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NOTES ON SELECTED BIOMEDICAL RESEARCH FACILITIES ON THE EUROPEAN CONTINENT, PART II: NANCY AND PARIS

By J. William Cox, CAPT, MC, USN, Chief of Medicine and Director of Research, US Naval Hospital, Philadelphia, Pennsylvania

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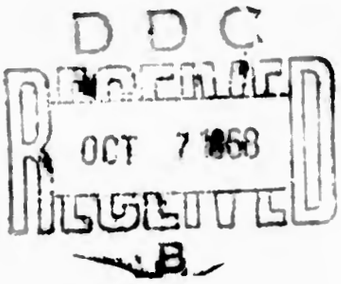

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NOTES ON SELECTED BIOMEDICAL RESEARCH FACILITIES ON THE EUROPEAN CONTINENT
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I. INTRODUCTION

This report presents selected features and impressions of the organization, facilities, personnel resources, mission and program of some clinical research facilities in France. The scientific liaison visits were made to Nancy in June 1968 immediately after the student revolt and general strike of May 1968, and to Paris in July immediately after the landslide victory of the Gaullist party in the elections of 30 June. The problems and issues were very candidly and openly discussed with me by the professors as well as by more junior members of the medical faculties with whom I had conferences. Perhaps it is a sampling error -- and I doubt that it is -- but I found well-organized, busy, efficient departments which were expertly administered. Each professorial contact revealed a gracious, considerate, and professionally outstanding person who was vitally concerned with progressive educational methods, and with modern techniques to improve the efficiency of the students' educational experience. I saw the facilities and experienced the atmosphere of enquiry which prevailed in the clinics and laboratories and at the bedside. I sensed the dedication and saw evidence of the professional competence of numerous members of the medical faculties manifested in a reasonable balance of clinical experience, fundamental and applied research, and teaching responsibilities. They were all aware of an ever-present truth -- no system is perfect; there is always room for improvement, and one either strives to achieve improvement or the system stagnates and deteriorates.

Quite frankly, I went to France reluctantly on the advice of an ONRL staff member. I went with some degree of scepticism and an animosity arising from events of recent years, and from my confused disappointment that the historic and traditional ties between our nations had been strained by what appeared to be unilateral and inappropriate French action. To my great surprise and delight, my experience in interpersonal professional, social, political, and commercial relations was outstandingly pleasant and rewarding. Of everywhere I have been, a genuinely warm and enthusiastic professional reception, a highly productive program, and gracious sincerity in the social amenities were collectively most consistently experienced in France. A sincere and informed concern for the future welfare of

medical education in France was apparent in all my contacts, as was a resolve to reach an effective solution. Unfortunately, to date no proposal or compromise have been accepted by the radical spokesmen of the rebellious student bodies, and it appears that they are demanding destruction of the system, not its reform. It also appears that this vocal minority would replace order and a reformable system with the chaos of educational anarchy. I know what the authorities have offered; I don't know what the radicals want which would be workable.

I agree fully with one professional European traveler, who stated that he is convinced that this reborn nation and her invigorated citizens deserve all the patience, all the support, and all the encouragement that can be given by the free world. This certainly applies to her medical scientific community -- an opinion far different from the one I held at the start of my liaison tour.

My orientation tours, briefings and conferences included the following: (1) The Service for Respiratory Insufficiency, Hôpital Maringer, Nancy; (2) the research facilities of the Dept. of Respiratory Pathophysiology, Univ. of Nancy Medical School; (3) the Dept. of Radiology and the Center for Research on Cardiovascular Surgical Techniques at Hôpital Broussais, Paris; (4) the Intensive Cardiopulmonary Care Center and the Pathology, Bacteriology, Pulmonary Function and Cardiac Catheterization Laboratories of the Dept. of Chest Diseases, Hôpital Laënnec, Paris; (5) the Coronary Care and Cardiac Intensive Care Center, Dept. of Cardiology, Hôpital Laribosière, Paris; and (6) the Center for Hematology and the Inst. for Research on Diseases of the Blood, Hôpital Saint-Louis, Paris. Addresses of these facilities are given in the Appendix.

II. ORGANIZATION, FACILITIES AND PERSONNEL RESOURCES, MISSION AND PROGRAMS FOR MEDICAL RESEARCH AND EDUCATION IN SELECTED LOCATIONS IN FRANCE

In the modern era until the start of World War I, France made great contributions to many fields of science, including biology and medicine, and had many great names linked to fundamental discoveries. The disastrous consequences of the first World War included a large reduction in the number of scientists and facili-

ities and personnel necessary for productive, modern scientific research. World War II aggravated the situation and dispersed the few teams which had remained intact and which worked with great alertness and initiative between the wars. The Nazi occupation deprived French scientists of the facilities and support necessary for their investigations.

After the liberation at the end of WWII, French national resources were necessarily devoted to economic reconstruction and development. The instability that prevailed until after 1950 perpetuated the period of quiescence in scientific research, and it is only since 1950 that it has regained forward momentum. Among French scientists, four recent Nobel Laureates, three in medicine and physiology, attest to the rebirth of French scientific vigor.

A. NANCY: UNIV. OF NANCY

The existing facilities of the Univ. of Nancy are a continuation of the University of the Dukes of Lorraine at Pont à Mousson, founded in 1572. The university-type activity ceased with the French Revolution, but began again early in the 19th century, and the University was recognized in 1854. Nancy became a part of France in 1766, and subsequently was fought over repeatedly, with many occupations in the 19th century. After the Franco-German War, its population was greatly increased by immigration of Alsatians and people from Metz. Nancy suffered relatively light damage in WWII and was liberated without great difficulty in September 1944, when university functions began to accelerate. The Medical Faculty is representative of the six medical schools in France. Members of medical faculties in the university hospital centers are involved with medical care, teaching and research in their departments. This multiple responsibility creates an environment for a balanced interplay of programs which benefit the standard of patient care, an objective which I have stressed in this and the Scandinavian series of reports. This objective is met expertly in Nancy through the excellent administration of the clinical patient care and diagnostic facilities and of the fundamental research laboratories by Prof. Paul Sadoul, Prof. of Clinical Respiratory Physiology, Medical School of the Univ. of Nancy, and Chief, Dept. of Respiratory Insufficiency, Hôpital Maringer.

1. Departmental Organization & Facilities

Two physical plants form a base for departmental operations. One, for fundamental research, is located in the building of the medical faculty. There, animal experiments and basic research are conducted on problems related to respiratory physiology, including test and evaluation of instruments and other technical advances in equipment for respiratory assistance. The other facility is clinically oriented and occupies the respiratory insufficiency pavilion of the Hôpital Maringer, which has a ward service for 150 patients, including a respiratory intensive care section. There are also a large outpatient clinic, a respiratory rehabilitation section which specializes in physical therapy and training to encourage diaphragmatic breathing, to increase efficiency in the work of breathing, and to facilitate ease and usefulness of the cough reflex.

In support of these patient care facilities, there is a very busy and well-equipped cardiopulmonary function laboratory, which includes the essential elements of a cardiac catheterization laboratory, a blood and respiratory gas analysis laboratory, and units for performance of tests of lung function, including spirometry, lung volume determinations, pulmonary alveolar ventilation, pulmonary membrane diffusion capacities, and pulmonary mechanics (compliance and resistance measurements).

The workload of the clinical facilities is extremely heavy. For example, diagnostic arterial punctures exceed 6000 per year, and there are at least two cardiac catheterizations per day. The 15-bed intensive care section was full, and demanded time-consuming but necessary procedures in the conduct of ventilatory assistance and related techniques for restoration of a state of pulmonary respiratory compensation in patients. The clinic consultation service, which I witnessed for an entire afternoon, evaluates in depth laboratory and historical data on approximately 30 patients three times weekly.

The equipment in support of these operations is modern and of many types and manufacture. The right piece of equipment to do the job required is available. Physical facilities are greatly overcrowded, and the Hospital is really an old building, a former 18th century abbey. A new

hospital with adequate, efficiently divided space is planned for completion in 1971. Similarly, there is great overcrowding of the research space at the Faculty of Medicine. Another disadvantage is the location of basic research facilities across the city from the Hospital. This situation will be corrected by the erection of a new building for the Faculty of Medicine to be completed in 1969.

2. Personnel and Programs

The number of specialists in the Dept. of Clinical Respiratory Physiology totals about 24. In addition, there are physicians in training as externs, interns, and as physicians undergoing advanced specialty graduate medical training. Some full-time staff members are oriented totally to the practice and clinical research aspects of respiratory insufficiency. Those of the Department whose primary interest and orientation lie in fundamental research in respiratory physiology are required, nonetheless, to take rotational obligations in support of the clinical and teaching functions of the Department. In other words, no physician is permitted to sequester himself in an ivory tower to lose contact with the primary concern of his profession, the patient. This policy, introduced by Sadoul, met with initial resistance, but is now accepted -- or tolerated -- because of the expert balance and tremendous opportunity for an integrated program of patient care, medical education and research. The frequency of the clinical assignment for the fundamental researcher is one week in six. The other five weeks, he is free to pursue his research without collateral responsibilities other than teaching at the undergraduate level.

I was struck by the fact that, with a diverse program with multiple projects in fundamental respiratory research and with many clinical management, diagnostic and research problems, Sadoul begins work at 0700 and returns in the afternoons to the medical school to coordinate, administer and direct a large basic research program and to discharge his professorial and university administrative functions. Sadoul also has extramural responsibilities as editor of Bulletin de Physiopathologie Respiratoire and Pres. of Societas Europaea Physiologiae Respiratoriae. Two nights a week, Sadoul is involved with a departmental conference

at which interesting diagnostic and therapeutic problems confronting the clinical facility are presented and discussed in depth, and at which a research symposium is conducted.

Several department members have been with Sadoul for almost ten years. Obviously, the balanced environment which exists is appealing and professionally rewarding. He also attracts (for periods of one to three years) physician-scientists from North America and elsewhere. There are now on the staff a French-Canadian pulmonary clinical physiologist and an American graduate engineer from MIT who is biophysically oriented. Names of scientists with whom I conferred, with a survey of their research activities, are presented below.

a. Service des Insuffisants Respiratoires: Mme. la Dr. Laxenair is Sadoul's first assistant physician in charge of inpatient care and the section for intensive care (Centre de Réanimation Respiratoire de Nancy). She is an expert in the techniques of ventilatory assistance, including the selection and proper use of the numerous different respirators of the volume-cycled type -- Engström (Sweden); SF-4 Respirateur (Sabath Fourès Laboratoires; Robert et Carrière, Paris); CELOG-2 (Robert et Carrière, Paris), and others. She is highly proficient at clinical diagnosis, bedside assessment, and treatment of respiratory insufficiency with the aid of certain measurements (P_aCO_2, P_aO_2, and/or S_aO_2)*. Her program also involves clinical teaching and research.

Mme. la Dr. Gimenez is concerned with new methods of respiratory rehabilitation and is in charge of the Rehabilitation Section. The success of the total program for pulmonary resuscitation, recompensation and rehabilitation is outstanding. Many patients have been returned to useful work who would otherwise have been dead or chronic respiratory cripples, totally incapacitated for ambulatory functions.

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* P_aCO_2 - partial pressure of CO_2, arterial blood in mm Hg (STP)
P_aO_2 - partial pressure of O_2, arterial blood in mm Hg (STP)
S_aO_2 - percent saturation (oxyhemoglobin) arterial blood

In the supporting clinical cardiopulmonary laboratory of the Service, Dr. J. Lacoste is the Head Physician. He has the MD and PhD degrees and a rich background in electronics and biomedical engineering. He designed an exceptionally sensitive, high-frequency response, infrared P_{CO_2} analyzer and an electromechanical carbon film recorder-projector which has four channels.* It is intenious, versatile and rugged. With these two items of equipment, P_{CO_2} of expired air may be accurately measured and recorded breath to breath. Other variables may also be recorded on simultaneous coordinates.

Dr. J. Schrijen is in charge of the large, well-equipped catheterization laboratory in which an average of two right heart catheterizations are performed daily with the aid of image amplification fluoroscopy and video-monitor image presentation. The versatile FLEICH Metabulator (Switzerland) and physiological recording and data storage equipment are excellent, as is the radiological equipment for cineangiocardiographic studies. In this connection, I was surprised to learn, first, that left heart catheterization by retrograde or transseptal techniques is not performed in this laboratory, and, second, that there is general conservative reluctance in France to use the procedure of lung biopsy in cases with diffuse pulmonary disease of uncertain etiology for diagnosis and correlation with clinical, physiological and radiographic data. The risk involved would appear less than some other operative and non-operative diagnostic procedures, and the information to be gained would be of real value to medical science. Study of lung biopsy specimens is potentially of great importance to the patient prognostically and therapeutically. Nonetheless, it is said to be rarely recommended or performed in this situation.

Dr. Pham conducted the outpatient follow-up and consultative service, and coordinated the physical findings, interval history and current laboratory data (spirometric,

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* manufactured by Le Controle de Chauffe, 17 rue Vernon, Alferville, France

alveolar ventilation, pulmonary airway resistance and compliance, and arterial P_{CO_2} and P_{O_2}) used to follow the course of patients recompensated from respiratory failure and released from the hospital. His clinic was efficient and patient evaluation was thorough. One or more junior associates were with Pham; progress notes and consultation reports were dictated and were characteristically comprehensive. Routinely a chest fluoroscopic examination was performed -- the equipment being right in the examining room of the clinic. Ample nursing and paramedical assistants were immediately available and all past medical records were available and frequently consulted.

b. Chaire de Physio-Pathologie Respiratoire de la Faculté de Médecine de Nancy (Prof. P. Sadoul) - Unité de Recherches de l'I.N.S.E.R.M.*: Medical scientists working in fundamental research in the Dept. of Clinical Respiratory Physiology under Sadoul usually hold positions under one of the public establishments of the Ministry of Social Affairs (INSERM) or the Ministry of National Education (CNRS)+. These appointments are, for example, "Attaché de Recherche à la DGRST" (or) "...à l'INSERM" and "Chargé de Recherche au CNRS." These are comparable to appointments such as Field Director, Post-Doctorate Fellow, etc., by our National Institutes of Health.

The recent and current research efforts which I observed are well conceived, timely and expertly executed. The laboratory space is woefully inadequate, but efficiently and equitably allocated to the various projects. The research equipment is excellent, and the new building with adequate laboratory space for the Department, to be finished in 1969, should provide for more efficient utilization of research personnel.

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* Research Unit of the National Health & Medical Research Institute

\+ National Center of Scientific Research

3. Research Areas:

Anthony M. Benis is an American hydraulic engineer with a PhD degree from MIT. His work is biophysically oriented, and his specific expertise is in the rheology of biological systems. His appointment to Sadoul's Department is "Attaché de Recherche à la DGRST." His experimental study is of rheological aspects of pressure-flow relationships in perfused, isolated lobes of the canine lung, using blood (at hematocrit 40-60%) and Dextran® solutions. Blood is not homogeneous, nor is it Newtonian in its flow characteristics; these properties of the fluid and possibly some change in the tube geometry produce pressure-flow curves which reflect marked increases in apparent viscosity (and resistance to flow) as the perfusion pressure falls or as the hematocrit is increased. Dextran solutions (Rheomacrodex or Macrodex) which when clear and used to perfuse rigid tube systems during in vitro studies, behave as a Newtonian fluid with linear pressure-flow relationships and uniform viscosity. Any departure from linear pressure-flow relations in the perfused lung could be interpreted to reflect changing conditions in the vascular geometry. At a set pulmonary venous pressure (P_v) of +10 cm H_2O and alveolar pressure (P_A) at +5 cm H_2O, repeated tests of the pressure-flow relationship for Dextran revealed it to be linear over a wide range of arterial perfusion pressure gradients (P_{a-v}). When the P_A and P_v were set so that they were equal (P_A and P_v both at +5 cm H_2O), absence of a post-capillary distending force ($P_v - P_A = 0$) relative to the venular compression force of P_A was associated with marked non-linearity and with an increased resistance as ΔP_{a-v} was reduced to and below 20 cm H_2O. At values for ΔP_{a-v} in excess of 20 cm H_2O, the pressure-flow relation was again strictly linear. It was concluded that this difference is the consequence of increased vascular resistance due to change in tube geometry, and not the consequence of a fluid factor because Reynolds numbers were all below 1000 -- well below the critical value for turbulent flow of Dextran in this system -- and because Dextran is a rigidly Newtonian fluid in constant tube or rigid capillary systems.

Pressure-flow relationship curves for blood in either the isolated, perfused lung or the capillary viscometer are clearly non-linear. The apparent viscosity,

and in parallel manner, the resistance to flow, rise steeply when ΔP_{a-v} is reduced in decrements. The effect is accentuated when the hematocrit is raised. The observed effects are large, and the data reemphasize that the rheological properties of blood are important hemodynamic variables which must be reckoned with in studies of the pulmonary circulation.

4. Mechanical Properties of Human Lungs: Physical Properties of Instruments for Ventilatory Assistance (Respirators):

R. Peslin and R. Martin are physicians with special interest and considerable experience in studies of the mechanical properties of human lungs in health and disease. They have also made a comparative study of the physical properties and performance characteristics of respirators in relation to their use in patients and normal subjects. Responses to artificial ventilation as regards alveolar ventilation, dynamic airway resistance, concentration of arterial blood gases and other physiological variables are correlated to instrument properties and performance.

One instrument in particular is worthy of mention, the CELOG-2*. This respirator is ab out the size of the US Bennett or Bird instruments, and its mechanism is also powered by a compressed air or oxygen source. It differs in mode of operation from other pressure-powered devices in that over a wide range of outlet resistance (in the external conduit) it delivers a predetermined volume of gas each cycle at a preselected cycle frequency. The expiratory value is also pneumatically controlled and allows rapid expiration at low pressure. Thus, a device for experimental and clinical use, capable of delivering a constant, predetermined tidal volume (0 - 1250 cc) during the inspiratory phase, irrespective of external conduit and airway resistance, at a predetermined cycle frequency (10 - 40/min.), is available commercially. The device is small (6 x 14 x 24 cm), light (10 lbs.), relatively inexpensive, and rugged. The expiratory valve is pneumatically controlled, of low resistance, and permits rapid expiration at low pressures. The CELOG-2 can develop a very high power level which exceeds 1 kgm/sec, permitting it to function essentially as a

* Laboratoires Robert et Carrière, 1 avenue de Villars, Paris

flow generator.

In clinical tests on patients with chronic respiratory hypercapnea, 30 minutes of assisted hyperventilation with air using a mask and the CELOG-2 respirator, and in other, similar tests using the Engström volume cycled respirator, the following results were noted at the end of 30 minutes:

Instrument	No. of Patients	Mean Changes at 30 Min. $\Delta PaCO_2$	ΔSaO_2	ΔpH
CELOG-2	12	-9.9 mm Hg	+7%	+0.08
" ENGSTROM	19	-5.4 mm Hg	+4.4%	+0.04

Other current research projects of the Department include: (1) a study by E. Reichart of the long-term effects of chronic experimental hypercapnea on electrolyte concentrations, total electrolyte stores and partition, and on bone composition. (2) A study by A. Lockhart et al. of hemodynamic effects of pharmacologic blockade of sympathetic nerve supply at rest and during exercise in patients with chronic lung disease. Selected recent references are listed in Section IV.

B. PARIS

My sampling of medical clinical research facilities in Paris proved exciting, and resulted in a broad and intensive itinerary which took me to institutes and clinical research activities of four institutions: Hôpital Broussais, Hôpital Laënnec, Hôpital Lariboisière and Hôpital Saint-Louis. Notes on the organization, facilities and research programs of the clinical research components visited in each are presented in the section below. Paris is alive with vigorous programs in medical research.

1. Centre d'Etudes des Techniques Chirurgicales, Hôpital Broussais-CNRS

The Cardiovascular Surgical Center of the Hôpital Broussais under Prof. Dubost is famous. Located in it in a relatively new, eight-story building is a field component of the National Center of Scientific Research (CNRS). This is the Center for research studies on surgical techniques under the direction of Dr. Daniel Daurent. Although located on the compound of a hospital, the Center represents one of the few pure experimental research departments included in my visits. In addition to the full-time professional staff of investigators, medical scientists who are also actively engaged in teaching and the practice of surgery use the facilities for their own experimental surgical investigations.

The physical plant and the efficiency of its subdivision, the diverse, modern equipment, and the adequate numbers of well-trained paramedical assistants all provide resources for an ambitious, well-organized, broad program of research and development in several fields oriented to the surgical sciences. Among these is a program for organ preservation, preparation for transplantation, and transplantation of heart, liver, kidney and lung. The particular research projects within this program explore both the technical and fundamental aspects of organ transplantation. Certain of these program elements are discussed in more detail below:

A second major program is a systematic study of fundamental and technological aspects of assisted circulation and their application to experimental left ventricular failure. The studies are quite advanced, and a next step will be development of a computerized servocontrol of the bypass pump for extracorporeal circulation. Sensing transducers for detecting and assessing physiological variables will have their signals fed to a multichannel input system of the on-line computer, which in turn will signal the electronic command system to effect automatic adjustments in the stroke volume, pressure pulse wave form, and frequency of the pump. This system will be discussed in greater detail below.

A third major program is related to a promising applied RDT&E effort on a modular membrane oxygenator which employs a paper membrane (cellulose acetate) impregnated with silicone.

A final program division consists of fundamental studies in applied cardiac physiology, particularly a study of coronary sinus pressure flow relationships under various stimulation conditions, and an attempt to define reflex mechanisms which may operate on the property of cardiac contractility.

Studies on the Technical Aspects of Organ Conservation, Preparation and Transplantation

Surgeons in this program are Prof. Charles Dubost and Drs. Jean-Paul Cachera and Alain Carpentier. Their attempts at heart transplantation began somewhat over three years ago with autotransplantations of fresh heart in the experimental animal. This resulted in development of surgical techniques which were so satisfactory that the purely technical aspects of the surgery were no longer a problem.

The work then moved along the lines of techniques for conservation and preparation of the heart to be transplanted as a homograft in recipient animals. A first step was the study of the survival by autograph transplants, at variable periods after attempted conservation under conditions of hypothermic and hyperbaric oxygen environments. The results after six hours of storage under the above conditions were excellent; results after 18 hours of storage were very poor, indicating a marked limitation in the techniques of hypothermia and hyperbaric oxygen environment for organ conservation.

More recently, attention has been focused on fresh transplantation employing immediate pretransplantation preparation of the heart for receipt by another animal. The preparation technique consists essentially of perfusion of the organ with antilymphocyte serum in a hypothermic and hyperbaric oxygen environment. To date, they have accomplished this in 150 experimental animals with excellent survival.

Still another facet of the problem has involved systematic studies in an attempt to define precisely the onset of a rejection crisis. So far, combined techniques and observations of the ECG, radiographic studies, enzymatic determinations, and clinical impressions have all failed to indicate singly or in combination the precise time of onset

of the rejection crisis. The group has moved now to more sophisticated physiological studies with implantation of flow meters and other sensing probes to measure physiological variables which may give the information desired.

Studies on Fundamental and Technical Considerations in Organ Conservation

The problem of organ conservation has been studied, using heart and liver. The experiments have dealt with a closed extracorporeal circulation system and a study of the organs' function while stored under hyperbaric and hypothermic conditions. The researchers have also employed measurement of lactic acid consumption and have subjected the tissue to correlative electron microscopic study. In brief, the results have been good for six hours of storage but poor for longer periods.

Other studies on organ conservation include those of Prof. J. Hamburger for kidney conservation; Dr. Milhaud for lung conservation, and finally, a deep freeze storage technique for heart under study by Dr. Cachera.

Carpentier, in a second phase of his work started three years ago, has used a technique of applying solutions to destroy or reduce the antigenetic material of pig donor heart valves, and has managed to adapt the donor aortic valves to the mitral valve sites of recipients. These grafts have a much reduced thrombogenic predisposition. The technique has been successfully applied in 15-25 human cases.

On the technological side, I was informed of a promising development in a highly sophisticated, complex apparatus designed by DeRouessard, an engineer in the Laboratoire des Etudes Cryotechnique de l'Air Liquide, a company near Grenoble. The apparatus permits perfusion of the organ under hyperbaric and hyperthermic conditions with such versatility that each separate physical variable, e.g., partial pressure, temperature, perfusion pressure, ambient pressure, etc., can be independently controlled. Drs. Jacques Hinglais and Laurent have surveyed the instrument's possibilities, but feel that it is far too sophisticated and complicated at the moment for the purpose and stage of their research.

Studies on Assisted Circulation, Fundamental and Technical Aspects

Hinglais and an engineering associate have developed and extensively tested a time and volume controlled extra-corporeal pump, the prototype of which was manufactured by Electronique Marcel Dassault, Saint-Cloud, France. The pump was demonstrated for me under experimental conditions and was quite amazing in its versatility and performance. It is used in conjunction with a remote electronic system control for monitoring and command signals; this system is connected to the electromechanical assembly of the extracorporeal actuator by cables, and provides for accurate control of the stroke volume, pressure pulse wave form, and time distribution characteristics of flow. The pump has a high frequency response, a minimal load sensitivity, even for pressures beyond the physiological range, and finally, adaptability to computer servocontrol. The various elements of the pump action are to be varied through signals from the external command system in response to computer signals determined by the computer program and the continuous input to the computer of the transducerized signals of physiological variables. The present, two-cable, coupled units which are operational are the extracorporeal pump mounted with its motor on a trolley, reduction gears and piston, and the remote control box for monitoring and command. The electromechanical pump includes elements of: (1) a hydraulic transmission between the piston and the auxiliary ventricle which is essential for volume control; (2) a dc motor to drive the piston, the position of which is precisely controlled electrically. In operation, the pump's performance is exact, and its pumping function characteristics can all be adjusted independently. An electronic synchronizer circuit is employed to trigger the stroke from the auricular wave signal of the ECG, or the pump stroke rate can be set at any desired frequency. The need to time the pump cycle precisely is met by modulating the command signal, which is visible on a cathode-ray oscilloscope screen. The push-pull phases (ejection phase-aspiration phase) durations can be varied continuously from a ratio of 1.3/1 to 1/7. The responsiveness of the pump to the command control signal generator is such that a plateau can be introduced at the end of the ejection phase, at the end of the aspiration phase, or both. The controls settings express the lengths of these plateaus as percent of the full cycle length selected; therefore,

the settings are independent of the adopted cycle length and its variation. The stroke volume of the pump can be varied continuously from 0 - 100 mliter, and the frequency from 0-250/min. In actual operation, the moment-to-moment pump performance is monitored by recording the trigger signal, command signal, and piston displacement; these signals are electronically integrated, and can be recorded as volume per stroke or volume per unit time, e.g., 15 sec.

A detailed study of experimental applications of the pump has been made in the dog; observations include measurement of hemodynamic factors, oxygen consumption, arterial flow in the circumflex coronary artery by means of an electromagnetic flow recorder, measurement of the cardiac output and radioactive chromium washout studies at coronary sinus catheterization under experimental conditions of sinus bypass in the open-chest dogs and of right heart bypass. Finally, the pump has been used in conjunction with atrial stimulation. Hinglais has come to the conclusion that so many physiological factors are important in circulatory assist that a number of variables must be continuously sensed, and that a system of computerized servocontrol of this versatile pump is essential for it to be safely and effectively used for circulatory assist by either left heart bypass or counterpulsation procedures. He is working now with simultaneous bloodflow signals, dimension signals derived from left atrial diameter, left atrial pressure signals and the oxyhemoglobin content of blood. The transducer signals of these monitored variables collectively control the command module and adjust the variables of the pump's function. Hinglais impressed me with the depth of his knowledge, and it was apparent that he has sufficient expert engineering assistance from a firm well known for its work in jet aircraft (Electronique Marcel Dassault) that a practical tool for adaptation to human treatment is very likely to come about and may represent a major advance.

RDT&E Studies on a New, Modular Type of Silicone-Impregnated Acetate (Paper) Membrane Oxygenator

This technological development employs units which are rated with a surface area capacity of 0.02 M^2, each capable of effecting for six hours a constancy of CO_2 transfer amounting to 60 ± 12 cc per minute and of O_2 transfer of 30 ± 8 cc per minute at a blood flow rate of 40 mliter per minute. The coupling together of 50 modules would permit this same, remarkable CO_2 transfer for a flow of up to 2000 mliter per minute.

It was apparent from my survey that fundamental and applied research oriented to improved techniques and instruments for diagnosis and patient care is moving rapidly at this institution.

2. Service de Radiologie de l'Hôpital Broussais

The facilities for cardiovascular radiology in the service of Prof. J. Ecoiffier are outstanding. The Hospital actually has two radiology services; one specializes in general diagnosis and therapy. I shall not detail all the equipment and physical facilities, but only enough to indicate that they are superb and must be a great joy to those who work in the department. There are six examination rooms, each fully equipped with an image intensifier, TV monitor, cinéfilm and roll changer film capability. Some rooms have biplane ciné- and roll film capability. The rooms are spacious; the X-ray tables are all of the remote control variety. There are five TV circuits and four automatic film processing units (Exomats). Reference to a published article in the Annales de Radiologie 9, p. 81, will give the reader a rough idea of the beautiful definition achieved in their selective arteriographic studies. Arteriography of the coronary system resulting in films showing an amazing quality and clarity of definition in vascular structures was demonstrated for me. On random film specimens pulled from routine files, all were of exceptional quality and definition.

Their technique for arteriography of the coronary vessels is interesting. The patient's arterial pressure is monitored by a transducer; pressure, the electrocardiogram and other desired physiological functions are monitored on a cathode-ray oscilloscope. The catheter through which the injection material is delivered is advanced to a position above the aortic valve. The assistance of an anesthetist is employed, with the patient intubated under light general anesthesia. When all is in readiness, pulmonary hyperinflation is produced equivalant to a strong Valsalva maneuver. The systemic blood pressure falls, and when it reaches 100 mm Hg or less, the power injection system for delivery of the contrast material is actuated. This procedure facilitates the flow of contrast medium into the coronary system and permits films to be obtained with exceptionally good definition of the coronary radicles.

3. Clinique de Pneumo-Phtisiologie, Hôpital Laënnec

This large department with clinical and research facilities is under the direction of Prof. Georges Brouet. It comprises: (1) an inpatient service of 150 beds for patients with chest diseases, disposed among four public wards, and a private patient unit with ten rooms; (2) a well-equipped, adequately staffed, eight-bed intensive care unit for management of respiratory insufficiency (Centre de Réanimation Respiratoire), using all advanced techniques for resuscitation and assisted ventilation; (3) a spacious, fully equipped respiratory function laboratory with adequate staff of technicians directed by Dr. Pierre Durous; (4) a fully-equipped cardiac catheterization laboratory with videomonitor and videotape recorder equipment to employ image intensifier fluoroscopic control and recording of catheter placement and of contrast studies; multichannel biophysical recording equipment is used for hemodynamic studies; (5) a bacteriology laboratory; (6) a pathology laboratory wherein morbid anatomical studies of lungs by quantitative methods is conducted with the aid of highly sophisticated instruments (Bignon, J., et al., Amer. Rev. Resp. Dis., in press). This component of the chest service is headed by Dr. J. Bignon, who has one assistant pathologist and four technicians; and (7) outpatient clinic spaces, professional and clerical offices, and library and conference room spaces, all of adequate size and well furnished.

The research areas of this department are both basic and mission-oriented. The research effort includes development and evaluation of instruments, equipment, and techniques employed in monitoring and managing severe respiratory insufficiency and its abnormal cardiovascular consequences, including arrhythmias. Clinical diagnosis, prognosis and treament are controlled by correlation to systematically collected physiological, biochemical and quantitative anatomic pathological data.

At present a major study is under way to ascertain which pathophysiological variables in patients with respiratory failure can be most efficiently and effectively monitored continuously in order to assess reliably the time course of cardiopulmonary function in relation to assisted ventilation and other treatment procedures.

Another prospective study has as its objective to define which reasonably convenient tests of pulmonary function are optimal for early detection and assessment of diseases affecting the physiological function and reserve of the respiratory system.

4. Service (Cardiologique) du Prof. Y. Bouvrain, Hôpital Lariboisière

This large department, devoted entirely to clinical cardiology and cardiological research, has had extensive experience with controlled observations of electrocardiographic responses to events during the hospital course of many patients with heart disease. The Assistant Chief of the department, R. Slama, and the head of the new facility for cardiac intensive care, R. Gourgon, have reported a considerable body of data bearing on incidence, precipitating events, nature, treatment and prognosis of cardiac arrhythmias in a series of articles published between 1964 and 1967 in Archives de Maladies du Coeur.

Gourgon, using the facilities at the C-V Research Center, Hôpital Broussais, is experienced in the physiological and technological aspects of extracorporeal assist employed in experimental graded left ventricular failure. He has developed a technique for establishing pulsed synchronous partial venoatrial bypass (with diastolic reinjection), and either isolated or combined bifemoral arterial counterpulsation (unidirectional). Partial venoatrial bypass without counterpulsation did not result in reduction of left ventricular pressure. Efficient arterial counterpulsation combined with partial venoatrial bypass always diminished left ventricular pressure. The summation effect of these two circulatory assistance procedures enhanced the efficiency of assisted circulation in graded experimental left ventricular failure.

Another aspect of circulatory assistance in heart failure currently under study in patients by Gourgon and colleagues is related to definition of the efficacy of and the indications for coupled pulse stimulation applied to the ventricle to produce controlled, repetitive ventricular extrasystoles and the resultant post-extra systolic potentiation. Similarly, Gourgon is studying factors which may indicate the use -- and those which may be prerequisite to the use -- of paired pulse stimulation applied to the atrium to achieve reduction in heart rate when conventional modes of treatment are ineffective.

The important studies of Gourgon and Coumel will now be expanded to analysis of the indications and efficacy of treatment modalities for cardiogenic shock. This study is made possible by the beautifully designed and completely

equipped intensive cardiac care facility, which includes a room with all the equipment for video-monitored and fluoroscopically controlled cardiovascular catheterization, for recording hemodynamic responses, and for analysis of O_2 consumption, blood gas tensions, O_2 saturation, etc. This facility consists of four sections: (1) a line of ten separate rooms with monitors for cardiac rhythm in which patients with known or probable acute myocardial infarction otherwise uncomplicated may be closely followed during the early days of their illness. These coronary care rooms are also used to monitor and closely observe patients with arrhythmias who have or may require an artificial cardiac pacemaker, but who are otherwise not in need of intensive, multiple procedures demanding continuous physician attention. (2) The offices, laboratories and other work spaces of the unit are on the opposite side of the coronary care rooms off a long hall which leads into (3) a large, circular room containing seven true intensive care bed units, each with overhead mounting of conduits which provide for multichannel monitoring of ECG, vascular pressures and other physiological variables. The controls and panels of the master receiving and recording console face the wall; and (4) one special unit for a single patient's intensive care with cardiac catheterization and image intensifier fluoroscopic equipment, equipment for measuring and recording multiple physiological and biochemical variables. This unit is housed in a large, rectangular room adjacent to the circular room, off the right side of the corridor. Rapid access to the single-patient room used for emergency procedures and intensive treatment of circulatory collapse may be either from the hall or from the large, circular room (seven-bed room).

5. Institut de Recherches sur les Maladies du Sang

This hematological research institute and its component clinical service (Service du Prof. Jean Bernard) at the Hôpital Saint-Louis are internationally renowned. Because of its great fame and because of the leukemia chemotherapy research program under CDR R.A. Burningham, MC, USN, at the US Naval Hospital, Philadelphia, I concentrated my effort at the Unit for Chemotherapy of the Leukemias while at the Hôpital Saint-Louis. This unit and the one at US Naval Hospital, Philadelphia, are participants in the worldwide, cooperative study on chemotherapy of leukemias, lymphomas, and Hodgkins disease carried out according to the protocols of the Acute Leukemia Group B (ALGB), sponsored by the USPHS National Institutes of Health (NIH).

The unit at the Hôpital Saint-Louis is under the supervision of (Mme.) Dr. M. Weil. The clinical service has an inpatient capacity of 140 beds. All therapy is carried out according to protocols, not all of which are ALGB protocols. The unit has accumulated vast experience in management of these malignant disorders, and has contributed a large body of data to the world literature, which helps to guide other centers with fewer patients.

To give an idea of the magnitude of the referred patient load to Bernard's service for treatment of these relatively rare, but tragic diseases, they treat an average of 150 new cases of acute lymphoblastic leukemia (mostly children) and 70 new cases of acute myeloblastic leukemia per year.

A practical point is that they do a diagnostic lumbar spinal puncture in all cases of acute lymphocytic leukemia, because there is such a high incidence of CNS involvement, even in the absence of symptoms and in spite of the presence of a hematologic remission.

A second point is the importance of dose limitation in use of a relatively new agent, rubidomycine (13,057 R.P. , derived from cultures of Streptomyces coeruleorubidus) which they have used for about three years in treatment of acute lymphocytic and acute lymphoblastic anemia. In 1966 they reported on results of treatment with rubidomycine in ten patients with advanced acute lymphoblastic leukemia who were resistant to most usual antileukemic drugs. Six of these ten patients, in whom the efficacy of rubidomycine could be evaluated, had either complete remission (four patients) or partial remission (two patients). This favorable response was evident in a remarkably short period of time, i.e., onset within five days and often complete within ten days. The dose was 1.0 mg/kg by IV infusion daily for five days. At this dose it was well tolerated with only one case showing a significant side effect (alopecia).

By 1967 they had experience with rubidomycine in over 80 patients, about half with resistant acute lymphoblastic and half with acute myeloblastic leukemia. A complete remission was achieved in 58% of the acute lymphoblastic and, surprisingly, in 51% of the acute myeloblastic cases. The dose schedule had been modified to 1 to 2 mg/kg

daily for three to eight days, followed by a maintenance injection of 1 to 2 mg/kg once weekly. At this dose, the side effects and toxic effects commonly encountered in leukemia therapy occurred in some as expected (alopecia and stomatitis), but in addition, bone marrow depression was particularly marked. Finally, when the total dose was in the range of 40 to 50 mg/kg, a severe cardiac disorder was very common, and subsequently it was apparent that at such a dose, 5% of the patients may die of myocardial toxicity. They now stress that the total dose of the schedule should not exceed 40 mg/kg; at this total dose, complete or partial remission may be anticipated in all children and in 85% of adults.

Other protocols for other malignant hematological disorders are being systematically explored. Their observations are carefully made and the experience accrued is extensive; the results achieved are hopeful and impressive. I am surprised that the 140-bed inpatient service is inadequate to cope with the patient load. Shortage of beds forces compromises and necessitates procedures being done in the outpatient clinic which should normally be done only on inpatient status. Nonetheless, the reputation of the unit and its success and contributions to achieving prolongation of improved, useful life warrant the additional risk even though the physical facilities are not sufficiently adequate to permit consistent adherence to standard indications for hospital admission.

III. SUMMARY AND COMMENTS

This report presents a survey of the departmental organization, professional personnel, physical and equipment facilities resources and research programs of selected clinical and research departments at various medical institutions of Nancy and Paris, France.

The vigor, scope and depth of the programs and the high quality and productivity of all elements of the seven organized departments which were visited attest to the fact that,at least in medical research, France has been reborn. The quality of physical facilities, the adequacy of advanced research equipment, and above all, the dedicated spirit and competence of professional people with whom I was privileged to confer were a revelation to me. Significant advances in fundamental and applied physiological research and in medical instrumentation technology were apparent in both cities.

The advanced developments which I noted in the basic and applied research and technological aspects of (1) organ conservation, (2) organ transplantation, (3) modalities for assisted circulation, (4) diagnostic and treatment facilities for intensive care of cardiac diseases and advanced respiratory insufficiency, and for malignant blood diseases are all evidence that French medical science has emerged from its long quiescence. The sublimation of traditional scientific greatness caused by the catastrophic events of two world wars and perpetuated by the priorities of economic recompensation until 1950, is no longer present in these medical research facilities. It is important to note that my explorations were not limited to national scientific showplaces. They were to working, striving, vigorous departments with manifestly outstanding professional leadership. The fact that this has all come about since 1950, in spite of all the difficulties which France has had, is the most remarkable impression I have.

This report also presents brief summaries of some of the specific investigations discussed, and includes a listing of departmental components visited and their addresses (Appendix), as well as selected, recent references (IV).

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APPENDIX

Addresses and Names (also in French) of Facilities Visited

NANCY

1. Dept. of Clinical Respiratory Physiology, Univ. of Nancy Medical School, 20 rue Lionnois, 54 Nancy, France

   - Chaire de Physio-Pathologie Respiratoire (Prof. P. Sadoul) de la Faculté de Médecine de Nancy

   - Groupe de Recherche de Physio-Pathologie Respiratoire de l'I.N.S.E.R.M.

2. Service for Respiratory Insufficiency (Prof. P. Sadoul) Maringer Hospital, 34 Quai de la Bataille, 54 Nancy, France

   - Laboratoire de la Fonction Pulmonaire

   - Centre de Réanimation Respiratoire

   - Clinique de Service des Insuffisants Respiratoires, Hôpital Maringer, 34 Quai de la Bataille, 54 Nancy, France

PARIS

1. Cardiovascular Surgical Center (Prof. Dubost) Broussais Hospital, 96 rue Didot, Paris 14, France

   - C.N.R.S., Centre d'Etudes des Techniques Chirurgicales (Prof. D. Laurent), Hôpital Broussais, 96 rue Didot, Paris 14, France

2. Dept. of Chest Diseases (Prof. G. Brovet), Laënnec Hospital, 43 rue de Sèvres, Paris 7

   Clinique de Pneumo-Phtisiologie (Prof. G. Brovet) Hôpital Laënnec, 43 rue de Sèvres, Paris 7

   - Centre de Réanimation Respiratoire

   - Laboratoire Troisier

   - Laboratoire de la Fonction Pulmonaire

   - Laboratoire de la Pathologie

3. Dept. of Cardiology (Prof. Y. Bouvrain), Lariboisière Hospital, 2 rue Ambroise-Paré, Paris 10, France

   Service du Prof. Y. Bouvrain, Hôpital Lariboisière, 2 rue Ambroise-Paré, Paris 10, France

   - Laboratoire Daniel Routier

   - Salle Daniel Routier (Service de Réanimation Cardiologie)

4. Institute for Research on Diseases of the Blood (Director: Prof. J. Bernard), Saint-Louis Hospital, 2 Place du Docteur-Fournier, Paris 10, France

   Institut de Recherches sur les Maladies du Sang (Pr. J. Bernard), Hôpital Saint-Louis, 2 Place du Docteur-Fournier, Paris 10, France

   - Unité de Chimiotherapie sur les Leucémies, Service du Pr. J. Bernard

5. Service de Radiologie de l'Hôpital Broussais, 96 rue Didot, Paris 14, France

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13. ABSTRACT

This report presents a survey of the medical research and development programs of seven departments at selected institutions in Nancy and Paris, France. The research and development areas reviewed include clinical respiratory and circulatory physiology, fundamental and technological aspects of organ conservation and transplantation, modalities of artificial circulatory assistance, chemotherapy of malignant hematological diseases, and facilities for intensive care of respiratory insufficiency and circulatory failure.

Each department was noted to have outstanding professional personnel, optimal equipment resources, and high quality productivity. The space allocations in the physical plants were suboptimal in only two departments.

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14. KEY WORDS	LINK A		LINK B		LINK C	
	ROLE	WT	ROLE	WT	ROLE	WT
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