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This report summarizes some of the physiological research being carried out at the Department of Experimental Research of the Semmelweiss Medical University and at other laboratories in Budapest; and at the Departments of Physiology, Pharmacology and Anatomy at the Medical School in Pecs.

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SOME ASPECTS OF PHYSIOLOGICAL WORK IN HUNGARY

During a trip in May 1972 I intended to visit several laboratories in Budapest, Pécs, Szeged and Debrecen, the sites of the four medical faculties in Hungary. Unfortunately, because of limitation in time and problems in scheduling, I was able to visit only certain laboratories in Budapest and Pecs, and the following will give a brief outline of the many things that I saw and heard about in these two centers.

I. Budapest

My own professional interest and previous contacts in Hungary had been mainly in the field of cardiovascular physiology, so that it naturally occurred that the major part of my visit there was involved in laboratories in this general area.

A. The Experimental Research Department of the Semmelweiss Medical University

This Department has been headed since its establishment in 1959 by Prof. A.G.B. Kovách, whose pervading interest throughout his professional life in research has been the investigation of mechanisms involved in shock. Until 1970 Kovach's Department was purely involved in research and graduate training, but since 1970 he has had the title of Professor; starting in the autumn of 1972 his Department will serve as a second department of physiology in the medical faculty and will be fully involved in the teaching of medical students. Incidentally, the Budapest medical faculty has approximately 400 students in each class, and this will mean that each of the two departments of physiology will handle 200 students. Kovách had just returned to Budapest in January 1972 after a year and a half in Philadelphia where he worked chiefly at the Johnson Research Foundation of the University of Pennsylvania. There, along with some young associates from his laboratory in Budapest, he initiated a collaborative project with Dr. Britton Chance on some of the metabolic effects of shock, particularly on mitochondrial oxidation reactions in various tissues. Kovach hopes for a continued collaborative effort among his and Chance's laboratories, the Cerebral Vascular Unit at Pennsylvania, and Professor Silver at the University of Bristol. This will involve investigations on the effects of hypoxia, stroke and shock upon brain function. Some of the details of Kovách's work with Chance are outlined below.

The work in Kovách's department includes cardiovascular, neurophysiological, biochemical, and metabolic studies, ranging from investigations of basic mechanisms to considerations of the alteration in physiological function during shock of various sorts. A large number of people are involved in these studies, some of which are summarized below.

1. Changes in cerebral mitochondria in hemorrhagic shock: A profound uncoupling of oxidative phosphorylation occurs early in shock, along with a high basic respiration. The oxygen consumption in different parts of the brain is affected differently.

2. The pressure dependence of blood flow: Studies are continuing on blood flow, as well as gland function, in the thyroid and the salivary glands during hemorrhagic shock.

3. Hypophyseal blood flow: This shows less sensitivity to carbon dioxide than does the blood flow of the brain. The flow in the anterior pituitary is less sensitive to pressure change than is that of the posterior pituitary. The flow is affected by somatic stimulation. In these experiments, local blood flow was measured by the hydrogen washout method.

4. Blood flow and capillary filtration coefficient (CFC) is skeletal muscle: During hemorrhage both these measures are reduced when hypotension is severe, in contrast with the findings of Mellander that CFC increases under these circumstances. The discrepancy in the results probably arises from the fact that in Mellander's experiments a somewhat different preparation was used than in these experiments, which were done by Dr. S. [illegible]iro.

5. Circulatory System Analysis: Dr. E. Monos has applied stochastic methods, along with analysis of auto- and cross-correlograms, to investigate the properties of useful and noise components of afferent and efferent neuronal activity (1). Monos is currently studying the effects of "random" modes of stimulation of efferent nerves on the quality and quantity of afferent output in autonomic nerves.

6. Electrical activity in sympathetic nerves supplying heart and forelimb: Drs. Kollar and Fedina have studied the differences in output to these two effector

organs during background activity and activation of the baroreceptor reflex, and during bleeding, cooling and stimulation of somatic afferents. Fedina has been active over the last several years in studies of both central and peripheral neuronal mechanisms involving the autonomic system.

7. Metabolic effects of hemorrhagic shock: Dr. P. Sandor is studying the effects of such shock on gluconeogenesis, oxygen consumption, and redox state of the perfused rat liver.

8. Splanchnic blood flow during hemorrhage: Dr. Hamar has investigated the effect of porto-caval shunt and finds that, following this procedure, in animals who survive the shock there is no mucosal necrosis as compared with the control animal, but at the same time there is no effect on survival rate. This obviously indicates that the intestinal necrosis is not as crucial a factor in causing death as has been supposed.

9. Continuous measurement of redox state of intact tissue: Kovách and Chance have modified Chance's original technique of measuring the redox states of pyridine nucleotide (PN) and flavoprotein (Fp). This consists of a so-called time-sharing fluorometric method, wherein the Fp signal refers to the mitochondrial space and the PN signal to the cytosolic space as well. They have used this technique to follow rapid perturbations of energy metabolism in the heart (2), and intend to apply it to liver, brain and other tissues, particularly in shock situations.

10. Comparative effects of adrenergic blocking drugs: Dr. Rubanyi, in collaboration with Kovách, has studied the action of this class of drugs in the pigeon and several other species of bird. In the pigeon, dibenzaline does not block norepinephrine and epinephrine except at very high (toxic) doses, and fails to block the cerebral ischemic reflex. Isoprenaline in low doses produces a rise in arterial pressure, while in high doses it causes a fall; it increases heart rate; a tachyphylaxis to the hypotensive effect occurs. Propranolol blocks the tachycardiac effect of isoprenaline, and reverses the dilator action of the latter to constriction. Therefore, in pigeons isoprenaline has both alpha and beta effects. While the significance of these observations in terms of pharmacodynamics is unknown, they are important in demonstrating that the concepts of drug action, in terms of specific receptors and their blocking agents, which have

been developed in particular laboratory mammals, are not necessarily adequate for other species, nonmammalian and mammalian as well.

Beyond these particular projects outlined above, a great deal of other work is being carried out in Kovách's active department.

B. The State Institute of Occupational Health in the Department of Experimental Physiology

Drs. A. Erdélyi and A. Mitsányi have been studying the characteristics of the arterial pressure rise in response to sciatic nerve stimulation. They have analyzed the frequency and voltage response relationships. Interestingly they find that in animals under anesthesia there is some depressor response in addition to the pressor response, while in the unanesthetized animal only a pressor response occurs after sciatic stimulation. They have some indication that two central mechanisms are involved in the pressor response. Both men have worked on the general problem of differential responses of sympathetic outflow to afferent stimulation (3, 4). They were formerly in Kovách's department and maintain close ties with him.

In the Toxicology Division of the Institute, Dr. G. Rabloczky and Dr. T. Jancso have been concerned with the development of the sensitivity to epinephrine in the chick embryo, problems of pulmonary circulation, and the relations of basal vascular tone to the response of blood vessels under different conditions.

C. Other Laboratories

In the Physiological Laboratory of the Department of Surgery of the Medical School, Dr. A. Juhász-Nagy has worked for some years on the regulation of coronary blood flow and particularly of the collateral flow, using a heat clearance technique for determination of the latter. For instance, he finds that stimulation of the stellate ganglia increases both total and collateral flow, while after propranolol, stellate stimulation decreases the total flow but with no decrease in "tissue flow." Changes in collateral circulation in response to norepinephrine and stellate stimulation depend to some extent upon the prevailing level of tissue flow. For instance, after occlusion of the anterior descending coronary artery mid-way along its length, if the tissue flow has been decreased markedly then norepinephrine causes an increase in flow, while it causes a decrease in flow if there has been only a small decrease in tissue flow after occlusion. Juhasz-Nagy has also investigated some aspects of the metabolic hyperemia in cardiac muscle.

The research laboratory of the Second Department of Medicine of the Medical Faculty, headed by Dr. L. Takács, is supported by the Academy of Sciences and consists of five people, of whom two are physiologists and three are clinicians. The emphasis in this laboratory is primarily in nephrology and cardiology.

Dr. T. Fenyvesi is investigating the inotropic and chronotropic effects of beta stimulation and blockade, and has evidence for a difference in the pharmacological actions on the two sets of receptors. For instance, the chronotropic response is more sensitive to beta blockade than is the inotropic.

Takács is studying the distribution of cardiac output in pregnancy, with the rubidium distribution method, and finds an increase in the proportion of cardiac output in the uterus. During hemorrhage the fraction of cardiac output to the uterus remains constant. Takács also is investigating the neutritive collaterals in rats following ligation of the femoral artery (5). He and his colleagues are also looking at the mechanisms of reactive hyperemia in the coronary circulation in dogs. They find a greater response under constant pressure perfusion than under constant flow perfusion.

Dr. P. Bencsáth, also working in Takács' laboratory, is interested in so-called denervation diuresis (6, 7), particularly the question whether the increase in sodium and water excretion is due to redistribution between cortex and medulla. There is apparently some medullary dilatation which may not be the primary factor. He concludes that either there is a direct action of catechol amines on tubular transport or there is a change in redistribution of glomerular filtration, but the latter is unlikely. There is no change in oxygen consumption of the kidney with denervation. Micropuncture studies have indicated a decrease in proximal tubular reabsorption of sodium, which may be a direct effect of the catechol amines on sodium transport.

In the Physiological Laboratory of the 3rd Medical Department of the University Medical School, Dr. M. Szentiványi has developed what he calls the modulator theory of adrenergic receptors. His evidence suggests that in coronary arteries and the vessels of the hind limb muscle only a single type of adrenergic receptor exists. For both types of vessel so far investigated, the innervation produces a direct constrictor effect when the muscle is at rest or at a low level of metabolic activity, and this constrictor effect has the standard characteristics of an alpha receptor mechanism. Szentiványi believes, however, that the beta response, i.e., vasodilation, observed especially in the coronary vessels after sympathetic stimulation, results from a transformation of the receptor in the artery as a result of action of some metabolic by-product when the metabolic rate increases. Much of his initial work has been published (8-10), and currently Szentiványi is working to isolate the active substance which brings about the alteration of the vascular receptors.

II. The Medical Faculty of Pécs

A. Department of Physiology

This Department, headed by Prof. K. Lissak, is of the highest international stature. Unfortunately, Lissak was away during my visit. The research activities of the Department are divided into three areas: neuroendocrinology, neurophysiology, and neurochemistry.

The interest of the neuroendocrinological group, which is headed by Dr. G. Telegdy, is aimed mainly at relations between certain aspects of behavior and the regulation of corticosteroid release by the adrenals. Along one line, they have shown that administration of corticoids to rats shortens extinction time (in avoidance responses), while ACTH and vasopressin delay extinction. At least part of this effect appears to be mediated through extra-hypothalamic (i.e., limbic) mechanisms.

Another topic is the role of a serotoninergic system in the response to stress and the production of ACTH. Serotonin (5HT) blocks the *in vitro* stimulating effect of ACTH or of adenohyphyseal extract on production of corticoid by the adrenals. 5HT introduced into the ventricles also blocks the stress effect of intraventricular saline. Likewise, the implantation of 5HT into the medial hypothalamus inhibits stress-induced corticosteroid secretion. Hence it is now thought that this serotoninergic system is inhibitory to ACTH production. Apparently the catechol amines block the stress response by increasing the level of 5HT in the hypothalamus.

Another interesting project is on the relationship between self-stimulation and stress as indicated by corticoid production. Self-stimulation is more effective than is passive stimulation of the lateral hypothalamus; passive stimulation also blocks the effect of histamine. The ontogenetic approach has revealed that the self-stimulation system develops at approximately the same time as does stress response to histamine, that is at about 15 days in rats.

The neurophysiological group is headed by Dr. Grastyan, who unfortunately was away at the time of my visit, and Dr. Angyan. They are concerned primarily with analysis of the learning process and the neural organization of reinforcement. Their main topics are (1) analysis of motor behavior through investigation of ipsiversive and contraversive movements, the so-called "double effect"; (2) self-stimulation as a model of the learning process; (3) analysis and correlation of sensory systems with respect to motivational states, by analysis of change in evoked potentials during different behavioral states such as sleep; (4) organization of motor behavior in terms of the mechanisms involved in "initiation" and "stop" behavior, as well as analysis of vegetative reactions such as arterial pressure during different behavioral states. In addition there is a special technical branch in the neurophysiological group headed by Dr. Kellenyi, who has developed such devices as tape systems and analog to digital converters.

B. Department of Pharmacology

The head of the Department, Prof. J. Porszasz, has been interested for some years in cardiovascular reflexes, including the central nervous mechanisms, and properties of the transmitter substances involved in these reflexes. Porszasz has recently been interested in the inhibition of sympathetic efferent activity by somatic and visceral afferent activity, and finds that the inhibition produced by the latter is much more long lasting than that produced by the former. He interprets this as indicating that more synapses are involved in the visceral afferent inhibition. The inhibition is decreased by alpha-adrenergic blocking agents, but is not influenced by atropine. Without anesthesia no inhibition is produced by somatic afferents, but inhibition is still produced by vagal afferent stimulation.

Dr. J. Szolcsányi has worked for some years on the mechanism of action of capsaicin on sensory receptors, and the production of desensitivity by this substance (11-13). Dr. F. Varga is studying mechanisms of drug absorption. Dr. Decsi is interested in transmitter substances in the central nervous system.

C. Department of Anatomy

While I had no opportunity for scientific discussions with this group, I should at least mention the two main lines with which I am acquainted. One is the extensive and outstanding work by Prof. B. Flerko in neuroendocrinology. The other is in developmental neurobiology being carried out by Dr. G. Székely, who has studied the relations between functional development of the nervous system and that of muscles (cf 14-16).

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