OTS: 60-11,895

JPRS: 2989

18 July 1960

ADAPTATION-DEFENSE MECHANISMS OF THE BODY

- USSR -

by P. F. Zdrodovskiy

Distributed by:

OFFICE OF TECHNICAL SERVICES
U. S. DEPARTMENT OF COMMERCE
WASHINGTON 25, D. C.

Price: $0.50

U. S. JOINT PUBLICATIONS RESEARCH SERVICE
205 EAST 42nd STREET, SUITE 300
NEW YORK 17, N. Y.

JPRS: 2989

CSO: 3892-N

ADAPTATION-DEFENSE MECHANISMS OF THE BODY

/Following is a translation of an article written by Prof. P. F. Zdrodovskiy, Active Member of the Academy of Medical Sciences USSR, in Vestnik Akademii Meditsinskikh Nauk SSSR (Herald of the Academy of Medical Sciences USSR), Vol. 15, No. 2, Moscow, 1960, pages 3-14./

Institute of Epidemiology and Microbiology imeni Gamaleya
AMS USSR

During the second half of the 19th century the eminent French physiologist Claude Bernard formulated his famous thesis that the most characteristic trait of all living creatures is their ability to preserve the constancy of their internal medium (milieu interieur) independent of external environmental changes. When the regulatory mechanisms which control the constancy of the internal medium are impaired for some reason or other, a disease emerges which ends in the death of the organism if the impaired equilibrium has not been restored.

Thus a disease originates, and when this occurs, as even Hippocrates indicated, the pathological process as a whole includes not only the disease per se, i. e., the injury to the organism, but also the fight to re-establish normal conditions.

To designate the force behind the propensity of the organism to ensure the constancy of its internal medium and its regulation, the American physiologist Cannon introduced a special term, "homeostasis." Thus, using modern terminology, a disease in its broader sense can be defined as a state of an organism with impaired homeostasis and with simultaneous mobilization of the means for restoring the normal internal medium.

It is clear from the above that in the study of diseases, together with problems of etiology, i. e., the causes of impaired homeostasis and internal medium, the study of mechanisms controlling the state of the internal medium and ensuring its restoration when impaired is particularly import-

ant. Hence, one can assume a priori that the homeostatic functions of the organism must be based on certain mechanisms of a stereotype character corresponding to its physiological structure.

Obviously, these general considerations are also fully related to infectious diseases which represent only a particular category of phenomena in the pathology of an organism. Hence, infectious forms of pathology, in spite of their inherent specificity, must also obey certain stereotype rules concerning homeostasis and, at any rate, cannot be considered independently.

What, then, are these stereotype mechanisms of homeostasis which ensure the regulation of the internal medium in norm and restore it in pathology?

One of the concepts offering a particularly promising means of generalization in this problem is the G. Selye concept of so-called stress -- a concept which the author believes constitutes the basis of a highly substantiated principle of neuro-humoral mechanism of homeostasis.

We shall give a brief description of this concept.

The Defense-Adaptation Mechanisms in the Teaching of Selye

The term "stress," rather unusual in biology and medicine, is borrowed by Selye from physics where this term designates tension, a derivative of force and resistance. As interpreted biologically, "stress" signifies a state of the organism resulting from interaction of injury and defense, and the factors which induce the state of stress are called in the Selye nomenclature "stressors."

As a result, in the interesting Selye concept, stress is characterized as a "state originating under the effect of some stressor and manifesting itself in the form of a specific syndrome which includes the sum total of changes which are created nonspecifically in the biological system" (Selye, 1956). In other words, the state of stress is characterized by a stereotype of symptoms specific to it, but this state may emerge in the organism in response to the most diverse, nonspecific influences.

Selye designates the symptomocomplex specific to stress as an adaptation syndrome, and divides it into: a) generalized adaptation syndrome (GAS), as a form of stress in the entire organism and b) local, or localized adaptation syndrome (LAS) identical with inflammation, as a form of stress on a limited part of the body.

The generalized and localized adaptation syndromes by no means oppose each other. It suffices to point out

that LAS frequently leads consecutively to GAS, and the latter in turn may affect the LAS.

The basic defense mechanism of the adaptation syndromes is connected with the action of the hypophyseal-adrenocortical system which, as stressed by Sayers (1950), plays the "most ubiquitous" role in homeostasis, in other words -- in regulating and protecting the internal medium in the Claude Bernard sense.

According to modern ideas, the hypophyseal-adrenocortical system effects its regulating and protective role under the control of the hypothalamic centers which are activated by corresponding neural, neurohumoral, or humoral influences induced by the stressor (see below).

The stimuli from the activated hypothalamus, in turn, are transmitted via the vascular system to the adeno-hypophysis, i. e., to the anterior glandular lobe of the hypophysis. This vascular system consists of so-called cortical blood vessels which connect the capillaries of the gray tuber of the hypothalamus with the capillaries of the adenohypophysis, when blood flows from the first to the second.

The mechanism of the hypothalamie stimulation is, according to the latest data, connected with special neurohormones formed in the posterior and medium part of the hypothalamus; and from there they are transferred with the bloodstream to the adeno-hypophysis via the vascular system (Guillemin and Rosenberg, 1955) discussed above.

As pointed out by Selye (1956), the hypophyseal adrenocortical system, functionally connected with the hypothalamic centers, effects its regulatory role according to the following scheme. The adrenohypophysis, stimulated into active state via the hypothalamus through neural, neurohumoral, or humoral pathways, begins under the effect of a general or local stressor to secrete intensively the adrenocorticotropic hormone (ACTH); this hormone stimulates the adrenal cortex inducing an enhanced secretion of an anti-inflammation hormone of the cortisone type, more correctly -- a hydrocortisone which reduces the connective-tissue reactivity.

In addition to it, the hypophysis secretes, on the one hand, the so-called growth hormone, or the somatotropic hormone (STH)*, and on the other hand -- an inflammation hormone of the desoxycorticosterone type is manifested in the adrenal cortex, while the cortex secretes aldosterone, all of them causing the reactivity of the connective tissue to rise.

*According to data of Scandinavian authors (Lundin et al., Schellin et al; 1954), the secretion of the somatotropic hormone (STH) by the adenohypophysis is part of the hormonal reaction in stress.

At the present time it is still a moot question whether the adrenal cortex secretes the inflammation hormones, desoxycorticosterone. The secretion of the considerably more active aldosterone by the adrenal cortex is controlled by the diencephalon (Farrel et al. 1956, 1958).

The adrenocorticotropic hormone plus the cortisone-type hormone effect the anti-inflammation action and can thus especially reduce the resistance of the organism to infection. At the same time the somatotrotropic and the inflammation hormones (corticoids) effect the inflammatory action by raising the resistance of the organism to infection.

The defense-adaptation reaction and the "adaptation syndrome" (according to Selye's terminology), of which the described reaction by the hypophyseal-adrenocortical system with a predominant falling-out of the cortisone-type corticoids is particularly characteristic, develops stereotypically in the organism under the effect of most diverse stressors, including factors of a physical, chemical, pharmacological, biological, as well as infectious-toxic order.

Thus, the adaptation syndrome with inherent protective mobilization of "adaptation hormones" may develop under all conditions which impair the homeostasis as well as the internal medium of the organism.

The starting mechanism for the hypothalamo-hypophyseal-adrenocortical system or its activation under stress undoubtedly can be humoral, as well as neuro-reflectory, though the immediate details of this mechanism have been studied by a relatively few (Selye, 1952, Long, 1952, Harris and Fortier, 1954). Selye, in particular, while confirming that stressors act on the hypophysis via humoral as well as neural means, indicates at the same time that any impairment of homeostasis, independent of its character, activates the ACTH secretion by the adenohypophysis.

According to Long (1952), the humoral mechanism is apparently connected with the relative ACTH and corticoid concentration in the blood and is thus related to the self-regulating systems; it exerts its influence directly on the hypothalamo-hypophyseal region. In contrast, the neural mechanism connected with the activation of the sympathetic nervous system and enhanced secretion of adrenalin induces a very rapid secretion of ACTH.

Inasmuch as various emotions (fear, rage, pain) as well as strong sound and light stimuli may activate a rapid secretion of ACTH (Harris and Fortier, 1954), the participation of the central nervous system (i. e., the cerebral cortex) in the activating mechanism of the hypothalamo-hypophyseal system seems to be beyond doubt.

Let us now turn to the characteristics of the adaptation syndromes and, discuss first of all, the "generalized adaptation syndrome" as described by Selye.

Generalized Adaptation Syndrome (GAS)

Selye distinguished in the dynamics of a generalized adaptation syndrome three phases which had received the following designations: 1) the alarm reaction, 2) the resistance reaction, and 3) the exhaustion reaction.

Each of these phases is characterized by definite symptoms:

1. The alarm reaction represents a sum of phenomena developing consecutively in a nonadapted organism under the effect of stressors and leading the organism to a state of resistance.

The alarm reaction has two stages: a) shock reaction developing directly after the harmful influence of the stressor and lasting from several minutes to 24 hours; the symptoms of this stage are: hypothermia, hypotension, increased permeability of the serous membranes of the capillaries, leukopenia, eosinopenia, gastrointestinal erosions, and catabolic phenomena in the tissues; b) the anti-shock reaction which takes place of the previous one is characterized by phenomena of anti-shock defense with removal of disturbances connected with the shock; the characteristics of this stage are: enlargement of the adrenal cortex with enhanced secretion of corticoids, predominantly of the same cortisone, a related involution of the lymphatic apparatus (lympholysis) with pronounced lymphopenia, increased elimination of corticoids with the urine, and a loss of weight.

2. The resistance phase is characterized by increased resistance to stress with the disappearance of the majority of morphological and biochemical changes of the previous phase. Thus, this phase is equivalent to a state of adaptation acquired by the organism in the previous phase. It must be noted in passing that the resistance phase may have a cross-character in relation to other stimuli-stressors. These stressors may lead to a state of increased resistance, or, inversely, to a state of increased sensitivity.

3. The exhaustion phase result from a protracted and excessive exposure of the organism to the stressor influence and is characterized by the loss of adaptation acquired during the previous phase.

These three phases of the adaptation syndrome during a prolonged influence of the stressor on the organism are presented graphically by Selye (Fig. 1).

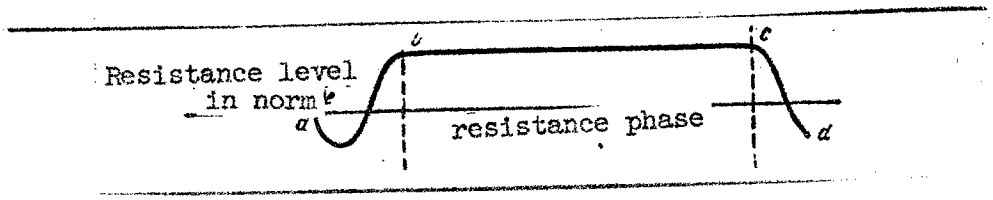

Fig. 1. Scheme of a generalized adaptation syndrome (according to Selye). Conditional designations: segment ab -- the alarm reaction; segment bc -- the resistance curve in GAS; segment cd -- the exhaustion phase.

As stated by Selye, the cited curve of the resistance change of the organism for the duration of the GAS was obtained by him in the following experiment which graphically concretizes the three-phasic character of the adaptation reaction as a whole.

One hundred rats were put in a refrigerated room with a temperature near the freezing point of water. During a 48-hour exposure to cold, the rats manifested typical phenomena of alarm. Thus, 10 rats, killed toward the end of the second day, showed: an enlargement of the adrenals with absence of fat in the cortex (symptom of increased secretion of corticoids), shrinking of the thymus gland (symptom of involution of the thymolymphatic apparatus), and ulcers in the gastric mucosa.

Within 48 hours 20 rats were removed, in order to ascertain their resistance to lower temperature as compared to the resistance they experienced in the refrigerator. It turned out that they were less resistant to this cold than the control rats. In other words, the rats at this stage showed lower resistance.

A selective check-up of the resistance of rats after five weeks of exposure elicited good resistance to low temperature not tolerated by control animals kept at the usual temperature. Thus, these observations showed an increased resistance to cold as compared to norm.

Finally, after a few months of existence in a refrigerated room, the rats lost their acquired resistance to cold under which they had lived for the past few months and began to perish. In other words, the experimental rats demonstrated the third phase of changes -- the exhaustion phase with loss of adaptation and reduction of resistance as compared to norm, with a loss of the reserves of "adaptation energy," as stated by Selye.

The phasic changes in the adrenals were very demonstrative in this experiment and in its analogues: during the phase corresponding to the alarm reaction, the lipoids disappeared from the adrenal cortex; during the resistance phase they accumulated excessively and, finally, during the exhaustion phase, the adrenal cortex was impoverished of lipoids.

These phasic changes during the adaptation syndrome manifest themselves not only under the influence of cold but under other stressors also, such as, for example, muscular overexertion, prolonged action of toxic substances, etc.

The described scheme of triphasic development of the adaptation-defense process represents a completely reliable generalization of factual data, as has been proven, in particular, by the reaction of the organism to prolonged moderate cold. Thus, under the influence of a very strong stimulus (stressor), the organism may perish while still in the alarm reaction phase, prior to the development of adaptation, i. e., during the shock stage.

Among the conditioning factors which modify the defense-adaptation process in various degrees or forms, Selye distinguishes internal and external factors.

The internal factors of this type include, in particular, the constitution, heredity, and prior exposures to stressors. The peculiarities of the stressor, diet, nutrition, climate, etc. belong to the external factors.

To illustrate this briefly, an identical quantity of the "inflammation" hormone -- desoxycorticosterone -- in a salt-free diet -- causes no significant changes in rats, while in rats kept on a diet rich in salt it causes hypertension and a marked affection of the kidneys.

Finally, it must be mentioned that the very defense-adaptation reaction can cause a pathologic condition if excessive or of insufficient intensity. Selye separates diseases of this origin into a special category of "adaptation diseases," -- more correctly, "adaptation defects." Examples of such adaptation diseases are various types of allergic affections with increased inflammatory reaction, obviously connected with the excessive formation of "inflammation" hormones of the desoxycorticosterone or aldosterone type in the adrenal cortex (rheumatism, hay fever, bronchial asthma, cutaneous allergic diseases, etc.).

Selye demonstrated in experiments on animals that excessive administration of desoxycorticosterone (mineralcorticoid) may produce cortico-vascular renal diseases, etc.

Let us now turn to the characterization of the local adaptation syndrome.

Local Adaptation Syndrome (LAS)

To study the rules of development of a local inflammatory adaptation process, Selye utilizes his method of creating an "inflammation sac" (granuloma pouch technique) in rats. In this method, the animal's back is shaved and 25 ml of air, together with an irritant (for instance, 0.5 ml of croton oil of definite concentration) are administered subcutaneously. As a result, an oval inflammatory tumor in the form of a granulation sac with an exudate is formed. This model permits a quantitative evaluation of the state of the inflammatory reaction by measuring the exudate and the area of necrosis. The latter is determined in percentages of affection in relation to the entire surface of the tumor measured planimetrically. It is understood that, parallel with macroscopic evaluation of the reaction, the tumor is examined by corresponding microscopic (histologic) methods.

After these remarks concerning method we shall pass to the analysis of the substance of the problem.

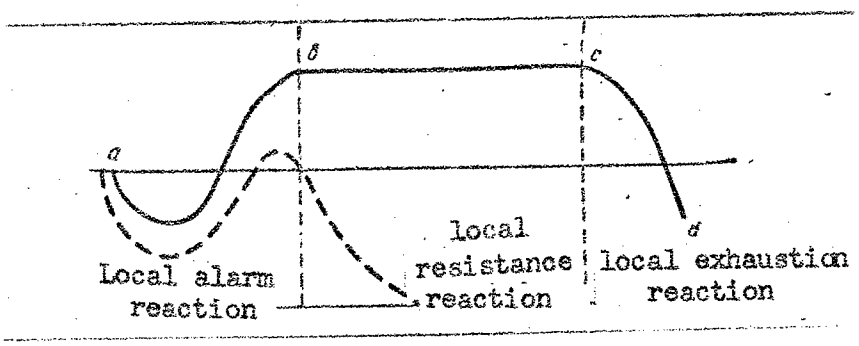

Fig. 2. Scheme of LAS (according to Selye). Conditional designations: straight line -- specific resistance; interrupted line -- cross-resistance; ab segment -- alteration, necrosis (atrophy); acute inflammation (hypertrophy and hyperplasia; bc segment -- chronic inflammation (hypertrophy and hyperplasia; cd segment -- degeneration, necrosis (atrophy).

In analogy with the generalized adaptation syndrome (GAS), a local adaptation syndrome (LAS) also has a triphasic course (Fig. 2).

The graphic scheme of a triphasic course of LAS is presented in detail by Selye in Fig. 2.

1. The local alarm reaction is composed of two stages:
a) the equivalent of shock stage develops directly after the effect of a strong stimulus and is characterized by alteration (regressive changes), frequent necrosis of cells and fibers of the connective tissue, as well as an edema in the area of the direct effect of the stimulus; this reaction represents the direct result of the injury and has no defensive character;
b) the equivalent of anti-shock reaction is characterized by the emergence and development of an acute inflammatory process with the presence of corresponding phenomena: hyperemia and stasis, exudation of plasma, and emigration of blood elements. With a continuing edema, the mesenchyma elements are transformed into an embryonic type of cells of a polyblast character. These phenomena correspond to the anti-shock stage of a generalized adaptation syndrome.

2. Local resistance phase in its initial stage is characterized by a rapid (a few hours) differentiation of polyblasts with the formation of cells of various types depending on the character and peculiarities of the stimulus (formation of fibroblasts, lymphocytic elements, macrophages, giant cells, etc.). Thus, for example, Indian ink stimulates formation of macrophages; mustard powder -- giant cells; croton oil - fibroblasts.

There is observed a marked "specific" resistance of the formed defense, granulation barrier to the necrotic dose of the homologous stimulus which had caused the inflammatory process. At the same time, a cross-resistance of the barrier to other stimuli is observed which causes formation of a granulation barrier of analogous histological structure; for instance, croton oil causes formation of cross-defense barrier to formic oil, mustard oil, bovine bile, etc.

Together with this process, a cross sensibilization of the defense barrier to stimul may be manifested which cause granulations of a different cellular composition, for instance, a defensive granulation membrane, caused by croton oil, can be necrotized by formaldehyde and China ink.

3. Local exhaustion phase. As a result of the inflammatory process there may be reparation (recovery) or, on the other hand, a necrotic disintegration of tissues; the latter represents an equivalent of the exhaustion phase and originates in those instances where an excessive stimulus exceeds the defense capabilities. As the result of such exhaustion, the defense granulation barrier is necrotized with eruption of the content of the inflammatory focus.

This triphasic character of the inflammatory process, with corresponding changes of the resistance of the Selye granulation barrier (1953), is illustrated by observing the fate of the "inflammatory sac" in rats caused by the administration of 0.5 ml. of two percent croton oil into the aerial cavity, and reinjection of the oil in similar doses at various periods. The results of related observations are summarized in Table 1.

Table 1

Number of rats	Periods of re-injection	Necroses: quantity in percentages	Necroses: area in percentages
100	--	40	9.0
20	2 hours	70	35.2
20	6 hours	50	9.1
20	7 days	0	0
20	14 days	30	7.8
20	28 days	43	8.5

After the first croton oil injection the skin resistance decreases during the first few hours (equivalent to the shock stage of the first phase); after seven days, rats show a pronounced resistance of the granulation barrier to repeated stimulation (second phase), and 14 to 28 days later the exhaustion phase emerges with loss of resistance (third phase).

Analogous to GAS, LAS reveals a high sensitivity to the effect of adaptation hormones in the inflammatory process. In this case cortisone inhibits the inflammation process (i. e., the formation of an exudate and a granulation barrier). In contrast, desoxycorticosterone and the somatotropic hormone enhance the inflammation process and the formation of a granulation barrier; desoxycorticosterone also exerts an antinecrotic effect.

Cortisone and somatotropic hormone balance each other in corresponding doses.

These effects of inflammatory and anti-inflammatory character are very graphically represented on the model of the "inflammation sac." Of the related separate details, the following merits special attention.

The anti-inflammation effect of cortisone is revealed upon introduction of insignificant doses (two ml) into the mass of the "inflammation sac;" introduction into the area

of one pole produces a diffuse effect on the entire "inflammation sac." The anti-inflammation effect of cortisone is manifested well when it is used during the process of the formation of inflammation, and not in regard to the already formed inflammatory focus. Finally, when croton oil is used, cortisone exerts only an anti-inflammation effect, and does not affect necrosis.

The following table composed by Taubenhous (1953) from combined data of the literature (Table 2), illustrates the effect of adaptation hormones on various connective-tissue elements.

Table 2

Hormone	General Effect	Fibroblasts	Collagen fibers	Basic substance
Somatotropic hormone	Stimulation	Large, with normal contour	Thickened, abundant	?
Desoxycorticosterone	Stimulation	Large, polygonal or star-shaped	Diminution	Alteration
Cortisone or hydrocortisone	Inhibition	Small	Inhibition	Inhibition

Table 3 illustrates the effect of adaptation hormones on exudation in experiments with the "inflammation sac" the related observations by Rindani (1953) are summarized.

Similarly to the generalized adaptation syndrome, activation of the hypothalamo hypophyseal-adrenocortical system with the secretion of corresponding adaptation hormones in a local adaptation process may proceed under the influence of humoral factors (a secretion of X-substances in the area of damaged tissues is presumed) and neurorefflectory mechanisms. In this connection it is interesting to note that, for instance, intravenous administration of histamine, secreted when tissues are damaged, very rapidly causes secretion of ACTH (Harris and Fortier, 1954).

In his report at the symposium on the mechanism of inflammation, Selye (1953) summarized the similar traits of a generalized and local (inflammatory) adaptation syndromes

as follows: 1) both syndromes represent nonspecific reactions which include injury and defense; 2) both syndromes have a triphasic course with phenomena of cross resistance and enhanced sensitivity during the adaptation phase; 3) both syndromes are particularly sensitive to the influence of adaptation hormes (ACTH, STH, corticoids); 4) if both syndromes develop simultaneously, their pronounced interaction is revealed.

Table 3

Hormone	Dose (in mg)	Average quantity of exudate (in ml)
Control	--	18
Hydrocortisone	5	2
Desoxycorticosterone	5	10
Hydrocortisone + desoxycorticosterone	5 5	5

Regarding the latter premise, Selye cites in subsequent publications (1956) very demonstrative experimental illustrations. Thus, upon reproduction of the "inflammation sac" in a rat via introduction of a mild stimulus (diluted croton oil) and a simultaneous creation of a state of general stress, for example through forced immobilization which acts as a very powerful stressor, then the inflammatory reaction disappears. When, however, the "inflammation sac" is reproduced in the rat via introduction of a strong stimulus (undiluted croton oil), then its combination with the same form of general stress produces an inflammation reaction of a violent course with extensive cutaneous necrosis and disintegration of the infiltrate. Control rats, not subjected to the general stress, show under these circumstances the usual "benign" development of the reaction in the "inflammation sac," less pronounced in the first instance and more pronounced in the second.

The Nature of the Anti-inflammation Effect of Medicinal Sleep

In the Institute of Surgery imeni A. V. Vishnevskiy, at the initiative of A. A. Vishnevskiy and under our guidance, scientific associate I. Ya. Uchitel' conducted during

the past few years on various experimental models numerous studies of the effect of medicinal sleep on the course of inflammatory processes of toxic, allergic, and infectious origin. The basic results of these studies led to a substantiated conclusion on the reduction of inflammatory processes under the influence of medicinal sleep. However, this protective effect was not observed on generalized infections and intoxications the course of which had often been even aggravated by sleep. To interpret the obtained results we expressed various ideas which basically did not, however, go beyond the limits of general statements on diverse variants of the reduction of the activity of the organism under the effect of the inhibitory exclusion of the cerebral cortex. These assertions, although basically correct, still indicated far less than the factual mechanisms causing the observed phenomena.

At this point, one must keep in mind that during the entire cycle of experimental studies we were interested not only, or even not as much, in the effect of medicinal sleep per se on the inflammatory and other infectious-toxic processes, as in the clarification via medicinal sleep of the general regulatory mechanism of inflammatory and infectious-toxic processes. Thus, medicinal sleep itself has become a method of clarification of certain general problems of infection pathology. The review and analysis of accumulated data on the effect of medicinal sleep, from the cited positions of the neurohumoral nature of the regulatory mechanisms of inflammatory and infectious-toxic processes, constitute the task of the present work.

Before discussing this analysis, we shall dwell first on the general characteristics of the experimental material and phenomena at our disposal.

The experiments were conducted on rabbits and monkeys. The rabbits were put to sleep with a mixture of urethane (10%) and veronal (0.75%). By means of repeated administration of the mixture, a continuous sleep was maintained for 24 to 72 hours, depending on the tasks of the experiment. The sleeping rabbits retained their corneal reflex and sensitivity to pain. The sleep in monkeys (Macaco rhesus) was induced with barbamyl. In its course the sleep was very similar to an analogous sleep in humans.

In the first series of experiments a study was made of the effect of medicinal sleep on the local reaction in rabbits upon intravenous injection of turpentine (0.1 ml), diphtheria toxin (100 reactive doses), and staphylococcus toxin (necrotizing dose).

In control animals turpentine in stated doses caused at the site of injection a markedly pronounced edematous

necrotic reaction, while the diphtheria and staphylococcus toxins produced an inflammatory - necrotic affection characteristic of these toxins. In sleeping animals the skin reaction to diphtheria and staphylococcus toxins was absent, as a rule, and, in experiements with turpentine, completely eliminated the edema reaction, but retained, as a rule, the necrotic affections of the skin. In addition, it was demonstrated that sleep inhibits the effect of leucotoxin and hyaluronidase which, as is known, increase the tissue permeability.

In the next series of experiments, the effect of medicinal sleep on various forms of allergic reactions was studied. The rabbits were sensitized with horse serum which was subsequently (after 12 to 14 days) repeatedly introduced intravenously, or in the cavity of the knee joint. Under these circumstances the control animals showed a markedly pronounced allergic reaction (edemic infiltration), or there was a corresponding allergic arthritis with marked enlargement of the joints. In contrast, sleeping rabbits showed only a mild cutaneous allergic reaction as a rule, and allergic arthritis was completely absent. Finally, the same series of experiments revealed that sleep completely prevents the development in rabbits of a cutaneous-hemmorrhagic Shwartzman reaction which was markedly pronounced in control animals.

In the third series of experiments, the effect of medicinal sleep on the development of local infectious processes was studied. With this in view, an intradermal and intra-articular infection of sleeping and control rabbits with virulent staphylococci was carried out. The result was that sleep completely prevented the development of an infectious-staphylococcus process in the skin as well as in the joints, while the control animal showed markedly pronounced intracutaneous foci and gonitis. The observations showed, however, that sleep only prevented the inflammatory reaction of the organism to the causative agent, but did not affect the viability of the latter (A. M. Ana'yev, I. Ya. Uchitel').

Still more clearly these phenomena were revealed in experiments with smallpox vaccine in rabbits and monkeys. Intradermal vaccination of sleeping rabbits and monkeys with smallpox detritus during a 72-hour sleep caused no reaction in contradistinction to control animals, but after awakening, the experimental animals developed a smallpox vaccination lesion. In other words, here also the medicinal sleep prevented the inflammatory reaction of the organism, but had no effect on the viability of the causative agent.

Thus, local inflammatory processes of toxic, allergic, and infectious origin, produced in the skin or in the joint

cavity, are completely eliminated or considerably reduced under the effect of medicinal sleep. Sleep does not merely prevent the destructive necrotic affections of tissues originating from chemical agents, such as turpentine, for example. At the same time, the medicinal sleep in no way affects the vitality of the micro-organisms, despite the complete prevention of inflammatory processes which are regularly induced under similar condition when animals are infected in their waking state. All this, taken as a whole, confirms the fact that medicinal sleep obviously diminishes the reactive property of the tissue of the organism, a definite level of which is essential to instigate an inflammatory process. We can state at this point that in this case we obviously deal with a diminution of the reactive property of the connective tissue.

We shall now turn to the results of other series of experiments.

As demonstrated by the observations of I. Ya. Uchitel', medicinal sleep, despite all that has been stated about its prophylactic effect in local inflammatory processes, as a rule not only fails to prevent but, rather accelerates and aggravates the processes of generalized infection or intoxication in sleeping animals. Thus, intradermal infection of sleeping rabbits with a small dose (0.1 ml) of virulent pneumococcus culture causes in them a fatal sepsis having a more rapid course than in controls. The same phenomenon is observed upon infecting rabbits with spores of the toxigenic culture of tetanus bacillus (intramuscular administration of spores in a calcium chloride solution).

It was further elicited that intravenous infection of sleeping rabbits with the smallpox vaccine virus differed from the experiments of intradermal infection with the same virus, in that intravenous infection frequently caused a specific encephalitis in the rabbits with a fatal exit, while the control rabbits tolerate without ill effects the intravenous infection with the same virus in similar doses.

Only experiments with the virus of fixed rabies occupied a particular place in the described series of observations. I. Ya. Uchitel' demonstrated that in suboccipital administration to sleeping rabbits of 1 Dlm virus of fixed rabies almost 50 percent of the animals survived while the majority of the waking rabbits, under the same conditions of infection, perished of rabies.

Thus, medicinal sleep prevents the development of inflammatory processes and at the same time, as a rule, aggravates the development and outcome of generalized infections and intoxications with a definite reduction of the reactive properties of the organism. At some time in the past

we attempted to explain this seeming paradox by the fact that during sleep the external and proprioreception was excluded, but the intero-reception remained intact. Therefore, the medicinal sleep prevents cutaneous and intra-articular infectious processes, but has no preventive effect when the virulent causative agent enters the internal tissues of the organism. However, this explanation, at best, was only half true.

We now turn to the latest data which led us to the most reliable path of understanding the mechanisms of the described phenomena connected with the effect of medicinal sleep.

We already knew from previous observations by I. Ya. Uchitel' (1954) that a bilateral perirenal novocaine blockade definitely reduces allergic reactions in rabbits sensitized with horse serum, if effected within six hours following the intra-dermal administration of the determining dose of the same serum. Under these circumstances, the area of allergic affections of the skin diminishes two to two-and-a-half times, as compared to the control. In subsequent observations by I. Ya. Uchitel', however, it became clear that the Artus allergic phenomenon, as well as the Shwartzman hetero-allergic reaction, do not develop in sensitized rabbits under conditions of artificial hypothermia with the temperature reduced to 26-28 for 24 hours. In other words, it was demonstrated that in allergic processes the novocaine blockade and hypothermia produce in rabbits the same preventive effect as does medicinal sleep.

As mentioned previously, we had no doubts from the very start of the experiments that the anti-inflammation effect of medicinal sleep must be connected with reduced reactivity of the organism -- to be more precise, with reduced reactivity of the connective tissues of the narcotized animals. It is perfectly obvious also that the cause of the elucidated anti-inflammation effect of novocaine blockage and hypothermia must be timed with an analagous reduction of reactivity.

It is well known at the same time that cortisone, the corticoid of the adrenal cortex, possesses anti-inflammation properties. On the other hand, the Selye conception of stress specifies an increase of corticoid production by the adrenal cortex under most diverse influences on the organism.

When we compare all these data, the question naturally arises, whether we are dealing in our experiments with a particular instance of anti-inflammation effects described by Selye in his concept of stress.

In the described states, the impoverishment of the

adrenal cortex cells in lipoids is particularly characteristic. Therefore, we set ourselves the task of morphological study of the adrenal cortex in medicinal sleep and in hypothermia. This task was successfully solved in the investigations of I. Ya. Uchitel' (the experimental part) and L. D. Krymskiy (the morphological part). In these studies the factual impoverishment of the adrenal cells in lipoids in medicinal sleep, as well as in hypothermia, was clearly established.

These cytomorphological and cytochemical findings elicited the fact that, in medicinal sleep as well as in hypothermia, an increased secretion of cortisone by the adrenal cells taxes place in the animals -- a factor which reduces the reactive potential of the connective tissue and produces an anti-inflammation effect of various intensities.

This point of view can reliably explain the above facts of aggravation of certain infectious processes in medicinal sleep. These observations were also made by I. Ya. Uchitel', particularly in her experiments with intradermal infection of sleeping rabbits, with a virulent pneumococcus culture and in intravenous administration of the smallpox vaccine virus. In both experiments the aggravating cause was obviously pathogenically connected with the reduction of the defense-inflammation reactivity of the connective tissue elements: in the first experiment, in the skin; in the second, in the capillary-vascular system of the brain. As a result, we observe in the first experiment a rapid development of pneumococcus sepsis, and in the second, a not infrequent formation of a specific encephalitis. One can assume that the occasionally observed postvaccination encephalitis has analogous etiology and pathogenesis, i. e., develops against the background of a hormonally reduced defense-inflammation potential.

There is also no contradiction to the described interpretation in the defense effect of medicinal sleep in experimental rabies. This infectious process develops in the cerebral cells and, under conditions of medicinal sleep, their reactivity is undoubtedly reduced, since a diffused cerebral inhibition is present. But the protective effect of sleep is realized only upon the use of minimal infectious virus doses, and not even in all animals. The absence of the defense effect of medicinal sleep in tetanus intoxication can be explained either by the particular strength of the tetanus stimulator of the nervous apparatus or by the timing of the action of the latter on the nervous apparatus which retains its reactivity level during medicinal sleep.

The anti-inflammation effect of medicinal sleep and hypothermia can be regarded as a particular instance of experimental elicitation of the above general rules, and, in summary, we are justified in confirming the Selye thesis on the neurohumoral regulation of inflammatory processes which are realized in the organism via the hypothalamo-hypophyseal-adrenocortical system. The activation of the latter, being accompanied by an increased secretion of inflammatory or anti-inflammatory biofactors of the adrenal cortex, may enhance or, inversely, reduce the inflammation process.

The precise mechanism of the anti-inflammation effect of medicinal sleep and hypothermia may be detailed as follows. According to the data by Selye (1954), pharmacological substances, particularly the soporific urethane used in our experiments, as well as cold, are in themselves stressors causing the activation of the hypophyseal-adrenocortical system. In addition, in medicinal sleep, the possibility of activation of the hypothalamic centers resulting from the inhibited state of the cerebral cortex must be evaluated.

In conclusion we shall note that it is also quite possible that the so-called novocaine blockade is essentially a sui generis stressor which exerts a beneficial effect on homeostasis via the same hypothalamo-hypophyseal-adrenocortical system, which obviously represents a universal regulator of the internal medium of the organism -- either by itself or under the control of the cerebral cortex. The basis for such interpretation of the novocaine blockade mechanism may be the fact that under experimental conditions the bilateral perirenal blockade may prevent in rabbits an allergic inflammation. However, this problem required special studies within the frame of investigation of the effect of novocaine blockade on the hypophyseal-adrenocortical system under the control of the morphological and biochemical tests available for this purpose.

Conclusion

The Selye concept of stress and of hypothalamo-hypophyseal-adrenocortical regulation of general and local defense-adaptation mechanisms deserves, in our opinion, close attention. Based on the principle of neurohumoral regulation, the Selye concept outlines, in particular, the path for concrete solution of the complex problem of regulatory bonds and the interaction of the central nervous system and "the connective tissue periphery" of the organism (including its free cells) which, as is known, plays a prominent role in the pathogenesis of infection and immunogenesis. We believe that this area of neurohumoral coordinations offers

the solution to the problem of physiological regulation of infectious processes concerning the whole organism. The examples cited in this review in regard to the clarification of our stated positions of the nature of the anti-inflammation effect of medicinal sleep are, in our opinion, sufficiently convincing illustrations.

As pointed out by Academician I. Khorvat (Czechoslovakia, 1955), neither purely humoral, nor purely neural concepts can interpret all processes observed in the organism. "In physiological processes," says the author, "the incretory system interacts with the neural system (in all cases) so indivisibly and intimately that they comprise a continuous, unified and integrated neurohumoral system."

Bibliography

Selye H., The Physiology and Patology of Exposure to Stress; a Treatise Based on the Concepts of the General -- Adaptation Syndrome, and the Diseases of Adaptation, Montreal, 1950.

Selye H., Heuser G., Fourth Annual Report on Stress. Montreal 1954.

Selye H., The Stress of Life, New York, 1956.

Jasmin G., Robert A., The Mechanism of Inflammation, an International Symposium. Montreal, 1953.

Asboe-Hansen G., Connective Tissue in Health and Diseases. Copenhagen, 1954.

Uchitel', I. Ya., In the book: Problems of Infection Pathology and Immunology. Moscow, 1954, Issue 2, page 71.

Uchitel', I. Ya., Krymskiy, L. D. Eksperimental'naya Khirurgiya (Experimental Surgery), 1956, No. 3, page 19.

Khrovat, I., Klinicheskaya Meditsina (Clinical Medicine), 1955, No. 4, page 10.

- E N D -