It seems, however, that this phenomenon like some other age effects described needs confirmation through more studies with higher numbers of observations.

EFFECTS OF REPETITIVE DESYNCHRONIZATION

Shifts in the temporal reference of the environment give rise for external desynchonization and internal dissociation of circadian systems which may continue for days or weeks, depending on the circumstances. In workers on rotating and night shifts, or in aircrews on long-haul transmeridian routes it might become kind of a permanent state for prolonged time periods. Therefore, it is only consequent to deal with the question of psycho-physiologic long-term effects of repetitive circadian desynchronization under the topic of this paper.

First of all, there have been some studies published from insects and rodents (13, 58, 59, 70, 119) in which shifts of lighting regimen varying in extent, direction and pattern repetition were introduced and resulting changes of longevity or life span measured. The results were not consistent, and somewhat surprising: Some experimental conditions caused significant reduction of life span, others no effect, or even prolongation. Speculatively, it was concluded that age of introduction of repeated shift regimen (earlier in life better than later), pattern of shifting (twice a week better than weekly), or inhibition of maturing processes could be responsible for the fact that repeated schedule shifts were harmless, life-shortening or even life-lengthening. Considering the extremity of these experiments one must conclude that animal research, so far, has not been very helpful in defining or predicting chronic desynchronization effects in man.

The extensive information available from shiftwork has been repeatedly reviewed in recent years, (1, 3, 5, 24, 34, 89, 101, 132, 144, 146, 147, 148). It has been considered to be rather inconclusive, the reason being a selection process involved in the recruitment or retaining of shiftworkers. In brief, the results can be summarized as follows.

In shiftworkers as compared to dayworkers there is

- an abnormal frequency of sleep problems;
- more often tiredness, restlessness, and minor nervous disturbances of transitory character;
- a higher number of digestive problems and gastro-intestinal disturbances (reported in some studies, only);
- both, lower and higher absenteeism;
- no higher mortality rate.

The most recent investigations found out that most of the disturbances associated with shiftwork

- had come into existence in the early periods of shiftwork;
- developed in predisposed individuals who often had shown indications of a similar symptomatology (sleep complaints, sensitivity to noise, gastro-intestinal irritability) before commencing shiftwork;
- were reduced, and well-being increased in "drop-outs" from shiftwork.

Some authors believe that statistics underestimate the problem because individuals unable to cope with shiftwork transfer to day work (self-selection), and conclude that shiftwork is a risk factor for predisposed individuals. They,also, propose to exclude those individuals from irregular working pattern who anamnestically indicate a disposition for sleep disturbance, digestive and intestine problems, and other symptoms of psychosomatic disorder.

Questionnaire studies in aircrews report, also, on a high incidence of sleep disturbances and gastro-intestine symptomatology (27, 93). However, health surveys did often fail to confirm, objectively, psychosomatic diseases to be a major factor for grounding or to deviate significantly in rate from a general population; they,also,did not discover sickness trends attributable to irregular work patterns or rhythm disruption (2, 18, 22, 120). One is inclined to assume that the difference to the industrial shiftwork situation could be due to the intense medical preselection of the aircrew population. Nevertheless, a specific screening procedure able to predict an individual's aptitude to cope with irregular work/rest schedules might still reduce the number and intensity of short- and long-term disturbances.

CONCLUSIONS AND RECOMMENDATIONS

Since air operations occur around the clock and over many time zones they interfere with the synchronization of the environmental and biological circadian timing systems. Subjectively, the post-transmeridian desynchronization may become manifest in a disturbance of those vegetative functions which like hunger, wakefulness and sleepiness, and evacuation of intestines are strongly daytime-related: They appear at unusual and unconvenient hours. Objectively, the "jet lag phenomenon" is characterized through transient changes of the circadian oscillation of body functions, the most significant of which are: displacement of rhythm on the temporal axis, change in the oscillation range, and alteration of the

24-hour mean. For mental and physical performance rhythms these changes mean lower functional values - i.e. a depression of the "readiness for efficiency" - at certain sections of the 24-hour cycle, and sometimes higher functional values at other daytimes. Where the readiness for efficiency is degraded, preflight performance level, if at all, may be obtained, only, with extra effort and higher physiological costs.

The following factors have been identified to affect the speed of re-entrainment (normalization) of biological rhythms: direction of flight, nature of function, characteristic of time cues, and individual features like personality and age. Moreover, it was demonstrated, objectively, that rapid return to the home base minimizes the disadvantageous effects of time zone flights because of shorter resynchronization times.

Long-termed professional activity on transmeridian routes, subjectively, may cause a higher incidence of sleep problems, nervous disturbances, and gastro-intestine complaints, particularly, in female crew members. Objectively, however, the rate of psychomatic diseases show no deviation from general population and seem to be no major factor for grounding; in addition, health surveys, so far, do not demonstrate sickness trends attributable to irregular working pattern or rhythm disruption. This seems to be different from the industrial shiftwork situation; the reason must be seen in the intense medical/psychological preselection and supervision of the aircrew population.

The present state of knowledge allows to give the following recommendations for the different parties engaged in transmeridian air transport operations.

- Passengers whose goal it is to hasten circadian resynchronization should shift the rest/activity cycle, in particular the timing of sleep and meals, to local conditions immediately after arrival at the final destination. They should relaxe for the first 24-hours, but otherwise make sure not to isolate from environmental time cues. Sufficient (extended) sleep during the first night seems essential; if necessary, this goal should be obtained through a hypnotic. Where it is possible, preadjustment by timing of sleep and meals before the flight can be helpful; this must be done, of course, in relation to the expected time shift.
- Aircrews, aiming to avoid time zone adjustment, should try to stay on home base pattern while on route and use any chance for sleep through naps and even short acting hypnotics; however, intake of sleeping aids should not be later than 12 hours before duty. Since night flying and irregular rest/activity pattern require extra effort one should keep away from additional stress. After return to the home base it is essential to utilize off-duty time sufficiently for rest and recreation.
- The management, engaged in keeping flight safety at maximum level, should take any pains to provide accommodations permitting crews on route to stay on home base pattern. As far as possible, schedules should be arranged for a rapid return to the home base; at home extended rest periods should be granted to allow biological rhythms to synchronize with the environment, again. Since irregular patterns seem to become more stressful with age, transmeridian flying should be reduced for crews above 50 years. Posting air crews overseas has been an elegant solution for most of the medical problems arising from time zone flying; its abolition was medically unwise.
- Flight surgeons, responsible for preservation of health and efficiency, should exclude from long-termed activity on transmeridian routes individuals with dispostion for sleep disturbances, gastro-intestine disorders and other psychosomatic complaints.
- Investigators, searching to improve the overall situation, should try to develop objective criteria for selection of individuals fit for duty with irregular rest/activity patterns, as in shiftwork and in flying on transmeridian routes.

A P P E N D I X

CIRCADIAN RHYTHM DISTURBANCE AS FACTOR FOR THE CONSTRUCTION OF FLIGHT PATTERNS

Formulas and Models

Realizing the fact that circadian rhythms in air operations may well have impact upon flight crew efficiency and therefore flight safety in general, several attempts have been made to assess the effects in computable forms and incorporate them into formulas of a broader validity. Basing on data from field studies, the formulas so far developed are covering such factors as resynchronization time (82, 135), rest period time (26, 49, 139), the potential physiologic load (103), and the optimal or maximal workload (111). A brief description of the various formulas will be given in the following sections.

Assessing resynchronization time. Derived from several studies in our own laboratory (82) a concept was developed which allows to appraise the average resynchronization time for several days after arrival in a new time zone. Basing on the findings that the course of adaption is not linear and re-entrainment occurs in relation to the number of time zones crossed the resynchronization rate is computed as follows: 50 % of the difference in pre- and postflight local time takes place within 36 to 48 hours after arrival; again 50 % of the residual difference is shifted within the following 48 hours; the same applies to the next two days, and so on. As an example, after a flight over 6 time zones, circadian rhythm has shifted 50 % or 3 hours on the second day, 75 % or 4.5 hours on the fourth day, and on the sixth day after arrival, 88.5 % or 5.25 hours.

This, of course, is not an exact estimation of the resynchronization time, but rather a rough approximation, a "rule-of-thumb" so to say. To develop a formula which is more precise and at the same time remains generally valid will be difficult.This is no surprising considering the great variety of resynchronization times with respect to the differences existing in individuals, body functions and flight directions. For scheduling transmeridian air operations, however, the formula offers a reasonable compromise of sufficient precision and easy applicability. Its great advantage is that it is based on a considerable amount of experimental data and that it covers not only physiological functions, but also performance rhythms.

Basing on results from field studies on body temperature rhythms after air travels, Sasaki (135) conceived a model which also permits an estimation of the resynchronization status in dependence on the time spent in a new time zone. In accordance with our findings, his data revealed evidence that resynchronization does not proceed linearly, but rather asymptomatically. Under the assumption that the rate of resynchronization is proportional to the number of traversed time zones, a differential equation is derived. Its solution for the condition that the traveller remains at the same location, as is the case for stopovers or for arrival at the destination, provides a relative simple model, combining exponential and constant components. The advantage of this formula lies in its convenience and in its feature to permit a prediction of the resynchronization status any time after arrival. It has, however, also one great disadvantage: It needs the empirical estimation of the time constant, which may considerably differ between individuals and between variables. Though derived from temperature studies only, the model may also be applied to performance rhythms, as tested in our laboratory by comparison of the predicted resynchronization rates with those actually measured.

Computing length of rest period. Buley's formula (26) for determining rest periods on long-distance air travel considers (in addition to circadian rhythmicity) several factors as significant for the physiological and psychological state of the air traveller after arrival. Those which are available for computation are included in his model: flight duration, local times of departure and arrival, and time zone translocation in excess of 4. It is obvious that by insertion of departure and arrival time, as well as number of time zones, circadian rhythmicity gains some weighting in this formula. In part it was derived from earlier studies (139) and in its improved form was applied to long-distance air travels by members of ICAO. As it has evolved the equation is: Rest period = Flight duration/2 + Time zones in excess of 4 + Departure time coefficient + Arrival time coefficient; or in symbolic form: $R = \Delta T/2 + (Z-4) + C_D + C_A$.

The coefficients are defined by dividing the 24-hours day in 5 sections and scoring them by numbers from 0 to 4 depending on their expected fatiguing effects. The validity of the formula has been tested by routine application, and the results were regarded as satisfactory. However, it has to be mentioned that its applicability cannot be extended on air crew scheduling, but rather remains restricted to the business traveller.

On the basis of the Buley's formula, Gerathewohl (49) developed "a simple calculator for determining the physiological rest period after jet flights involving time zone shifts". The underlying formula includes, in addition, to the components of the ICAO model, three more factors: the age factor, the flight direction (east-bound versus west-

bound displacement), and also traversed time zones less than four. The extended formula reads: Rest period = Travel time (in hours) + Departure time coefficient + Number of time zones + Arrival time coefficient + Geodirectional coefficient + Age coefficient; or reduced to the symbolic from: $R = T + C_D + N_{tz} + C_A + G_C + A_C$.

The geodirectional coefficient takes into account the different resynchronization rates observed between east- and west-bound flights. Hence, travelling from West to East contributes twice as many credit points to the summation. The age coefficient ranges from 1 to 4 corresponding to classification with increasing age. Credit for time shifts is already given with 1 time zone crossed and then "is graded as a cyclic function" with more time zones added.

Estimating physiologic load. A completely different approach was chosen by Mohler (103) in 1976. Utilizing the data which he derived from airline pilots on world flights, he developed a multiplicative and additive formula resulting in a "physiological index" giving the predicted overall pattern level of difficulty and pointing to critical segments within the pattern. The purpose of this index was to serve as an aid in constructing flight patterns, indicating to the constructors when a pattern or segment has the potential of imposing high physiological loads. As major critical tiring factors in long-distance flights the following are included in the formula a) multiple night flights (necessitating day sleep), b) number of time zones traversed, and c) layovers after an evening arrival. Multiple transits, pattern in excess of 7 days, flights in an easterly direction and the first flight of a pattern are also considered significant enough to contribute to the computation of the index. The calculation procedure is performed in 7 steps, each with many detailed conditions. Thus, a condensation to a simple symbolic form appears rather difficult, though, no doubt, the computation per se can easily be handled. As preliminary criteria for the grade of load, values are given reflecting, easy, heavy, and definitely severe indices. For a general application, there may be some hesitation remembering the fact that the baselines of this model were derived from very specific airline flight patterns with many segments. Thus, when applying the formula, for instance, to a rapid round trip between Frankfurt and Los Angeles, the resulting index did not reflect satisfactorily the high load on the crew of such a flight. This consideration does not question the validity of the model for other patterns. On the contrary, it may be seen as a start in the right direction and as a promising step in quantifying factors contributing to fatigue which otherwise are neglected or under-emphasized.

Defining optimal (maximal) workload. Nicholson (111) has developed an approach to quantify optimal and maximal workload for flight patterns including several segments and for aircrews operating world-wide. The workload is obtained from the duty periods and the number of days on route, time zones remain unregarded. Optimum workload is defined as the cumulated duty hours for days on route above which sleep difficulties may be encountered; maximum workload is reached when cumulated duty hours do not allow acceptable sleep patterns. Nicholson claims that during world-wide flights many factors may affect well being and efficiency of aircrew, but that of prime importance is the maintenance of an acceptable sleep pattern which can be achieved, only, through an appropriate timing of duty periods. In his formula, calculation of workload is given by (number of days on route $\pm$ 1) times average duty hours per day. Thus, for flight patterns with several days on route, a table is derived indicating optimum and maximum of the accumulated duty hours for each day of the tour. As Nicholson pointed out, the effects of irregular duty hours and time zone changes received sufficient weighting in his formula as reflected by the reduction of the average workload for the whole tour with increasing duration.

Rest/Duty Regulations

Constructors of flight patterns are basically confronted with two aspects of the involvement of circadian rhythms in air operations. Simply, they may be called: shifted work and shifted time. The first aspect implies flight duty to be performed at abnormal daytimes within the 24-hour rest/activity cycle. The second aspect must be considered, when flight patterns include transmeridian routes.

There is general agreement that flying at unusual daytimes is more stressing than doing the same operations during normal hours, and probably there are no rest/duty regulations, issued by airlines or legislators, which do not take into account that this is one of the major fatiguing factors. To compensate for its impairing effects, all official regulations principally have incorporated the same expedients: reduction of flight duty hours, elongation of the subsequent rest period, and limitation of the number of night flights.

Some disagreement only exists in defining night flights, i.e. in stipulating what is the beginning and what is the end of the night, or how many flight hours have to be spent during night so that the flight will be conceded as night duty time. There are also minor divergencies where the 24-hour period is divided into sections and gradually differentiated with respect to causing more or less fatigue. Thus, the number of sections may differ between some regulations, amounting from 2 to 5 per day, and a time period between 22.00 and 24.00 hour may count as most fatiguing, whereas according to other regulations the most

difficult time starts not before 24.00 hour. As stated above, all these differences are minor and to not question the general acceptance of circadian rhythmicity as a factor potentially influencing performance and efficiency when operations are conducted as night- or shiftwork. The literature on rest/duty regulations, so far available, encourages to the conclusion that this aspect is taken seriously and is sufficiently considered.

In view of this fact, it seems somewhat surprising that only few of the national and international rest/duty regulations, presently in force, seem to cover the aspect of circadian rhythmicity specifically evolving from operations on transmeridian routes. There are some reasons, however, conceivably responsible for this denial. First, considering the enormous variety of flight schedules and routes all over the world, it becomes obvious that a regulation satisfying the need for practicality and the demand for general validity appears rather difficult to develop. Secondly, regulations reflect a compromise regarding the various and sometimes divergent interests of the parties involved. Third, there is not yet unanimity among experts as to the extent these factors may touch flight safety through impairing crew efficiency.

To give an example, how the aspect of circadian rhythmicity in transmeridian operations is incorporated into legislation, the German rest/duty regulations are cited (6).

As a general rule for flight crews on transmeridian routes, the regulations imply that resynchronization to new time zone must not be enforced but instead aircrews return as fast as possible to their home base. This applies only on the premises that sufficient rest time is provided within each 24-hour period away from home. To prevent sleep deficits, 14 hours rest time are considered the minimum under these conditions, and the operator is obliged to supply quarters which can be shielded from light and noise during local daylight hours. Upon returning to home base, the minimum rest period will be extended, if one or more flight segments have been spent in time zones differing from home base by 4 or more hours. The minimum rest period required by regulation, will then be calculated by multiplying the largest time zone difference while on duty with the factor 8. Thus, if the largest difference has been 6, for instance, the minimum rest period will be 6 x 8 = 48 hours;or with the largest difference being 12 time zones, the rest period requires 12 x 8 = 96 hours. The factor is, primarily, established on findings with respect to resynchronization times; based on body temperature rhythm it allows normalization of circadian system of at least 50 % at the home base. Beginning a new duty period the conditions with respect to residual desynchronization is almost equal and practically independent of the number of time zones crossed before. In applying these principles, the regulations pursue the following objectives:

1. to keep shifting of circadian rhythms at a minimum while on duty in time zones different from home base;

2. to grant a rest time upon return with sufficient resynchronization of the biological timing system to start duty again.

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PSYCHOSTIMULANTS

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RESUME.

Cette revue des notions actuelles sur les psychostimulants débute par un aperçu historique et géographique.

Les données sur les bases neuro-chimiques de la vigilance sont ensuite abordées en distinguant le différents systèmes de médiateurs impliqués dans la conduction synaptique.

La méthodologie des essais thérapeutiques portant sur les psychotropes est ensuite abordée, et suivie de l'étude des effets observés lors de l'utilisation des différents types de produits disponibles : nooanaleptiques, nootropes, thymoanaleptiques et adjuvants métaboliques.

Après avoir tenté d'intégrer ces données à un modèle général de la vigilance faisant intervenir les concepts de capacité de traitement et de filtrage, l'article conclue par les indications et contre-indications de l'usage des psychostimulants.

1 - INTRODUCTION HISTORIQUE.

La recherche de moyens artificiels pour améliorer les performances de l'homme est un phénomène que l'on retrouve dans toutes les cultures. A l'origine, elle relève de l'herboristerie empirique, la consommation de certaines plantes s'accompagnant d'effets jugés favorables, celles-ci sont retenus comme utiles. Plus tard, au cours du 19ième siècle, les développements de la chimie ont conduit à l'extraction des principes actifs puis à l'étude de leur structure chimique et enfin à leur synthèse.

1.1 - On peut schématiquement classer les stimulants naturels en grandes catégories :

- La caféine.
Son usage est universellement répandu, on la trouve dans le thé, dans l'aire de culture chinoise, dans le café qui voit son origine en Abyssinie la noix de Cola en Afrique, la Guarana et le Maté en Amazonie. Sous forme de café et thé, son usage s'est répandu en Europe au 16ième siècle. La synthèse de la caféine a été réalisée en 1820.

- Le tabac.
Originaire du Mexique et utilisé pour les cérémonies sacrées, il a été introduit en Europe après la découverte du Nouveau Monde où on l'utilisa à l'origine comme thérapeutique. Son principe actif est la nicotine.

- L'arec ou betel.
Son usage se circonscrit à l'Asie du Sud-Est. La noix d'Arec contient un alcaloïde : l'Arecoline.

- L'alcool.
Bien que ses effets à forte dose soient plutôt dépresseurs, il joue également un rôle activant par levée des inhibitions, son usage est également très général.

- Le coca.
C'est la plante divine de l'empire Inca, chiquée, elle permettait de vaincre la fatigue et d'éliminer la faim. Son principe actif est la cocaïne synthétisée en 1855. Son usage a été popularisé par BENTLEY puis FREUD qui en fit l'apologie.

A ces stimulants propres au système nerveux, il convient d'ajouter l'EPHEDRINE synthétisée en 1885 par NAGAI et KANAO, qui s'étaient intéressés à l'extrait végétal de l'ephedra réputé en médecine traditionnelle chinoise pour son effet stimulant respiratoire et cardiaque. Dérivant de ce produit, toute une lignée a vu le jour avec l'Adrenaline en 1901, puis l'Amphétamine en 1931.

1.2 - Depuis plusieurs années, divers produits ont été reconnus pour un effet psychostimulant parallèle à celui de leur destination première : l'exemple de l'Iproniazide classique. Il s'agit à l'origine d'un antituberculeux qui se révéla dès 1952 posséder une action antidépressive.

Depuis, de nombreuses molécules ont été étudiées, parfois sans hypothèse, pour rechercher empiriquement leurs propriétés psychotropes éventuelles.

A ces recherches empiriques s'ajoute maintenant une approche théorique à visée explicative : la neurochimie que nous envisagerons d'abord sous son aspect le plus général, avec les mécanismes de la transmission synaptique, puis plus spécifiquement en abordant les différents systèmes qui peuvent rendre compte des effets stimulants des produits.

2 - RAPPEL DE NEUROCHIMIE.

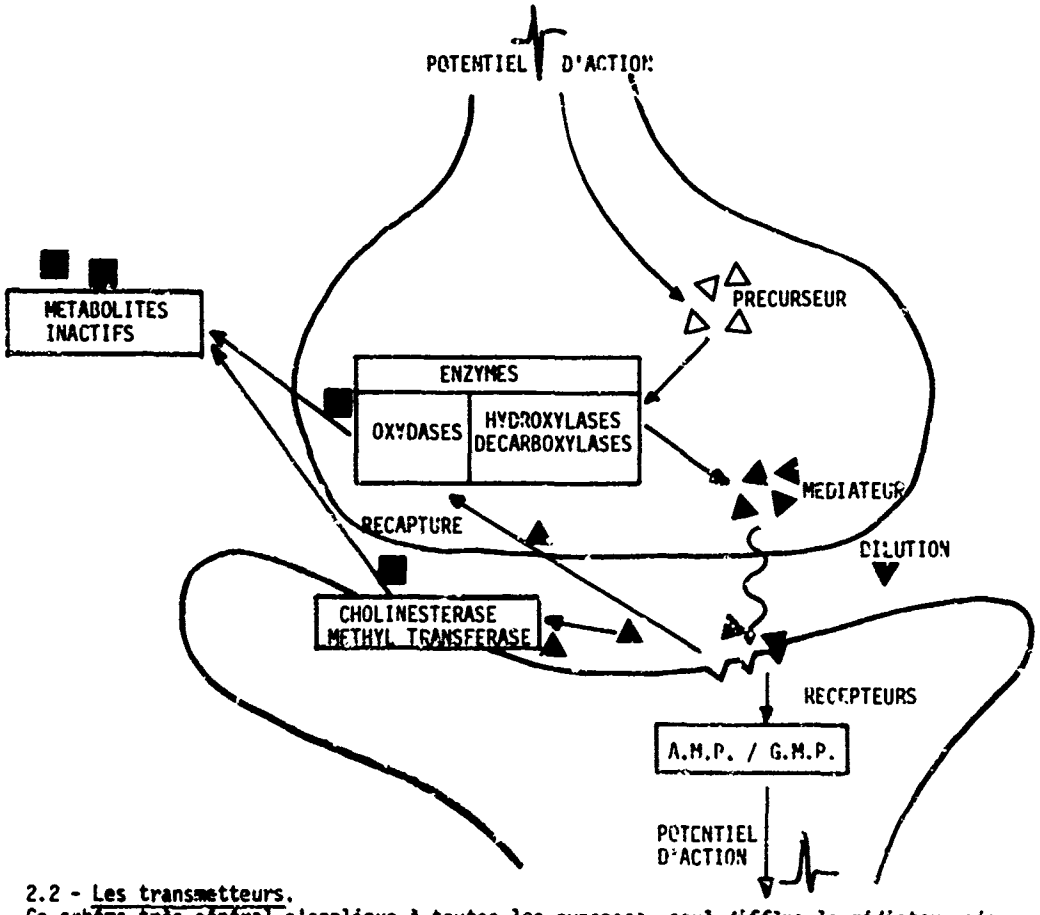
2.1 - La transmission synaptique.

On sait que le système nerveux est constitué d'un réseau de cellules appelées neurones, spécialisées dans la génération et la conduction d'un phénomène électrique : l'influx nerveux. L'existence de ce réseau implique celle de communication entre ces neurones. Dans l'immense majorité des cas, celle-ci ne s'effectue pas à l'aide d'une conduction par contiguïté du potentiel électrique, mais par l'intermédiaire de corps chimiques secrétés par la cellule amont excitant la cellule située en aval.

On appelle synapse la région qui regroupe les parties de ces neurones contigus : terminaison de l'axone, bouton dendritique et l'espace qui les sépare.

L'examen au microscope électronique a permis de mettre en évidence de petites vésicules dans les terminaisons axoniques, et des microdosages ainsi que des examens microscopiques en fluorescence ont révélé l'existence de substances chimiques appelées médiateurs sécrétées par le neurone amont et excitant le neurone aval.

Le schéma général est le suivant : des corps appelés précurseurs existent à l'intérieur du neurone et sont transformés par une succession de réactions enzymatiques en médiateur. Celui-ci est libéré par l'influx nerveux et après avoir traversé l'espace dendritique agit sur une structure réceptrice du neurone suivant, qui à son tour déclenche des réactions mettant en jeu deux corps : Adenine Monophosphorique (AMP) et Guanine Monophosphorique (GMP), recréant une dépolarisation membranaire génératrice de l'influx nerveux. L'excès de médiateur va devoir être détruit de façon à ce que l'effet soit limité dans le temps. Cette inactivation s'effectue par trois voies : la diffusion et dilution dans le milieu extracellulaire, la dégradation enzymatique et enfin la recapture par le neurone presynaptique.

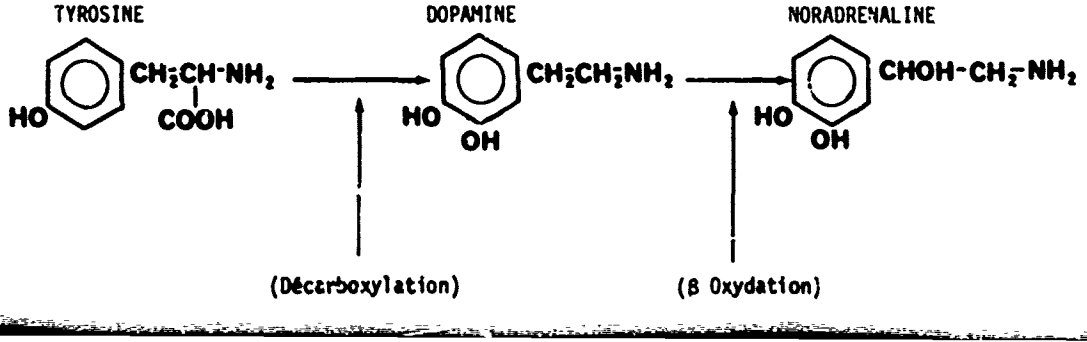


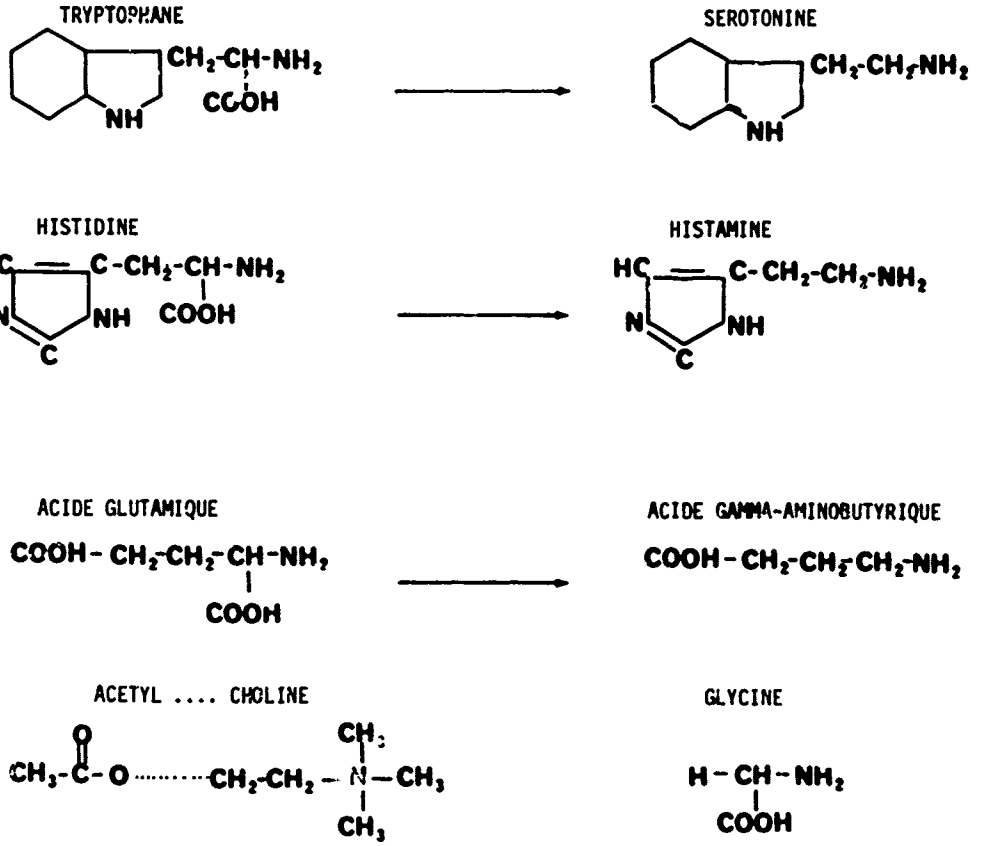
2.2 - Les transmetteurs.

Ce schéma très général s'applique à toutes les synapses, seul diffère le médiateur mis en jeu ; on a pu regrouper en systèmes les ensembles de neurones possédant le même médiateur.

On peut classer ces médiateurs en quatre catégories répondant à leurs familles chimiques.

- un premier groupe comprend des corps relativement simples constitués autour d'un acide aminé aromatique, ce sont les Monoamines. Parmi celles-ci, on distingue celles qui sont dérivées de la Tyrosine et celles qui sont issues du Tryptophane. De la Tyrosine sont issues la Dopamine et la Noradrenaline, et du Tryptophane la Serotonine.
- d'autres médiateurs sont issus également d'amino-acides, ainsi la Glycine et l'Histamine.
- l'Acetylcholine est un ester acetique de la choline, elle-même dérivée d'un Ammonium quaternaire.
- une classe assez hétérogène regroupe d'autres dérivés d'amino-acides et des peptides.





2.21 - Système dopaminergique.

Il regoupe les régions de la substance noire, le système strié, le globus pallidus, l'amygdale, le rhinencéphale et les régions de l'hypothalamus ; récemment, HÖKFELT a décrit des liaisons de ce type dans la zone limbique (1972) et le cortex préfrontal.

On sait le rôle du système strié dans la régulation motrice, l'insuffisance de DA entraîne un syndrome parkinsonien, par contre son excès amène des comportements stéréotypés et des troubles psychiques du type paranoïde.

D'autre part, la DA inhibe par son action sur l'hypothalamus la sécrétion de la luteine releasing factor (LRF) et de la prolactine. Enfin, le rôle de la région limbique dans la régulation des besoins et celui de la région préfrontale laisse présumer du rôle de la DA dans les processus mentaux (MATTHYSSE et KETY - 1973).

2.22 - Système noradrénergique.

Il prend en grande partie son origine dans un noyau appelé locus coeruleus et de là, émet des faisceaux descendants vers la moelle et ascendants vers pratiquement toutes les régions du système nerveux central. Il faut noter l'extrême diffusion du réseau, il est possible que d'un seul neurone dépendent tous les neurones corticaux. On peut donc présumer de son rôle de coordination globale. C'est lui qui règle l'éveil et la phase paradoxale du sommeil qui correspondrait à l'activité onirique.

Un autre groupe de neurones est lié à la région hypothalamique et joue un rôle sur la régulation endocrinienne en facilitant le LRF et l'ovulation. Il exercerait également son contrôle sur la thermogénèse et certains comportements primitifs : faim, soif, sham - rage.

2.23 - Système Sérotoninergique.

Ses cellules d'origine sont groupées dans la région médiane du tronc cérébral qui reçoivent elles-même des neurones noradrénergiques. Les voies suivant des trajets analogues à ceux des systèmes noradrénergiques. On peut donc prévoir des interactions importantes entre ces deux systèmes. Le système sérotoninergique commande le sommeil à ondes lentes, il inhibe l'activité sexuelle et l'agression : son rôle est donc adverse de celui de la noradrénaline.

2.24 - Système Cholinergique.

Sa distribution est elle aussi très large, on trouve des synapses cholinergiques pratiquement partout là où existent des liaisons noradrénergiques. Le système cholinergique joue un rôle dans les comportements d'éveil, mais son action est plus nuancée, il permet une adaptation correcte des actes alors que le système NA a essentiellement une fonction d'activation globale.

Les études sur le développement du cortex ont montré que les structures cholinergiques apparaissent plus tardivement que les autres, ce qui traduirait bien leur caractère plus évolué.

2.25 - Autres médiateurs.

Leur distribution et leur rôle sont moins connus. On peut les grouper en deux catégories :

a) La première comporte des acides aminés :
   - L'Histamine dérive par décarboxylation de l'histidine. Son rôle comme médiateur a été suggéré par les études de SNYDER (1972). L'existence de voies ascendantes histaminergiques vers le cortex laisse penser que ce système pourrait jouer un rôle dans les mécanismes d'éveil.

- L'acide gamma-aminobutyrique (GABA) est un dérivé de l'acide glutamique, après décarboxylation et hydroxylation. Il jouerait un rôle inhibiteur sur la transmission synaptique (ROBERTS - 1975). Les synapses GABA ergiques sont largement distribuées dans le système nerveux. On pense qu'il existe des rapports étroits entre le système GABA et le système dopaminergique.
- La Glycine est un acide aminé très simple. Les synapses utilisant ce médiateur se situeraient principalement dans la moelle épinière et joueraient un rôle inhibiteur (WERMAN - 1967).

b) Le second groupe rassemble des corps plus complexes, assemblages d'acides aminés. Ces polypeptides sont traditionnellement rattachés aux sécrétions hormonales, mais on sait qu'ils peuvent également jouer le rôle de médiateurs - GUILLEMIN a proposé de les nommer cybernines. Ils sont localisés électivement dans la région hypothalamique, mais on les rencontre dans d'autres régions du système nerveux central.

Le rôle de ces corps sur le comportement a été discuté récemment lors d'un colloque de l'INSERM (GOURDJI - 1978).

L'ACTH et la Vasopressine joueraient un rôle dans les phénomènes de mémorisation, la Prolactine et les Endorphines joueraient sur les facteurs émotionnels.

Cette brève revue montre la complexité et les nombreuses interactions existant entre les médiateurs. La distribution des effets en fonction des localisations anatomiques est loin d'être évidente. Le caractère monolithique de chaque système, constitué d'un ensemble de neurones connectés à l'aide d'un neuromédiateur unique jouant à chaque étape un rôle excitateur ou innibiteur, peut, lui-même être mis en question ; SZABADI (1978) a proposé un modèle qu'il nomme "agonisme-antagoniste" selon lequel un même médiateur pourrait exercer des effets à la fois positifs ou négatifs sur des sites récepteurs postsynaptiques distincts. Cette hypothèse permettrait d'expliquer les effets paradoxaux en fonction des quantités de neuromédiateurs, ainsi que la succession dans le temps de phases excitatrices et inhibitrices après l'application d'un seul produit.

2.3 - Mode d'action des psychotropes.

L'existence de la barrière hémoencéphalique interdit le passage direct de neuromédiateurs ingérés ou injectés au niveau de la synapse. Une action médicamenteuse ne peut donc être envisagée à partir de ces produits, la seule possibilité est une intervention sur leur génèse ou leur devenir. Les études portent principalement sur les monoamines et sur l'acetylcholine.

Au niveau de la génèse des transmetteurs, les facteurs suivants peuvent être abordés :
- le fonctionnement métabolique de neurones doit être satisfaisant
- le précurseur du transmetteur doit être disponible
- le système enzymatique de transformation, principalement les décarboxylases, doit être efficace
- le stockage du transmetteur doit être assuré

Une fois libéré du neurone presynaptique, le transmetteur doit pouvoir transmettre son information, ce qui implique que l'on peut agir sur :
- la disponibilité des sites récepteurs post-synaptiques
- le déclenchement des systèmes Adenyl et Guanine monophosphoriques

Enfin, le surplus de neurotransmetteur doit être inactivé. Il sera possible d'agir sur ce point, soit en modifiant les enzymes qui sont chargés de sa dégradation, soit en jouant sur le mécanisme de recapture.

Ces différentes voies d'abord seront détaillées lors de l'étude des différents produits.

3 - METHODES D'ETUDE.

En face d'un produit susceptible d'exercer des actions psychostimulantes, plusieurs démarches devront être effectuées avant que les essais sur l'homme soient engagés. L'examen de la formule chimique permet parfois une prédiction des effets, mais ce moyen est soumis à de nombreux aléas ; la relation entre structure et efficacité est en effet loin d'être précise. C'est au niveau des essais sur l'animal que vont apparaître les premières informations concernant la toxicité, la pharmacodynamie du produit (absorption, métabolisme, taux sanguin, dégradation excrétion) et surtout les effets sur le comportement. Les animaux ayant reçu les produits sont soumis à des tests bien standardisés (SIMON - 1978). Les psychostimulants induisent une hyperactivité observable, soit directement, soit mesurée objectivement par comptage des mouvements, ils facilitent l'apprentissage et le conditionnement et sont antagonistes des hypnotiques. Certains psychostimulants ont pour effet de déclencher des mouvements stéréotypés de léchage, mastication, ce sont les amphétaminiques, les autres sont rangés dans la catégorie des neurostimulants.

Lors des études sur l'homme, les techniques d'observation des effets peuvent être classées en trois groupes : l'évaluation clinique directe ou dirigée à l'aide d'échelles d'appréciation, les méthodes psychométriques et les relevés physiologiques.

- Les méthodes d'observation clinique sont essentiellement utilisées en psychiatrie sur des malades. Lors des études porta t sur des sujets sains, on s'appuie plus volontiers sur les deux autres.
- Les procédures psychométriques comprennent des tests d'efficience tels que mesures de temps de réaction, de l'attention, de la mémoire, de la capacité de décision, et des questionnaires qui portent soit sur des traits relativement permanents de la personnalité, soit sur des états actuels.
- Les techniques d'enregistrement physiologiques portent surtout sur l'électroencéphalographe, la fréquence cardiaque, la résistance cutanée et certains dosages biochimiques.

L'étude objective des psychotropes en général, et des psychostimulants en particulier, doit s'appuyer sur des règles précises de méthodologie, les résultats obtenus pouvant être soumis à de nombreux biais.

Il faut savoir qu'il est plus difficile de mettre en évidence des effets chez l'homme sain que chez le malade, chez ce dernier, en effet, le produit agit en tant que correcteur d'un trouble, le plus souvent facile à observer. Chez le sujet sain au contraire, on n'observera souvent qu'une exagération d'une fonction normale. Une technique utilisable est alors d'observer les effets compensateurs d'un produit vis-à-vis d'une situation qui serait susceptible de perturber son équilibre : prolongation d'une tâche, fatigue physique, privation de sommeil, prise de produits favorisant le sommeil, etc...

Une autre difficulté vient de ce que l'on nomme "l'effet Placebo" ; il s'agit des modifications de l'état d'un sujet auquel a été administré un produit inactif (Placebo), ou des effets additionnels que peut entraîner un produit actif. On considère qu'environ un tiers de la population présente ce phénomène, il est donc nécessaire de le contrôler lors de l'étude d'un produit.

On distingue (GUELFI - 1978) plusieurs niveaux de contrôle expérimental qui correspondent à des exigences distinctes :

- dans les essais ouverts, le prescripteur, le sujet et l'observateur connaissent la nature du produit utilisé
- dans les essais avec insu, à côté du ou des produits actifs, on distribue un Placebo ayant même apparence. Il peut s'agir d'un simple insu où seul le malade est dans l'ignorance de la nature active ou non du produit, d'une évaluation en insu ou seul le prescripteur est au courant, et enfin de double insu où aucun des protagonistes ne possède d'informations. Cette technique permet seule d'éviter tout effet de suggestion.

L'organisation de l'essai est définie par un plan expérimental (DEFAYOLLE - 1978) qui peut, soit porter sur des groupes de sujets distincts ayant reçu les diverses formes médicamenteuses, soit sur des observations portant sur les mêmes sujets ayant reçu successivement les différentes formes.

Ce plan devra tenir compte du nombre des mesures effectuées (avant, pendant, après traitement), des conditions auxquelles sont soumis les sujets (fatigue, etc...), de la durée écoulée entre la prise du produit et l'observation de la durée de l'imprégnation (effet aigu ou chronique).

4 - ETUDE DE QUELQUES PRODUITS.

Il convient dans un premier temps de situer les psychostimulants parmi l'ensemble des produits à action psychotrope. LEWIN, en 1928, décrivait cinq catégories :

Les EUPHORICA : opium, cocaïne, ...
Les HYPNOTICA : gardenal
Les INEBRIANTIA : alcool
Les PHANTASTICA : belladone - Peyolt
Les EXCITANTIA : café, tabac, ...

Plus récemment, DELAY et DENIKER proposent une classification en trois grands groupes : Psycholeptiques, Psychoanaleptiques et Psychodysleptiques.

Les premiers abaissent le niveau de fonctionnement du système nerveux, on y range les hypnotiques caractérisés par leur action sur le sommeil, les anxiolytiques ou tranquillisants, et les neuroleptiques qui sont des thérapeutiques antipsychotiques.

Les Psychodysleptiques regroupent les Hallucinogènes et enfin les Psychoanaleptiques sont doués de propriétés excitantes et recouvrent la notion de psychostimulants.

Parmi ceux-ci, on distingue deux grandes classes selon que la stimulation s'exerce sur les capacités cognitives ou sur l'humeur ; dans le premier cas, il s'agit de nooanaleptiques, dans le second de thymoanaleptiques.

Ce sont essentiellement les nooanaleptiques qui nous retiendront ici, nous les diviserons en trois catégories :

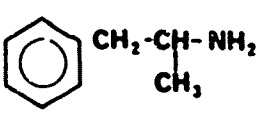
- Les stimulants de la vigilance ou nooanaleptiques proprement dit
- Les stimulants des facultés cognitives ou nootropes
- Les régulateurs du fonctionnement neuronal

A : Nooanaleptiques.

Les produits les plus étudiés appartiennent à la classe des amphétamines. Il ne faut toutefois pas négliger l'importance des stimulants naturels, caféine et nicotine, quand cela ne serait qu'en raison de la grande fréquence de leur emploi. Enfin, d'autres produits présentant des propriétés excitantes ou vis-à-vis du système nerveux central seront passés en revue.

4.11 - Amphétaminiques ou Psychamines.

Ce sont des dérivés qui présentent une analogie de structure avec la noradrénaline. Le chef de file est l'Amphétamine



Deux heures après absorption par voie orale, on observe le maximum de la concentration sanguine. Le produit s'accumule électivement dans le cortex cérébral et le thalamus et environ les 2/3 sont éliminés par voie urinaire (on en trouve encore une semaine après la prise).

Les amphétamines agissent par trois voies (BROOKES - 1977). La première et la plus importante accélère la libération des catécholamines dans l'espace synaptique. Il s'y ajoute une inhibition de la recapture des produits en excès et enfin une inhibition de la synthèse de la Dopamine et de la Noradrénaline. Il n'existe pas d'effet d'inhibition des Monoamine-oxydases ni d'action sur le système sérotoninergique.

Ces phénomènes rendent compte de deux aspects très importants :
- la stimulation des systèmes noradrénergiques d'éveil
- l'épuisement consécutif lié à une libération importante du médiateur sans resynthèse compensatrice

Les effets de l'amphétamine portent essentiellement sur la vigilance, on observe une diminution de la sensation de sommeil, une augmentation de l'efficacité psychomotrice et un moindre sentiment de fatigue après effort.

Sur le plan psychométrique, EYSENCK (1960) ne relève pas de différences importantes sur le plan perceptif en dehors d'une plus grande réactivité pupillaire à la lumière. CARL et TURNER, dès 1936, observent pour des doses modérées (10 mg) une amélioration des facultés cognitives, mais l'effet inverse avec des doses trois fois plus fortes. Ils notent également une facilitation de l'apprentissage dans un test de codage et des modifications de l'humeur dans un sens favorable, les sujets se sentent en effet plus calmes, relaxés, moins fatigués et plus sociables. L'effet le plus net est la diminution de la détérioration des performances de surveillance lors de tâches prolongées, décrit en 1950 par MACKWORTH. Pour J.F. MACKWORTH (1965), l'amphétamine modifierait moins le niveau initial des performances que leur détérioration. Le produit n'influe pas sur le taux des fausses détections et exercerait un effet analogue à la connaissance des résultats.

Des conclusions analogues avaient été faites par PAYNE et HAUTY en 1954 pour une tâche de poursuite motrice sur quatre indicateurs. Un groupe ayant reçu de l'amphétamine ne présentait pas de dégradation après deux heures, alors que celle-ci se manifestait par un groupe contrôle sans médicament. NEAL et PEARSON observant, en 1966, le même effet sur une tâche de détection de cinq nombres impairs successifs, avec comme tâche complémentaire le repérage de sons de longue durée au milieu de sons de durée plus brève.

IVY constate qu'après 20 heures de garde ou de conduite automobile, la prise de 10 mg d'amphétamine entraîne une amélioration de l'équilibre de la coordination oculomotrice en poursuite tridimensionnelle, et une diminution des temps de réaction de choix. Le produit permet également de minimiser les effets de la privation de sommeil, ainsi que l'a montré KORNETSKY et ses collaborateurs (1959). Après 68 heures de privation, l'amphétamine permet une amélioration dans un test du type barrage, dans une épreuve de codage et lors d'un test de réponse psychomotrices à 10 stimuli et 10 réponses.

Ces effets favorables ne doivent toutefois pas masquer les inconvénients de l'utilisation de l'amphétamine. Elle exerce en effet des effets sur le système végétatif (tachycardie, sécheresse de la bouche, troubles digestifs) et surtout elle peut entraîner des troubles psychopathologiques tels que l'anxiété, et même l'apparition de psychoses délirantes. Sans aller jusque là, on relève parfois une dispersion de l'attention. On observe régulièrement des troubles du sommeil et une perte d'appétit. Toutes ces manifestations peuvent être attribuées à un surdosage, mais il faut savoir que la détermination de la dose efficace comporte une importante part d'aléa, les effets à dose constante dépendent en grande partie des facteurs de personnalité et de l'état mental actuel du sujet.

Il convient donc d'être très prudent dans l'usage de ce produit, d'autant plus que même bien dosé, il entraîne deux conséquences fâcheuses : un état d'épuisement consécutif à l'effet bénéfique qui peut d'ailleurs expliquer certains effets paradoxaux de sédation, et surtout une assuétude qui peut entraîner de véritables toxicomanies. Les premières ont été notées au JAPON dès 1954.

Les cas se sont étendus vers les années 1968 à la Scandinavie puis à la Californie. Le produit est maintenant classé au tableau B.

En dehors de l'amphétamine, d'autres produits ont été employés. Pratiquement tous ont le même effet et les mêmes inconvénients. Citons le prolintane, la pémoline, le méthylphénidate. Selon NICHOLSON (communication personnelle), seul ce dernier produit, à la dose de 20 mg, exercerait un effet sur le sommeil, il diminuerait sensiblement la phase de sommeil paradoxal correspondant aux activités de rêve.

Le méthylphénidate agirait sur la recapture élective de la Dopamine (PEREL - 1977), il est principalement utilisé pour l'effet paradoxal qu'il présente chez les enfants hyperactifs. Chez ceux-ci, le produit exercerait un effet normalisant, se traduisant par une amélioration de la focalisation de l'attention et une diminution de l'agitation (BARKLEY R.A. (1977) ; GABRYS J.B. (1977)).

Récemment, on a proposé l'utilisation d'un précurseur des catécholamines : la L-Dopa ; elle diminuerait la durée du sommeil sans sensation de fatigue, augmenterait l'anxiété, stimulerait la motricité, l'effet serait donc très proche de celui des amphétaminiques (ZARIFIAN - 1975).

Enfin, les produits beta-stimulants (Salbutamol) exerçant leur action au niveau du récepteur post-synaptique, montrent un effet analogue (FELINE - 1977).

4.12 - Stimulants naturels.

Il s'agit d'un groupe très hétérogène sur le plan chimique. Les modes d'action sont également variables, excitants ou désinhibiteurs. Le café, la nicotine et l'alcool seront envisagés dans un premier temps puis seront passées en revue quelques substances médicamenteuses dont l'emploi pourrait être envisagé comme stimulant de la vigilance.

a) La caféine est une triméthylxanthine : elle est utilisée sous forme de décoction de grains de café torréfié ou de feuilles séchées de thé.

La caféine est bien connue par ses effets toniques sur les systèmes nerveux et cardiorespiratoire. Il faut ajouter qu'elle possède des propriétés diurétiques.

Dès 1912, HOLLIGSWORTH étudiait les effets de la prise de café sur les performances évaluées par techniques psychométriques. Il constatait que pour des doses modérées (1 tasse), il obtenait une accélération des capacités associatives ; l'effet était obtenu 1 à 3 heures après la prise et il se prolongeait durant 6 à 7 heures.

A coté de cet effet favorable, il notait un accroissement des erreurs lors d'une épreuve de temps de réaction de choix et une diminution de la coordination oculomotrice.

Des effets analogues sont décrits par GILLILAND en 1939, amélioration de la vitesse d'exécution d'opérations numériques, augmentation de la mémoire immédiate des chiffres, mais diminution de la précision motrice - WEISS (1962) rapproche les effets de la caféine de ceux de l'amphétamine. Bien qu'appartenant à des familles différentes, ces deux produits ont des modes d'action analogues - AMMON (1973) a montré les effets stimulants de la caféine sur les systèmes adrénergiques périphériques ; cet auteur relève, comme pour l'amphétamine, une impression de meilleur rendement intellectuel accompagné d'un sentiment de tension.

b) Le tabac : il est généralement admis par les fumeurs que le fait de fumer permet de meilleures performances, surtout sur le plan de l'attention. La nicotine agirait en bloquant la fixation de l'acétylcholine sur le recepteur post-synaptique et exercerait son effet en deux temps, d'abord excitant puis déprimant.

HULL, en 1924, comparant les résultats de fumeurs et de non fumeurs, constata dans les deux groupes qu'une pipe entraînait une accélération de l'exécution d'addition chez les fumeurs et un ralentissement chez les non fumeurs. Dans les deux groupes, il constatait une légère diminution de la précision, la mémoire des chiffres et la vitesse d'apprentissage était moins bonne.

CARVER (1934) montre également un accroissement des erreurs dans les calculs et une moins bonne coordination oculomotrice après 3 cigarettes ou un cigare.

Plus récemment, JOHNSTON (1966) montra que l'usage du tabac diminue l'efficience dans une tâche de poursuite motrice. Le même effet négatif est constaté par ANDERSON (1975) pour une tâche d'apprentissage verbal. Par contre, d'autres auteurs décrivent des effets favorables sur les temps de réaction (MYRSSEN 1972).

Un dernier point doit être signalé : c'est l'action protectrice qu'exercerait le tabac contre la dégradation des performances lors des tâches prolongées - TARRIERE (1964) a montré que les fumeurs maintenaient stables leurs performances à une tâche de surveillance et de tracking, alors que les témoins se détérioraient. Ce résultat a été retrouvé partiellement par TONG (1977) avec cette réserve que le niveau de base des performances de fumeurs était plus bas que celui des non fumeurs. On est en droit de se demander dans quelle mesure l'effet de motivation réactivé par le fait de fumer n'explique pas en partie cet effet.

L'usage du tabac ne peut pas être envisagé vraiment comme une thérapeutique psychotrope, toutefois, son usage chez les fumeurs peut constituer une aide lors de tâches prolongées en gardant à l'esprit le caractère toxique de la nicotine sur le plan cardiovasculaire, et les risques cancérigènes liés à cette habitude.

c) L'alcool : son usage est universellement répandu, que ce soit sous forme de vin, de bière ou de spiritueux.

Le mode d'action de l'alcool serait lié à la fixation d'une enzyme nécessaire au métabolisme de la dopamine, entrainant la formation d'un corps de même nature que les opiacés (DAVIS - 1970). Après absorption, on constate dans un premier temps une phase d'excitation cérébrale, d'augmentation de la confiance en soi, de la loquacité, et c'est à ce titre que nous le faisons entrer dans les psychostimulants.

On a pu de même constater une augmentation du travail à l'ergométrie et une diminution de la fatigue, ainsi qu'une moindre sensibilité aux stimuli douloureux (BAISSET - 1965).

Cette augmentation des capacités n'est toutefois qu'apparente. Pour des alcoolémies de l'ordre de 0,80 gr., nous avons relevé avec DINAND (1969) un ralentissement des temps de réaction visuel, un accroissement du nombre des erreurs à un test d'attention (barrage de trois lettres), ainsi qu'une diminution de l'efficacité de l'apprentissage. Dans cette étude, les aptitudes les plus détériorées se révélaient être celles qui faisaient appel aux fonctions les plus élaborées. A dose plus importante, il entraîne une dépression, voire le coma. Même dans la première phase, il y a dégradation des performances objectives, c'est dire que seules des tâches grossières pourront être effectuées.

d) La cocaine : c'est la mastication de la feuille de cola qui a permis aux indiens de combattre les envahisseurs espagnols, elle est toujours pratiquée dans les pays Andins pour surmonter la fatigue. En Europe, c'est l'alcaloïde qui est utilisé. Son usage au XIX siècle était considéré comme normal.

L'usage de la cocaine dans un premier temps produit une euphorie accompagnée de désir d'action, secondairement, on note l'apparition d'une lassitude physique et psychique, avec dégradation des fonctions intellectuelles (LEWIN - 1964).

La cocaine agit en inhibant la recapture de la Noradrénaline et de la Dopamine. Elle fait partie des toxiques majeurs.

4.13 - Médicaments Neurostimulants.

Nous citerons pour mémoire la strychnine qui accroitrait les perceptions sensorielles et la picrotoxine qui ne sont pas utilisées comme psychostimulants. Par contre, de nombreux produits ont vu le jour récemment ; ils ont tous une action stimulante globale et ne présentent pas les inconvénients des psychamines.

Nous avons pu montrer (1978) l'effet correcteur de l'amineptine sur la diminution de vigilance induite par certains produits psycholeptiques mineurs tels que les tranquillisants, et CAILLE (1978) a mis en évidence les propriétés psychoanaleptiques d'une nouvelle molécule, le 3726 C E R M, dont la structure chimique s'apparente à celle des beta bloquants. Une étude est actuellement en cours pour étudier ce produit concurremment avec la caféine et la méthylphénidate. Le Diethyl-amino-ethanol (DEANOL) et les produits apparentés ont montré leur efficacité dans certains cas d'asthénie. Ils amélioreraient la capacité de concentration tout en régularisant le besoin de sommeil (SCHUBERTH J. - 1978). Ils agiraient comme précurseurs de l'acétylcholine (EICHHOLTZ - 1962).

La Parachloro-phénylalanine (PCPA) est un inhibiteur de la synthèse de la sérotononine, elle exerce un effet antagoniste sur le sommeil et son usage a pu être envisagé comme éveillant.

4.2 - Nootropes.

Le concept de nootrope a été proposé par GIURGEA (1972). Cette classe de produit exercerait une action élective sur les facultés cognitives, sans répercussion sur le sommeil. Ces produits sont en général des dérivés de médiateurs synaptiques autres que ceux de la série des psychamines.

4.21 - Le Piracetam est apparenté à l'acide gamma aminobutyrique, il favoriserait le turn-over de l'A.T.P. et la formation des acides nucléiques dont le rôle a été proposé dans la fixation mnémonique. Le produit se fixe électivement au niveau du cortex cérébral et faciliterait les liaisons interhémisphériques. MINDUS (1976) a pu montrer que la prise du produit améliorait les performances mentales chez des sujets normaux lors de l'exécution de tâches psychomotrices.

4.22 - Les produits à effet cholinergiques ont récemment été étudiés (DAVIS - 1978), partant de l'hypothèse que la diminution de l'efficience du système cholinergique pouvait expliquer des troubles amnésiques du vieillard, on a pu vérifier que la Physostigmine qui est un cholinomimétique ou inhibiteur de la cholinesterase exerçait un effet favorable sur la mémoire à long terme de l'homme. SITARAM, la même année, obtient des résultats identiques, avec la choline et l'arécoline qui favorisent l'apprentissage verbal d'une séquence de 10 mots. Par contre, un antagoniste, la scopolamine, entraîne un effet inverse.

SCHUBERTH, déjà cité, montre les effets antagonistes de la scopolamine et de la physostigmine. La première pertuberait le stockage d'informations nouvelles sans toutefois altérer la mémoire immédiate et détériorer les informations déjà stockées en mémoire à long terme. Il observe des troubles de l'attention, toutefois moins marqués chez les sujets hypovigilants par privation de sommeil ou soumis à des températures élevées. Il constate également une diminution du sommeil paradoxal. La Physostigmine, à l'inverse, compense les effets de la privation de sommeil, réduit les hallucinations causées par la scopolamine, rétablit le sommeil paradoxal et exerce un effet éveillant. Les effets sont toutefois variables en fonction du rythme circadien.

4.23 - Les Polypeptides sont étudiés depuis peu. Nous mentionnerons à titre d'exemple les recherches menées par KASTIN (1975) et ses collaborateurs sur la fraction protéique commune entre les hormones corticotropes et mélanotropes. Ce Polypeptide : l'ACTH 4-10, qui ne comprend qu'une chaine de 7 acides aminés aurait un effet positif sur la mémoire, l'attention est meilleure durant les tâches soutenues et la résistance à l'ennui s'accroit (MILLER - 1974). Le même auteur, en 1976, montre, sur une tâche continue de détection, que le produit accroit le pourcentage de détections correctes et fait décroitre celui des erreurs par excès ou défaut. Une étude plus poussée, axée sur la mémorisation, montre que l'amélioration porte plus sur les tests à structure spatiale et numérique que sur ceux mettant en oeuvre des stimuli verbaux.

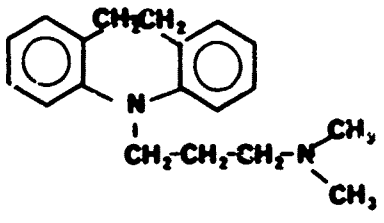
L'ACTH 4-10 exercerait son action surtout au niveau de la réticulée thalamique sans répercussion végétative.

La voie d'étude des Polypeptides apparaît très féconde, tant sur le plan des stimulants que sur celui des anxiolytiques. Toutefois, leur emploi reste encore difficile en l'absence de forme facilement administrable.

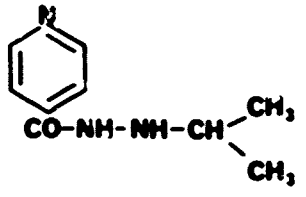
4.3 - Thymoanaleptiques.

Bien qu'ayant une action élective sur l'humeur, ces produits exercent une action tonique générale. On peut les diviser en deux grandes classes.

IMIPRAMINE



IPRONIAZIDE



4.31 - Les dérivés de l'Imipramine se caractérisent chimiquement par une structure tricyclique comportant un atome d'Oxygène ou d'Azote dans la portion centrale.

Ils agissent en s'opposant au recaptage des catécholamines, d'autre part, ils sont antagonistes de l'acétylcholine, de l'histamine et de la sérotonine.

Leur action est lente, environ une semaine ; ils entraînent des effets latéraux de type atropinique : tachycardie, sécheresse de la bouche, sueurs, troubles de l'accomodation, constipation. On note souvent de l'insomnie et parfois de l'anxiété.

4.32 - Les inhibiteurs de la monoamine oxydase, dont le nom caractérise le mode d'action, se caractérisent chimiquement par la présence d'un groupement hydrazine : R - NH - NH - R - Leurs effets se manifestent par l'accumulation des catécholamines et de la sérotonine par non destruction. Ils n'exercent pas d'effet sur le système cholinergique.

Ils induisent des effets secondaires analogues aux précédents, mais surtout d'ordre tensionnel. Certains aliments doivent être bannis : le café, le chocolat, les bananes et les fromages.

Tout ceci rend difficile, voire impossible, l'emploi de ces produits à des fins non thérapeutiques.

4.4 - Adjuvants métaboliques.

On regroupe sous cette rubrique les produits qui ne sont pas directement liés au système nerveux mais qui permettent le fonctionnement normal de toute cellule et en particulier du neurone.

- Certains ions minéraux, tels que le Potassium, le Sodium le Calcium et le Magnésium, déterminent l'équilibre entre les milieux intra et extracellulaires. Dans les conditions normales, il est exceptionnel qu'une carence existe.

- La nutrition de la cellule s'effectue grâce au métabolisme des glucides et on peut penser que l'apport de produits intermédiaires du cycle de combustion puisse être un appoint utile : bien entendu, on trouvera les sucres, eux-mêmes glucose, fructose, mais aussi l'Adénosine triphosphor e, les acides glutamique, aspartique, succinique, etc....

- L'apport de produits de base est nécessaire pour la construction des cellules elles-mêmes - Acides aminés, tryptophane, méthionine, phénylalanine, glycine, acides nucléiques.

- Enfin, il peut être utile d'apporter des régulateurs métaboliques qui modulent les combustions tels que la centrophénoxine, l'heptaminol, sans oublier les vitamines C et celles du groupe B, ainsi que certaines hormones anabolisantes (corticoïdes et hormones males).

Tous ces produits entrent plus ou moins dans les compositions de médicaments appelés défatigants, leur efficacité est modérée sur le plan biochimique, mais ils peuvent constituer une aide au moins psychologique chez des sujets éprouvant le besoin d'un soutien lors de situation requerrant une activité mentale soutenue.

5 - MODELE EXPLICATIF.

Au cours du paragraphe précédent, nous avons vu que plusieurs produits étaient susceptibles d'améliorer l'efficacité des différents maillons de la chaîne de traitement de l'information : réception, stockage et opérations intellectuelles. A l'exception des nootropes, encore mal connus, et des adjuvants d'efficacité mineure, tous ces produits agissent sur l'activation générale, on a vu en effet le rôle important que jouent les systèmes catécholinergiques dans les mécanismes d'éveil. Dans le modèle que nous avons exposé précédemment (DEFAYOLLE - 1968), le concept d'activation jouait un rôle central et l'on se souvient de la relation curvilinéaire qui existait entre celle-ci et les performances. LEGEWIE, la même année, proposait d'appliquer ce schéma à l'efficacité des psychotropes.

Selon ces modèles et dans le cas qui nous intéresse, celui des stimulants, on doit s'attendre à un effet positif chez les sujets sous-activés, et négatif chez les suractivés.

Par sous ou suractivés, LEGEWIE entend un facteur de personnalité stable se recoupant en gros avec les deux types d'introvertis (suractivés) et d'extravertis (sous-activés) d'EYSENCK. Il faut généraliser ce schéma aux aspects dynamiques, et y faire intervenir également la tâche, l'environnement, la motivation, etc...

On peut ainsi rendre compte de l'effet paradoxal de détérioration par surdosage relatif de l'activation.

Notre hypothèse attribuait la courbure de la fonction à l'effet antagoniste de deux fonctions, l'une de la capacité de traitement évoluant dans le même sens que l'activation, et l'autre de capacité de filtrage se dégradant avec cette activation. C'est ce dernier phénomène qui rendrait compte de la décroissance de la deuxième partie de la courbe.

Un moyen d'éviter la détérioration des performances par hyperactivation pourrait être de renforcer les processus de filtrage.

Ceux-ci semblent être sous la dépendance du système cholinergique, c'est vers des produits appartenant à cette catégorie qu'il y aurait lieu de s'orienter.

Nous n'avons envisagé que les effets directs sur les performances, il ne faut pas négliger ceux qui, s'exerçant à un niveau moins élevé d'intégration, peuvent modifier celles-ci.

Les phénomènes d'activation s'accompagnent généralement de manifestations neurovégétatives gênantes : sudation, troubles digestifs, tachycardie, pouvant constituer pour le sujet des stimulations parasites qui viennent perturber son efficience. Il faut ajouter à celà les phénomènes moteurs, les tremblements qui constituent en eux-mêmes un handicap à l'exécution de tâches nécessitant une coordination motrice précise.

Le schéma qui vient d'être présenté aborde le problème sous son aspect neuropsychologique, ce serait une erreur de le considérer comme suffisant, le pôle biologique ne rend pas compte de l'aspect symbolique qui est propre à l'homme.

La dimension sémantique, la signification, revêtent une importance certaine. Jouer sur la capacité de traitement, le filtrage en les augmentant, ne préjuge pas des objets sur lesquels portent ces processus ; l'augmentation du potentiel d'un individu ne signifie rien s'il n'est pas dirigé dans une direction souhaitable, il peut se manifester sous forme d'efficacité, d'anxiété ou d'agressivité, et cette direction ne dépend pas nécessairement de phénomènes biochimiques. L'usage de produits médicamenteux ne résoud donc qu'une partie du problème de l'augmentation de l'efficience.

6 - INDICATIONS DES PSYCHOSTIMULANTS.

L'usage des psychostimulants peut être motivé par deux raisons qui, schématiquement, coïncident avec les deux grandes classes de produits qui ont été envisagées précédemment : les nooanaleptiques et les nootropes.

- Dans le premier cas, le problème central est celui du maintien de la vigilance, soit pour éviter sa dégradation au cours de tâches prolongées, soit pour éviter un endormissement lié à une perturbation des rythmes normaux du sommeil et de la veille.

Dans ce dernier cas, l'usage des amphétaminiques est évidemment le plus efficace, mais il faut garder à l'esprit que ces produits peuvent entrainer des troubles par hypervigilance avec non focalisation de l'attention et des effets latéraux nuisibles : troubles des coordinations psychomotrices, pertes de l'appétit, anxiété, agitation. De plus, leurs effets sont suivis d'une période de dépression physique et intellectuelle. Ces produits ne devraient donc être employés qu'exceptionnellement, pour des durées relativement brèves et leur dosage adapté à chaque utilisateur.

Pour un usage plus soutenu, le stimulant naturel qu'est la caféine apparait d'un maniement plus souple, mais là aussi il faut se garder d'un surdosage. Nous avons vu que le tabac ne pouvait pas être considéré comme un psychostimulant vrai, mais que chez les habitués, il constituait une aide utile.

- Lorsque le but est d'améliorer les performances intellectuelles, le problème est plus complexe, les nootropes sont d'introduction récente, leur application souvent difficile et mal codifiée. Bien qu'à notre avis ils représentent une voie d'avenir, on devra se contenter de médications plus mineures, certains neurostimulants et les adjuvants métaboliques peuvent être employés.

Quels que soient les produits utilisés, il existe un risque de dépendance pharmacologique.

On définit la pharmacodépendance comme un "état psychique et quelquefois physique résultant de l'interaction entre un organisme vivant et un médicament. Cette interaction se caractérise par des modifications du comportement et par d'autres réactions qui engagent toujours fortement l'usager à prendre le médicament de façon continue ou périodique afin de retrouver ses effets psychiques et quelquefois d'éviter le malaise de la privation" (EDDY - 1965).

La tolérance est caractérisée par une diminution de l'efficacité du produit entrainant une augmentation de sa consommation.

On distingue la dépendance psychique, qui relève d'un désir de plaisir ou d'évitement de malaise, de la dépendance physique, ou assuétude, qui se manifeste par des troubles importants lorsque l'usage du produit est interrompu.

En ce qui concerne les psychostimulants, seuls les psychamines, la cocaine et l'alcool (tout au moins dans la phase initiale) entraînent une dépendance physique.

Pour les autres produits, les effets agréables qu'entraînent leur usage peuvent entrainer une dépendance psychique qui peut rendre difficile la suppression de l'habitude, c'est une raison supplémentaire pour n'envisager leur usage que dans des circonstances exceptionnelles. Avant de recourir aux moyens pharmacologiques, il faudra toujours se demander s'il n'est pas possible de modifier les conditions d'exécution des tâches : horaires, difficulté et formation des personnels qui se révèlent souvent plus efficaces et moins nocifs.

Le meilleur activant du système nerveux est certainement la motivation et c'est dans cette voie qu'il faut essayer d'œuvrer.

C'est seulement dans l'impossibilité d'agir par ces moyens non agressifs que l'on pourra avoir recours aux aides pharmacologiques.

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PSYCHOSTIMULANTS

by

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SUMMARY

This review of the state-of-the-art of psychostimulants starts with a brief historical and geographical survey.

The basic neuro-chemical data on vigilance are then dealt with, and the various systems of mediators involved in synaptic conduction, differentiated from each other.

The methodology of therapeutic tests on psychotropes is then tackled and the effects induced by the use of the various types of drugs available noo-analeptics, nootropes, thymoanaleptics and metabolic adjuvants are considered.

After an attempt at incorporating these data into a general model of vigilance including the data handling capacity and filtering concepts, the paper ends with the indications and contraindications as to the use of psychostimulants.

1. HISTORICAL BACKGROUND

The search for artificial means capable of improving man's performance is a phenomenon to be found in all cultures. Originally, it comes under empirical herb therapy and when the consumption of certain plants is followed by effects regarded as favourable, these plants are considered useful. Later on, in the course of the 19th century, the developments which took place in the field of chemistry led to the extraction of their active principles, then to the analysis of their chemical structure, and finally to their synthesis.

1.1 Natural stimulants can be broadly classified as follows:

Caffeine

It is used on a world-wide basis. It is found in tea in the area of Chinese culture, in coffee which originated in Abyssinia, in the Kola-nut in Africa, in Guarana and Maté in Amazonia. Its use in the form of coffee and tea spread to Europe in the 16th century. The synthesis of caffeine was achieved in 1820.

Tobacco

Originating in Mexico and used for sacred ceremonies, it was introduced in Europe after the discovery of the New World and was originally used for therapeutic purposes. Its active principle is nicotine.

Areca or betel

Its use is limited to South-Eastern Asia. The Areca nut contains an alkaloid: Arecoline.

Alcohol

When taken in large quantities its effects are rather depressant. However, it plays also an activating role by removing inhibitions. It is also used widely

Coca

It is the holy plant of the Inca empire and when chewed it is supposed to overcome fatigue and suppress hunger. Its active principle is cocaine which was synthesized in 1855. Its use was popularized by Bentley, then by Freud, who put forward justifications for its use.

To these stimulants, which are peculiar to the nervous system, ephedrine should be added. It was synthesized in 1885 by Nagai and Kanao, who were interested in the vegetable extract from ephedra famous in traditional Chinese medicine for its stimulating respiratory and cardiac effect. Derived from this substance, a whole family began to appear, with Adrenalin in 1901, then Amphetamine in 1931.

1.2 For the last few years it has been recognized that various products exert a psychostimulant effect parallel to their primary purpose, for example Iproniazide. It was originally used against tuberculosis, but proved to have an anti-depressive action as early as 1952.

Since then a large number of molecules have been studied, sometimes without starting from a given assumption but with a view to determining empirically possible psychotropic properties.

These empirical investigations are now complemented by a theoretical approach for explanatory purposes. This is neurochemical and we shall first consider its most general aspect, including the mechanisms of synaptic transmission, and then from a more specific standpoint, by dealing with the various systems likely to account for the stimulating effects of the products.

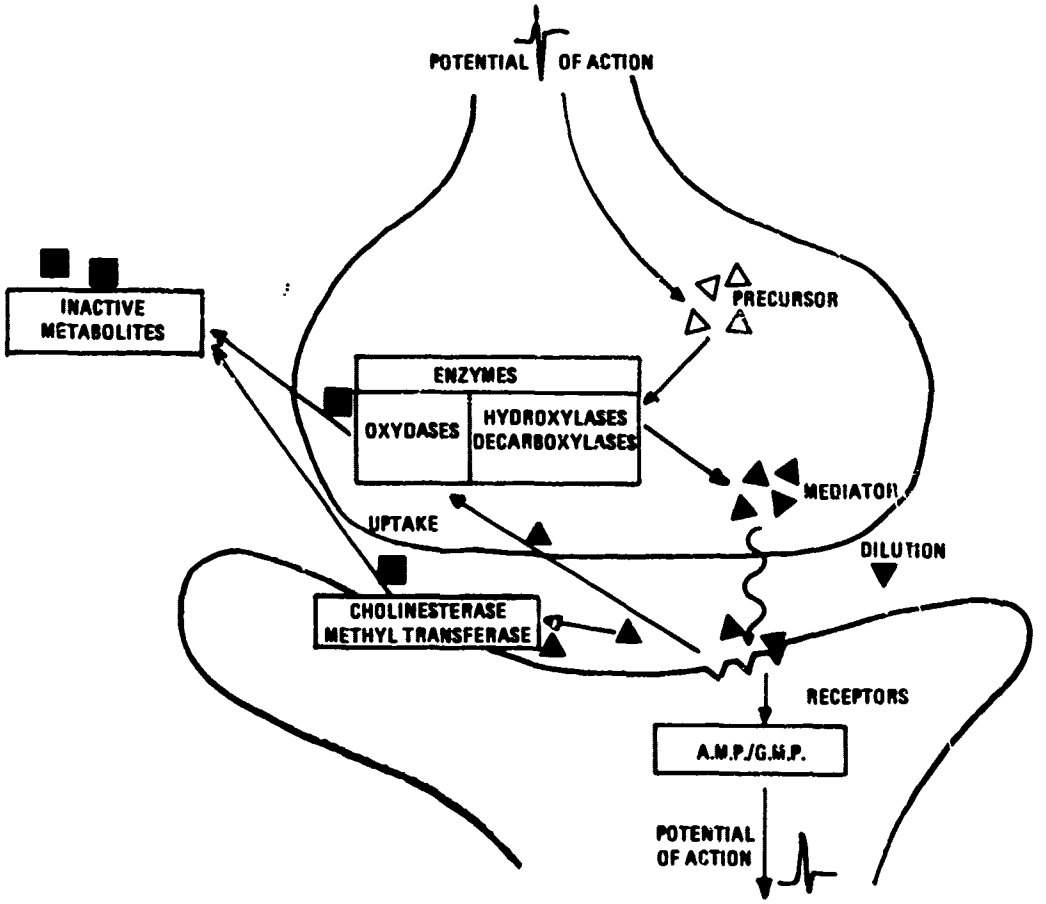
2. NOTIONS OF NEURO-CHEMISTRY

2.1 Synaptic Transmission

It is well-known that the nervous system is made up of a network of cells called neurons, specialized in the generation and conduction of an electric phenomenon the nerve impulse. This network implies a communication between the neurons. In most cases communication is not established by conduction of the electric potential by contact, but through chemical substances discharged by the upstream cell which excites the cell located downstream.

We call synapse the area in which the parts of these adjacent neurons are grouped: ending of axon, dendrite and the space which separates them.

Investigations with an electronic microscope have revealed the presence of small vesicles in the axon endings, and quantitative micro-analyses, as well as microscopic examinations under flouorescent conditions, have revealed the existence of chemical substances called mediators, discharged by the upstream neuron and exciting the downstream neuron.



The general pattern is as follows. Within the neuron, there are bodies called "precursors" which are transformed into mediators through a series of enzymatic reactions. These mediators are released by the nerve impulse and, after passing through the dendritic space, act upon a receptor structure of the following neuron. In its turn, the latter triggers a series of reactions involving two substances, monophosphoric adenine (MPA) and monophosphoric guanine (MPG), and re-creating a membrane depolarization generative of the nerve impulse. The excess mediator must be destroyed so that the effect may be limited in time. This inactivation is achieved through three processes, diffusion and dilution in the extra-cellular medium, enzymatic degradation and, finally, uptake by the presynaptic neuron.

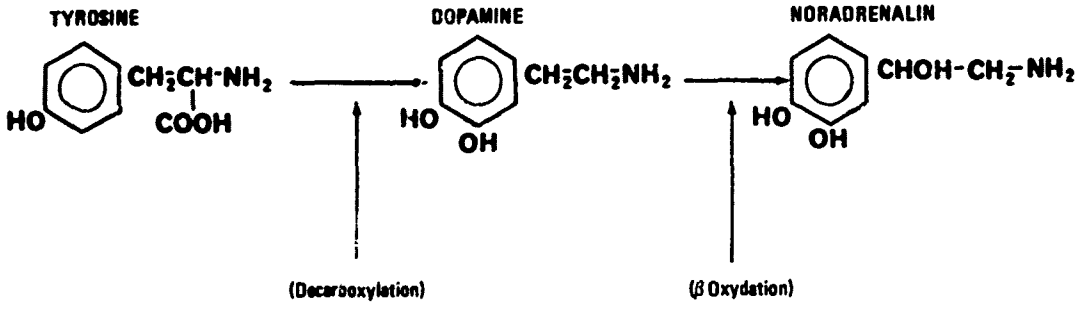
2.2 Transmitters

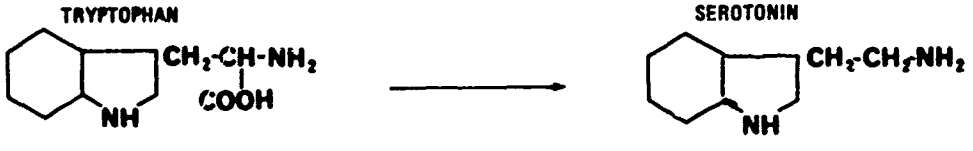
This broad pattern applies to all the synapses. The only difference lies in the mediator involved. The sets of neurons possessing the same mediators have been grouped in systems.

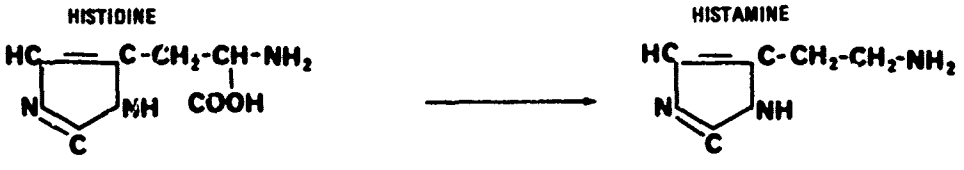
Mediators can be classified in four categories depending on their chemical families.

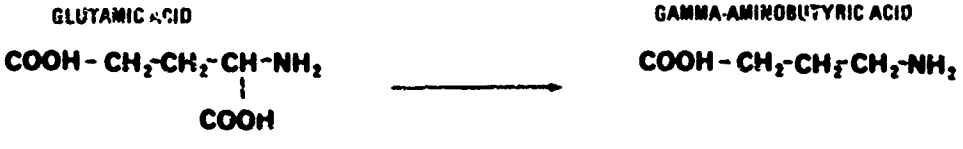
- the first group called Monoamines includes relatively simple bodies, centred on an aromatic amino-acid. Among monoamines, those derived from Tyrosine are differentiated from those derived from Tryptophan. Dopamine and Noradrenalin are derived from Tyrosine, and Serotonin from Tryptophan.
- other mediators are also derived from amino-acids, for example Glycine and Histamine.
- Acetylcholine is an acetic ester of choline which is itself derived from a quaternary ammonium.

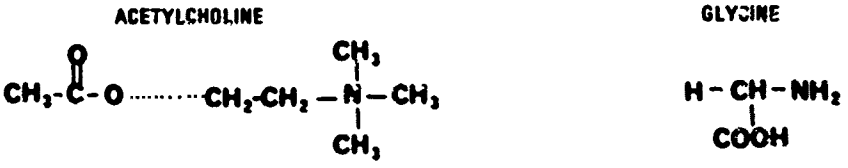
a rather heterogeneous class includes other derivatives from amino-acids and peptides.











2.2.1 Dopaminergic System (DA)

It includes the regions of substantia nigra, the striated system, the globus pallidus, the amygdalla, the rhinencephalon and the regions of the hypothalamus; Höfkelt has recently described connections of this type in the limbic zone (1972) and the prefrontal cortex.

The role of the striated system in motor regulation is well known. An insufficient amount of DA brings about a Parkinsonian syndrome. On the other hand, an excess of DA induces stereotyped behaviours and psychic disturbances of the paranoid type.

In addition, through its action on the hypothalamus, DA inhibits the secretion of the luteine releasing factor (LRF) and prolactin. Finally, in view of the role of the limbic zone in the regulation of mood, and of the prefrontal zone, DA is assumed to be involved in mental processes (Matthysse and Kety 1973).

2.2.2 Noradrenergic System

It originates largely from a nucleus called locus coeruleus, and, from there, it sends out bundles directed downwards towards the medulla, and upwards towards almost all the regions of the central nervous system. The very high diffusion of the network is to be stressed. All the cortical neurons may depend upon a single neuron. It can therefore be assumed that it plays an overall coordination role. It is responsible for the regulation of wakefulness and of the REM (rapid eye movement) phase of sleep which is supposed to correspond to the oniric activity.

Another group of neurons is associated with the hypothalamus area and plays an active part in the regulation of endocrinous activities, by facilitating the LRF and ovulation. It is also supposed to control thermogenesis and certain primitive behaviours such as hunger, thirst and sham rage.

2.2.3 Serotoninergic System

Its original cells are gathered in the medial region of the brain stem which receives itself noradrenergic neurons. The paths are similar between these two systems to those of the noradrenergic systems. Considerable interactions between these two systems can therefore be anticipated. The serotoninergic system controls slow wave sleep, and inhibits sexual activities and aggressiveness. Consequently, its action is contrary to that of noradrenalin.

2.2.4 Cholinergic System

It is also spread widely. Cholinergic synapses are to be found almost wherever noradrenergic connections exist. The cholinergic system is involved in wakefulness, however, its action is more subtle, as it allows a suitable adaptation of behaviour whereas the NA system performs essentially an overall activation function.

Studies on the development of the cortex have revealed that the cholinergic structures appear later than the others, which would bear evidence of a more advanced character.

2.2.5 Other Mediators

Their distribution and role are less well known. They can be classified in two categories:

(a) The first category includes amino-acids:

Histamine, derived from histidine by decarboxylation. Its role as a mediator was suggested by Snyder's studies (1972). The existence of histaminergic paths going up towards the cortex leads one to assume that this system might be involved in the wakefulness.

Gamma-aminobutyric acid (GABA) is a derivative of glutamic acid, after decarboxylation and hydroxylation. It is assumed to have an inhibiting influence on synaptic transmission (Roberts 1975). GABA-ergic synapses are spread widely in the nervous system. Close relations are supposed to exist between the GABA system and the dopaminergic system.

Glycine is a very simple amino-acid. The synapses using this mediator are assumed to be mainly located in the spinal cord and to have an inhibiting action (Werman 1967).

(b) The second group includes more complex bodies, which are combinations of amino-acids. These *polypeptides* are traditionally related to hormonal secretions. However, it is recognised that they can also perform a mediator function. It was proposed by Guillemin to call them cybernines. They are selectively located in the hypothalamus, but they can also be found in other regions of the central nervous system.

The influence of these bodies on behaviour has been discussed recently during an INSERM colloquium (Gourdji 1978).

ACTH and vasopressin are assumed to play a part in memory processes, whereas prolactin and endorphines are supposed to exert an influence on emotion.

This brief survey shows the complexity of, and numerous interactions between mediators. The distribution of effects depending on anatomic locations is far from evident. The very monolithic character of each system made up of a set of neurons connected through a single neuromediator playing an existing or inhibiting part at each stage, may be questioned. Szabadi (1978) proposed a model which he calls "agonism-antagonist", according to which a single mediator might have both positive and negative effects on distinct postsynaptic receptor sites. Such an assumption would account for the paradoxical effects according to the amounts of neuromediators, as well as for the succession, in time, of exciting and inhibiting phases after the application of a single product.

2.3 Mode of Action of Psychotropes

The existence of the blood brain barrier prevents the direct transit of neuromediators, either ingested or injected, to the synapse level. Therefore, no medicinal action from these products can be noted. The only possibility consists in acting either on their genesis or on their evolution. Research in this field deals mainly with monoamines and acetylcholine.

At the stage of the genesis of the transmitters, the following factors can be considered:

the metabolic operation of the neurons must be adequate
the precursor of the transmitter must be available
the enzymatic transformation system, especially decarboxylases, must be efficient
transmitter storage must be effected.

Once released from the presynaptic neuron, the transmitter must be able to convey its information, which implies that it is possible to act on:

- the availability of the post-synaptic receptor sites
- the activation of the monophosphoric Adenyl and Guanine systems.

Finally, the excess neurotransmitter must be neutralized. This can be achieved either by modifying the enzymes in charge of its degradation, or by acting on the uptake mechanism.

These various approaches will be considered in detail when the different products are studied.

3. METHODS OF STUDY

When faced with a product likely to have a psychostimulant action, several steps have to be taken prior to undertaking tests on man. Sometimes, an analysis of the chemical formula provides a means of predicting effects. However, this method is hazardous, because the relation between structure and efficiency is far from accurate. The preliminary information on the toxicity and pharmacodynamics of a product (absorption, metabolism, blood rate, degradation, excretion) and, in particular, on its effects on behaviour will be provided by tests on animals. After absorbtion the animals are subjected to standardized tests (Simon 1978). Psychostimulants induce hyperactivity which can be either directly observed or objectively measured by counting movements. They facilitate learning and conditioning and are antagonistic to hypnotics. Certain psychostimulants trigger stereotyped licking or chewing motions. These are the amphetaminics. The other psychostimulants are classified in the neurostimulant category.

When tests are carried out on man, the techniques used to observe the effects can be broken down into three groups, clinical evaluation, either direct or controlled by rating scales, psychometric methods and physiological records.

Clinical observation is mainly used in psychiatry on patients. Within the framework of studies performed on healthy subjects, and other two methods are preferred.

Psychometric procedures include efficiency tests such as measurement of reaction time, attention, memory, decision-making capability, together with questionnaires concerned either with relatively permanent personality features, or with present conditions.

Physiological recording techniques are mainly concerned with electro-encephalographs, heart rates, skin resistance and biochemical quantitative analyses

The objective study of psychotropes at large, and psychostimulants in particular, must use precise methodology, since the results obtained can be biassed in many ways.

It should be pointed out that it is more difficult to bring out effects on a healthy subject than on a sick subject. As regards the latter the action of the product will be the correction of a disturbance which is most often easy to observe In a healthy subject, on the contrary, it is the exaggeration of a normal function which is often observed It is then possible to apply a technique which consists in observing the compensatory effects of a product regarding a situation likely to impair the subject's balance prolonged task, physical fatigue, sleep deprivation, absorption of sleep inducing drugs, etc.

Another difficulty arises from what is called "the placebo effect". This effect concerns either the modifications of the state of a subject who has been given an inactive substance (Placebo), or the additional effects which can be induced by an active substance. It is believed that approximately one third of the population is affected by this phenomenon. It is therefore necessary to test it every time a substance is investigated.

There are several levels of experimental testing (Guelfi 1978) which correspond to precise requirements:

in *open tests*, the nature of the product used is known by the prescriber, the subject and the observer.

in blind tests, a Placebo assuming the same appearance as the active product(s) is given in addition to this (these) product(s). This may be either a *single blind* test, in which the patient does not know whether the product is active, or a *blind evaluation*, in which only the prescriber knows whether the product is active, or, finally, a *double blind* test in which none of the parties are aware. This is the only technique which prevents any suggestion effects.

The test is organized according to an experimental programme (Defayolle 1978) which may involve either distinct groups of subjects having received the various forms of drugs, or observations on the same subjects having received successively the various forms of drugs.

In this programme, the following factors will have to be considered: number of measurements (prior to, during and after treatment), conditions to which the subjects are subjected (fatigue, etc.), interval of time between the absorption of the product and the observation of the impregnation time (acute or chronic effect).

4. STUDY OF A FEW PRODUCTS

In the first stage, a place must be assigned to the various psychostimulants among the products with a psychotropic action. In 1928, Lewin described five categories:

EUPHORICANTS:	opium, cocaine, etc.
HYPNOTICS:	gardenal
INEBRIANTIANTS:	alcohol
PHANTASTICANTS:	belladonna Peyolt
EXCITANTS:	coffee, tobacco, etc.

More recently, Delay and Deniker proposed a classification in three broad categories: Psycholeptics, Psychoanaleptics and Psychodysleptics.

The products of the first category reduce the level of performance of the nervous system. They include hypnotics, characterized by their action on sleep, anxiolytics or tranquillizers, and neuroleptics which are antipsychotic therapeutic substances.

Psychodysleptics include hallucinogens. Finally, psychoanaleptics have excitant properties and correspond to the notion of psychostimulants.

Among the latter, two broad classes can be distinguished according to whether stimulation is exerted on cognition or on the mood. In the former case, nooanaleptics are concerned, in the latter case, thymoanaleptics.

We shall deal essentially with nooanaleptics, which we shall divide into three categories:

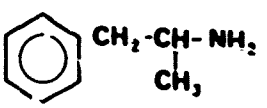
vigilance stimulants, or nooaleptics proper
cognition stimulants, or nootropes
neuronal performance regulators

4.1 Nooanaleptics

The most thoroughly studied products belong to the class of amphetamines. However, the importance of natural stimulants such as caffeine and nicotine should not be overlooked, in view of their high frequency of use. Finally, other products having excitant properties or exerting an action on the central nervous system will be reviewed.

4.1.1 Amphetaminics or Psychamines

These derivatives bear some resemblance in structure with noradrenalin. The leading product in this category is amphetamine.



Two hours after ingestion, the highest blood concentration is observed. The product accumulates electively in the cerebral cortex and the thalamus, and approximately two thirds is eliminated by the urinary system (traces are still to be found one w'.κ after its ingestion)

Amphetamines have a threefold action (Brookes 1977). The first and most important action is the acceleration of the release of catecholamines in the synaptic space. The second action is an inhibition of the uptake of excess products, and the third and last action is an inhibition of dopamine and noradrenalin synthesis. There is no inhibition effect on monoaminoxidases, nor any action on the serotoninergic system.

These phenomena reflect two extremely important aspects:

the stimulation of the noradregenic systems of wakefulness

the subsequent exhaustion, resulting from a considerable release of the mediator, without any new compensating synthesis.

The effects of amphetamines are essentially felt on vigilance. The sensation of sleep is reduced, psychomotor efficiency is improved, and the feeling of fatigue consequent upon efforts is lessened.

From a psychometric standpoint, Eysenck (1960) did not record marked differences in perception, except higher pupillary reactivity to light. As early as 1936, Carl and Turner observed an improvement of the cognitive faculties corresponding to moderate quantities (10 mg), but noted a reverse effect with quantities three times higher. They also noted improved learning ability in a coding test, and favourable modifications of the subject's mood. The subject feels calmer, relaxed, less tired and more sociable. The most evident effect is the reduction of the monitoring performance deterioration during prolonged tasks, as described in 1950 by Mackworth. Mackworth, J.F. (1965) believes that amphetamine modifies the deterioration of performance rather than the initial level of performance. This product does not affect the rate of wrong detections and is supposed to have an effect similar to the knowledge of results.

Similar conclusions had been made in 1954 by Payne and Hauty concerning a motor tracking task on four indicators. After a period of two hours, no performance deterioration was noted in a group having been given amphetamine, whereas such deterioration was apparent in a control group without drugs. In 1966, the same effect was observed by Neal and Pearson for a task in which five successive odd numbers had to be detected with, as an additional task, the identification of long duration sounds among short duration sounds.

It was noted by Ivy that, at the end of a twenty hours watch or car driving, the absorption of 10 mg of amphetamine improves the balance of oculomotor coordination in three-dimensional tracking, and reduces the selection response times In addition, this product minimizes the effects of sleep deprivation, as shown by Kornetsky and his collaborators (1959) After 68 hours of deprivation, the absorption of amphetamine results in an improvement in a "cancellation" type test*, in a coding test and in a psychomotor/test comprising 10 stimuli and 10 responses.

In spite of these favourable effects, the drawbacks related to the use of amphetamine should not be overlooked. In fact, amphetamine has an action on the vegetative system (tachycardia, mouth dryness, digestive troubles) and, above all, it can induce psychopathological troubles such as anxiety or even psychosis accompanied by delirium. Without going to such extremes, difficulties in attention focusing can be noted. Sleep disturbances and loss of appetite are common occurrences. All these signs can be attributed to an overdose. However, it must be stressed that the determination of the right dose is associated with a number of hazards, as, with the same dose, the effects achieved are largely dependent upon the subject's personality factors and present mental state.

Consequently, this product should be used with great caution, especially since, even in right amounts, it brings about two adverse consequences a state of exhaustion consequent upon the beneficial effect, which, incidentally, may account for certain paradoxical effects of sedation, and especially an addiction which may lead to toxicomania Such cases were noted for the first time in Japan as early as 1954. About 1968, these cases spread to Scandinavia, then to California. The product is now classified.

In addition to amphetamine, other products have been used. Almost all of them have the same effect and the same drawbacks Let us mention prolintane (5 10 mg), pemoline (20 40 mg), methylphenidate (10 12 mg) and fencamfamine (10 20 mg). According to Nicholson (private information), only the two latter products in the doses indicated have an action on sleep. They reduce appreciably the REM phase of sleep corresponding to the dreaming activity.

Methylphenidate is supposed to act on the elective uptake of dopamine (Perel 1977). It is mainly used for its paradoxical effect on hyperactive children. In the latter case, this product may have a normalizing effect, resulting in improved attention focusing and reduced restlessness (Barkley, R.A. (1977); Gabrays, J.B. (1977).

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* Test in which the subject must strike out given signs or letters in a text.

The use of a precursor of catecholamines has been proposed recently: it is the L-Dopa; it is reported to reduce the duration of sleep without any feeling of fatigue, to increase anxiety, and to stimulate motoricity. Its effects would therefore be very close to those of amphetamines (Zarifian 1965).

Finally, similar effects are revealed by beta-stimulants (Salbutamol) which exert their influence at the level of the post-synaptic receptor (Feline 1977).

1.1.2 Natural Stimulants

They belong to a group which is very heterogeneous from the chemical standpoint. Their modes of action are also variable. They have either exciting or disinhibiting effects. To start with, coffee, nicotine and alcohol will be considered, then a few medicaments will be reviewed, the use of which could be contemplated for vigilance stimulating purposes.

(a) *Caffeine* is a trimethylxanthine and is used either in the form of a decoction of roasted coffee beans, or in the form of dried tea leaves. It is well known for its tonic effects on the nervous and cardio-respiratory systems and in addition, offers diuretic properties.

As early as 1912, Hollingsworth studied the effects of coffee ingestion on human performance, by means of psychometric methods. He noted that, for moderate doses (1 cup), the associative abilities are improved. The effect was obtained after one to three hours following the ingestion of coffee and went on during six or seven hours.

Apart from this beneficial effect, he noted an increased number of errors during a selection response test, and a reduction of oculomotor coordination.

Similar effects were described by Gilliland in 1939. Accelerated performance of numerical operations, improved immediate memory of figures, but reduced motor precision Weiss (1962) compared the effects of caffeine with those of amphetamine. Although they belong to different families, these two products have similar modes of action. Ammon (1973) demonstrated the stimulating effects of caffeine on the peripheral adrenergic systems: as in the case of amphetamine, this author noted an impression of improved intellectual efficiency accompanied by a feeling of tension.

(b) *Tobacco*. It is generally admitted by smokers that smoking results in improved performance, especially as regards attention. It is assumed that nicotine acts by blocking the fixation of acetylcholine on the post-synaptic receptor, and that its action takes place in two stages: first excitation, then depression.

When comparing the results obtained with smokers and non-smokers, in 1924, Hull noted in the two groups that the smoking of a pipe resulted in accelerated addition performance among smokers, and slowed down addition performance among non-smokers. In both groups, he noted a slight reduction in precision memory of figures and speed of learning.

Carver (1934) also demonstrated an increase of computation errors and a reduction of oculomotor coordination after 3 cigarettes or one cigar.

More recently, Johnston (1966) demonstrated that the use of tobacco leads to reduced efficiency in a motor tracking task. The same negative effect was observed by Anderson (1975) for a verbal learning task. On the contrary, favourable effects on reaction times were described by other authors (Myrssen 1972).

A last point should be highlighted. The protective action likely to be exerted by tobacco against performance deterioration during prolonged tasks. Tarriere (1964) demonstrated that the performance of smokers remained steady in a monitoring and tracking task, while the performance of control subjects deteriorated. The same result was partly obtained by Tong (1977), with the reservation that the basic performance level of smokers was lower than that of non-smokers. We are justified in wondering to what degree the motivation effect, re-activated by smoking, might account partly for this effect.

The use of tobacco as psychotrope therapeutics cannot be seriously contemplated. Its use by smokers may provide a certain degree of assistance during prolonged tasks, although one should bear in mind the toxic character of nicotine from a cardiovascular point of view, and the cancerigenic hazards associated with this habit.

(c) *Alcohol*: its use is widely spread, in the form of either wine, beer, or spirits.

The mode of action of alcohol is supposed to be related to the fixation of an enzyme necessary to the metabolism of dopamine. This induces the formation of an opiate analogue (Davis 1970) Following the absorption of alcohol, a phase of cerebral excitation, increased confidence and loquaciousness is noted in the first stage, and this is why we include it in the category of psychostimulants.

Increased work has been established by ergometry, as well as reduced fatigue and decreased sensitivity to painful stimuli (Baisset 1965).

However, this increase of abilities is only apparent. For blood level about 800 mg/l, we noted, with Dinand (1969) a slowing down of visual reaction times, a rise in the number of errors in an attention test ("cancellation" test with three letters), together with a reduction of learning efficiency. This study revealed that the most deteriorated aptitudes are those related to the most elaborate functions. Higher doses induce a state of depression or even coma. Even during the first phase, a deterioration of objective performance is observed, that is to say only rough tasks can be carried out.

(d) *Cocaine*: chewing cola leaves enabled the Indians to fight against their Spanish invaders; this practice is still used in Andean countries to overcome fatigue. In Europe, it is the alkaloid which is used. Its use was regarded as normal in the 19th century.

The use of cocaine first induces a state of euphoria accompanied by a will to act, then physical and psychic weariness, with a deterioration of the intellectual functions (Lewin 1964).

Cocaine exerts an action by inhibiting the uptake or noradrenalin and dopamine. It is listed among major toxic products.

4.1.3 Neurostimulating Medicines

As a reminder, let us mention strychnine, which is thought to increase sensory perceptions, and picrotoxin. These two substances are not used as psychostimulants. However, many products have been recently developed; all of them have an overall stimulating action without the drawbacks created by psychamines.

We have been able to demonstrate (1978) the corrective effect of *amineptine* on the impairment of vigilance induced by certain minor psycholeptic products such as tranquillizers, and Caille (1978) revealed the psychoanalptic properties of a new molecule, the 3726 CERM, the chemical structure of which has points in common with that of the beta adrenoceptor antagonists. Within the framework of investigations in progress, this product is being studied in conjunction with caffeine and methylphenidate. Diethyl-amino-ethanol (DEANOL) and the related products proved to be efficient in certain cases of asthenia. They are thought to improve the concentration ability while regulating the sleep requirement (Schuberth, J. 1978). They are supposed to act as precursors of acetylcholine (Eichholtz 1962).

Parachloro-phenylananine (PCPA) is an inhibitor of the synthesis of serotonin: it has an antagonistic action on sleep and its use as a stimulant of vigilance can be contemplated.

4.2 Nootropes

The concept of nootrope was proposed by Giurgea (1972). This class of products is reported to have an elective action on the cognitive faculties, without any consequential effects on sleep. These products are generally derivatives of synaptic mediators, other than those belonging to the group of psychamines.

4.2.1 Piracetam is related to the gamma aminobutyric acid. It is thought to exert of favourable action on the turn-over of Triphosphoric Adenosine, and the generation of nucleic acid which is supposed to play a role in mnemonic fixation. This product settles electively in the cerebral cortex and is thought to facilitate interhemispheric connections. Mindus (1976) demonstrated that the absorption of this product improves mental performance in normal subjects carrying out psychomotor tasks.

4.2.2 Products exercising a cholinergic action have recently been studied (Davis 1978), based on the assumption that the decreased efficiency of the cholinergus system may account for amnesic troubles in old people. It has been established that Physostigmine, which is a cholinomimetic, or cholinesterase inhibitor, has a favourable influence on man's long term memory. During the same year, Sitram obtained identical results with choline and arecoline which help the verbal learning of a sequence of 10 words. On the contrary, scopolamine, which is an antagonistic product, brings about a reverse effect.

The antagonistic effects of scopolamine and physostigmine have been demonstrated by Schuberth (already mentioned). The former product is reported to affect the storage of new information, although it does not impair the immediate memory, and to damage the information already stored in the long term memory. Schuberth observed disturbances of attention, although less marked in subjects suffering from hypovigilance induced either by sleep deprivation or by high temperatures. He also noted a reduction of REM sleep. On the contrary, Physostigmine compensates the effects of sleep deprivation, reduces the hallucinations caused by scopolamine, restores REM sleep and exercises a stimulating effect on vigilance. These effects are nevertheless variable with the circadian rhythm.

4.2.3 Polypeptides have not been studied until recently. For the sake of example, let us mention the research work conducted by Kastin (1975) and his collaborators on the proteinic fraction which corticotropic and melanotropic hormones have in common. This Polypeptide ACTH 4-10 which is only made up of a chain of 7 amino-acids, is thought to have a positive effect on memory attention is improved during sustained tasks, together with resistance to boredom (Miller 1974). In 1976, based on a continuous detection task, this author demonstrated that this product

increases the percentage of correct detections and decreases the percentage of errors by excess or default. A more thorough study, centred on memorization, revealed that tests with a spatial and numerical structure are improved to a higher degree than tests involving verbal stimuli.

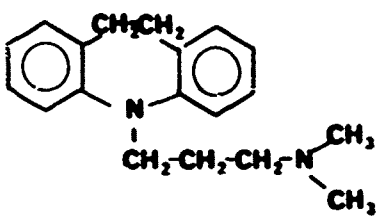
ACTH 4-10 is thought to exercise its action mainly on the thalamic reticula without any repercussion on the vegetative system.

Research on Polypeptides seems to be very promising as regards both stimulants and anxiolytics. However, for lack of a suitable form of administration, their application is still difficult.

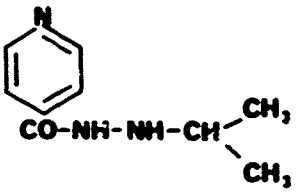
4.3 Thymoanaleptics

While they exert an elective action on the mood, these products have also a general tonic action. They can be divided into two broad classes:

IMIPRAMINE



IPRONIAZIDE



4.3.1 The chemical characteristic of *Iminazine* derivatives is a three-cycle structure containing an atom of oxygen or nitrogen in its central part.

Their action is twofold. They counteract the uptake of catecholamines, and they are antagonistic to acetylcholine, histamine and serotonin.

This action is slow: one week approximately. They induce side effects of the atropinic type, tachycardia, mouth dryness, perspiration, impairment of accommodation, constipation. Insomnia and sometimes anxiety are observed.

4.3.2 Inhibitors of monoamine oxydase. Their name defines their mode of action. They are chemically characterized by a hydrazine group: R – NH – NH – R. They are responsible for the accumulation of catecholamines and serotonin due to non-destruction. They do not exert any effects on the cholinergic system.

They induce secondary effects similar to those mentioned above, especially as regards blood pressure. Certain items of food have to be ruled out: coffee, chocolate, bananas and cheese.

For all these reasons, the use of these products for non-therapeutical purposes is difficult, not to say impossible.

4.4 Metabolic Adjuvants

This heading includes all the products which are not directly related to the nervous system although they are necessary to the normal performance of any cell, particularly the neuron.

Certain mineral ions such as Potassium, Sodium, Calcium and Magnesium play a determinant part in the balance between intra- and extra-cellular media. Under normal conditions, a deficiency is exceptionally found.

The nutrition of the cell involves the metabolism of glucides, and the input of intermediary products of the combustion cycle may well be regarded as a useful contribution. Sugars, which include glucose, fructose are to be found, of course, but also triphosphoric Adenosine, as well as glutamic, aspartic, succinic etc. acids.

The supply of basic products is necessary to the building up of the cells themselves: amino-acids, tryptophane, methionine, phenylalanine, glycine, nucleic acids.

Finally, it may be useful to provide metabolic regulators in order to modulate combustion, for example, centrophenoxine and heptaminol, as well as vitamins C and those of the B group, and certain anabolistic hormones (corticoids and male hormones).

All these products are present, to some degree, in the composition of medicine called antiasthenics. Their biochemical efficacy is moderate; however, they may provide some degree of assistance, at least psychologically, to subjects experiencing the need of support in situations requiring sustained mental activity.

5. EXPLANATORY MODEL

As mentioned in the previous paragraph, certain products are capable of enhancing the efficiency of the various links in the data processing sequence: input, storage and intellectual operations. With the exception of nootropes, which are still insufficiently known, and adjuvants, the efficacity of which is minor, all these products exert an action on activation in general. In fact, we have noted the important part played by catecholinergic systems in the mechanisms of wakefulness. In the model which we presented previously (Defayolle – 1968), the activation concept played the principal part, and the curvilinear relation between activation and performance was stressed. In the same year, Legewie proposed the application of this pattern to the efficacy of psychotropes.

According to this model, and in the case with which we are concerned – that of stimulants – we must anticipate a positive effect in hypo-activated subjects, and a negative effect in hyper-activated subjects.

By hypo- or hyper-activated, Legewie means a stable personality factor corresponding broadly to the following two types: introverts (hyper-activated) and extroverts (hypo-activated), as defined by Eysenck. This pattern must be extended to the dynamic aspects, and incorporate the task, the environment, the motivation, etc..

It is thus possible to account for the paradoxical effect of deterioration by relative overdose of activation.

According to our assumption, the curvature of the function was ascribed to the antagonistic effect of two functions: the data processing capacity evolving in the same direction as activation, and the screening capacity deteriorating with activation. It is the latter phenomenon which seems to account for the die-away of the second part of the curve.

A means of avoiding performance deterioration might consist in reinforcing the filtering processes.

These seem to be under the control of the cholinergic system: therefore, research should be oriented towards products belonging to this category.

We have considered only direct effects upon performance; however, the effects exerted at a lower level of integration must not be overlooked as they can modify performance.

Activation phenomena are usually accompanied by unpleasant neuro-vegetative manifestations: perspiration, digestive troubles, tachycardia likely to create interference stimulations affecting the subject's efficiency. In addition to these, motor phenomena, such as tremor, impede the performance of tasks demanding precise motor coordination.

The pattern which has just been presented deals with the neuropsychological aspect of the problem. We would be wrong if we regarded it as sufficient, because the biological pole does not account for the symbolic aspect which is peculiar to man.

The semantic aspect significance assumes an unquestionable importance. Modulating the data processing capacity and filtering by increasing them does not relate directly to the objectives pursued by these processes. Enhancement of a human being's potential is pointless unless it is oriented in a desired direction. This potential may assume the form of efficiency, anxiety or aggressiveness, and this form does not necessarily depend on biochemical phenomena. Therefore, the use of drugs provides only a partial solution to the problem of efficiency enhancement.

6. INDICATIONS OF PSYCHOSTIMULANTS

The use of psychostimulants can be motivated by two reasons which, in outline, coincide with the two broad classes of products considered above: nooanaleptics and nootropes.

In the first case, the major problem is that of the maintenance of vigilance, either to avoid its deterioration during prolonged tasks, or to avoid the induction of sleep resulting from a disruption of the normal rhythms of sleep and wakefulness. In this case, the use of amphetaminics is obviously the most efficient. However, it should be borne in mind that such products may lead to hypervigilance induced disturbances, with lack of attention focusing, as well as prejudicial side effects: psychomotor disorder, loss of appetite, anxiety and agitation. In addition, their effects are followed by a period of physical and intellectual depression. These products should therefore be used only on an exceptional basis, for relatively brief periods, and in quantities adapted to each user.

For prolonged use, the natural stimulant provided by caffeine seems to offer more flexibility, although the danger of an overdose must also be avoided. As mentioned earlier in this paper, tobacco cannot be considered as a true psychostimulant; however, it is of useful assistance to habitual smokers.

When the purpose in view is an enhancement of intellectual performance, the problem is more complex. Nootropes have only been recently introduced, and their application is often difficult and inadequately codified. While, in our opinion, they may hold good promises for the future, we shall have to be content with medications of lesser efficiency; some neurostimulants can be used, together with metabolic adjuvants.

Whatever may be the products used, there is always a risk of pharmacological dependence.

Pharmacological dependence is described as "a psychic and sometimes physical state resulting from the interaction between a living organism and a drug. This interaction is characterized by behavioural modifications and other reactions which always compel the user to take the drug continuously or periodically in order to find again its psychic effects and sometimes to avoid the discomfort created by deprivation". (Eddy - 1965).

Drug tolerance is characterized by a lowering of the product efficacy, leading to increased consumption.

One differentiates between psychic dependence, related to a wish to experience enjoyment or avoid discomfort, and addiction, which leads to considerable disturbances when the use of the product is interrupted.

As far as psychostimulants are concerned, only psychamines, cocaine and alcohol (at least in the initial phase) create a physical dependence.

As regards the other products, the pleasant effects created by their use may lead to a psychic dependence, and the suppression of the habit may be difficult; this is an additional reason why their use should only be considered under exceptional circumstances. Prior to resorting to pharmacological means, the possibility of modifying the conditions under which the tasks are performed should always be considered: schedule or work, level of difficulty, training of personnel; such solutions are often more efficient and less harmful.

The best stimulant of the nervous system is unquestionably motivation, and efforts should be made in this direction.

Pharmacological aids should be used as a last resort, when we find ourselves faced with the impossibility of acting through these non aggressive means.

HYPNOTICS AND THE MANAGEMENT OF DISTURBED SLEEP

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Over the past few years there has been increasing interest in the effect of drugs on performance, and with hypnotics interest has centred around residual effects after sleep - the so-called 'hangover'. There is little doubt that many of the currently available hypnotics modify well-being and impair performance during the early part of the day after overnight ingestion, but it is not so widely appreciated that impaired performance may persist well into the working day, and to the evening, and that there may be difficulties in appreciating that performance is impaired. Residual effects have tended to be accepted as an inevitable concomitant of an effective hypnotic, but the need to avoid impaired performance in those who carry out skilled work has prompted the search for hypnotics with effects on performance which are minimal or contained within the sleep period.

We are concerned with the occasional use of hypnotics by those who carry out skilled work. The benzodiazepines are the most likely to prove useful, and, though many were introduced as anxiolytics, it would appear that most, if not all, modify sleep. However, careful consideration must be given to the choice of an hypnotic, as a drug with a short duration of action without residual effects on performance is required. The effect of hypnotics on performance is an important consideration, and several centres using different techniques to assess impaired performance in man are involved in such studies. There is wide agreement on the appearance and persistence of impaired performance with benzodiazepines, though we will be concerned mainly with studies on visuo-motor coordination - a skill particularly sensitive to hypnotics. Studies on visuo-motor coordination have provided comparative data on many of the benzodiazepines available as hypnotics, though performance from other laboratories, as well as other studies, will be included to indicate their appropriate clinical use.

PERFORMANCE STUDIES

In the assessment of visuo-motor performance in man (Borland & Nicholson, 1974) subjects position a spot inside a randomly moving circle displayed on an oscilliscope. The movement of the spot is controlled by a hand-held stick, and an error signal, proportional to the square of the distance between the spot and the centre of the circle, controls the difficulty of the task by modulating the mean amplitude of the movement of the circle. Such studies are usually carried out in healthy subjects who are required to avoid alcohol, and are not involved in any other form of therapy. Subjects familiar with such skills require several days of practice to reach a steady level of performance, but inexperienced subjects may require 2-3 weeks. The effects of the drug should be studied over several hours, and involve 5 or 6 assessments of performance. With visuo-motor coordination each assessment involves a tracking run of 10 min, and the mean amplitude of the task over the final 500 secs may be taken as the performance measure. Experiments are separated by at least a week, and trials are double blind with placebo and drugs being presented in identical form and in random order.

Barbiturates. Though barbiturates may be of less importance now in the management of insomnia, they are nevertheless used to a considerable extent. It is important to realise that with the usual dose ranges residual effects on performance are likely, and that decrements in performance are related to dose, both in their persistence and in their severity at given time intervals after ingestion. In the context of residual effects on performance heptabarbitone is of particular interest as it has a relatively short half life (3.7 h) compared with most of the other barbiturates used as hypnotics (Clifford, Cookson & Wickham, 1974), and, so among the barbiturates, it is likely to have the least persistent effects on performance. However, though there is no substantial accumulation with the 200 mg dose (Breimer & DeBoer, 1975), decrements in performance have been detected 10 h after ingestion. The usual dose range for heptabarbitone is 200-400 mg, and with 400 mg decrements in performance may persist to, at least, 19 h after ingestion. Impaired performance at the 10 h interval increases over the dose range 200-400 mg, and though at 13 h no decrement in performance can be established with 200 mg, impaired performance is seen with 300 and 400 mg (Fig 1). Similar decrements in performance in visuo-motor coordination have been observed with pentobarbitone sodium (Borland & Nicholson, 1975a).

Other studies with barbiturates have also shown persistent impairments of performance (Von Felsinger, Lasagna & Beecher, 1953; Kornetsky, Yates & Kessler, 1959; McKenzie & Elliott, 1965; Malpas, Rowen, Joyce & Scott, 1970; Bond & Lader, 1972; Hart, Hill, Sye Wilkinson & Peck, 1976), and it is evident that impaired performance persists much longer with the higher doses which are still within the usually accepted therapeutic range. The effects of barbiturates given over-night need careful attention, and residual impairments of performance may be an inevitable sequel of their use.

Benzodiazepines. Studies on the effect of diazepam, flurazepam hydrochloride and nitrazepam on performance in man have also been carried out using visuo-motor coordination, and show that the persistence of impaired performance with diazepam is much less than that with flurazepam hydrochloride and nitrazepam (Fig 2). With 10 mg diazepam impaired performance is observed for a few hours after ingestion, but with nitrazepam and flurazepam hydrochloride impaired performance persists well into the next working day. The limited duration of impaired performance with diazepam is of particular interest, as though it has promoted initial effects on performance its relatively short equilibration half life (De Silva, Koechlin & Bader, 1966) is associated with recovery within a few hours (Borland & Nicholson, 1975b; Clarke & Nicholson, 1978). It would also appear that subjects retain their ability to appreciate their impaired performance with diazepam, and so, overall, it may prove to be useful as an hypnotic for those who carry out skilled work.

On the other hand impaired performance with nitrazepam persists throughout the next working day, and with daily administration there is evidence of accumulation. With flurazepam hydrochloride recovery of performance is seen during the early afternoon, but there is also substantial accumulation of its major

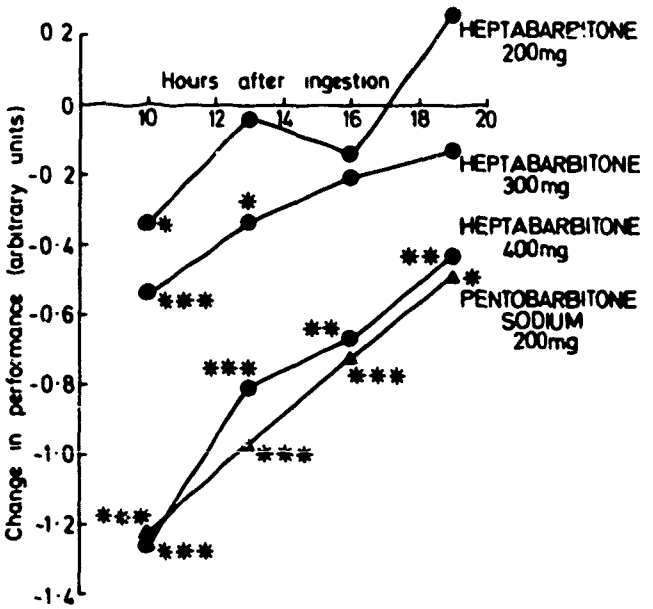


Fig 1
Change in performance (arbitrary units) in visuo-motor coordination after ingestion of 200, 300 & 400 mg heptabarbitone, and 200 mg pentobarbitone sodium (Significance levels * P < 0.05, ** P < 0.01 and *** P < 0.001).

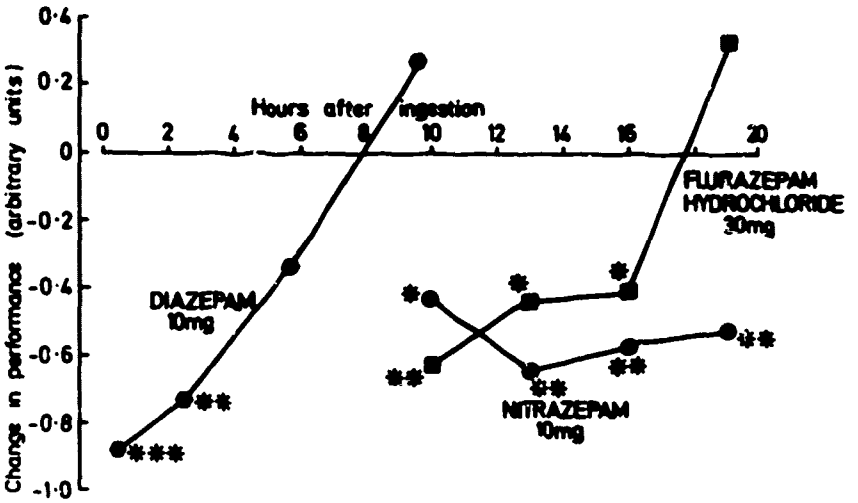


Fig 2
Change in performance (arbitrary units) in visuo-motor coordination immediately after ingestion of 10 mg diazepam, and during the morning after the overnight ingestion of 30 mg flurazepam hydrochloride and 10 mg nitrazepam (Significance levels * P < 0.05, ** P < 0.01 and *** P < 0.001).

metabolite with daily ingestion (Breimer, 1977). It is also important to realise that with nitrazepam subjects may consider that it is no longer exerting a deleterious effect on their performance even though their performance is impaired, whereas with flurazepam hydrochloride subjects would appear to be able to assess changes in their performance and identify impaired performance (Borland & Nicholson, 1975a). The residual effects of nitrazepam and flurazepam hydrochloride suggest that performance of complex skills may well be impaired throughout most of the working day with overnight ingestion of doses which are within the normal

therapeutic range, and these observations have been supported by other workers (Malpas, Rowen, Joyce & Scott, 1970; Bond & Lader, 1973).

Diazepam and its hydroxylated metabolites. Though N-desmethyldiazepam (nordiazepam) is the major metabolite of diazepam, and, like diazepam, possesses hypnotic activity, the other metabolites are of considerable interest (Fig 3). Comparative studies have been carried out on the effects of diazepam,

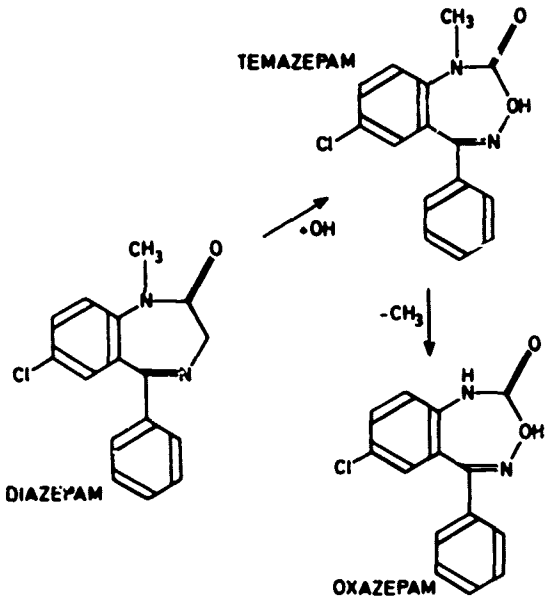


Fig 3
The hydroxylated metabolites of (a) diazepam are (b) 3-hydroxydiazepam (temazepam) and (c) 3-hydroxy,N-desmethyldiazepam (oxazepam).

3-hydroxydiazepam (temazepam) and 3-hydroxy,N-desmethyldiazepam (oxazepam) on visuo-motor coordination in man. With the overnight ingestion of 5 & 10 mg diazepam, 10 & 20 mg temazepam, and 15 & 30 mg oxazepam visuo-motor coordination is not impaired the next day, but there is a trend of impaired performance 10 h after ingestion of temazepam when the dose range is extended to 30 mg, and performance the next day is impaired with 15 mg diazepam and 45 mg oxazepam overnight (Figs 4-6).

An important point is that the three benzodiazepines, diazepam, temazepam and oxazepam, have dose ranges free of residual effects, and this observation is supported by studies on their immediate effects on performance. With the ingestion of 10 mg diazepam and 20 mg temazepam recovery occurs within a few hours, and, though with 30 mg oxazepam absorption may be delayed, performance recovers within 6-7 h (Fig 7). These observations are in agreement with other studies. Similar results have been reported with diazepam on performance related to driving (Seppälä, Kortilla, Häkkinens & Linnoila, 1976), and in a variety of tasks including auditory vigilance and reaction time (Hart, Hill, Bye, Wilkinson & Peck, 1974). With temazepam the results with visuo-motor coordination are comparable with those of Hindmarch (1975), and other workers have observed the slow onset of impaired performance with oxazepam (Nolander & Duvhök, 1976).

Nordiazepam and its precursor, potassium clorazepate. With nordiazepam (5-10 mg) it is difficult to be certain of effects on performance, though over several hours a gradual decline in performance may appear (Fig 8). Similarly, with the overnight ingestion of potassium clorazepate (15 mg), there is no immediate residual impairment, but performance levels may decline during the day (Borland & Nicholson, 1977; Clarke & Nicholson, 1978). It would appear that nordiazepam (Tansella, Zimmerman-Tansella & Lader, 1974; Palva & Linnoila, 1976), and potassium clorazepate have limited effects on performance, and though they may impair the ability of subjects to maintain a high level of performance over several hours, this effect may be overcome by increased effort.

STUDIES ON SLEEP

To establish the effectiveness of the benzodiazepines which could be useful for those involved in skilled activity, studies on sleep have been carried out in healthy volunteers. Subjects are usually required to refrain from napping and undue exercise, and to abstain from caffeine and alcohol on the days which involve sleep recordings. The studies are carried out in laboratories which are usually sound attenuated and may be temperature and humidity controlled. Electroencephalography is used with electrodes placed according to the 10:20 system. The electromyogram (submental musculature) and the electro-oculogram are also recorded to differentiate between rapid eye movement (REM) and slow wave sleep. The record is analysed by 30 sec epochs into sleep stages. The studies have been published in detail elsewhere, but Table 1 summarises the effect of diazepam and its hydroxylated metabolites in dose ranges free of residual effects on performance, as well as that of nordiazepam and its precursor, potassium clorazepate.

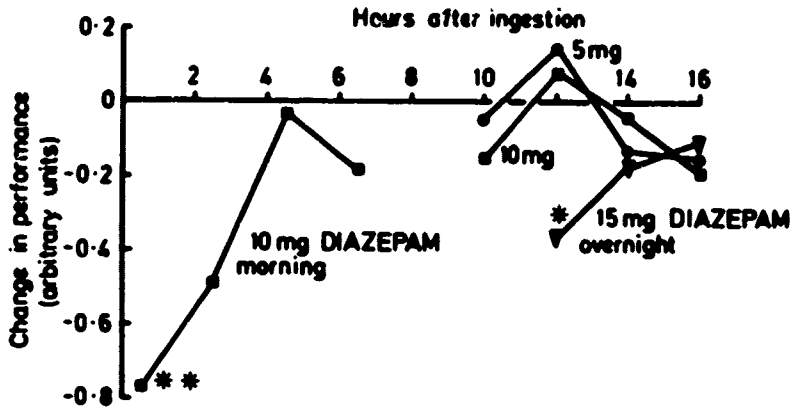


Fig 4
Change in performance (arbitrary units) in visuo-motor coordination immediately after ingestion of 10 mg diazepam, and during the morning after overnight ingestion of 5, 10 & 15 mg diazepam (Significance levels * P < 0.05; ** P < 0.01 and *** P < 0.001).

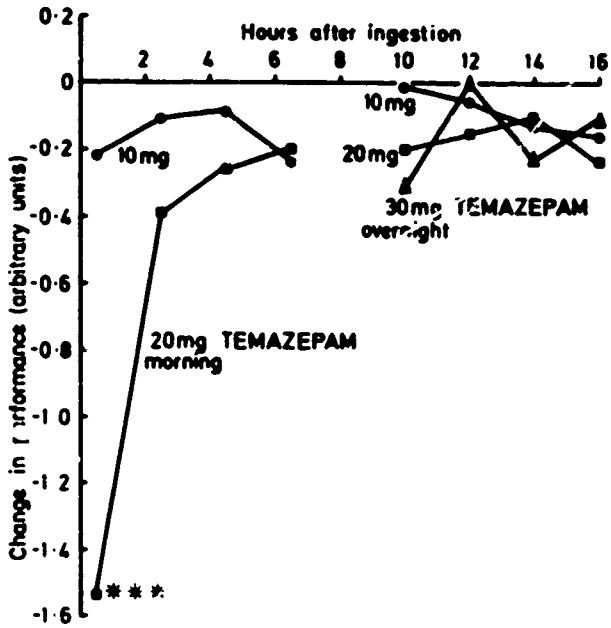


Fig 5
Change in performance (arbitrary units) in visuo-motor coordination immediately after ingestion of 10, 20 & 30 mg temazepam (Significance levels * P < 0.05; ** P < 0.01 and *** P < 0.001).

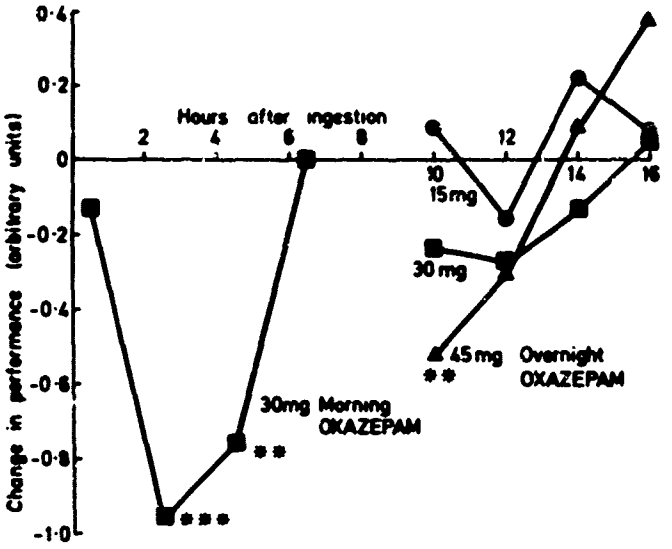


Fig 6
Change in performance (arbitrary units) in visuo-motor coordination immediately after ingestion of 30 mg oxazepam, and during the morning after overnight ingestion of 15, 30 & 45 mg oxazepam (Significance levels * P < 0.05, ** P < 0.01 and *** P < 0.001).

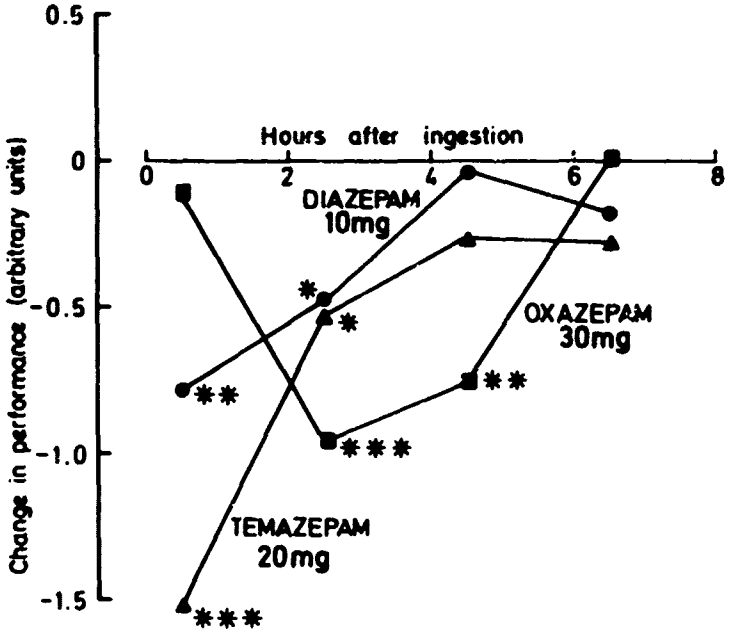


Fig 7
Change in performance (arbitrary units) in visuo-motor coordination immediately after ingestion of 10 mg diazepam, 20 mg temazepam and 30 mg oxazepam (Significance levels * P < 0.05, ** P < 0.01 and *** P < 0.001). These are the maximum doses of each hypnotic which are unequivocally free from residual effects on performance after overnight ingestion.

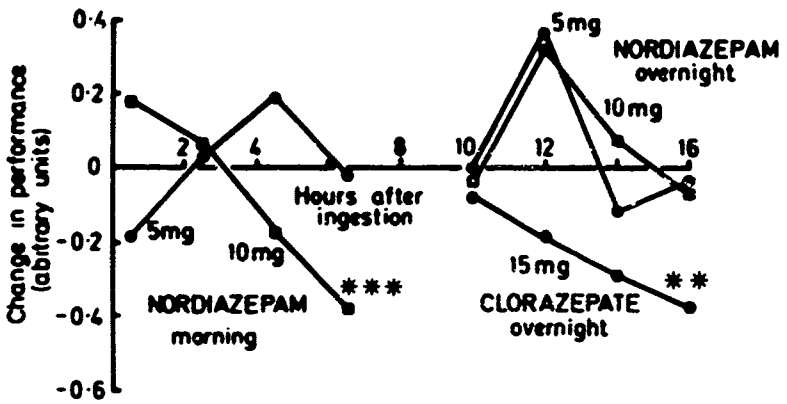


Fig 8

Change in performance (arbitrary units) in visuo-motor coordination immediately after ingestion of 5 & 10 mg nordiazepam, and during the morning after the overnight ingestion of 5 & 10 mg nordiazepam and 15 mg potassium clorazepate (Significance levels * $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$).

Diazepam and its hydroxylated metabolites. The effect of diazepam (5-10 mg) is limited to the night of ingestion (Nicholson, Stone & Clarke, 1976). Total sleep time is marginally increased, and sleep onset latencies and awakenings are reduced. There are no other effects. Diazepam has a limited, though useful, hypnotic activity in man in which awake activity is depressed. With temazepam (10-20 mg) there is an increase in total sleep time, and sleep onset latencies and awakenings are reduced. Temazepam reduces the duration of drowsy as well as awake activity, and the effect of drowsy sleep is seen throughout the night. Like diazepam (5-10 mg), there are no effects on slow wave and REM sleep, except that the appearance of the first REM period is delayed (Nicholson & Stone, 1976). Oxazepam (15-30 mg) has a marked effect on sleep. It increases total sleep time and reduces the duration of awake activity and of drowsy sleep (Nicholson & Stone, 1978). There is no evidence of change in slow wave or REM sleep, and it is not possible to establish an effect on sleep onset latency - a finding consistent with pharmacokinetic data which suggests slow absorption.

Nordiazepam and its precursor, potassium clorazepate. Both drugs shorten sleep onset latencies and reduce awakenings, while latency to stage 3 is also reduced by nordiazepam. Nordiazepam (5-10 mg) and potassium clorazepate (15 mg) reduce the duration of awake activity and drowsy sleep, and there are increases in total sleep time. No effects are observed on REM sleep, except that the appearance of the first REM period is delayed by potassium clorazepate. The effect of 10 mg nordiazepam and 15 mg potassium clorazepate would appear to be comparable, and each modifies sleep for about 28-30 h after ingestion (Nicholson, Stone, Clarke & Ferres, 1976).

SLEEP DURING THE DAY

It is well established that the response of man to many drugs varies with time of day (Reinberg & Halberg, 1971), and that the effectiveness of a drug may exhibit circadian rhythmicity. Circadian activity has been observed with the barbiturates (Pauly & Sheving, 1964), and a benzodiazepine (Marte & Halberg, 1961), and so it is possible that circadian effects may influence the activity of hypnotics in man. The relative activity of hypnotics during the night may not be reflected at other times of the day, and it is in this context that studies on the effect of diazepam and two closely related benzodiazepines, its hydroxylated metabolites 3-hydroxydiazepam (temazepam) and 3-hydroxy,N-desmethyldiazepam (oxazepam) have been extended to sleep during the day. Though it is appreciated that such studies may not accurately reflect the patterns of sleep disturbance under operational conditions, they do nevertheless provide some indication of the likelihood of an hypnotic being effective at times other than when the rest period coincides with the circadian desire for sleep. In these studies experiments involved one afternoon. The subjects slept at home for the night preceding the afternoon sleep, and reported to the laboratory at 12.30 h. The subjects retired to bed at 14.00 h, and the lights were turned off immediately. They were allowed to rise from bed at 20.00 h.

Hypnotic activity during the day of diazepam and its metabolites differ, and these differences may not relate to the effect of the drugs on sleep during the night. Diazepam reduces awake activity and only marginally increases total sleep time at night (Nicholson, Stone & Clarke, 1976), whereas during the day there is a marked increase in total sleep time with reduced drowsy (stage 1) sleep. On the other hand temazepam and oxazepam have less hypnotic activity during the day than would be expected from night-time studies

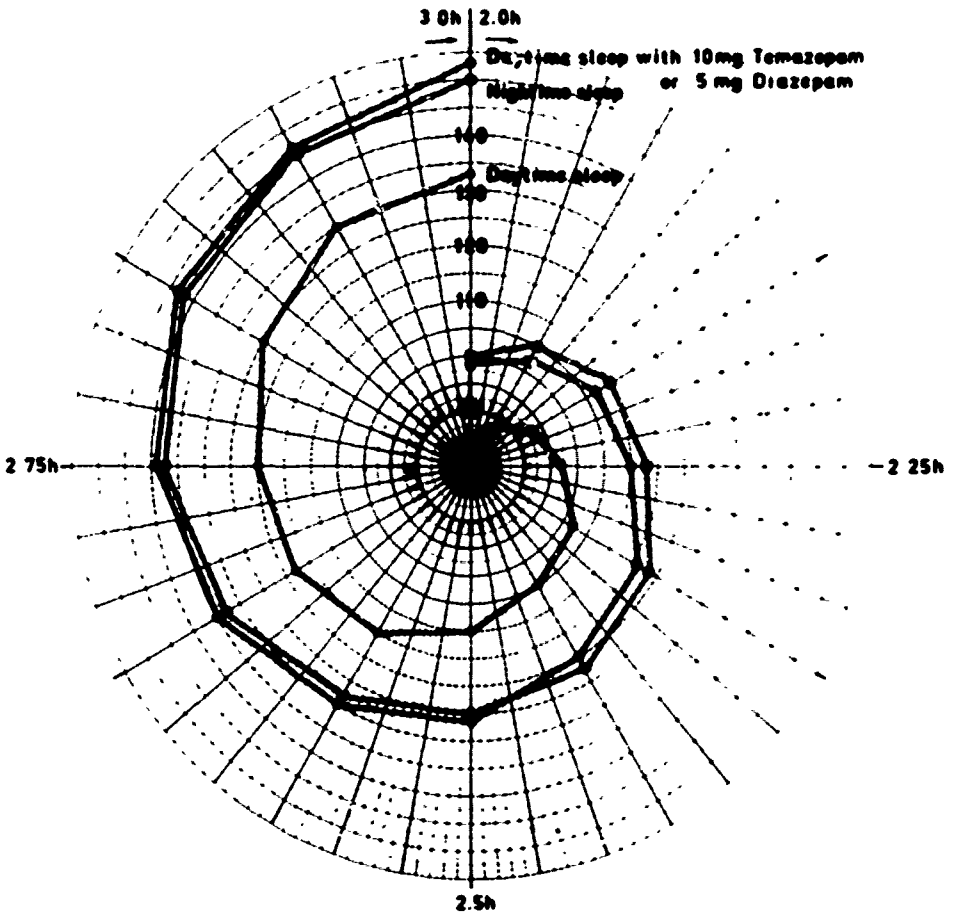


Fig 9
Sleepolarogram: change in duration of the combined sleep stages 2, 3, 4 and REM for 2.0-3.0 h of an afternoon sleep from 1400 h.

It can be seen that the sleep time (ie total stage 2, 3, 4 and REM) for both day time and night time sleep increase up to the first 3 hours in bed. At the end of the 3 hour period the total sleep time for day time sleep is just over 130 minutes whereas that for night time sleep is about 150 minutes. The effect of drugs at this time is that day time sleep with 10 mg temazepam or 5 mg diazepam produces the same total sleep as that which would be expected with night time sleep without drugs.

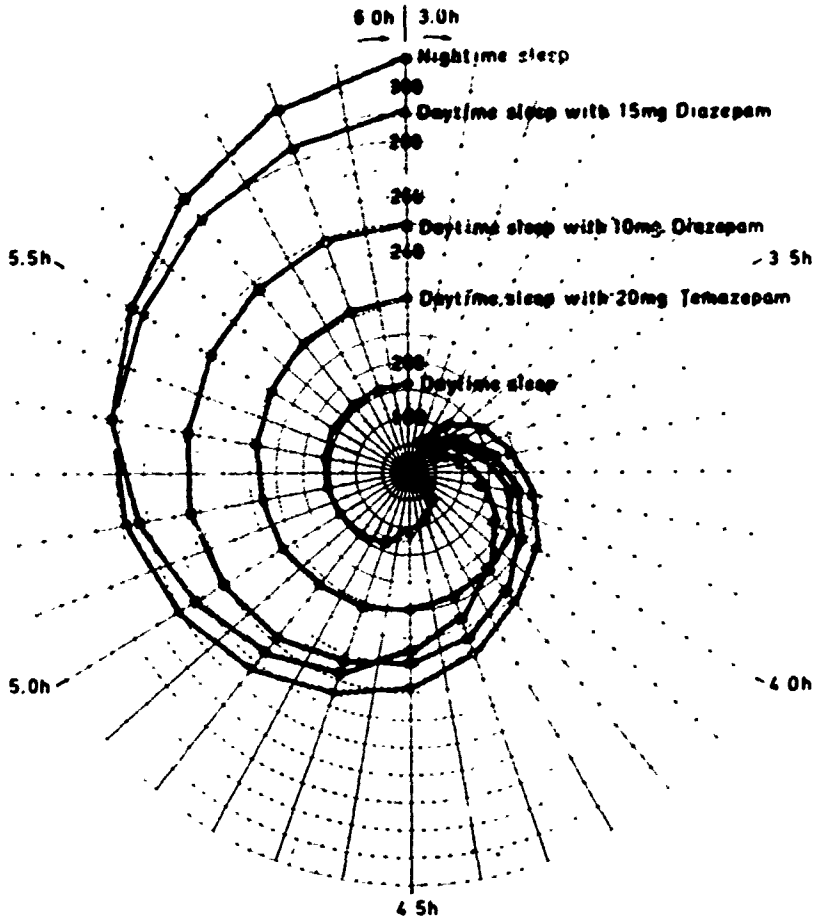


Fig 10
Sleepolarogram: change in duration of the combined sleep stages 2, 3, 4 and REM for 3.0-6.0 h of an afternoon sleep from 1400 h.

The period from 3-6 hours presents very different pictures concerning the effectiveness of these drugs. Over the period of time the total amount of sleep obtained during the day has increased to 190 minutes but has remained constant during the last hour and a half, whereas with night time sleep there is an increasing amount of sleep during the whole of the 6 hour period and that by the end of the 6 hour period the total amount of sleep is about 310 minutes. An analysis of the effectiveness of the drugs show that with 20 mg temazepam during day time sleep there has been a useful increase in sleep, but this has occurred during the first 4 hours and that during the last 2 hours of the day time sleep period there was little, if any, increase. On the other hand with 10 mg diazepam the amount of sleep during the day increases up to the 5 hour interval and with 15 mg diazepam the amount of sleep is increasing even toward the end of the 6 hour period. With the 15 mg dose of diazepam the total amount of sleep approximates that which would be obtained at night time without the use of drugs.

	DIAZEPAM		TEMAZEPAM		OXAZEPAM		NORDIAZEPAM		POTASSIUM CLORAZEPATE
	5	10	10	20	15	30	5	10	15
Increased Total Sleep Time		(*)	(*)	**		**	*	***	**
Reduced Sleep Onset Latency	**	**	***	***			***	***	*
Decreased Latency to Stage 3							*	*	
Increased Latency to REM				***					**
Reduced Awake (Stage 0)	*	*	*	*				*	*
Reduced Drowsy (Stage 1)			**	**		***		***	**
Increased Stage 2			*	*		**		*	**

Table 1

Effect of diazepam and related 1,4-benzodiazepines (mg) on sleep in healthy man. Changes in sleep measures are given as significance levels (* P < 0.05, ** P < 0.01, *** P < 0.001).

(Nicholson & Stone, 1976, 1978). With temazepam there is no increase in total sleep time, though the distribution of sleep stages is changed with reduced awake activity and drowsy sleep, while with oxazepam total sleep time is increased without changes in awake activity or drowsy sleep. It would appear that diazepam preserves, or even enhances, its hypnotic effect at night for sleep during the day, but that oxazepam increases total sleep time without reduced awake activity and drowsy sleep, and that temazepam reduces awake activity and drowsy sleep without an increase in total sleep time.

There may be several explanations for the relative changes in the hypnotic activity of such similar drugs between day and night, but the question arises whether the effect of oxazepam and temazepam, but not diazepam, are modified by circadian influences. A priori it would be expected that drugs with similar structures, like diazepam and its hydroxylated metabolites, would be affected in the same manner by circadian rhythmicity, but Muller (1973), in a comparison of the activity of a long and a short-acting barbiturate in the rat, showed that the short-acting drug, hexobarbitone, produced the longest sleeping time when given at the end of the light period, whereas the long-acting drug, phenobarbitone, produced the longest sleeping time when given at the early part of the light period. These differences in activity were related to changes in liver structure between the early dark period and the early light period. Phenobarbitone given at the beginning of the light period produced no changes, but the same dose given at the beginning of the dark period led to dilatation and fragmentation of the endoplasmic reticulum.

Similar mechanisms may be involved in the differential effects of diazepam and its metabolites on sleep during the day and during the night, as it is the metabolism of diazepam only which gives rise to a long-acting metabolite, N-desmethyldiazepam (nordiazepam). It is possible that diazepam, temazepam and oxazepam are metabolised in a similar manner at the same time of the day, but that nordiazepam with its peculiar long half-life of several days may not be susceptible to the same influences, and so the effect of temazepam and oxazepam may vary from that of diazepam at certain times of ingestion. It is not possible to pursue these considerations further with the data available, but the studies suggest, at least, that circadian influences may be relevant to the differential activity of closely related hypnotics in man at various times of the day.

CONCLUSIONS

It is evident from these studies carried out in healthy man, that some guidelines can now be given for the occasional use of hypnotics in the management of sleep when impaired performance the next day would be unacceptable. The prolonged effect of nordiazepam and potassium clorazepate would suggest that these compounds are more appropriate in the management of insomnia secondary to anxiety, in which a persistent daytime anxiolytic effect with minimal effects on performance is required, while diazepam and its hydroxylated metabolites, temazepam and oxazepam, are appropriate in the management of disturbed sleep when a residual effect during the day after overnight ingestion is to be avoided.

However, there are certain points which should be taken into consideration in the use of hypnotics. With daily ingestion of diazepam (5-10 mg), its long-acting metabolite, nordiazepam, could accumulate, and so the dose of diazepam should not only be kept within 10 mg as residual effects are observed above this range, but it should not be repeated at intervals of less than 48 h or given more than twice in seven days. Diazepam would appear to be particularly useful for sleep at unusual times of the day. Oxazepam (15-30 mg) is also without residual effects, but the relatively slow absorption of the drug, and the lack of effect on sleep onset latencies may reduce its usefulness, though otherwise it is an effective hypnotic. Temazepam (10-20 mg) has a useful hypnotic effect, and, like oxazepam, as the advantage that its metabolism is not complicated by a long-acting metabolite, and so daily ingestion is unlikely to be contraindicated. However, it is important to stress, as with all hypnotics, that it is the individual response of each patient which is paramount, particularly if they are involved in skilled activity.

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MANAGEMENT OF IRREGULAR REST AND ACTIVITY

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MANAGEMENT OF IRREGULAR REST AND ACTIVITY

INTRODUCTION

A significant biomedical aspect of air operations (military or commercial) is that operations are conducted without regard for the clock. Furthermore, such disregard is further complicated by the fact that such disregard is conducted on schedules which, for the typical aircrewman, lack any important degree of regularity. Aircrews therefore, are likely to be working at any time of the day or night and do not even have the limited advantages of being on "shift" work, which is not uncommon in industry. Nicholson (1), in examining the problem with particular focus on transport operations, states:

"The irregularity of work in air operations presents many problems in the management of aircrew. With short-haul routes, services relate to the hours of business and commerce, and duty hours are often outside usually accepted times of work, while with long-haul operations, duty may start at any time of the day or night, and crews have to cope with repeated time zone changes. There is little doubt that adequate sleep is vital in the adaptation of aircrew to irregular work and rest, and that circadian variations of function may influence their effectiveness at certain times of the day."

"It is only recently that serious effort has been made to understand the problem. It is now no longer true to say that the only generally agreed facts are that we do not like disturbed sleep, and that sleep loss tends to make us sleepy: but it is true that disturbances in performance cannot be easily demonstrated after sleep disturbance, and that this has tended to minimize the importance of the problem. Sleep disturbance modifies circadian functions, impairs response to stress and upsets the normal sense of well being, and so it is likely that the measurement of performance is insufficiently sensitive to detect important changes. Inability to detect performance decrement after sleep loss suggests that disturbed sleep, or even loss of sleep, may be of little operational importance but this is not a reasonable conclusion. It is more likely that performance is maintained by greater effort or by concentrating attention on some aspects of the problem for a limited time, and it is in this way that the integrated performance of aircrew may be impaired."

For several years, the staff of my laboratory have been examining these problems in both airlift and tactical operations. It should be stated at the outset that grossly irregular operations occur less often in tactical than in airlift operations, particularly in the peacetime environment, so much of the material presented here will be taken from airlift studies. We can be sure, however, that in wartime, tactical operations around the clock can be expected, so lessons learned from airlift can indeed be useful. Of critical concern in my laboratory are those variables in the behavioral or biochemical domains which are, broadly speaking, cyclic in nature, either because there is an underlying periodicity or because the way in which the USAF employs its aircrews introduces some cyclic features. My presentation will be oriented specifically toward military air applications, though the related science is indeed fascinating.

The operational goal which we must address is to determine on a quantitative basis the impact of mission duration/mission cycling on mission effectiveness. The qualitative aspects of this problem are well known to operational users of weapons systems. In practice, users develop rules and schedules for employing crews in weapons systems based on this qualitative understanding of crew limitations, refine these through experience, and arrive at a workable compromise between mission requirements and crew capabilities. The goal set by operational managers is to avoid crew fatigue and loss of efficiency. Systems designers borrow from operational experience in designing new weapon systems. The result at both the design and operational levels are, however, best guesses. A quantified description of crew capability in the area of mission duration/mission cycling will improve the coupling of crew duty-time limits and weapons system capability based on operational criteria. The kinds of variables which must be considered are shown in Table I.

TABLE I

List of Factors Contributing to Periodicity in Military Air Operations

I. Work/rest
   a. W/R duration--round the clock
   b. Work period duration
   c. Task load and time course variation
   d. Shift work
   e. Contingency demands
   f. Repeated cycles across long periods

II. Sleep
   a. Sleep duration
   b. Stage deprivation
   c. Sleep deprivation
   d. Split sleep
   e. Daytime sleep
   f. Depletion of reserves
   g. Sleep environment

III. Time-anchored variables
   a. Day-night cycles
   b. Time zone
   c. Adaptation to new schedules

The research and development objective we must pursue is to define envelopes of acceptable duty schedules for aerospace and ground operations, the modification of these envelopes by cyclic and time-

anchored factors, and the effects on crew performance within these envelopes resulting from other single and multiple environmental (physiologic) stresses. Mission duration, mission cycling, and task characteristics are the critical aspects within which these effects should be defined. This problem area is in a considerable state of flux as a consequence of an ongoing reformulation of concepts about the effects of factors like work/rest cycles, task loading, and rest/recovery requirements on aircrew efficiency. The reformulation is focused on the need to sort variables into primary and secondary stressors and to establish the time course of performance decrement for these stressors singly and in combination.

In the remainder, we shall focus on airlift and tactical operations studies, dealing with the former first, because that historically is where this line of research started.

PART I

AN ILLUSTRATIVE STUDY

In a separate study (to be discussed later in this paper), we collected data from 100 airlift missions in which C-141 aircraft commanders used an activity log to report in half-hour blocks their activities on and off duty around the clock for 20 days, which included at least one entire multi-day mission. Ten such packets of data involving missions to the Far East were selected from a large group of 61 and used to perform a sort of desk-level simulation of transport operations (2).

First, a model mission was empirically derived by obtaining modal times for eating, sleeping, and flying on each successive day. Intervals between these activities were alloted to functions such as "crew rest," "on the flight line," "clearing operations," and similar aircrew duties arranged in the appropriate sequence. The resulting model was cross-checked against mean times for each activity obtained from the entire 61 aircraft commanders. Then, eating times, sleeping times, and flying times reported by the 10 pilots selected for detailed analysis were sorted into two groups, at home or on temporary duty (TDY) away from home, converted to percentages, and plotted on a time scale.

We found that the model mission is made up of six flights (legs) consisting of a long and medium length leg outbound, and a short and 3 medium length legs inbound. In-transit time was six days, and the complete cycle, including predeparture and post-mission crew rest, was eight days. Flight time was 38 hours out of the 144 hours in transit. Inflight and sleep periods, which provide the maximum contrast in activity, were identified.

The times for flights, meals, and sleep onset during the six days in transit are plotted on the same 24-hour scale. The following findings were obtained. They come from a "simulation" but are only one step away from real data.

a. Work. The primary work of aircrews is flying a mission leg. The model mission yielded the following picture:

Normal work day (GMT)		1600-0100 Z
Mission work:	leg 1	2000-0630 Z
	leg 2	0145-0830 Z
	leg 3	2330-0200 Z
	leg 4	0500-1130 Z
	leg 5	1315-1830 Z
	leg 6	1300-1845 Z

b. Meals The typical meal times (GMT) for breakfast, lunch, and supper at home base were 1430, 2000, and 0230, respectively. Meal times on the mission (not necessarily a typical meal, e.g., lunch at lunch time) were: 1200, 1730, 2000, 2000, 2100, 2100, 0030, 0200, 0400, 0600, 0700, 0900, 0930, and 1100 Z.

c. Takeoff times. The typical takeoffs at home base peaked at 1400 and 0000 Z. Takeoff times on the missions were 1300, 1315, 2000, 2330, 0130, and 0500.

d. Sleep onset. The typical time reported for sleep onset at home base was 0630 Z. Sleep onset times for the mission were: 1200, 1600, 2030 (lunch time at home), 2400, 0130, 0800, and 1000 Z.

e. Sleep duration. To our surprise, sleep durations at home and on a mission were quite similar, in this analysis. It ranged from 4 hours or less to 13 hours, peaking at 8 hours. We shall examine this in more detail subsequently.

It appears that the "model" mission indicates that a transport pilot going out on an extended mission enters into an unpatterned schedule of living and working. In the face of this psychological and physiological confusion, the aircrewman can adopt one of three strategies:

1. He can remain on a home base schedule, but this puts him out of step with the pattern at every stopover point and is sometimes physically impossible because, for example, he is flying when the home base schedule says he should be sleeping.

2. He can shift to the local schedule at each stopover, but this produces conflicts with the previous schedule, so that he may find himself eating or going to bed too soon, or having to defer eating or sleeping despite a physiological need. (Furthermore, this does not alter the lack of patterning. We reprogrammed eating and sleeping on this basis in the "model" mission and derived a different but equally unpatterned daily schedule.)

3. He can anchor his schedule to the airplane's flying schedule, a compromise which our data say he has, in fact, adopted even in the face of the consequent disruption.

Clearly none of these strategies solve the problem. It is further complicated by unproductive periods during extended missions. These are reported surprisingly often.

What are the consequences of this disruption? It is well known that changes in the pattern alter cyclical physiological functions. These alterations have been detected in many studies, but the effect in the psychomotor domain--a loss in piloting skill--remains elusive. We know from our field studies of aircrewmen that they are largely dissatisfied with their lot when flying extended missions and are most satisfied back home. We think that the appropriate laboratory experiments and field studies remain to be performed. The reader should go back and look at Nicholson's statements in the introduction as he ponders this question.

PART II

ADDITIONAL STUDIES: AIRLIFT

During the period 1969-1972, my laboratory conducted a series of studies on airlift operations. The impetus for work was the entry of the C-5 into the operational inventory. It's on-board crew rest provided an opportunity for double-crew operations, with one crew "at rest" while the other flew a portion of the mission. This suggested modifications in crew duty regulations. We flew double-crew missions in both the C-141 and the C-5, collecting data on sleep, fatigue, performance, and biomedical changes. We also performed a number of other studies.

The initial double crew studies were performed in a C-141 outfitted with a crew rest facility in the cargo area. Six experimental transport missions were flown on routes generating various combinations of long and short legs. Crews followed a 4/4 or 16/16 work/rest schedule, modified only by operational constraints. The aircraft flew through the system with minimum ground times. Missions required 55-60 hours to complete, with flying time averaging 43 hours. Crew performance was evaluated by an on-board flight examiner's rating form. Subjective fatigue was measured on a 20-point rating inventory every 4 hours. Sleep EEG's were recorded on two navigators and were supplemented by self reports from all crew members. Urine samples were collected from all crew members at 4-hour intervals starting 2 hours before departure. Urinalysis consisted of epinephrine, norepinephrine, 17-hydroxycorticosteroids, sodium, potassium and urea, all expressed as a ratio against creatinine.

The behavioral aspects will be reported first (3). There were no statistically significant differences attributable to the two widely different work/rest schedules. The schedules were selected to span an "envelope" of work periods, the 4/4 chosen since it would surely modify on-board sleep and the 16/16 chosen because it approximated the normal duty day of a single crew. We were satisfied that operational needs and crew preference could be used to select work/rest schedules within this envelope. There were no statistically significant differences in the flight examiner's performance ratings. This supports the position of Nicholson, reported at the beginning of this paper.

Subjective fatigue increased rapidly during the first 18 hours, and stabilized there after at a level indicating moderate persistent fatigue not relieved by on-board sleep. It was also influenced by crew position, with the aircraft commander reporting the most fatigue. Longer legs also produced more fatigue.

Sleep findings were most interesting. Hours of sleep for mission days were 1.8, 6.2, and 5.2, respectively, and for recovery days 9.8, 9.3, and 8.9, respectively, compared to 7+ hours reported typically prior to the mission. Special attention should be given to the information on the qualitative aspects of sleep.

"The EEG sleep tracings not only supported the self-reports on sleep loss, but also showed a reduction in both deep and "dream" sleep. Though limited to only two crewmembers on three missions, the EEG results are highly suggestive and indicate that care must be taken in planning flights involving double crews. The sleep literature is full of studies which show that loss of deep sleep may result in people becoming physically uncomfortable, withdrawn, and less aggressive, while REM deprivation may result in people becoming less integrated and less interpersonally effective. This loss of deep sleep and REM sleep during both work/rest schedules is disturbing, for previous laboratory work would predict "better" sleep on the 16/16 schedule. Perhaps during flight, the schedule is less important than the actual flight conditions of noise, turbulence, interruption of circadian cycles, interpersonal crew interactions or concern about aircraft responsibility."

"We are aware of only one other study involving the analysis of work/rest cycle effects on flight crews in an operational setting. It also used double-crew transport mission. Atkinson et al. (4) conducted a two-mission study of 5 and 2 days duration in prop and jet aircraft, respectively, at about the same time we were operating our missions. They used a 20-hour duty day (a 10/10 schedule, approximately) in the propeller-driven aircraft and a 24-hour duty day (a 12/12 schedule, approximately) in the jet transport. Their paper focused on sleep effects. They found, in general, progressively less sleep during successive sleep periods, more sleep disturbance for the crew working during the normal sleep period, and a slow recovery (return to normal sleep durations), with the recovery taking longer for the crews working the 20-hour duty day and for those individuals with greater sleep disturbance during the mission. In some cases recovery took up to five days. They recommend against short duty periods because of the aggravation of sleep pattern disturbances inherent in such schedules. They advise a 12/12 schedule, which keeps the crews entrained with the 24-hour day (though one crew must reverse its work/sleep pattern) and provides a longer block of time in which to sleep the normal amount. It is clear that factors beyond work/rest schedules per se need to be considered."

The stresses of the mission appeared to conceal changes associated with time zone stress, if such is relevant to transport operations.

"Though not tested statistically, there was an increase in subjective fatigue which took place during the first day of the mission and then stabilized at a value in the middle of the scale for the rest

of the mission. There was some recovery on day 1 of the postflight period and additional recovery on day 2. Postflight day 2 shows a circadian shift which resembles day 1 of the mission. We suspect that the onset of subjective fatigue followed a normal circadian cycle during mission-day 1, but that there was no recovery during the remainder of the mission because of the stress of the mission combined with the stress of poor sleep."

On the biochemical side (5), we had data clearly revealing anticipatory stress, revealed primarily in the epinephrine (E) data. E increased 131% on day one (with the elevation evident in the initial mission samples) and then dropped back to +37% and +54% on days two and three. Increased stress was seen in the aircraft commanders (+47% compared to a crew mean of +38% for inflight values). No effects related to work/rest cycle were seen. Stress was greater for the crews flying during the night (at home base). Pre-existing circadian variability persisted, with flight having a modifying effect, primarily in terms of elevated excretion rates and some dampening of amplitude. Recovery required 4-5 days, lagging by a day behind subjective fatigue measures, and matching the return of post-mission sleep duration to its normal value.

In the papers on the parallel sets of double-crew missions flown in the C-5, we published first on the biochemical aspects (6). These missions were 65+ hours and can be characterized as involving a great deal of delay and frustration for the crew, caused by problems attendant with the entry of any major new aircraft into the operational inventory. Therefore, analyses were made on a mission by mission basis. Work/rest cycles this time were 5/5 and 12/12. Among the findings of interest for this paper were:

(a) Anticipatory stress was again evident

(b) Flying during home base night-time was more stressful

(c) C-5 crews were less stressed biochemically than C-141 crews, probably due to considerably better on-board crew rest facilities

(d) Physiologic entrainment remained the primary determinant of physiologic responsiveness to the mission stress.

An early publication in the C-141 series had focused on oral temperature as an index of nonspecific stress (7). In that study, we found a small but statistically significant hypothermia clearly present by the second day of the mission and parallel to subjective fatigue (with a small lag). There was a trend (not statistically significant) toward flattening of amplitude and toward a small phase shift (additional lag), a finding we have obtained occasionally in nearly all cyclic variables under study.

In the study now being reported (8), we examined oral temperature again. Oral temperature is an administratively easy measure:

"Oral temperature, a practical biomedical index (since its measurement does not greatly conflict with crewmembers' duties), is known to be sensitive to both endogenous and exogenous influences. In an earlier paper, we reviewed the pertinent literature on body temperature responses to prolonged flight and to work/rest and wakefulness/sleep cycles similar to those used in the present studies, finding that (a) body temperature, mental efficiency, psychomotor performance, and subjective fatigue are interrelated phenomena, (b) body temperature under certain conditions serves to predict mental efficiency and psychomotor performance, (c) body temperature depression is typical of nonspecific stress, and (d) sleep deprivation, which acts in the manner of a nonspecific stressor, modifies but does not obliterate body temperature periodicity . . . Van Loon (1963) in a study of nonflying personnel found flattening (diminished amplitude) of the body temperature day-night curve when the sleep/wakefulness schedule was inverted. This finding is pertinent to the present case . . . In the C-5 studies, body temperature and subjective fatigue at a late time showed parallelism, a phenomenon implying common mechanisms. As pointed out previously, subjective fatigue is thought to relate to activities in the reticular formation of the brain stem which spread to the hypothalamus, thereby influencing endocrine and sympathetic nervous system activities. As is well known, body temperature regulation involves hypothalamic, endocrine, and autonomic nervous system activities. Sleep and wakefulness are also known to relate to activities in the reticular formation. Interrelationships between such dissimilar functions as oral temperature and subjective fatigue are, therefore, to be expected."

However, the utility of oral temperature is not nearly as striking in this study, because of the statistical problems created by difficulties in pooling missions to obtain aggregate averages. The other factor of interest is that on entrainment (periodicity). In this and the earlier papers (7, 8, 9) it underwent specific examination and led to the conclusion we have reached several times: entrainment is a primary determinant of both physiologic and behavioral responsiveness but in these studies remained locked on the home base clock, resistant to shifting through susceptible to the disruptive influences of poor and/or reduced sleep.

In the studies just reported, we were examining double-crew missions. The more conventional transport missions are operated with single crews, each crew flying a portion of the mission and turn the aircraft over to another crew at an intermediate ground stop where the first crew goes into "rest" and the second crew continues the mission. This is called "staging" and we examined its effects in a separate study (10). Transport crews flying 100 missions maintained a log on work and rest on an around-the-clock basis starting 12 hours prior to the mission and ending after 3 days of post-mission rest. Ninety missions were flown to Southeast Asia and 10 to Europe. Average mission time was 6.7 days, during which average flying time was 44.5 hours. The typical full cycle including pre-mission and post-mission rest was 9.1 days.

Table II shows that mission flying accounted for only 20% of total cycle (mission) time. In general, military transport aircrewmen spend approximately ½ of a block of days on a mission flying the airplane, 1/5 of the time on related duties, and over ½ in an "off-duty" status, for crew rest at stages. Though Table II does not highlight this fact, almost 1/3 of the mission time ("time-away") is spent sleeping during crew rest at stages (crew rest stations). Twenty percent of the missions required 12 or more days,

illustrating perturbations to the flow of crews (not planes) through the military airlift system as a result of stage delays and shuttles (turn-arounds).

Time spent in pre- and post-flight duties contributes to crew workload. The average total time for these duties is 21.1 hours for each mission. This breaks out close to 2 hours for the combination of pre- and post-flight per leg, which is in the expected range. The total hours are not insignificant; they are 1/10 of the total mission cycle time.

Codes were provided for two kinds of "waiting" while on a mission. The first was for waiting in an off-duty status at stages when the aircrewman had, in essence, run out of things he needed or wanted to do. The average value is 7.3 hours, though half of the reports (the median value) were 2.2 hours or less, including approximately 40% where none was reported. The second was for waiting on the flight line, or ramp-pounding. The mean total time for the full mission cycle for ramp-pounding is 4.1 hours (approximately 1 hour per stage segment), which is not excessive. There were occasional reports of 10 or more hours.

The third category of off-duty time while on a mission is called "other" in Table I. The mean is 32.9 hours. Of this, 9.9 hours were devoted to meals; 20.4 were expended on personal activities like shopping, sight-seeing, or showering and shaving; and 2.6 hours were miscellaneous. Overall, this block accounts for approximately 1/5 of the total time away from home, exclusive of "waiting" and sleep.

TABLE II

Overall Summary of Mission Cycle Times

Activity	Average Hours Per Cycle		% of Total Cycle	
Pre-/post-rest (2.4 days)	(57.8)		(26.4)	
at home	55.1		25.5	
sleep		25.4		11.6
other		29.7		13.6
(errors/missing)	2.7		1.2	
Away on mission (6.7 days)	(160.8)		(73.6)	
off-duty	89.2		40.8	
sleep		49.0		22.4
waiting		7.3		3.3
other		32.9		15.1
Flight line	25.2		11.5	
pre-post		21.1		9.6
ramp-pounding		4.1		1.9
Fly mission	44.5		20.4	
Squadron work	1.9		0.9	
Total time (9.1 days)	(218.6)			

The preceding table provides a general picture of the distribution of various kinds of work and non-work time. Sleep is an area of considerable interest. Changes in sleep quality and quantity during a mission are one measure of the physiologic cost of a mission. Table III presents these data.

TABLE III

SLEEP PER STAGE OR PER DAY

	Average Number of Hours	Reports of 12 Hours or More	"Naps" Reported (2 Hours or Less)
Pre-departure Mission Stages			
	6.8	2%	18%
1	7.4		
2	7.2		
3	7.8	4%	17%
4	7.8		
5	7.5		
Post-Mission Day			
1	9.9	32%	1%
2	9.2	13%	2%
3	8.9	6%	2%

Almost a fourth of the time away from home is spent sleeping (see Table II), equal to the time inflight. Table III shows that sleep during the mission increases somewhat, but that the dramatic change occurs

during the post-mission period, where the means on 3 successive days are 9.9, 9.2, and 8.9. This demonstrates the cumulative physiologic cost incurred during the mission. This cost is further demonstrated by the incidence of sleep periods greater than 12 hours, which are quite high (32%) on the first post-mission night.

The sleep data indicates that a mission constitutes a significant physiologic load and that during the course of a mission a physiologic debt develops, despite the fact that regular periods are provided for sleep and rest. A variety of "stressors" act upon transport crewmembers, including such factors as the mission work, the 30-hour day, circadian conflicts, altered sleep schedules, off-duty activities, variations in sleep environments, the situational stress of time-zone translocation, and others we cannot identify. Providing a rest period based on a crewmember's home station habits does not automatically insure sufficient rest during a mission. Continuing attention must be given to sleep and rest problems in the airlift environment.

The previous study dealt with long-haul missions requiring several days and utilizing the regular aircrew resources (personnel on active duty). The motivational structure is not often examined when such studies are conducted, but it plays a role. Regular aircrews operate in a motivational context where management demands combine with intrinsic motivation to get the job done. Rayman (11) reports a study in which "irregulars" performed short-haul missions on a demanding schedule and where the motivational structure included monetary incentives, enhanced supporting resources, and a "show them it can be done" kind of intrinsic motivation. This involved civilian aircrews flying emergency resupply in Southeast Asia. These crews worked a 14-17-hour day flying three or four 1.4 hour shuttles with 1 hour turnaround at home base, four days in a row with the fifth day off, logging not less than 145 hours of flying time per month and exceeding 200 hours per month in some cases, for two months. Data were collected on blood pressure, pulse and pulse pressure and were usually within normal limits. The men were observably tired at the end of each day, and reported feeling tired, but recovered with one night of sleep. Other miscellaneous clinical measures yielded values which were unremarkable. Questionnaires yielded a lack of "undue fatigue," and the concensus was that they could have continued for approximately another month. Among Rayman's conclusions were:

(a) . . . "crew duty limitations, at best are established by experience . . ."

(b) Maximum support facilitates continued performance (my rephrasing) . . . "all extra duties normally assigned to the airmen should be discontinued . . ."

(c) Avoid perturbations such as schedule changes, ramp delays, takeoff delays (my rephrasing).

There is no doubt a short, sustained "surge" with maximum support and an enhanced motivational structure can, as this study demonstrates, result in monumental efforts by aircrewmen. The reader is aware of the facilitating effect of a war.

PART III

ADDITIONAL STUDIES: TACTICAL OPERATIONS

More recently, my laboratory has been engaged in studies of tactical fighter operations, to include deployments, sortie surges, air-to-ground, etc. The first of these studies (12) involved deployment of F-4D's from New Mexico to Germany, 30 days of NATO exercises, and redeployment to New Mexico. Our full subjective and urinary battery was employed. Significant increases in subjective fatigue (34%), an increase (41%) in post-deployment sleep (the average for the first night in Germany was 12 hours) and comparable increases in E, NE, 17-OHCS, and urea were seen as the result of deployment. Similar but less exaggerated effects were seen on redeployment. Overall, however, the values indicated crewmembers were only moderately stressed, partly because management optimized departure and arrival times so as to facilitate resynchronization to the local clock.

In July 1976, we performed a study (13) during the employment of an A7-D squadron in a sortie surge exercise. Included was a simulated round robin deployment followed by two weeks of multiple missions per day. Subjective fatigue increased within each day as a function of number of sorties flown, but there was recovery during each night of sleep (in a normal, home-base environment). There was, however, no night-time flying. Under these conditions, crews had no problems coping with the demands of the exercise, from a biomedical point of view.

The next study (14), we participated in the employment of the A-10 in a 12-day joint Army-Air Force exercise involving extensive air-to-ground operations. Subjective fatigue scores showed increased fatigue during each day, a trend toward minor cumulative fatigue across days for pilots flying more than one mission per day, but good recovery during each night of sleep. Not uncommonly, there was a more substantial fatigue in the afternoon, and pilots reported feeling "washed out." This and the finding on multiple missions per day suggest some caution in employing A-10 pilots in this mode. The biochemical measures gave evidence of anticipatory stress and flight stress, but indicated only moderate physiologic activation. Acceleration stress was also evaluated. The A-10 is, of course, not a high-performance fighter, but when G stress is expressed as G level x time. In combination with the demands of low-level "jinking," this form of acceleration stress was an important contributor to within-mission fatigue. Overall, however, the pilots were able to cope with the demands of the exercise. The absence of night missions and the opportunity to obtain night-time sleep in a normal sleep environment undoubtedly contributed to this.

In 1978, we participated in a sortie surge (15) involving F-4's in Korea. The exercise lasted 15 days. Eight two-man crews served as subjects though the entire wing was exercised. Subjective fatigue for pilots increased within a day and more gradually across days, but never exceeded moderate fatigue. Multiple sorties per day enhanced feelings of fatigue. Oral temperatures indicated daily mild hypothermia, a gross indicator of nonspecific stress discussed earlier. Heart rate and blood pressure did not change significantly. Again, however, crewmen obtained normal sleep in the normal home base environment. In general, crewmen were able to cope with the demands of the exercise.

Again in 1978, we participated in a sortie surge (16) in Germany, code name Salty Rooster. Involved was a wing of F-4's surging for 12 days, with many multiple missions per crew per day during the first 4 days. Subjective fatigue ratings showed increased fatigue during the day, recovery following a normal night of sleep, and no evidence of cumulative fatigue across days. In general, feelings of fatigue increased relative to the number of sorties flown in a day, with the 3rd sortie being most fatiguing, the 3rd or 4th mission late in the afternoon suggesting that crews were indeed being taxed. Once again, crewmen could cope with the demands of the exercise, but the heavy schedule early in the exercise suggested the need for some biomedical caution.

PART IV

THE ISSUE OF SLEEP

We have been leading the reader gently toward what has become for us a central issue: sleep, during a mission or during an exercise; sleep during the nights of an exercise/mission or after an extended mission. Consider the following data in Tables IV and V:

TABLE IV

SLEEP EFFECTS: AIRLIFT OPERATIONS

Name/Date	A/C	Type Exercise	Significant Sleep Effects	Probable Explanation
Cold Shoulder I Early 1970	C-141	Sim C-5 ops, 54 hrs, double crew	Post = 9.8, 8.9, 8.9	Workload; poor inflight sleep
Channel missions Spring 1970	C-141	Routine 6½ days, single crew	Post = 9.9, 9.2, 8.9	Workload; time away from home; variable duty day
Cold Shoulder II Early 1971	C-5	C-5 OT&E, 75 hrs, double crew	Post = 11.8, 8.8, 8.9	Workload; frustration; poor inflight sleep
Blue-Gold Apr-May 1977	C-5	Aerial refuel, 32/44/56 hrs	Post = 11.2 (9.2; 15.8)	Workload; poor inflight sleep

TABLE V

SLEEP EFFECTS: TACTICAL EXERCISES

Name/Date	A/C	Type Exercise	Significant Sleep Effects	Probable Explanation
Crested Cap Sep 75	F-4D	30-day deploy CONUS-Eur	1st night - 12 hrs Eur 1st night - 11 hrs CONUS	Predeparture workload Extended flight duration
Sortie Surge Jul 76	A-7D	Simulated deploy 2 wks CONUS	Nonsignificant trend	Multiple sorties; normal sleep period/ environ.
JAWS II Nov 77	A-10	Joint exercise 10 days CONUS	None	Within mission workload; normal sleep period/environ.
Commando Rock Feb 78	F-4D	Surge, 15 days Korea	None	Multiple sorties; normal sleep period/ environ.
Salty Rooster Feb 78	F-4D	Surge, 13 days Germany	None	Multiple sorties; normal sleep period/ environ.

It can be seen that multi-day missions with atypical sleep periods in marginal sleep environments, compounded by many other stressors exacts a cost which is demonstrated by sleep duration (Table IV). It can also be seen that multiple stressors in circumstances where normal sleep times in normal sleep environments can be obtained results in good tolerance for the burden imposed on aircrewmen.

The substance of our concern with sleep, the consequences of poor sleep and the ameliorative aspects of period good sleep, is amply supported by a remarkable AGARDograph by Johnson and Naitoh (18). They present a detailed review of the aeromedical findings in the section entitled "Aircrew Operation Studies and Partial Sleep Loss." In reviewing the studies from this laboratory and from the UK (RAFIAM, Preston, Atkinson, and others), they state that:

" . . . the concept of "physiological cost" emphasized by Hale and his coworkers highlights the coping mechanism of the body to unusual conditions. While "cost" implies these physiological responses are detrimental, there are little data to indicate that the changes reported by Hale and his associates have long-term detrimental effects. Though it may still be too early and too complex to accomplish, it would be of help in evaluating the physiological cost of missions if Hartman and his colleagues could

develop a numerical scale for labeling a stress response as "mild," "moderate," or "severe," depending on the excretion rates of catecholamines and 17-OHCS. Another question that needs attention is that of determining what part of the "cost" is due to the usual stressors of flight, that due to sleep deficit, and that resulting from the interaction of the two. It should also be remembered that consistent physiological and biochemical changes from this amount of sleep loss per se have been difficult to find."

Later, they make the following point about the relationship between altered sleep and maintenance of performance:

"What are the consequences of working at the high workload or at the level of workload which interferes with obtaining an acceptable sleep pattern? In his 1970 review paper in the proceedings of a conference for the NATO Advisory Group for Aerospace Research and Development (AGARD), Nicholson indicated that there was at present no conclusive evidence from the aeromedical literature showing that limited sleep deficits, which may be experienced with workloads just above the zone, would lead to decrement in performance during flying."

Nicholson has, of course, modified his position a bit since that time. (See quotation in the introduction.)

Johnson and Naitoh go on in the next section to discuss recovery from partial sleep loss. This section begins:

"The problem of adequate recovery function studies following sleep loss has been discussed. The problem is even more acute for partial sleep loss. Most researchers have stressed the need for adequate rest and sleep before beginning another mission, but few have presented data to support specific recommendations."

After reviewing several studies, they provide the following summary:

"In summary, partial sleep loss appears to be a part of most aircrew operations, especially those involving time-zone crossings. Of far more significance than the actual amount of sleep loss is the disruption of the usual sleep-wakefulness cycle. Sleep appears to be fragmented and often scheduled for unusual hours. Flights during usual sleep periods tend to be associated with a greater accumulation of sleep disruption and sleep deficit raise the "cost" of the mission both in terms of increased physiological stress-related responses and by higher levels of fatigue. Subjective feelings of fatigue are the major findings whether sleep reduction occurs in a laboratory or in an operational setting. Double crews help to reduce sleep loss and permit sustained flights of two or more days, but these flights appear to have an optimal period of about 48 hours. Short work-rest cycles such as 4 work/4 rest lead to sleep deficit and should be replaced by cycles that allow for uninterrupted sleep periods of 6 or more hours."

Natani, in a review of research* on human behavior relevant to space flight, makes a number of interesting points regarding the effects of stress on sleep:

1. Lester, Burch, and Dossett (1967) reported that deep, or slow wave sleep is virtually eliminated during a state of subjective stress, such as the period before a critical examination for medical students. Usually after an acute stress of this type there is a rebound of slow wave sleep on succeeding nights which may compensate for the loss while under stress.

2. Hartman (1971) and Harris, Pegram and Hartman (1971) have found reductions in deep sleep during extended flying missions. They have interpreted this effect and the subsequent length of time taken for recovery as an index of depletion of physical reserves or the physical cost of a stress inducing activity.

3. The Antarctic work suggests that a year or more is required before slow wave sleep returns to baseline levels in the men who winter at the South Pole. Thus, the men at the Amundsen-Scott Station may be experiencing a continual depletion of reserves with an accumulating state of chronic fatigue. This view is consistent with the Soviet suggestion that CNS exhaustion occurs in the Antarctic.

4. The similarity of the subjective complaints obtained under conditions of sensory isolation/deprivation, Antarctic wintering, toxicity, and fatigue suggests that all of these effects have a common neurophysiological basis, i.e., a lowered CNS efficiency, which is subjectively experienced primarily as a disturbance in sleep quality with feelings of apathy, irritability, lassitude, and negative mood.

5. Both the extended flight studies and the work in the Antarctic suggest that as long as a significant level of stress exists sleep patterns will remain disrupted and prevent recovery, leading to a continual depletion of physical reserves.

Natani goes on with an extended and provocative discussion of measurement problems relative to assessing stress effects, a discussion which will be of considerable value upon the imminent publication of this review.

PART V

SUMMARY

There is a great deal more literature which can be cited--and to some degree this paper has been somewhat cavalier in reporting largely on studies from this laboratory. Nevertheless, it seems time to bring the status quo into focus and to consider how commanders and planners at all levels can manage the problem

*Personal communication. Natani, K., Assessment paradigms, psychometric, neurometric, neuropsychological: strategies for selecting for technical proficiency and psychological adaptability in space worker candidates.

of irregular rest and activity. First, the status quo: the problem breaks out into four subcategories, based on mission duration:

a. Tactical missions (repeated cycles in one day)

b. Strategic missions (one to four days per cycle)

c. Airlift (one week)

d. Ground-based centers (basically shift work)

Each category will be discussed separately. The term work/rest will be used as a less cumbersome substitute for "irregular rest and activity."

a. Work/rest cycles (tactical aircraft).

Operational requirements for brief, multiple missions in tactical aircraft within a single day generate special crew fatigue problems related to high workloads and high hazards per mission, mission scheduling rules, acute fatigue effects across a sequence of missions within a day, and required rest and recovery schedules. In-house laboratory studies have generally focused on crew workload/hazard studies per mission and have not generally demonstrated (or sometimes even investigated) a buildup of cumulative fatigue across missions as this relates to rest requirements and circadian (time-of-day) factors.

An integrated body of data providing a set of rules which can be applied across the board to all new tactical aircraft or new operational missions is not available. In addition, the effects on performance of being subjected to multiple stressors repeatedly on a time scale consistent with operational practices has not been adequately studied. Furthermore, the duration and kind of rest between such exposures has not been evaluated. This is an essentially undeveloped area which needs: (a) a careful, critical integration of existing studies, which are fragmentary at best; and (b) a program of research and development to fill in the gaps so that rules (possibly in the form of mathematical models) can be developed.

As a first step, a diverse and scattered body of technical information related to this program element must be identified, pulled together, and used to develop an integrated picture of the current state-of-the-art on this problem. This integrated summary will provide a basis for planning studies on work/rest schedules. It will be important to conduct such studies within the context of multiple stressors from environmental sources and to keep the program field-oriented, probably by accomplishing a substantial part of the work in field studies. The product of these studies should be general rules for work/rest and multiple stress effects which can guide the formulation of operational concepts relative to the crews.

b. Work/rest cycles (nuclear A/C, AWACS, SAC missions, etc.)

Present bomber systems and future aerospace systems involving operational requirements for missions lasting from one to four days, manned in some systems with two crews (flight crews up front and mission crews aft, in the case of AWACS), generate special fatigue problems related to the work/rest cycles and to task complexity/criticality. Inflight rest accommodations and work/rest schedules appear to be particularly important. These are likely to involve quite different concepts where there are two kinds of crews. These problems are taking the form of (a) acceptable work schedules, and (b) crew size; these are usually alternate facets of the same question. In-house laboratory studies have not been sufficiently comprehensive because (a) questions from design and operational Air Force elements have been presented piecemeal, and (b) applicable research has not been broad enough to cover all elements of the problem. In general, however, research performed on problems in airlift operations and ground-based centers will provide data applicable to this area.

c. Work/rest cycles (transport aircraft).

Operational requirements for extended missions in transport aircraft for periods from 4 days to two weeks (multiple flights per mission) result in recurring problems on mission scheduling policies, duty time per flight, flight time per month, and related questions on crew composition and crew manning ratios. The problems commonly originate in the form of concern over flight fatigue and/or crew workload, both aspects being presented in a rather nonspecific form. In-house laboratory studies have been tailored to the specific complaint/system/mission configuration, which has made it difficult to develop general principles.

Approximately 2 dozen applicable studies have been conducted in the past 15 years on the factors in transport operations which contribute to piloting decrement. These studies have identified a multiplicity of on-duty and off-duty factors which impose a burden upon aircrewmen; to date flying fatigue per se has not emerged as a primary problem, but the non-flying burden has been demonstrated to contribute to significant motivational deficiencies which in turn have an effect on overall mission effectiveness. One of our studies (2) demonstrated that transport crews go into an unpatterned living and working schedule on these kinds of missions, but follow-on studies to demonstrate the psychological cost have not been accomplished, so the relevance of this factor to work/rest problems has not been evaluated. The feasibility of performing acceptably on a broken sleep schedule has been satisfactorily demonstrated in several studies, provided the total amount of sleep is adequate, but it is accompanied by a reduced tolerance for additional stresses which needs further study. An extensive literature review on circadian effects has failed to show an operationally meaningful change in crew efficiency. Circadian effects are easily demonstrated on biologic parameters and are accompanied by a small, tolerable loss in performance, but the interaction with other stresses (probably an additive performance loss) has not been adequately studied. Studies on the performance effects of flying through time zones have given mixed results, and it frequently suffers from limited scope as well as methodologic deficiencies. These "time zone" effects additional study in the operational context, and especially in the context of multiple stresses, but time zone stress probably will be resolved as a secondary stressor similar to circadian effects. All of these studies have led to the formulation of a third category, cumulative fatigue, standing midway between acute and chronic in the usual

medical sense. Work/rest cycles appear to be an important variable in cumulative fatigue, but effects over months need study.

We are in better shape here than in the tactical and strategic area, in the sense that we can define the studies which need to be done. Studies should be conducted to identify problems related to sleeping and resting in flight and in enroute BOQ's, since recovery from work has been shown to be the key factor in recent research. We need more research on the environmental envelope for adequate sleep. The operational utilization of an all-jet airlift force and advanced systems involving airborne-command-post concepts will put flying crews in more direct conflict with time-anchored stressors. General problems involving the objective and subjective aspects of cumulative fatigue (conceptually distinct from either acute or chronic fatigue) should be studied. Many of these factors are clearly secondary stressors, so these kinds of studies can await the availability of resources. Field studies riding "piggy-back" on real operational missions to ensure the validity of the findings should be conducted opportunistically, utilizing operational exercises as they occur within the operational commands.

d. Work/rest cycles for crews in electronic, communications, and surveillance centers (ground-based)

We have addressed this problem in my laboratory in only two field studies but it is important because it offers clues to the stress effects of "mission" crews in AWACS, C^3, NEACP, etc. Task-loading is particularly important in this area. The tasks commonly require the more complex forms of discrimination and decision-making and are critical. The problems come up with each proposal on ground-based centers. Acceptable work/rest cycles are significantly altered by task factors, but work-schedule and manning decisions are usually made in relation to space constraints imposed by the facility itself and its geographical location (e.g., a remote Minuteman installation). It is particularly important to define the acceptable work/rest cycle envelope while providing a capability for extended operational (contingency) periods.

A rather large body of literature in related aviation activities is available, including studies conducted in-house and on contract by ESD, some work supported by AMRL, FAA, and USAF studies on air traffic control, Navy studies in air traffic control, for battle command centers, and in submarines, as well as less formal USAF operational studies on small group performance. Crew effectiveness, motivation, subjective changes, morale, and remote-station factors have been evaluated. The initial need is for an integrated compendium of the existing literature, written in user language. Studies to fill the gaps, most probably in the area of crew effectiveness during "crises" can then be instituted.

The extensive body of literature pertaining to this effort urgently needs to be assembled and integrated in order to provide general ground rules which can be used to establish concepts of systems management related to crew requirements. This integration will also provide the definition of requirements for further research and development, which must consider both the manning and management of crews during routine operations, and the capabilities of crews to function during extended periods of crises.

In general, then, I feel that an acceptable data base on transport operations is becoming available because of continued research on the C-141/C-5. Because some transport data will be applicable to multi-crew operations of one to four days, an acceptable data base will gradually become available in this sub-area. Tactical air operations are currently receiving less attention but the effort is growing; it will require a good deal of work to dev lop the appropriate data base. Fragments of data on ground-based centers are scattered through the technical literature. To collect and collate these pieces and to fill in the missing elements with special studies will also require a good deal of work.

The significant constraint in this general area is the requirement to perform a major part of this research in operational settings with operational personnel. This is vital to obtaining meaningful data, but is frequently difficult to arrange. Substantial management support is needed to meet this requirement.

The above discussion describes the current situation as I see it in broad categories of military operations. The next step will be to summarize my views with regard to cyclic variables having an impact on aircrews--contributors, if you will, to irregular rest and activity.

Sleep. The studies from this laboratory have paid particular attention to sleep. A summary statement on sleep must necessarily be multifaceted.

a. Sleep reduction, sleep disturbance, changes in stage patterning, reduction in sleep duration, sleep at atypical times relative to home base, and poor sleep environments are all primary aircrew stressors in military operations. Split sleep is one way crewmen cope with sleep problems.

b. Adequate sleep, or even somewhat marginal sleep, is of major significance in maintaining operational effectiveness.

c. Good sleep in the post-mission period or after operational exercises is essential for recovery and subsequent readiness for the next mission/exercise.

d. Self-reports on sleep are the easiest, most practical measure of the effect of missions/exercises on crews.

Cost. In this laboratory, we use the concept of cost as a global approach to all the stress effects we see in a study. We think of it primarily in physiological terms. We assess it in several ways.

a. Increased sleep during the mission/exercise, if such is feasible.

b. Carry-over of subjective fatigue across sleep periods (cumulative fatigue).

c. Altered biochemistry (increased excretion rate, attentuation of amplitude, phase shifts).

d. The time course of recovery, to include the return of sleep duration, subjective fatigue ratings, and biochemical measures to normal values. Typically in day-time tactical operations with reasonable work days, it is accomplished in one day. Typically in multi-day transport missions it occurs in 3 to 4 days, though the biochemical measures oscillate around normal values for an additional 2 or 3 days. The bomber/AWACS/C^3/MEACP remains relatively indeterminant at this time.

Performance Effects. They are elusive. Part of the problem is that we get little hard data in field exercises. Part of the problem is that such data when available relate to second-order measures (e.g., sleep) in a gross way only. Furthermore, we probably do not have the proper scaling, nor the proper time intervals. But probably the most important aspect is that crewmen compensate--they maintain performance in the face of stressors, but at a cost.

Subjective vs. biochemical measures. These are two classes of second-order measures of changes in operational effectiveness.

a. They seem to relate in a qualitative sense. We haven't seen large disturbances in biochemistry, for example, without concomitant changes in self-reports on fatigue or sleep.

b. The time courses, the underlying time domains, are different. We don't have a usable time base accommodating both classes of measures at this time.

c. Equally important, we won't have the required correlating scales for the measures, even if we found the proper time bases.

d. It may be a fruitless chase, if we attempt to go beyond qualitative comparisons.

Secondary Stressors. It is my position that many of the cyclic factors about which we are concerned in military aviation operations are secondary stressors, i.e., they become a stressor only when a primary stressor is already having a significant effect, and then their only impact is additive to primary stressor effects. I would offer a final study at this point (19), a study for which only portions of the data have been published because of design limitations in the situation in which the study was conducted. Four experienced transport pilots flew for 24 hours continuously in a C-130 simulator, flying 11 legs of 2 hours duration. Each pilot began in a different quarter of the day. Performance during the cruise portion of each leg and an ILS approach at the end of each leg were scored. Performance during cruise degraded slowly and did not influence performance. The changes in performance were much more interesting. Graphic records (from the simulator plotting board) of the last four minutes of each ILS (instrument landing system) approach were scored for deviations from the prescribed flight path. The maximum score was nine. Table VI presents the ILS approach data for the early morning hours of each mission.

TABLE VI

Mean ILS Scores (3 approaches) for Each Pilot

Pilot #	Mission Start Time	Approach Number	Mean Approach Score
1	2400	2,3,4	6.7
2	1800	4,5,6	6.3
3	1200	6,7,8	6.0
4	0600	8,9,10	4.3

The indications in these data are that: (a) Pilot #1 with the least mission time (least fatigue ?) performed best. The next two pilots (#2, #3) performed almost as well even though they had 6 and 12 additional hours of mission upon reaching the low part of the zone of circadian periodicity. Pilot #4 performed poorest, and was at approximately 20 hours into the mission. This suggests that the circadian stressor impacts performance (overcomes compensatory mechanisms) only after a significant degree of fatigue is present. Fragmentary data? Yes. Provocative data? Yes!

I would propose that the following cyclic variables are secondary, impacting man only if primary stressors are already taking their toll:

a. Duration of the duty day beyond 16 hours; note that this also suggests that you cannot assess the effect of a 20-hour duty day, for example, unless you also consider where it occurs on the clock.

b. Task load, when variable and with reasonably short peak periods.

c. Contingency demands (e.g., an emergency; e.g., an exercise; these are the two extremes), again when variable and with reasonably short peak periods.

d. Day-night cycles

e. Time-zone transition, perhaps.

Finally, we must address the question of how one might manage aircrews, given all the problems associated with irregular rest and activity. At the USAF School of Aerospace Medicine, we emphasize provisions for good sleep, preferably at times appropriate to the previous duty period and some balance of local and home base time. For example, the Crested Cap commanders did at least two successful things: (a) scheduled the arrival in Germany to provide for debriefings, meals, brief relaxation, and bed-time consistent with local sleep schedules--after a demanding, long duty day of preparations for deployment and the trans-Atlantic flight; (b) set aside 12 hours for rest/sleep on the first night after arrival. We recommend

delivering fresh pilots to the exercise/engagement arena if immediate missions are contemplated--if this is possible (we are still studying the feasibility of this approach). We recommend "tracking the psychological and physiological status of crews to look for growing cumulative fatigue. We recommend "tracking" the efficiency of sleep--how do crews feel after sleep? How much are they getting? We strongly recommend realistic post-mission or post-exercise rest periods, up to 3 days. We recommend considering long, demanding duty days be scheduled with one eye on the clock, and with a careful appraisal of pre-mission activity/work. We recommend enhancement of sleep and rest facilities away from home base, enhancement of all support facilities, and provision of an adequate number of well-trained, unfatigued support personnel. We recommend minimizing all ground delays, for whatever reason. We recommend reducing the duty day in the face of high environmental stress.

Nicholson (1) says the key is the appraisal of duty hours, with emphasis on acceptable sleep patterns, adding cautionary notes about the changes in sleep behavior in crewmen over 40. He suggests that some hypnotics may be useful for some crewmen, but that more research is needed.

Rayman (11) suggests that: (a) we accept operational experience regarding aircrew duty rules unless there are unequivocal research findings against it; (b) that an on-scene flight surgeon be provided for "hands-on" evaluations of crew members, particularly after the early period of an extended exercise; (c) that the flight surgeon attend to fatigue signs and provide briefings; (d) that the best possible food, quarters, and inflight provisions be available; (e) that grounding for fatigue be a joint decision of the flight surgeon, operations officer, and the crew member concerned; (f) that simple medical monitoring be employed; (g) that all extra duties be suspended; (h) that delays be minimized; and (h) that quarters be located as close as possible to the operations building. Finally, we can infer from Rayman that significant gains can come from enhancing the motivational structure.

There are enough suggestions here to keep all of us and all wing commanders for a considerable period of time. I come back to the importance of sleep.

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BIBLIOGRAPHY ON INTENSIVE AIR OPERATIONS - PROBLEMS OF SLEEP, VASOVAGUES AND CIRCADIAN RHYTHMS

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INTRODUCTION

This bibliography has been compiled by the Defence Research Information Centre (DRIC) to provide literature references on the problems of sleep, wakefulness and circadian rhythms during intensive air operations in support of AGARD Lecture Series 105. The symposium is intended for those concerned with the management of civil and particularly military personnel who have to cope with irregular work and rest. It is also intended to provide an understanding of the physiological processes involved in the adaption of man to disturbed sleep and wakefulness and consider approaches to the management of the problem.

The bibliography has been compiled using the data bases listed below via terminals to the computerized information networks available at DRIC. Abstracts or descriptors are given where available on the file. An author index is included. Only articles in English or where an English translation of th. title has been provided are included.

Citations are presented in two sections: Part 1: References by the Lecturers, contains items of interest written by the seven authors of the papers given at AGARD LS 105. Part 2: Additional references, contains references on the problems of sleep, wakefulness and circadian rhythms during intensive air operations except those in Part 1.

SOURCES AND AVAILABILITY OF REFERENCES LISTED

Relevant items have been selected from the following data bases:

BIOSIS (Biosciences Information Service), a general biological file covering biology, zoology, medicine and related areas. The file was covered for the period 1973 to December 1978.

Excerpta Medica covers the entire field of human medicine and related disciplines. It consists of articles from over 3,500 biomedical journals published throughout the world. The file was covered for the period 1975 - to December 1978.

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45. CHANGES IN THE 24-HOUR RHYTHM AFTER TWO TRANSATLANTIC FLIGHTS IN RAPID SEQUENCE (EFFECTS OF TWO SEQUENTIAL TRANSATLANTIC FLIGHTS ON CIRCADIAN RHYTHM OF BODY FUNCTION AND PERFORMANCE)
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Institut fuer Flugmedizin, Bad Godesberg, West Germany, 21st International Congress on Aviation and Space Medicine, Munich, West Germany, September 17-21, 1973, Preprints 338-339. 7 refs.
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Klein, K.E.
European Space Research Organisation, Paris,(ESRO-TT-35), 123-139
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49. RESYNCHRONIZATION RATES OF A PSYCHOMOTOR TEST RHYTHM IN MAN FOLLOWING TRANSLONGITUDINAL FLIGHTS
Rosenblatt, L.S., Klein, K.E., Winget, C.M., Hetherington, N.W., Beljan, J.R.
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Aerospace Medicine, Vol.43, No,2,1972, 119-132
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Klein, K.E., Bruener, H., Gunther, E., Jovy, D., Mertens, J., Rimpler, A., Wegmann, H.M.
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56. INVESTIGATION OF AIRCRAFT CREW FATIGUE ON LONG - DISTANCE FLIGHTS WITH JET AIRCRAFT.
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Civil aviation/Commercial aircraft/*Flight crews/*Flight fatigue/*Flight stress (biology)/*Jet aircraft/Psychophysiology.

58. INVESTIGATIONS ON STRESS IMPOSED ON AIRCREW IN CIVIL JET AIRCRAFT DURING LONG-RANGE FLIGHT - REPORT ON RESULTS ON THE NORTHERN ATLANTIC ROUTE (STRESS IMPOSED ON AIRCREW IN CIVIL JET AIRCRAFT DURING LONG FLIGHT)
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Deutsche Versuchsanstalt Fur Luft - Und Raumfahrt, Bad Godesberg DLR-FB-65-44. 10-1965, 67 pp.
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60. DIAZEPAM AND 3-HYDROXYDIAZEPAM (TEMAZEPAM) AND SLEEP OF MIDDLE AGE.
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Nicholson, A.N., Stone, B.M.
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63. DIFFERENTIAL EFFECTS OF BENZODIAZEPINES ON SLEEP AND PERFORMANCE IN HEALTHY MAN.
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Br. J.Clin, Pharmacol., 1978, Vol.5, No.5, 469-472.
*Oxazepam/*Drug comparison/*Sleep/*Task performance/*Rem sleep/*Stage 1 sleep/*Stage 2 sleep/*Stage 3 sleep/Stage 4 sleep/*Diazepam/*Temazepam/*Placebo.

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Br. J. clin. Pharmac., Vol.6, 1978, 325-331.

66. IRREGULARITY OF WORK AND REST
Nicholson, A.N.
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Borland, R.G., Nicholson, A.N.
Br. J. clin. Pharmac., Vol. 4, 1977, 86-89.

68. EFFECT OF DIAZEPAM AND FOSAZEPAM (A SOLUBLE DERIVATIVE OF DIAZEPAM) ON SLEEP IN MAN
Nicholson, A.N., Stone, B.M., Clarke, C.H.
BRIT.J.CLIN. PHARMACOL, No. 3-4, 1976, 533-541.
The effect of diazepam (5 mg and 10 mg), and fosazepam (60 mg and 80 mg), a soluble derivative of diazepam, on sleep was studied in 6 healthy adult males using electroencephalography for sleep measures, and analogue scales for subjective assessments of well being and sleep quality. The effect of diazepam was limited to the night of ingestion, but the effect of fosazepam was carried over to the next night and so modified sleep for about 30 hr after ingestion. Effects on total sleep time were limited to the night of ingestion. There were increases with diazepam (10mg) (P= 0.05) and with fosazepam (60 mg and 80 mg) (P= 0.001). For the night of ingestion sleep onset latencies were shortened, and awakenings were reduced by both drugs. The latency to stage 3 was shortened by fosazepam (60 mg and 80 mg) (P= 0.05). The low and high dose of each drug reduced the duration (min) of stage 0 sleep (P= 0.01), but fosazepam also reduced the duration (min) of stage 1 sleep (P= 0.001), and there was an increase in stage 2 sleep (P= 0.01). With fosazepam there were no effects on the duration of stage 3, but there was evidence that stage 4 activity was reduced during the recovery night after ingestion of fosazepam (80 mg). No effects were observed on REM sleep. Subjects reported an improved sense of well being during the day after ingestion of diazepam and fosazepam, and with fosazepam they reported improved sleep. Correlations were calculated for sleep measures and subjective assessments.

69. EFFECT OF A METABOLITE OF DIAZEPAM, 3 HYDROXYDIAZEPAM (TEMAZEPAM), ON SLEEP IN MAN.
Nicholson, A.N., Stone, B.M.
BRIT. J. CLIN. PHARMACOL, No. 3-4, 1976, 543-550.
The effect of 3 hydroxydiazepam (temazepam, 10 mg and 20 mg) on sleep was studied in 6 healthy adult males using electroencephalography for sleep measures, and analogue scales for subjective assessments of well being and sleep quality. The effects were compared with diazepam (5 mg and 10 mg). Effect on total sleep time was restricted to the night of ingestion. There was no change in total sleep time after temazepam (10mg), but with 20mg total sleep time was increased (P = 0.01). Sleep onset latencies and awakenings were markedly reduced. Temazepam reduced the duration (min) of state 0 (P = 0.05) and stage 1 (P = 0.01) sleep, and the effect on stage 1 was seen during each two hourly interval of sleep (P = 0.05). No effects were observed with stage 3, 3+4 and REM sleep, except that the appearance of the first REM period was delayed with temazepam (20mg) (P = 0.001). The subjects, as a group, reported improved sleep, but subjective assessments of well being were not altered. Correlations were calculated for sleep measures and subjective assessments.

70. EFFECT OF N-DESMETHYLDIAZEPAM (NORDIAZEPAM) AND A PRECURSOR, POTASSIUM CLORAZEPATE, ON SLEEP IN MAN.
Nicholson, A.N., Stone, B.M., Clarke, C.H., Ferres, H.M.
BR J Clin Pharmacol, Vol, 3, No. 3, 6.1976, 429-438.
The effect of N-desmethyldiazepam (nordiazepam, 5 and 10 mg) and potassium clorazepate (15 mg, a precursor of nordiazepam) on sleep was studied in six healthy adult males.
Electroencephalography (EEG) was used for sleep measures, and analogue scales were used for subjective assessments of well-being and sleep quality. Effects on total sleep time were limited to the night of ingestion. There were increases with nordiazepam (5 and 10 mg) (P = 0.05) and 0.001 respectively), and with clorazepate (15 mg) (P = 0.01). Sleep onset latencies were shortened, particularly with nordiazepam, and awakening to stage 0 activity was reduced, by both drugs. The latency to stage 3 was reduced by nordiazepam (5 and 10 mg) (P = 0.05). There were no effects of nordiazepam (5 mg) on the duration (min) of sleep stages. Nordiazepam (10 mg) and clorazepate (15 mg) reduced the duration of stage 0 and stage 1, and there were increases in stage 2. Reduced stage 1 and increased stage 2 sleep were observed during the recovery night. No effects were observed with stage 3, but there was evidence that stage 4 activity was depressed on the recovery night only. No effects were observed on REM sleep, except that the appearance of the first REM period was delayed with clorazepate (15 mg) P = 0.01). The effect of nordiazepam (10 mg) and clorazepate (15 mg) were comparable, and each modified sleep for about 28-30 h after ingestion. 4 With nordiazepam (10 mg) and clorazepate (15 mg) the subjects, as a group, reported improved sleep, but subjective assessments of well-being were not altered. Correlations were calculated for sleep measures and subjective assessments.

71. PERFORMANCE AND IMPAIRED PERFORMANCE.
Nicholson, A.N.
BRIT. J. CLIN. PHARMACOL, No. 3-4 1976 521-522
*Pharmacotherapy/*Psychedelic agent/Performance.

72. BEHAVIOURAL SEQUELAE OF METHAQUALONE IN MAN AND IN THE MONKEY (MACACA MULATTA).
Borland,R.G., Nicholson, A.N., Wright, C.M.
Br. J.Clin,Pharmacol, Vol. 2, No. 2, 4.1975, 131-141
Residual effects in man of methaqualone hydrochloride (400 mg) were studied by adaptive tracking and by reaction time.
Performance was measured at 10 h, 13 h, 16 h, 19 h, and 34 h after the overnight ingestion of the drug. There was no evidence of impaired performance on adaptive tracking from 10 h to 19 h, but enhanced performance (P = 0.001) was observed 34 h after ingestion. With reaction time an increase (P = 0.01) was observed 10 h and a decrease (P = 0.05) was observed 19 h after ingestion. Effects in the monkey (Macaca mulatta) of methaqualone (20 and 30 mg/kg body weight) were studied by a delayed matching task in which total response time was measured. No consistent effects on matching behaviour or on total response time were observed 2 h after intraperitoneal injection. The studies suggest that methaqualone hydrochloride may be a valuable hypnotic for occasional use by persons involved in skilled activity.

73. COMPARISON OF THE RESIDUAL EFFECTS OF TWO BENZODIAZEPINES (NITRAZEPAM AND FLURAZEPAM HYDROCHLORIDE) AND PENTOBARBITONE SODIUM ON HUMAN PERFORMANCE.
Borland, R.G., Nicholson, A.N., Wright, C.M.
Br. J. Clin, Pharmacol, Vol.2, No. 1, 2.1975, 9-17
The residual effects of two benzodiazepines, nitrazepam (10 mg) and flurazepam hydrochloride (30 mg), and pentobarbitone sodium (200 mg) were studied by adaptive tracking and by reaction time. Performance was measured at 10 h, 13 h, 16 h, 19 h and 34 h after ingestion of each drug. Impaired performance on adaptive tracking was observed at 10 h, 13 h, 16 h and 19 h after nitrazepam and pentobarbitone sodium and at 10 h, 13 h and 16 h after flurazepam hydrochloride. Enhanced performance was observed at 34 h after nitrazepam and pentobarbitone sodium. Increased reaction time persisted to 16 h after nitrazepam, flurazepam hydrochloride and pentobarbitone sodium and reaction time was also increased at 34 h after nitrazepam and pentobarbitone sodium. During the morning immediately after ingestion, the subjects as a group were able to differentiate correctly between placebo and drugs, but they were not able to assess accurately the persistence of the residual effects of nitrazepam and pentobarbitone sodium. Flurazepam hydrochloride would appear to be a more promising benzodiazepine than nitrazepam for use as a hypnotic by persons involved in skilled activity. There was a rapid recovery of performance during the afternoon and, unlike pentobarbitone sodium and nitrazepam, subjects retained the ability to recognize impaired skill.

74. LONG-RANGE AIR TO AIR REFUELLING A STUDY OF DUTY AND SLEEP PATTERNS
Mills, N. H., Nicholson, A.N.
AGARD conference proceedings. Vol. 146, 1974, A14-1-A14-9
Human

75. HUMAN PERFORMANCE AFTER A BARBITURATE (HEPTABARBITONE)
Borland, R.G., Nicholson, A.N.
Br. J.Clin. Pharmacol., Vol.2, No. 1, 1974, 209-215.
The residual effects of heptabarbitone given overnight were studied by an adaptive tracking technique. Decrements in performance were observed at a 10 hr interval after 200 mg, at 10 hr and 13 hr intervals after 300 mg and at 10 hr, 13 hr, 16 hr and 19 hr intervals after 400 mg of the drug. Decrements in performance at each interval and the persistence of the effects were dose related. Subjective assessments of performance correlated with measured performance, but the subjects, as a group, over estimated their performance after placebo and heptabarbitone. With heptabarbitone (400 mg) highly significant decrements in performance persisted to the 19 hr interval after ingestion, but subjective assessments of performance to the 19 hr interval did not differ significantly from subjective assessments of control activity of the day before. Individual blood concentrations of heptabarbitone did not give a significant correlation with individual performance decrements, although the blood concentrations and performance decrements at each dose were related.

76. DUTY HOURS AND SLEEP PATTERNS IN AIRCREW OPERATING WORLD-WIDE ROUTES.
Nicholson, A.N.
Aerospace Medicine., Vol.43, 1972, 138-141.

77. PHYSIOLOGICAL CONSIDERATIONS OF DISTURBED SLEEP WAKEFULNESS CYCLES IN THE AERO SPACE ENVIRONMENT
Nicholson, A.N.
Man in space. Proceedings of the Fourth International Symposium on basic environmental problems of man in space, Yerevan, USSR, 1-6 October 1971 (Dist. By Univelt, San Diego, Calif.
Human.

78. INFLUENCE OF DUTY HOURS ON SLEEP PATTERNS IN AIRCREW OPERATING IN THE LONG HAUL TRANSPORT ROLE. A STUDY OF SINGLE CREW OPERATIONS AND DOUBLE CREW CONTINUOUS FLYING OPERATIONS (INFLUENCE OF DUTY HOURS ON SLEEP PATTERNS IN FLIGHT CREWS DURING LONG DURATION FLIGHTS)
Nicholson, A.N.
AGARD, rest and activity cycles for the maintenance of efficiency of personnel concerned with Military Flight Operations, 11.1970, 11 pp
*Flight crews/*Flight fatigue/*Human performance/Physiological effects/Stress (physiology)/ Work-rest cycle.

79. DOUBLE CREW CONTINUOUS FLYING OPERATIONS: (i) A STUDY IN AIRCREW SLEEP PATTERNS; (ii) MILITARY IMPLICATIONS.
Atkinson, D.W., Borland, R.G., Nicholson, A.N.
Aerospace Medicine, Vol. 41, 10.1970, 1121-1126
Continuous flying operations, in which crews sleep aboard the aircraft instead of sleeping at route stations, provide an operational capability independent of positioned crews. Such missions may lead to sleep difficulties and it is concluded from two missions operated by Royal Air Force Air Support Command that the optimum duration is 48 hours. In the case of a fast strategic transport aircraft this provides a world-wide capability.

80. MILITARY IMPLICATIONS OF SLEEP PATTERNS IN TRANSPORT AIRCREW.
Nicholson, A.N.
Proc. Roy. Soc. Med., Vol. 63, 1970, 570-572.

81. SLEEP PATTERNS OF AN AIRLINE PILOT OPERATING WORLD-WIDE EAST-WEST ROUTES.
Nicholson, A.N.
Aerospace Medicine, Vol. 41, 1970, 626-632.

82. APPRECIATION OF THE EFFECTS OF CHANGES IN WORK REST SCHEDULES UPON VARIOUS CIRCADIAN RHYTHMS BY AUTO ESTIMATION TECHNIQUES (FATIGUE, ETC.) AND AUTO MEASUREMENT.
Reinberg,A.
Arch.Mal.Prof.Med.Trav.Secur.Soc. Vol. 38, No.1-2, 1977, 145-146.
*Circadian rhythm/*Fatigue/*Work table/*Oil industry/*Worker/*Shift worker/*Working time.

83. ADJUSTMENT OF PHYSIOLOGICAL CIRCADIAN RHYTHMS TO SHIFTS IN THE WORK REST SCHEDULE EVERY 3-4 DAYS IN OIL REFINERY OPERATORS.
Reinberg,A., Vieux, N., Laporte, A., et al
Arch.Mal.Prof, Vol. 37, No. 6, 1976, 479-494.
7 healthy adult men (from 21 to 36 yr; mean = 26.4), oil refinery operators volunteered to perform self measurements at fixed clock hours (1 hr, 5 hr, 9 hr, 13 hr, 17 hr 21 hr) 5 times/24 hr (not during sleep), both at work and at home, every day, during 8 consecutive weeks. The participants were given sheets and instruments to document the following variables: mood and fatigue (self rating); random number addition test, heart rate, oral temperature, peak expiratory flow, grip strength, systolic blood pressure (self measurements). 5 of these participants have been shift working for 7 mth to 3 yr with the following timing (given in the rotation order): normal day from 7 hr to 3 yr with the following timing (given in the rotation order); normal day from 7 hr 45 to 16 hr 30; night shift from 21 hr to 6 hr; morning shift from 6 hr to 13 hr; evening shift from 13 hr to 21 hr. The shift duration has been (and still is) 3-4 days (rapid rotation). The other two participants (controls) were working a normal day only. Time series thus collected (15,000 measurements) were analyzed using the cosinor as the main statistical method. Endpoint and confidence interval estimates for circadian acrophase, phi, (phi = timing of the peak in the 24 hr scale), amplitude and mesor, M (M = 24 hr rhythm adjusted mean) were computed transversally for each day and each variable. A Delta psi phase shift in the work rest schedule (Delta psi of socio ecologic synchronizers) is followed by an acrophase shift, Delta psi, of the studied variables. The adjustment of phi following a Delta psi = 8 hr is very rapid (within 1 or 2 days) both after a phase delay (Delta psi from the normal day to the night shift) or a phase advance (Delta psi from the night shift to the morning shift). Quick adjustment is usually observed among shift workers, representing in fact selected subjects; presumably this ability has a genetic origin. The temporal relationship between phi of the studied rhythms are not altered by Delta psi leading to the conclusion that this aspect of the temporal structure is not altered. However, the phis are gathered around mid work during the normal days and the evening shifts but before mid work during the night shifts and after midwork during the morning shifts. This lack of coincidence in time between phis and mid work (working hours scheduled at a wrong time) may contribute to produce a certain type of fatigue during night and morning shifts; it suggests also that the work per se is a rather poor synchronizer by comparison with the socioecologic dependant work rest schedule. In subjects able to adjust quickly the rapid rotation of shifts seems to be well tolerated from a chronophysiological point of view. This fact has to be kept in mind since, socially as well as psychologically, the acceptance of the rapid rotation is better than the conventional weekly shift. A biological index to detect quick adjusters does not exist as yet. Individual variations in the speed of adjustment after a Delta psi has to be taken into consideration in studies involving manipulations of synchronizers.

84. ENDOCRINE CIRCADIAN RHYTHMS IN UNUSUAL CIRCUMSTANCES OR ENVIRONMENT.
Reinberg, A.
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85. EVALUATION OF CIRCADIAN DESYNCHRONIZATION DURING TRANSMERIDIAN FLIGHTS.
Reinberg, A.
Arch. Mal. Prof., Vol. 32, No. 4, 4.1971, 390-393.

86. EVALUATION OF CIRCADIAN DISCHRONISM DURING TRANSMERIDIAN FLIGHTS.
Reinberg, A.
Stud.Gen. (Berl), Vol. 23, No. 11, 1970, 1159-1168.

87. EVALUATION OF CIRCADIAN DYSCHRONISM DURING TRANSMERIDIAN FLIGHTS (CIRCADIAN RHYTHMS SYNCHRONIZATION CHANGES IN HUMAN BIOLOGICAL AND PHYSIOLOGICAL FUNCTIONS DURING TRANSMERIDIAN FLIGHTS)
Reinberg, A.
12th, Open meeting of working group V, symposium on biological rhythms, and symposium on nutrition of man in space, Prague, Czechoslovakia, 1.-24 May 1969, Pub. by North-Holland Publishing Co., 8 refs. 172-174.
Biological effects/*Circadian rhythms/Conferences/*Flight time/Life sciences/Physiological/ responses/*Synchronism.

88. BIOLOGICAL RHYTHMS - REVIEW OF SOME RECENT DATA (BIOLOGICAL RHYTHMS IN MAN, ANIMALS AND PLANTS).
Reinberg, A.
Revue De Medicine Aeronautique et Spatiale, Vol.7, 1968, 127-130. 59 refs.
*Activity cycles (biology)/Aerospace medicine/Animals/*Circadian rhythms/Conferences/ Environmental engineering/Plants (botany)/*Psychological effects/*Social isolation.

89. CIRCADIAN AND LOW-FREQUENCY RHITHMS IN HUMAN PHYSIOLOGY
Halberg, F., Reinberg, A.
J. Physiol (Paris), Vol.59, No.1. Supply., 1967, 117-200.

90. INTERRELATIONSHIPS BETWEEN BIOLOGICAL RHYTHMS WORK-REST SCHEDULES AND TASK PERFORMANCE.
Weitzman, Elliot, D.
Montefiore Hospital and Medical Center Bronx NY Dept of Neurology, 11.1977.
*Biological rhythms/*Rest/*Work/*Performance (Human)/Test facilities/Test methods/Test equipment/Naval personnel/Psychophysiology/Naval watch.

91. RELATIONSHIP OF THE CIRCADIAN RHYTHMS OF SKIN AND CORE BODY TEMPERATURES UNDER ENTRAINED AND FREE-RUNNING CONDITIONS IN MAN.
Czeisler, C.A., Weitzman, E.D., Moore-Ede, M.C., Krauss, A.L.
Fed. Proc, Vol. 36, No. 3, 816.
*Circadian rhythms/*Skin temperature/*Exercise/*Body temperature/Volunteer.

92. THE RELATIONSHIP OF SLEEP AND SLEEP STAGES TO NEUROENDOCRINE SECRETION AND BIOLOGICAL RHYTHMS IN MAN.
Weitzman, E.D., Boyar, R.M., Kapen, S., Hellman, L.
Recent Prog. Horm. Res. Vol. 31, 1975, 399-446.

93. ACUTE REVERSAL OF THE SLEEP-WAKING CYCLE IN MAN - EFFECT ON SLEEP STAGE PATTERNS (HUMAN SLEEP PATTERN CHANGES DUE TO ACUTE SLEEP-WAKING CYCLE REVERSAL).
Goldmacher, D., Kripke, D.F., McGregor, P., Mogaire, C., Weitzman.
Archives of neurology, Vol. 22, 6.1970, 483-489. 29 refs.
*Circadian rhythms/*Human reactions/Rapid eye movement state/*Sleep/Sleep deprivation/ *Wakefulness.

PART 2. ADDITIONAL REFERENCES

94. SUSTAINED OPERATIONS AND SLEEP DEPRIVATION - EFFECTS ON INDICES OF STRESS
Francesconi, R.P., Stokes, J.W., Banderet, L.E., Kowal, D.M.
Aviation Space, and Environmental Medicine, Vol. 49, 11.1978, 1271-1274. 19 refs.
Urine samples were analysed to evaluate the effects of sleep deprivation and additional stress imposed on two groups of highly trained and motivated military personnel deprived of sleep while sustaining performance of their assigned military tasks under simulated conditions. One group is informed that the sustained operations challenge can persist to 86 hr, while the other is told that the sustained operations scenario will not exceed 42 hr. The results suggest that anticipation and perception of the experimental situation affects the common urinary indices of stress (17 - hydroxycorticosteroids, catecholamines). More importantly, similar effects are noted for sympathicoadrenomedullary and adrenocortical activity. Moreover, the responses are affected by situational uncertainty and apparent cumulative fatigue.

95. DAYTIME STATE AND NIGHT-TIME SLEEP, A SLEEP STUDY AFTER A MARATHON GROUP EXPERIENCE.
Glaubman, H., Hartmann, E.
Percept Mot. Skills, Vol. 46, No.3.1, 6.1978, 711-715.
The nocturnal sleep of 9 subjects was recorded under two conditions following a "normal" weekend and following a weekend in which the subjects participated in a psychodynamic marathon group activity. Differences between the two experimental conditions were found for sleep latency and on one measurement of D-latency. Both latencies were reduced after the marathon group. No differences were found on the remaining 12 measurements. These findings tend to reaffirm the stability of sleep patterns under various pre-sleep conditions.

96. SLEEP, MOOD, AND FATIGUE DURING A 14-DAY He-O2 OPEN-SEA SATURATION DIVE TO 850 fsw WITH EXCURSIONS TO 950 fsw.
Townsend, R.E., Hall, D.A.
Undersea Biomed, Res. Vol. 5, No.2, 6.1978, 109-117.
To obtain information on sleep, mood, and performance of divers and surface support personnel during deep dives in the open sea, 12 divers and 12 surface support personnel were monitored during a 14-day open-sea saturation dive using the U.S. Navy Deep Diving System, Mark 2, Mod 0. Divers lived in the deck decompression chambers at 850 fsw equivalent and made 5 days of excursion wet dives to approximately 950 fsw via the Personnel Transfer Capsule. Electroencephalographic and self-report measures of sleep, and measures of mood, anxiety, and 4-choice reaction time performance were obtained during a predive base-line period and throughout the dive and decompression. Results suggested that, unless personnel are rotated, there are limitations to the practical duration of very deep open-sea saturation dives caused by the accumulation of sleep debt, fatigue, and loss of psychological vigor.

97. SLEEP PATTERNS IN THREE ACUTE COMBAT FATIGUE CASES.
Schlesberg, A., Benjamin, M.
J, Clin. Psychiatry, Vol. 39, No. 6, 6.1978, 546-549.
A preliminary report is presented on the sleep patterns of three combat fatigued patients with recurrent nightmares, insomnia, low frustration thresholds and impotence. All the patients had undergone acute partial sleep deprivation prior to their breakdown. The results show severe deficiency in REM sleep and absence of stage 4 sleep. EMG was usually high with numerous body movements and bursts of tachycardia throughout the night.
Nightmares occurred in stage 2. Total effective sleep time was between 129' and 250'. Most of the sleep was in stage 2, and patients woke up with the feeling that "they had not slept at all". It is hypothesized that acute partial sleep deprivation prior to breakdown was an important predisposing factor, and that chronic partial sleep deprivation was a constant aggravating factor of combat fatigue. Replacement therapy for the specific deficient sleep states is proposed.

98. SLEEP DEPRIVATION AND SUSTAINED OPERATIONS: EFFECTS ON INDICES OF STRESS.
Francesconi, R.P., Stokes, J.W., Banderet, L.E., Kowal, D.M.
Army Research Inst. of Environmental Medicine, Natick Mass, USARIEM-M-22/78, 2.1978. 19 p.
Two groups of highly trained and motivated military personnel were deprived of sleep while sustaining performance of their assigned military tasks in a laboratory simulation, one team (i) was sleep deprived for 42 hours while the second team (ii) was deprived of sleep for two consective 39 h periods separated by a 33 h rest interval. Six-hour urine samples were collected on a 24 h basis after an appropriate control period for each team. During sleep deprivation subjects were required to perform their assigned military tasks on a sustained basis for the duration of the scenario. Results indicated that their anticipation and perception of the experimental situation affected the common urinary indices of stress.

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99. PROBLEMS IN MAINTAINING THE ALERTNESS OF AIR FORCE PERSONNEL. - THE ORGANIZATION OF WORK SCHEDULES DURING LONG-DISTANCE FLIGHTS.
Papin, J.P.
AGARD, Meeting, Scuola Militare di Sanita Aeronautica, Rome, Italy, 24 February 1976.
Riv. Med. Aeronaut. Spaz, Vol. 40, 1977, 153-164.

100. STRESS RESPONSES OF PILOTS FLYING HIGH-PERFORMANCE AIRCRAFT DURING AERIAL COMBAT MANEUVERS.
Burton, R.R., Storm, W.F., Johnson, L.W., Leverett, S.D., Jr.
Aviat. Space Environ. Med., Vol. 48, No. 4, 4.1977, 301-307.
In aerial combat maneuvers (ACMs), at Luke AFB, Az, eight pilots flew their two F-15 aircraft against nine pilots in three F-106 aircraft. A total of nine flights, consisting of 23 ACMs, were accomplished in 5 successive days. The degrees of fatigue, stress, and sympathetic activity were quantified using both subjective analyses and the biochemical constituents in the urine of the pilots of the F-15 or F-106. Biochemical indicators, reported per 100 mg creatinine, included: epinephrine, norepinephrine, 17-OHCS, urea, inorganic phosphate, sodium, potassium, and sodium/potassium ratio. The F-106 pilots exerted more relative effort than did the F-15 pilots--effort which appeared to be associated with high-G experience. Both groups of pilots were equally fatigued following ACMs; however, only the fatigue of the F-106 pilots was directly correlated with the length of the ACM. Sympathetic and stress responses during the ACM--similar for both groups of pilots--showed postflight increases of 54% in epinephrine, 19% in norepinephrine, and 20% in 17-OHCS over preflight values, thus suggesting a moderate stress response. Resting levels of these same indicators, for days the pilots did not fly and for pre-ACM values, were similar but higher than control values previously reported for other stressful activities. By late afternoon, postflight values for these indicators had returned to near-preflight levels.

101. THE FLIGHT FATIGUE.
FATIGA DE VUELO. DATOS NEUROFISIOLOGICOS DE INTERES DIAGNOSTICO.
Herrero Aldama, P.
ARCH. NEUROBIOL. 1977, Vol. 40, No. 3. 197-216
Flight fatigue is regarded as a multicausal syndrome, with a common factor consisting in the attention affectation. It is expected, in this sense, that the new EEG techniques, when approaching the neurophysiologic supports of such an affectation in a deeper way than the traditional electroencephalography, will allow a useful complementary diagnosis. The diagnostic value of a series of proposed tests concerning cardiology, body temperature, ophthalmology, psychology, clinical and biochemical neurology is criticized, all of these being considered of relative usefulness. A series of neurophysiologic data related to the attention and alpha rhythm, monotony of the stimuli, difficulties or lack of sleep shown by conventional EEG or VCN, fatigue due to the rupture of the biologic rhythms when flying westward and vice versa, and the conditions of sleeping, time-table and modalities of the sleeping profile are considered. The individual differences in this respect are evaluated and the possibility of training effects and the various functions are taken into account.

102. INVERSION OF THE SLEEP WAKEFULNESS PATTERN: EFFECTS ON CIRCADIAN VARIATIONS IN PSYCHOPHYSIOLOGICAL ACTIVATION.
Akerstedt, T.
ERGONOMICS, Vol.20, No.5, 1977, 459-474.
Thirty-six habitually dayworking railway repairmen were exposed to a 3 week period of nightwork. The subjects were studied with respect to circadian rhythms in catecholamine excretion, body temperature, subjective alertness and mood. For half the group the measurements covered one 24 h period before nightwork, the first week of night work, the third week of night work, and the first week after return to day work. For the other half measurements were made during the first and third day week after the night work. During day work weeks all variables exhibited pronounced circadian variation, peaking in the early afternoon, with the exception of body temperature which reached its maximum in the evening. During the first week of night work the day-oriented pattern of adrenaline excretion persisted but the mean 24 h level was increased and day sleep levels were very high. By the third week of night work the circadian pattern had flattened out at a very low mean level. For noradrenaline excretion considerable adjustment (comparable to an inversion) to night work was seen with high night values. For body temperature, selfrated alertness and mood circadian functions flattened out during night work. It was concluded that all variables were strongly affected by the exposure to night work and that adrenaline excretion indicated a stress response of the organism. With reference to other studies it was also concluded that adrenaline excretion is not easily phase-shifted through a three week spell on night work, while noradrenaline in contrast appears to adjust very rapidly.

103. SOME EFFECTS OF SLEEP DEPRIVATION ON TRACKING PERFORMANCE IN STATIC AND DYNAMIC ENVIRONMENTS.
Collins, W.E.
J. APPL. PSYCHOL. Vol. 62, No. 5, 1977, 567-573.
The influence of 34 and 55 hr of sleep deprivation on scores derived from manually tracking the localizer needle on an aircraft instrument was assessed under both static (no motion) and dynamic (whole-body angular acceleration) laboratory conditions. In each of 2 experiments, 20 young men, equally divided into control and sleep-deprived groups, were tested in an enclosed rotator, in darkness with the exception of the illuminated tracking display. Significant decrements in dynamic performance were uniformly obtained after 24 hr and more of sleep loss. Static scores were less consistently impaired. Administration of d-amphetamine after 55 hr of sleep loss reduced error for both static and dynamic tracking; although performance at both tasks remained poorer for sleep-deprived subjects, their static tracking scores did not differ significantly from control subjects 2 hr after drug ingestion. The study indicates clear performance impairment for an aviation - related task after a night without sleep. Impairment is generally greater with increasing amounts of sleep loss and is more pervasive in motion environments.

104. STRESS AND SLEEP
Schneider, D.
SCHWEIZ. ARCH. NEUROL. NEUROCHIR. PSYCHIATR, Vol. 121, No. 1, 1977, 47-54.
For this paper, psychophysiological relationships between stress and sleep are considered with reference to clinical psychiatric problems. Answers to the first question - how does sleep affect the tolerance of stress in the waking stage? - are provided by sleep deprivation experiments. The latter show that total sleep deprivation has a great influence on stress. However gradual partial sleep deprivation to a sleep time of 5 hr seems well tolerated by most individuals. In some special cases the author found subjects well adapted to the workaday world who could live with briefer sleeping periods. Because of experimental problems, the second question - how does stress affect sleep? - is more difficult to answer. Anxiety is one of the most important factors deteriorating sleep under conditions of stress. This reduced sleep is in turn stressful for waking behaviour. Thus, the relationship between stress and sleep. 2 factors separated for scientific investigation, is essential and especially important in the problem of insomnia.

105. TIME ZONE CHANGE AND SLEEP
Sasaki, M., Endo, S.
JIKEIKAI MED.J., Vol. 24, No. 2, 1977, 129-143.
This study investigated the effects of time zone changes of sleep. The subjects were 6 male civilian aircraft occupants, aged 24-47 years. After time zone change with geographical time difference of 7 hours (between Tokyo and San Francisco), all night sleep studies were undertaken in San Francisco. The results are summarized as follows: 1) Disturbance in intra-sleep cycle as a whole, though mild. 2) Tendency to easy awakening in the night and to interruptions of sleep. 3) Slight increase in SREM (sleep-rem REM), especially in the first half. 4) Slight decrease in SREM (sleep REM). 5) Tendency to slight delayed REM Sleep latency and shortening and unstability in the duration of REM Sleep in the first half. 6) Tendency to keeping a high level of pulse rate in the first half (observed in two subjects). These changes are considered to need various investigations in the future. It seems first of all that 'disturbance in circadian cycle' may have a bearing on it. It is time zone change which produces various discrepancies between chronobiological and physiological clocks. And the thus resulting disorder of sleep exhibits disturbance in its inherent rhythms, providing us with findings of interest, which are highly suggestive of clinical significant for insomnia.

106. INTERINDIVIDUAL DIFFERENCES IN CIRCADIAN PATTERNS OF CATECHOLAMINE EXCRETION, BODY TEMPERATURE, PERFORMANCE, AND SUBJECTIVE AROUSAL.
Akerstedt, T., Froeberg, J. E.
Biol. Psychol, Vol. 4, No. 4, 12.1976, 277-292.
Interindividual differences in circadian rhythms of urinary catecholamine excretion, performance, self-ratings of arousal and oral temperature were studied in 80 subjects divided into three groups--morning--active, evening-active, and intermediate. Catecholamine excretion, body temperature, and self-ratings of arousal exhibited pronounced circadian variations. Morning-active subjects exceeded other groups in the 24 h level of adrenaline excretion but crest phases did not differ, occurring close to 13.00 h. No differences between groups were found for noradrenaline excretion. Crest phases occurred close to noon. Self-rated alertness exhibited a significantly earlier (14.12 h) crest phase for morning-active than for evening-active subjects (16.09 h). The performance did not differ between groups.

107. PHYSIOLOGICAL INDEX AS AN AID IN DEVELOPING AIRLINE PILOT SCHEDULING PATTERNS.
Mohler, S.R.
Aviat. Space Environ. Med., Vol. 47, No. 3, 3. 1976, 238-247.
A multiplicative and additive formula has been developed for assisting in the development of schedules for airline pilots and flight engineers. The formula is based on freshness/tiredness data derived from aircrews on world flights. It should materially assist those who develop the schedules to avoid, where possible, finalizing those crew patterns that would impose a severe physiologic load on cockpit personnel. The objective of the application of the formula is to assure that crew members retain adequate "physiologic reserve" in the course of flying various segments of a pattern. This enables them to absorb the stresses of schedule delays or disruptions, as well as unforeseen operational problems and flight emergencies.

108. AVIATOR PERFORMANCE BIOCHEMICAL PHYSIOLOGICAL AND PSYCHOLOGICAL ASSESSMENT OF PILOTS DURING EXTENDED HELICOPTER FLIGHT.
Kimball, K. A., Andersom, D. B.
AGARD Conference proceedings, 1976, Vol. 180, 1976, AB-1-AB-15.
Human, Diet, Sleep.

109. EFFECTS OF TEMPORAL STRESSORS ON VIGILANCE AND INFORMATION PROCESSING.
Alluisi, E.A., Coates, G.D., Morgan, B.B, Jr.
Vigilance: theory, operational performance, and physiological correlates. New York, Plenum Press, 1977.

110. EFFECTS OF TIME ZONE CHANGES ON PERFORMANCE AND PHYSIOLOGY OF AIRLINE PERSONNEL.
Preston, F.S., Bateman, S.C., Meichen, F.W., Wilkinson, R., Short, R.V.
Aviation Space and Environmental Medicine, Vol. 47, No. 7, 1976. 763-769.
Human/Menstrual/Cycle/Nopipreazole/Hydro/Chloride/Cent-Depress-Drug.

111. FATIGUE, CIRCADIAN RHYTHM, AND TRUCK ACCIDENTS.
Harris, W.
Vigilance: theory, operational performance, and physiological correlates. New York, Plenum Press, 1977.

112. IMPROVEMENT OF ALERTNESS IN SAILORS DURING NIGHT WATCHES BY MEANS OF FOOD AND DRINKING REGIMENS, INCLUDING BIOLOGICALLY ACTIVE CONCENTRATES.
Mitkova, M.
BULL. INST. MARIT.TROP. MED. GDYNIA, Vol. 27, No. 1, 1976. 17-24.
It is stated that by food and drinking intervention (including biologically active food and drinking concentrates) we are able to help the sailor's body to a certain extent, to adapt itself to work under especially aggravated occupational conditions. This is extremely important for the peak moments of strain, esp. during night watches. This fact must not be underestimated in the complex of measures in fatigue prophylaxis, in the improvement of alertness to maximal working capacity with a view to ensure safe ship voyages.

113. PSYCHOMOTOR TEST PERFORMANCE AND SLEEP PATTERNS OF AIRCREW FLYING TRANSMERIDIONAL ROUTES
Buck, L.
AVIAT. SPACE ENVIRON. MED., Vol. 47, No. 9, 1976, 979-986.
Pilots and flight attendants flying scheduled services between Vancouver and Tokyo and between Toronto and Rome were tested on a tracking task before and after flights in each direction. Flights were included in schedules involving both 24 h and 7 d layovers at the overseas station. During these periods, they recorded their sleep patterns. The data showed that, following flight, subjects made an immediate attempt to adapt their behaviour to local time and the changes in their performance scores could be interpreted on that basis. It was concluded that behavioural circadian rhythms adapt rapidly to a new time zone.

114. SLEEP DISTURBANCES OF COCKPIT PERSONNEL AFTER TRANSMERIDIAN LONG DISTANCE FLIGHTS.
Schaffler, K., Renemann, H.H.
MED.KLIN., Vol. 71, No. 46, 1976, 1985-1995.
Functional complaints of flying personnel that are attributable to sleep disturbances or that promote the latter are less the result of the sum of sleep deficiency, and more the consequence of an imbalance of the distribution of the 1 to 4 stages of sleep (orthodox sleep) and of dream sleep (paradoxical sleep, REM sleep). The lack of the latter is a particular indicator of sleep disorders. Taking sleeping tablets (especially barbiturates) and alcohol greatly disturbs the balanced distribution of sleep stages and the hoped for effect of refreshing sleep is disappointed. But short periods of sleep of about 6 hours can lead to adequate regeneration via optimal distribution of the states of sleep. By optimizing sleep the shifting of the phases and the attenuations of the amplitude of the physiological oscillations can be suppressed. The demonstration of an endocellular sleep mechanism under pacemaker control shows the existence of a close bond of the many periodic oscillation processes of the human body with exogenous influences (time oscillators). The quality of sleep can be improved by the effects of self s . dy, the personal way of life and by learning autogenous training. Counterbalancing of the sleep deficit is difficult, as sleep of longer duration does not help with the distribution of the stages and the recuperative value that is bound up with it.

115. VIGILANCE. THEORY, OPERATIONAL PERFORMANCE, AND PHYSIOLOGICAL CORRELATES. INTRODUCTION. BACKGROUND OF THE SYMPOSIUM.
Mackie, R.R.
Vigilance: theory, operational performance, and physiological correlates. New York, Plenum Press, 1977.

116. WAKEFULNESS SLEEP RHYTHM AND MODE OF LIFE.
Benoit, O.
REV. PRAT. Vol. 26, No. 27, 1976, 1945-1954.
Wakefulness and sleep follow a 24 hour rhythm. Environment (activity, social life) is the main synchronizing factor. Level of wakefulness, psychomotor performance and mood vary periodically and in a foreseeable manner with time of day. Sleep follows certain structural laws in its course but its duration and pattern depend somewhat on time. There are many interrelationships between wakefulness and sleep. Duration and quality of sleep, and the nuisances which act on it also influence the wakefulness function. Conversely wakefulness level, conditions of diurnal activity stress and anxiety influence sleep. Disturbances in sleep wakefulness cycle are provoked by professional constraints (night work, work in shifts, etc). They vary with each person but in certain cases may prevent any adaptation to anything but diurnal work.

117. PREDICTION OF PILOT PERFORMANCE: BIOCHEMICAL AND SLEEP-MOOD CORRELATES UNDER HIGH WORKLOAD CONDITIONS --- DURING AIRCRAFT CARRIER LANDINGS.
Brictson, C.A., McHugh, W.B., Naitoh, P.
AGARD, Simulation and Study of High Workload Operations. 10pp
Aircraft carriers/*Aircraft landing/Flight stress (biology)/*Performance prediction/ *Pilot performance/*Psychophysiology/Sleep/Statistical analysis/Stress (psychology)/ Work capacity.

118. CIRCADIAN RHYTHMS OF CATECHOLAMINE EXCRETION, SHOOTING RANGE PERFORMANCE AND SELF RATINGS OF FATIGUE DURING SLEEP DEPRIVATION.
Froeberg, J.E., Karlsson, C.G., Levi, L., Lidberg, L.
BIOL.PSYCHOL., 1975, Vol. 2, No. 3, 175-188.
Circadian rhythms in urinary catecholamine excretion, performance and self ratings were studied in 2 experiments with a total of 29 subjects who were deprived of sleep for 72 hr. Adrenaline excretion and fatigue ratings showed the most consistent circadian variations; noradrenaline and performance rhythms were more irregular. The average crest phase for adrenaline excretion was around 1400 hr, for noradrenaline about 0800 hr, for performance 1700 hr and for fatigue 0500 hr. 24 hr levels of performance and 'subjective arousal' decreased over the 3 days of sleep deprivation, while adrenaline excretion levels increased.

119. PSYCHOBIOLOGICAL CIRCADIAN RHYTHMS DURING A 72 HOUR VIGIL.
Froeberg, J.E., Karlsson, C.G., Levi, L., Lidberg, L.
FORSVARSMEDICINE, Vol. 11, No. 3, 1975, 192-201.
Circadian rhythms in urinary catecholamine excretion, oral temperature, performance, and subjective arousal (self ratings of alertness and fatigue) were studied in 32 subjects deprived of sleep for 72 hours. Adrenaline excretion, oral temperature, and subjective arousal showed consistent circadian variations. Performance rhythms were also apparent, although more irregular, in some of the measures. Noradrenaline excretion had no significant circadian rhythm. The crest phase for adrenaline excretion was between about 1200 and 1500 hours, for subjective arousal and performance about 1600-1700 hours, and for oral temperature about 1700-2300 hours. There were significant correlations between oral temperature, performance, and subjective arousal.

120. RESEARCH NOTE: THE INTERACTIONS AMONG STRESS, VIGILANCE, AND TASK COMPLEXITY.
Kennedy, R.S., Coulter, X.B.
HUM. FACT., Vol. 17, No. 1, 1975, 106-109.
A simple (one channel) or a complex (three channel) vigilance task was administered with or without threat of shock to a large group of flight students. It was found that a larger absolute decrement was obtained in the complex task, but the relative decrements were equivalent for both. One channel monitoring was better overall than three channel monitoring in the nonstressed condition. Stressed subjects performed better than nonstressed, and this enhancement was greater for three channel monitoring.

121. VARIATIONS OF SOME PARAMETERS OF THE OCULAR SYSTEM IN RELATION TO FATIGUE DURING LONG TRANSMERIDIAN FLIGHTS.
Boissin, J.P., Abbas, L.
REV. MED. AERONAUT. SPAT., Vol. 14, No. 54, 1975, 65-67.
*Aviation/*Vision/*Fatigue/*Intraocular pressure/*Circadian rhythm.

122. SUSTAINED PERFORMANCE AND RECOVERY DURING CONTINUOUS OPERATIONS
Morgan, Ben. B.,Jr., Coates, Glynn,D.
Old Dominion Univ Norfolk Va Performance Assessment Lab. ITR-74-2, 12.1974. 47 pp
The two sections of the report represent the reproduction of papers presented at the 82nd annual meeting of the American Psychological Association. New Orleans, Louisiana, 30 August - 3 September 1974 and the 18th annual meeting of the Human Factors Society, Huntsville, Alabama 15-17 October 1974. Both papers are based on studies of continuous work and recovery conducted at the Performance Research Laboratory, University of Louisville, Louisville, Kentucky. Results summarized herein suggest that performance decrements during 36 hr of continuous work and sleep loss will vary between 11 and 35% depending upon the time of day at which the continuous-work session begins. It is also suggested that appropriately scheduled military personnel will be able to maintain acceptable levels of performance during 36 hr of continuous field operations and that these personnel will require 6 to 8 hrs of sleep before they are ready to return to duty.

123. INFLUENCE OF CHANGING TIME ZONES ON AIR CREWS AND PASSENGERS.
McFarland, R.A.
Aerospace Medicine. Vol. 45, 6.1974. 648-658. 30 refs.
Age factor/Airline operations/Biochemistry/*Circadian Rhythms/*Flight crews/Flight fitness/*Flight stress (biology)/In-flight monitoring/*Passengers/Physiological effects/Sleep/Stress (physiology)/Time dependence.

124. SIGNAL DETECTION EFFICIENCY IN THE MORNING WATCH. EFFECTS OF PRIOR SLEEP, DIURNAL RHYTHM AND FATIGUE. Colquhoun, W.P., Hamilton, P., Edwards, R.S.
Royal Naval Personnel Research Committee London, OES-10/74, 5.1974, 33p.
An experiment was carried out to determine whether staying awake before the morning (0400-0800) watch (a custom observed in submariners on prolonged patrols) is likely to exert a detrimental effect on operations such as sonar monitoring carried out continuously throughout the watch. Even when sleep had been taken, general performance levels in the morning watch were markedly different from those in a watch held from 2000 to 2400 the previous evening. Detection rate was substantially lower throughout the watch, and the degradation during the second half of the watch at times exceeded 50 per cent when compared to 'fresh' performance at the start of the previous evening watch.

125. CIRCADIAN VARIATION IN PRESUMABLY HEALTHY YOUNG SOLDIERS
Kanabrocki, E.L., Scheving, L.E., Halberg, F., Brewer, R.L., Bird, T.J.
Arkansas Medical Center, Little Rock, and Minnesota School of Medicine, Minneapolis, 2.1974. 64 pp.
A group of thirteen young soldiers was standardized for approximately thirty hours with rest time. Each man was sampled at three-hour intervals throughout one 24-hour period; this involved the measurement of oral temperature, radial pulse, blood pressure, intraocular pressure and minute ventilation. One year later another study was performed similarly on twelve men over a 72-hour period. A great majority of the many variables analyzed demonstrated a significant fit to a 24-hour cosine curve. From this same analysis, one was able to estimate three rhythmic parameters and their confidence limits; these included the acrophase (crest of best-fitting cosine), the amplitude and the mesor (computer-determined over-all mean). The significance of these data is discussed.

126. EFFECTS ON SUSTAINED PERFORMANCE OF 48 HOURS OF CONTINUOUS WORK AND SLEEP LOSS.
Morgan, B.B.,Jr., Brown, B.R., Alluisi, E.A.
HUM. FACT. Vol. 16, No. 4. 1974, 406-414
The work efficiency of 10 subjects during a 48 hour period of continuous work, and sleep loss was assessed using the synthetic work technique. Performance during the period of stress was found to be significantly influenced by the circadian rhythm. Decrements first occurred after approximately 18 hr of continuous work, and performance decreased to an average of 82% of baseline during the early morning hours of the first night. Performance improved to about 90% of baseline during the daytime of the second day but decreased to approximately 67% during that night. All measures of performance recovered to baseline levels following a 24 hr period of rest and recovery.

127. TWENTY-FOUR-HOUR RHYTHMS OF RECTAL TEMPERATURE IN HUMANS: EFFECTS OF SLEEP-INTERRUPTIONS AND OF TEST-SESSIONS.
Aschoff, J, Fatranska, M, Gerecke, U, Giedke, H.
Pfluegers Arch, Vol. 346, No. 3, 1974, 215-222.

128. 12 AND 24 H RHYTHM IN ERROR FREQUENCY OF LOCOMOTIVE DRIVERS AND THE INFLUENCE OF TIREDNESS.
Hildebrandt, G, Rohmert, M, Rutenfranz, J.
Int. J, Chronobiol., Vol. 2, No. 2, 1974, 175-180.

129. ULTRADIAN RHYTHMS IN EXTENDED PERFORMANCE.
Orr, W.C, Hoffman, H.J, Hegge, F.W.
Aerospace Medicine, Vol. 45, No. 9, 1974, 995-1000.
Eleven healthy young, male volunteers participated in an experiment which involved continuous monitoring of heart rate and performance on a complex vigilance task. Subjects were instructed to continue in the experiment for 48 hr or until they felt they could go no longer. All subjects completed at least 21 hr and 2 went for 44 hr. Heart rate and behavioral measures were subjected to complex demodulation analysis to determine the phase and amplitude characteristics of cyclic activity with a period in the range of 90 min + or - 5 min. The primary findings were a rather marked increase in the amplitude of the 90 min rhythm, in both heart rate and performance measures, as the time on task increased, reaching their highest level near the end of the run. This response pattern was found in over three fourths of the analyses done, and was independent of the total duration of the experiment. It is felt that this marked amplitude rise is indicative of a cumulative stress response. In most subjects, the heart rate response did appear to show some similarity of patterning with at least one of the behavioral measures. Only 5 subjects showed an obvious dissociation between heart rate and the behavioral responses. There was, however, greater concordance of response patterning among the behavioral measures.

130. INTERINDIVIDUAL DIFFERENCES IN CIRCADIAN FATIGUE PATTERNS OF SHIFT WORKERS.
Ostberg, O.
Br. J, Ind, Med, Vol. 30, No. 4, 10.1973, 341-351.

131. STRESS, ADRENOCORTICAL ACTIVITY AND SLEEP HABITS.
Goodyear, M.D.
Ergonomics, Vol. 16, No. 5, 9.1973, 679-681.

132. THE EFFECTS OF NOISE AND OF LOSS OF SLEEP UPON THE OBSERVATIONS OF 3 SOURCES OF SIGNALS WITH UNEQUAL PROBABILITIES
Robert, G, Hockey, J.
Royal Naval Personnel Research Committee, London, OES-11/74, 10.1973, 16 pp DRIC-BR-51849.
Three groups of 12 naval ratings had to monitor 3 sources of signals, and to report each time they detected a signal. A source was checked by pressing the corresponding key and looking for a dull red flash. One group worked with and without noise. The other group worked after a night without sleep and after normal sleep. Noise has a beneficial effect in making the man concentrate more on the most probable source of signals. But noise has a detrimental effect in increasing the number of misses in the second half of the experimental period. Whereas loss of a night's sleep has only detrimental effects. It stops the man from concentrating more on the most probable source of signals. And it makes him require more evidence before he reports a signal.

133. PERFORMANCE, RECOVERY AND MAN-MACHINE EFFECTIVENESS
Dodek, Richard, A.
Texas Tech Univ Lubbock Center of Biotechnology and Human Performance. Semi-annual progress rep 3.1973. 22 pp.
The project is concerned with the assessment of human performance and recovery capabilities under relatively long duration conditions (two hours or more). Varying work/rest schedules and environments are among the variables manipulated, and the results relate to the doctrine of continuous operations. During this reporting period, a report was prepared describing the results of a study of 8 and 16 hours of continuous work; experiments were continued to ascertain the effects of methyl scoppolmine on (animal) response decrements; a report was begun on the relation between circadian rhythms and performance on a physical loading task; and research continued on heat stress limits for sedentary operations. Three papers were presented at meetings, three published, three accepted for publication, and four were submitted. This progress report contains a list of 27 topics of potential military relevance derived from the studies conducted from 1968 to the present.

134. EFFECTS OF SLEEP LOSS AND STRESS UPON RADAR WATCHING
Bergstroem, B., Gillberg, M., Arnberg, P.
J. APPL. PSYCHOL., Vol. 58, No. 2, 1973, 158-162.
Detection performance in a 40 min radar watching task was studied using 20 soldiers, divided into 2 matched groups. The experimental group was deprived of sleep for 78 hr and both groups were then subjected to stress induced by unpleasant electric shocks. It was hypothesized that the effects of sleep loss and stress oppose each other through dearousing and overarousing, respectively. Results indicated significant impairment of performance when subjects were deprived of sleep, but they indicated an improvement under stress. Changes were accompanied by small but reliable heart rate reduction and elevation respectively, thus lending support to the hypothesis.

135. A THEORY OF FATIGUE.
Cameron, C.
Ergonomics Vol. 16, No. 5, 1973, 633-648.
Human/Sleep/Habits/Stress/Anxiety.

136. SPECIFICATION OF VARIATION PATTERNS OF PHYSIOLOGICAL AND PERFORMANCE MEASUREMENTS IN SLEEP LOSS.
Saito, Y.
J. Hum. Ergol., Vol. 1, No. 2, 12.1972, 207-216.

137. SUBMARINE CREW EFFECTIVENESS DURING SUBMERGED MISSIONS OF SIXTY OR MORE DAYS DURATION. (EFFECTS OF CONFINED SUBMARINE ENVIRONMENTS ON CREW PERFORMANCE AND BIOLOGICAL PROCESSES DURING PROLONGED SUBMERGENCE).
Weybrew, B.B.
Naval Submarine Medical Center, Groton, Conn, NSMRL-686-281071, 11.1972. 29 pp.
Circadian rhythms/*Controlled atmospheres/*Human performance/*Long term effects/Morale/*Physiological responses/Sleep deprivation/Stress (psychology/*Submarines.

138. FATIGUE IN SUSTAINED TACTICAL OPERATIONS.
Petersen, Peter B.
Army Combat Developments Command Medical Service Agency Fort Sam Houston Tex, Doctoral thesis, 6.1972. 170 p.
Concepts for future U.S. tactical operations envision man's capabilities as encompassing rapid acclimation, fatigue reduction, changed wake-sleep cycles, and changes to the circadian cycle under sustained and continuous operational requirements. U.S. forces must be able to deal with an enemy who may have these capabilities. The study focuses on concepts for the reduction of fatigue in its various stages in sustained tactical operations, techniques of leadership, and on measures to prevent fatigue.

139. HUMAN FACTORS IN LONG-DISTANCE FLIGHTS.
Mohler, S.R., Cierebiej, A.
Ind. Med. Surg, Vol. 41, No. 6, 6.1972, 11-17.

140. EFFECTS OF 72-HOUR PARTIAL SLEEP DEPRIVATION HUMAN BEHAVIORAL AND PHYSIOLOGICAL RESPONSE MEASURES/FINAL REPORT/(EFFECTS OF PARTIAL SLEEP DEPRIVATION ON BASIC BIOLOGICAL RHYTHMS USED FOR DETERMINING PERFORMANCE OF SIGNAL DETECTION TASKS).
Frazier, T.W., Benignus, V.A., Every, M.G., Parker, J.F., Jr.
Walter Reed Army Inst. of Res. 50 pp
*Circadian rhythms/Fourier analysis/*Human performance/*Signal detection/*Sleep deprivation/ Spectrum analysis/Stress (physiology).

141. ENCEPHALOGRAPHIC INVESTIGATIONS OF HUMAN ADAPTATION TO A CHANGED DIURNAL CYCLE (ADAPTATION PERIOD TO INVERTED WORK-REST CYCLE OBSERVED WITH ENCEPHALOGRAPH, NOTING EFFECT OF BRAIN BIOELECTRIC ACTIVITY CIRCADIAN RHYTHMS STABILITY).
Chernikova, V.P.
Kosmicheskaia Biologiia i Meditsina, Vol. 6, 1972. 38-42. 5 refs.
*Activity (biology)/Activity cycles (biology)/Adaptation/*Bioelectricity/*Brain/*Circadian rhythms/*Electroencephalography/Relative biological effectiveness (RBE)/Sleep/Stress (biology)/ Synchronism/Wakefulness/*Work-rest cycle.

142. BIOLOGICAL RHYTHMS IN AEROSPACE MEDICINE.
Lomonaco, T.
Minerva Med., Vol. 63, No. 7, 1972, 430-435.

143. THE EFFECT OF SLEEP LOSS AND THREAT-INDUCED STRESS UPON TRACKING.
Bergstroem, B.
Scand, J. Psychol, Vol. 13, No. 1, 1972, 54-60.

144. PHYSIOLOGICAL CHANGES DURING OPERATIONAL FLIGHTS OF LONG DURATION.
Auffret, R.
AGARD Conference Proceedings, Vol. 101, 1972, 9-1-9-12.
Human/Stress/Heart/Rate.

145. A STUDY OF RECOVERY FUNCTIONS IN MAN.
Harris, William, O'Hanlon, James F.
Human Factors Research Inc, Goleta, Calif, (402185) Technical Memo. 4.1972. 89 pp.
Concepts of sustained and continuous military operations were examined with respect to relevant literature. In particular, the objectives were to predict behavioral and biological impairments which might result in those operations; and to determine whether the period necessary for recovery following a sustained operation can be ascertained from the literature. It was concluded that those objectives could not be met due to inadequate information. Nonetheless, the literature did provide data which suggest that certain severe impairments may be experienced by soldiers engaging in sustained and continuous operations. It also provided guidelines for the design of studies to collect the required information. Finally, this review led to a call for serious reevaluation of the current concepts of continuous operations.

146. THE EFFECTS OF A 48-HOUR PERIOD OF SUSTAINED FIELD ACTIVITY ON TANK CREW PERFORMANCE.
Ainsworth, L.L., Bishop, H.P.
Human Resources Research Organization Alexandria Va, HUMRRO-TR-71-16, 7.1971. 111 pp.
A 48-hour field experiment was conducted to determine the effects of sustained activity on the performance of tank crews in communication, driving, surveillance, gunnery, and maintenance activities. Moving surveillance and some driving activities showed statistically significant performance deterioration over a 48-hour period of work without sleep. The experiment showed that the diurnal rhythm of the subjects did not affect performance significantly. The results of the experiment support a broad conclusion that tank crews using present equipment can maintain operational proficiency during 48 hours of sustained activity.

147. SIMULATED TIME-ZONE SHIFTS AND PERFORMANCE ABILITY - BEHAVIORAL, ELECTROENCEPHALOGRAPHIC AND ENDOCRINE EFFECTS OF TRANSIENT ALTERATIONS IN ENVIRONMENTAL PHASE (MENTAL CALCULATING ABILITY, MOTOR COORDINATION, AND AUDITORY PERCEPTUAL ACUITY OF HUMAN SUBJECT DURING LONG DURATION FLIGHT SIMULATION).
Berkhout, J.
AGARD, rest and activity cycles for the maintenance of efficiency of personnel concerned with military flight operations, 11.1970. 1 pp
Circadian rhythms/Human factors engineering/*Human performance/*Human reactions/*Stress (physiology)/Work-rest cycle.

148. FATIGUE AND STRESS IN AIR TRAFFIC CONTROLLERS.
Grandjean, E.P., Wotzka, G., Schaad, R., Gilgen, A.
Ergonomics, Vol. 14, No. 1, 1.1971. 159-165.

149. CIRCADIAN VARIATIONS IN RENAL EXCRETION OF MAGNESIUM, CALCIUM, AND PHOSPHORUS DURING A 3-DAY FLIGHT --- ONBOARD C-5 AIRCRAFT.
Giannetta, C.L., Jayanthinathan, V.S.
School of Aerospace Medicine, Brooks AFB, Tex. SAM-TR-74-38. 11 pp.
C-5 Aircraft/Calcium/*Circadian rhythms/Flight crews/Magnesium/Metabolism/Minerals/ Phosphorus/*Renal function /Stress (physiology)/Urine.

150. EFFECT OF TIME ZONE CHANGES ON THE SLEEP PATTERNS OF BOAC/B. 707 CREWS ON WORLD-WIDE SCHEDULES
Preston, F.S. Bateman, S.C.
Aerospace Medicine, Vol. 41, No. 12, 12.1970, 1409-1415.

151. CHANGES IN ATTENTION ALLOCATION IN A MULTICOMPONENT TASK UNDER LOSS OF SLEEP
[illegible]key, G.R.
Br. J. Psychol, Vol. 61, No. 4, 11.1970, 473-480

152. REST AND ACTIVITY CYCLES FOR THE MAINTENANCE OF EFFICIENCY OF PERSONNEL CONCERNED WITH MILITARY FLIGHT OPERATIONS (REST AND ACTIVITY CYCLES FOR MAINTAINING EFFICIENCY OF MILITARY FLIGHT OPERATIONS PERSONNEL).
AGARD, CP-74-70, 11.1970. 110 pp.
*Fatigue (biology)/Flight fatigue/*Human factors engineering/Human reactions/Human tolerances/*Operator performance/Sleep/Sleep deprivation/*Work-rest cycle.

153. TECHNICAL EVALUATION REPORT ON AGARD AEROSPACE MEDICAL PANEL SPECIALIST MEETING ON REST AND ACTIVITY CYCLES FOR THE MAINTENANCE OF EFFICIENCY OF PERSONNEL CONCERNED WITH MILITARY FLIGHT OPERATIONS
Benson, A.J.
AGARD, Conference Proceedings No. 74, 11.1970. 7 pp.
Three main categories of work and rest schedules of flying personnel and ground based personnel concerned with flight operations are discussed: (a) laboratory investigations of physiological variables and task performance during normal and abnormal work-rest schedules. (b) in-flight studies of aircrew operating long-haul transport aircraft, and (c) duty cycles in Air Traffic Control Tasks.

154. INFLUENCE OF WORK-REST SCHEDULING AND SLEEP LOSS ON SUSTAINED PERFORMANCE. (WORK-REST SCHEDULING AND SLEEP LOSS EFFECT ON OPERATOR PERFORMANCE IN WATCHKEEPING AND ACTIVE MULTIPLE VISUAL TASKS)
Alluisi, E.A.
Aspects of human efficiency: Diurnal rhythm and loss of sleep: Proceedings of the Symposium, Strasbourg, France, 12-17 July 1970. London, English Universities Press,Ltd.,1972. 199-2141.13 refs
Circadian rhythms/Conferences/Human behaviour/Memory/Mental performance/*Operator performance/Sensory perception/*Sleep deprivation/Stress (physiology)/*Task complexity/*Visual tasks/*Work-rest cycle.

155. LOSS OF SLEEP AND COMBAT EFFICIENCY - EFFECTS OF THE WORK/REST CYCLE. (SLEEP LOSS AND WORK-REST CYCLE EFFECTS ON COMBAT EFFICIENCY, CONSIDERING PSYCHOMOTOR REACTIVITY, VIGILANCE AND DECISION MAKING CAPACITY).
Gaille, E.J.P.,Quideau, A.M.C.,Girard, J.F.J.,Grubar, J.C.,Monteil, A.C.
Aspects of human efficiency: Diurnal rhythm and loss of sleep; Proceedings of the Symposium Strasbourg, France, 12-17 July 1970. English,Universities Press,Ltd., 1972. [illegible] refs
Alertness/*Combat/Conferences/*Decision making/*Human performance/Human reactions/Human tolerances/Military psychology/*Psychomotor performance/*Sleep deprivation/*Work-rest cycle.

156. TIME ZONE DISRUPTION AND SLEEP PATTERNS IN PILOTS
Preston, F.S.
Trans, Soc, Occup, Med, Vol. 20, No. 3, 7.1970, 77-86.

157. PSYCHOLOGICAL FACTORS IN THE AIR TRANSPORTATION OF TROOPS.
Pozner, H.
Proc. R. Soc. Med, Vol. [illegible], No. 6, 6.1970, 572-574.

158. THE EFFECTS OF STRESS FATIGUE ON PERFORMANCE IN A SIMULATED DRIVING SITUATION
Heimstra N. W.
Ergonomics, Vol. 13, No.2, 3.1970, 209-218.

159. HUMRRO STUDIES IN CONTINUOUS OPERATIONS
Haggard, Donald F.
Human Resources Research Organization, Alexandria, Va., HUMRRO Professional Paper-7-70, 3.1970. 15 pp.
A laboratory study and a field study were conducted to obtain data on performance decrements on tank crew tasks during 48 hours of continuous combat operations, and to examine the degree of decrement in terms of its effect on tactical efficiency. Experience in the studies illustrates the need for increased efficiency in obtaining human factors information, demanded by the increasing complexity of military tactics and equipment.

160. SLEEP LOSS AND CEREBRAL EXCITABILITY.
Owen, M, Bliss, E.
Am. J, Physiol, Vol. 218, No. 1, 1.1970, 171-173.

161. PSYCHOLOGICAL, PSYCHOPHYSIOLOGICAL, AND BIOCHEMICAL CORRELATES OF PROLONGED SLEEP DEPRIVATION
Kollar, E.J.,Pasnau, R.O.,Rubin, R.T.,Naitoh, P, Slater, G.G.,Kales, A.
Am. J. Psychiatry, Vol. 126, No. 4, 10.1969, 488-497.

162. TIME-ZONE EFFECTS ON THE LONG DISTANCE AIR TRAVELER (EFFECTS OF RAPIDLY CROSSING NUMEROUS TIME ZONES ON BIOLOGICAL RHYTHMS OF LONG DISTANCE AIR TRAVELER).
Gerathewohl, S.J., Siegel, P.V.
Federal Aviation Administration, Washington, D.C. FAA-AM-69-17, 9.1969. 13 pp.
*Air transportation/*Biological effects/*Circadian rhythms/*Flight fatigue/Jet aircraft/Stress (psychology).

163. BIOLOGICAL RHYTHMS (CIRCADIAN RHYTHM PROBLEMS IN MILITARY TROOP TRANSPORT AND AEROSPACE MEDICINE).
Kratochvil, C.H.
AGARD, Aeromedical aspects of troop transport and combat readiness, 10.1968.
Activity cycles (biology)/*Aerospace medicine/Air transportation/*Armed forces/Bibliographies/*Circadian rhythms/Conferences/*Military technology/Physiological responses/Stress (physiology).

164. TROOP TRANSPORT OPERATIONS (AEROMEDICAL ASPECTS OF STRATEGIC AND TACTICAL OPERATIONAL CONDITIONS FOR MILITARY TROOP TRANSPORT).
Dhenin, G.H.
AGARD, Aeromedical aspects of troop transport and combat readiness, 10.1968.
Acclimatization/*Aerospace medicine/*Air transportation/Altitude sickness/*Armed forces/Carbon monoxide/Circadian rhythms/Conferences/Flight fatigue/Freighters/Great Britain/Heat Tolerance/Helicopters/*Military technology/Passenger aircraft.

165. THE TIME ZONE AND CIRCADIAN RHYTHMS IN RELATION TO AIRCRAFT OCCUPANTS TAKING LONG-DISTANCE FLIGHTS.
Mohler, S.R., Dille, J.R., Gibbons, H.L.
Am. J. Public Health, Vol. 58, No.8, 8.1968, 1404-1409.

166. EFFECTS OF LIMITED SLEEP DEPRIVATION ON PERFORMANCE OF SELECTED MOTOR TASKS.
Holland, G.J.
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167. SUBJECTIVE AND OBJECTIVE REACTIONS TO DISTURBANCES OF CIRCADIAN RHYTHM FOLLOWING LONG-DISTANCE FLIGHTS FROM EAST TO WEST AND VICE VERSA.
Lavernhe, J., Bellanger, G., Peteghem, J Van.
Presse Med, Vol. 76, No. 7, 2.1968, 347-348.

168. CIRCADIAN RHYTHMS AND MILITARY MAN (CIRCADIAN RHYTHMS AND MILITARY MAN - PERFORMANCE DECREMENT OF COMBAT TROOPS INDUCED BY HIGH SPEED FLIGHT THROUGH MULTIPLE TIME ZONES).
Kratochvil, C.H.
AGARD, Behavioural Problems in Aerospace Medicine, 10.1967, 10 pp.
*Armed forces (United States)/Bibliographies/Body temperature/*Circadian rhythms/*Combat/Conferences/Dreams/Drugs/Excretion/*Flight/*High speed/*Human performance/Physiological responses/Rapid eye movement state/Sleep/Supersonic flight/Supersonic transports.

169. INFLUENCE OF SLEEP DEPRIVATION AND WORK ON PERFORMANCE IN VIGILANCE TESTS.
De Renzi, E., Faglioni, P.
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Schreuder, O.B.
Aerospace Medicine, Vol. 37, No. 4, Suppl, 4.1966, 1-44.

172. EXPERIMENTAL STUDIES OF THE FUNCTION OF CONCENTRATION MAINTENANCE 3. INFLUENCES ON THE DEPRIVATION OF SLEEP.
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This Lecture Series No.105 on the subject of Sleep, Wakefulness and Circadian Rhythms is sponsored by the Aerospace Medical Panel of AGARD and implemented by the Consultant and Exchange Programme.

The Lecture Series is intended for those concerned with the management of civil, and particularly military personnel, who have to cope with irregular work and rest. It will provide an understanding of the physiological processes involved in the adaptation of man to disturbed sleep and wakefulness, and consider approaches to the problem of management including the use of drugs.

The lectures will fall into three subject categories: Sleep, wakefulness and circadian rhythms. Physiological and psychological aspects - Adaptation of man to disturbed sleep and circadian rhythmicity Management of irregular rest and activity.

In the first part attention will be given to the physiological basis of sleep, wakefulness and circadian rhythms and the psychological correlates including performance relevant to personnel involved in skilled activity. The second part will review studies on the adaptation of man to unusual patterns of rest and activity with special reference to present day situations, and the third part will attempt to provide a basis for the management of disturbed rest and the rationality for the use of drugs.

The series is designed for a wide range of interests in both the civil and military context, and for the land, sea and air environments. It is intended that the participants will include managers and operations staff as well as medical officers.

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