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ABSTRACTS

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The structure of the intracardiac nervous system

Studies by a modification of the Bielschowsky method have revealed the following evidence concerning the single layers of the cardiac wall and the blood vessels of the heart in specimens from different vertebrate species.

In every one of the three layers of the wall of the heart, and especially in the epicardium and endocardium, receptors of various shapes occur, belonging mostly to the vagal sensory system, and in a smaller part to the first thoracic spinal ganglia. The number of receptors is particularly high in the atrial epicardium, where the terminal rami of the thick, myelinated fibres form mainly dendritic ramifications. In the endocardium there are also such receptors, in which the fine terminal rami show tuft-like arrangement. The receptors in the myocardium are similar to muscle spindles, and are located in the area of the atrial septum. The myocardial efferent fibres form terminal rings, or, tapering off, adhere to the sarcolemma like the motor fibres of the *Anamnia*. Most of the ganglia occur in the area of the atrial epicardium. The ganglionic cells, among which many special forms occur, are mostly of the Dogiel I, and in a smaller number of the Dogiel II type. Most of the interneuronal synapses made up by the preganglionic fibres of vagal origin form spirals and pericellular plexi but terminal rings and buttons are not uncommon, either, particularly in the area of the venous sinus.

The cardiac vessels are rich in efferent fibres, specialized receptors could be demonstrated exclusively in the wall of the coronary artery and the left coronary vein. The receptors of the coronary artery are thick myelinated fibres terminating in buttons lying close to the inner part of the adventitia. The receptors of the coronary veins are dendritic ramifications extending over a large surface, and terminating with fine fibrils in extensive neurofibrillar lamellae.

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The nervous control of coronary circulation

It has been shown earlier that, in agreement with the histological data, the intracardiac ganglia and the sympathetic preganglionic fibres running to them play a decisive role in the innervation of the coronaries. The vagus does not participate in coronary innervation. The preganglionic fibres running to the intracardiac adrenergic ganglia are the constrictor fibres of the coronaries, while those running to the intracardiac cholinergic ganglia are the dilators. Stimulation of the preganglionic fibres causes constriction or dilatation, without altering the metabolism of the heart. As opposed to this, stimulation of the sympathetic postganglionic fibres innervating the myocardium, and the intracardiac administration of adrenaline cause an increase of coronary flow, which is a secondary consequence of the increased cardiac metabolism, of the release of metabolites. This metabolic dilatation takes place at the capillary level. In the tortoise, whose coronaries have no capillaries, adrenaline exerts exclusively its primary effect, causing vasoconstriction.

The coronary constrictor fibres maintain a constant vasomotor tone, the blocking of which by surgical or pharmacological methods results in coronary dilatation.

The circumstance that the adaptation of the coronary system — which consists first of all in meeting the increased demand resulting from increased cardiac activity — takes place also without any external nervous effect, made it doubtful whether the vasomotor fibres had any physiological role in coronary control. It was especially the role played by the coronary constrictor fibres that had to be elucidated, because their excitation leads even to a reduction of the blood supply to the heart.

It has been shown that whenever the general sympathetic tone is increased, *i.e.* blood pressure is raised, together with other sympathetic nerves the coronary constrictors are also stimulated. Thus coronary res stance increases in connection with the increase in blood pressure following the clamping of the common carotids. One of the important physiological roles played by the coronary constrictor nerves is that in the case of an increase in general sympathetic tone the resulting coronary constriction so-to-say brakes down the dilatory response to the increase of metabolism. Correspondingly, the O_2 consumption of the heart, recorded by means of the densitometer, remains at an optimum level.

The other important role played by the coronary constrictor fibres is the maintenance of perfusion pressure at an optimum level during the state of enhanced sympathetic activity. The increase in the tension of the coronary

wall resulting from the elective stimulation of coronary constrictors, or from the increase in coronary pressure leads namely to an excitation of the mechanoreceptors of the coronary wall, to a reflex fall of blood pressure. This reflex is extinguished by vagotomy. Thus, the above fine reflex interplay facilitates a fine correlative interaction between coronary resistance and peripheral vascular resistance, *i.e.* blood pressure.

The precise adjustment of coronary flow to the changes in cardiac metabolism is well-known. Although the adaptation, being the property of blood vessels, takes place without any nervous effect, the most important physiological role of the coronary constrictor fibres is to ensure this metabolic adaptation. In our experiments the hyperaemic reaction following the interruption of coronary flow served as the measure of metabolic adaptation. In the state of increased constrictor tone following unilateral or bilateral carotid clamping a great increase in the hyperaemic response could be observed. In contrast, surgical or pharmacological interruption of the constrictor pathways (stellectomy, intracoronary administration of dibenzylamine or hexamethonium) was followed by a considerable decrease, or even total abolition of the hyperaemic response. In the latter case restoration of the coronary tone by the intracoronary injection of vasopressin led to a revival of the hyperaemic response. Thus, a constant coronary constrictor tone is an essential prerequisite of coronary metabolic adaptation, without which the O_2 consumption of the heart under stress is also unfavourable, the oxygen debt is increased.

One of the most surprising results of the experiments was that the coronary constrictor tone had been extinguished the hyperaemic responses not only decreased, but in most cases disappeared. For this condition neither the closure of the arteriovenous shunts, nor the collateral flow coming into existence during the interruption of flow can be held responsible. On the one hand namely, following the cessation of the coronary constrictor tone, the O_2 content of sinus blood did not decrease, but increased, and, on the other hand, the fall of coronary pressure was the same in the control experiments as following the extinguishing of this tone. In contrast to this, the slope of the flow-curve having been smoothed following the cessation of the coronary constrictor tone suggests that the coronaries behaved as rigid tubes.

In our opinion this "rigidity" of the coronaries is a process analogous to what happens during a coronary attack. In both instances it is an inadequate adjustment to cardiac metabolism of coronary flow which is in the focus of the events, without real decrease in flow. (For the human disease this has been shown by PELLEGRINI.) On the basis of our experimental evidence the development of angina pectoris is believed to take place in the following manner. In some way the coronaries have become insensitive to the tonic impulses of the vasoconstrictors, and, similarly to what happens when the

constrictor pathways are interrupted, a "rigidity" of the coronaries occurs. Such a peripheral uncoupling of the coronary constrictor tone may be also the result of an overstrain, an exhaustion of the constrictor system. It has been found namely that repeatedly protracted increases of the coronary constrictor tone result in an insensitivity to the constrictor impulses and in rigidity.

In our experiments the coronary "rigidity" appeared not immediately after the cessation of the constrictor tone, but only after the gradual decrease of the hyperaemic response. Correspondingly, the cessation of the constrictor tone is not the direct cause of rigidity, but it is merely the initiator of a mechanism, which ultimately leads to coronary rigidity. The fact that the phenomenon can be induced also by the intracoronary injection of physiological saline indicates that after the sympathetic coronary constrictor tone ceased the changes in the NaCl and water content of the blood vessels lead ultimately to "rigidity". Hypoxia and minute thrombi in the heart produced a similar effect.

Studying the correlation between arteriosclerosis and this experimental angina pectoris, it has been found that in the isolated heart of rats maintained on atherosclerotic diet the rigidity did not develop more often and easier than in the normal controls, provided the morphological change was not severe. Increasing the severity of the change, it was easier to induce "rigidity". In grave atherosclerosis the coronaries were *a priori* rigid, insensitive to the metabolic stimulus of an interruption of flow, though by no means in every case. All these lend support to the old clinical observation that angina pectoris may develop also in the heart free from arteriosclerosis, and that severe arteriosclerosis is not always associated with angina pectoris. Thus, arteriosclerosis can promote the development of angina pectoris, of coronary "rigidity", but cannot be identified with it.

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The reflexes of the heart

The mechanoreceptors located in the areas of coronary circulation, atria and great vessels are the starting points of reflex mechanisms playing a decisive role in the regulation of peripheral circulation. On the basis of our studies carried out for several years, two groups of cardiac and circulatory reflexes may be distinguished, viz. 1. the buffer reflexes, the representant of which is the carotid sinus reflex, and 2. the stabilizer reflexes, represented by the coronary sinus stabilizer reflex (SCSR), first described by the present

authors. The buffer reflex is characterized by the short duration of the depressor effect, as well as by the gradual increase in the reflex response to the increase in stimulus intensity, while the stabilizer reflex is characterized by the long duration of the hypotensive response, the "all or nothing" nature of the effect, the trigger-like action and the extreme sensitivity to general anaesthetics. Beside the SCSR a further reflex but of a buffer nature (coronary depressor reflex) can be elicited from the area of coronary circulation. The latter reflex, whose receptors are presumably in the wall of the coronary arteries, can be separated from the SCSR not only haemodynamically and on the basis of the sensitivity to anaesthetics, but also on grounds of the central nervous localization. As that of the buffer reflexes in general, the centre of the coronary depressor reflexes is in the area of the vasomotor centre in the brain stem, thus the reflex persists after a transversal cut across the pons. In contrast to this, in the case of the SCSR the intactness of the mesencephalic structures is a necessary condition.

According to our investigations, the receptors of the coronary chemoreflex (Bezold—Jarisch reflex), that have not been localized precisely before, are identical with the receptors of the SCSR. It has been shown that the Bezold—Jarisch reflex continues to behave in the same manner as the SCSR even after the brain stem has been cut at an appropriate level.

Evidence has been obtained to show that at the junction of the left atrium and pulmonary veins, as well as in the wall of the latter, there are receptors of circulatory reflexes of stabilizer nature, essentially identical with the SCSR. In response to the stimulation of these receptors blood pressure is stabilized at a low level and the oxygen saturation of arterial blood is considerably diminished. For the latter phenomenon, observable also at the elicitation of the SCSR, presumably an opening of pulmonary arteriovenous shunt is responsible. A similar decrease in arterial oxygen saturation never takes place in response to the buffer reflexes, and these reflexes, unlike the SCSR, are inactive also on the arteriovenous shunts of the extremities. From these and other facts it is concluded that the fall in blood pressure is based on the participation of different vascular areas in the cases of the stabilizer and the buffer reflexes.

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Effect of endogenous vasoactive substances on the coronary fraction of cardiac output

Employing SAPIRSTEIN's ^{86}Rb indicator fractionation method, the effect of certain endogenous vasoactive substances on the coronary fraction

of cardiac output has been studied in the rat. From the values for cardiac output and blood pressure, coronary flow and resistance were calculated.

Angiotensin II (0.1 and 0.55 μg/kg/min intravenously) slightly increased the coronary fraction, but had no effect on blood flow and resistance. Serotonin creatinine sulphate (0.4 to 10.0 mg/kg, intraperitoneally) was effective in the highest dose only; it increased blood flow and coronary flow, but decreased the resistance. Norepinephrine was applied in doses of 20, 100 and 500 μg/kg, intraperitoneally; the two smaller doses slightly increased the fraction, the highest significantly increased coronary blood flow and diminished the resistance. Epinephrine (100 and 500 μg/kg, intraperitoneally) dilated the coronaries and increased coronary flow. In response to the higher dose the fraction increased.

In earlier experiments it has been shown that after bleeding, as well as in tourniquet shock the coronary fraction of cardiac output was significantly higher than in the controls. None of the agents tested could by itself produce that effect.

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Studies of the revival of the automatism of frog hearts arrested by the Stannius II ligature

It has been observed that after the second Stannius ligature has been placed ventricular automatism is revived in but about 40 per cent of the cases.

Comparison of the cation composition of the ventricles starting to beat spontaneously after the second Stannius ligature (potassium, 104.6 $\pm$ 7.9 meq/l; sodium, 71.0 $\pm$ 25.8 meq/l) with that of hearts failing to resume their function (potassium, 103.3 $\pm$ 8.9 meq/l; sodium, 64.4 $\pm$ 15.1 meq/l) and with the normal values (potassium, 105.1 $\pm$ 7.7 meq/l; sodium, 56.7 $\pm$ 17.8 meq/l) revealed no significant difference in the three experimental groups.

Measurement by microelectrodes of the transmembrane and action potentials has shown that at the base of the ventricle the transmembrane potential values are grouped around two maximums, 45 to 55 mV (27.6 per cent of the measurements), and 65 to 75 mV (44.8 per cent). As opposed to this, at the apex the values are between 65 to 80 mV in 90 per cent of the cases.

The action potentials from fibres of low transmembrane potential showed slow diastolic depolarization, which, according to data in the literature, is characteristic of atrial fibres.

Thus the explanation of the revival of automatism is to be sought in the presence of atrial type fibres among the ventricular muscle fibres.

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Enzyme activity in cardiac ganglia

The localization in the cardiac ganglia of cholinesterases, alkaline and acid phosphatases has been studied. The cholinesterases were identified by the GEREBTZOFF and COUPLAND and HOLMES modifications, the alkaline and acid phosphatases by the GOMORI–TAKAMATSU and the GOMORI method, respectively. Both kinds of cholinesterase were bound to be represented in the cardiac ganglia. On the basis of their cholinesterase activity, two types of cells have been distinguished. With the cholinesterase active type I cells only the body of the cell, with type II the body as well as a process show strong cholinesterase positive reaction. The strong cholinesterase activity of the synaptic areas is readily demonstrable in the cat, particularly following vagal stimulation, or 1 to 8 hours after bilateral vagotomy. The synaptic zones displaying strong activity are somewhat bigger than the morphologically demonstrable synapses, and the intensive activity extends also to preganglionic fibre's preterminal segment which is in contact with the body of the cell. The cholinesterase active cell types I and II are shown also by the alkaline phosphatase reaction. It is, however, undecided whether the two cell types are the same. As compared with other cellular surfaces, the synaptic spaces show no alkaline phosphatase activity. The acid phosphatase reaction is strong in the nerve fibres, and the cholinesterase active type I cells also display acid phosphatase activity.

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Electron microscopy of the impulse conducting system and nervous elements of the heart

In the rat and the guinea pig no fundamental difference has been found to exist between the conductor fibres and the common muscle fibres of the heart. The ultramicroscopic components are the same in the two types of fibre. There are, however, definite differences in the quantity and location of myofibrils, in the organization of the endoplasmic reticulum, in the distribution of mitochondria, and in the connexion between fibres, *etc.* At certain points of the system, the structure of the conductor fibres shows significant differences. The most typical conductor elements are to be found in the sinus node. There are also certain species differences between the rat and the guinea pig. A parallelism may be established in many respects between the ultramicroscopic and the physiological data.

In certain areas of the heart, and especially of the conducting system, the amount of nerve fibres shows considerable variations; the largest number occurs in the Aschoff—Tawara node. There is a certain difference between the individual and the collective innervation of the nerve fibres. No subneural junctions have been found in the heart, but specific elements have been detected. So, for example, near the sinus node cells similar to chemoreceptor cells, and adjacent to the Aschoff—Tawara node swollen axons similar to the Herring bodies could be observed. In the latter granules corresponding morphologically to adrenaline have been demonstrated.

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The effect of hypoxia on coronary blood flow

In dogs with crossed circulation and isolated perfusion of the head, the effect on coronary circulation of isolated cerebral and isolated trunk hypoxia has been studied. In response to isolated cerebral hypoxia, coronary flow decreased and coronary resistance significantly increased. After the relief of hypoxia coronary dilatation with a significant diminution of coronary resistance occurred. Under isolated trunk hypoxia coronary flow was considerably increased and coronary resistance decreased. Cardiac output increased slightly in isolated cerebral hypoxia, and significantly in isolated trunk hypoxia. Blood pressure increased significantly in both cases.

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The influence of duodenal osmoregulation on cardiac activity and blood pressure

The intraduodenal injection of hyper- and hypotonic solutions lowers the mean arterial blood pressure. The pressor reflex evoked by clamping the two common carotids, as well as the hypertensive response to stimulation of the splanchnic nerve are also significantly diminished. Meanwhile, the heart rate increases, and in the ECG depressed R waves, and in leads 2 and 3 elevated P waves appear. The phenomenon persists for more than 1 hour.

The phenomenon is thought to be caused by inhibitory impulses from the osmoreceptors of the duodenal mucosa reaching the vasomotor centre *via* the vagus, lowering its tone. This view is supported by the observation

that bilateral cervical vagotomy abolishes the above phenomenon. The humoral nature of the effect could be ruled out in dogs with crossed circulation. The investigations supply an explanation of the development of the dumping syndrome.

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Regulation of the fibrillatory tendency of the heart in hypoxia

The correlation between arterial hypoxia and the tendency to atrial and ventricular fibrillation has been studied following total or partial elimination of the nervous control of cardiac activity. The tendency to fibrillation was established by estimating the so-called fibrillatory threshold, *i.e.* the weakest electrical stimulus still capable of evoking fibrillation.

In situ the heart of anaesthetized cats showed under the effect of arterial hypoxia an increased tendency to fibrillation while in the heart-lung preparation the tendency to fibrillation diminished parallel with the decrease of the O_2 saturation of arterial blood. In isolated ischaemia or hypoxia of the head the tendency to fibrillation increased, whereas it decreased in isolated hypoxia of the torso.

Acute denervation of the heart, bilateral cervical vagotomy, or atropine treatment prevented the enhancement of fibrillatory tendency by hypoxia, whereas sympathectomy or dibenzylamine treatment had no influence on it.

Thus, for the increase of the tendency to fibrillation in hypoxia a hypoxia of the central nervous system is responsible in the first place, through stimuli reaching the heart decisively by vagal mediation.

The above apply to initial hypoxia. In chronic hypoxia the tendency to fibrillation is decreased, presumably as a result of an exhaustion of nervous centres.

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Correlation between myocardial hypoxia and the catecholamine level

In rats under ether anaesthesia the intravenous injection of vasopressin causes coronary constriction and the resulting myocardial hypoxia alters the ECG tracings in that the ST segment and the T wave are elevated. Comparing

the elevation of the T wave with the control ECG tracings, dose-response curves have been plotted. *Vasopressin* $ED_{50} = 1.1$ (0.83 — 1.45) U/kg.

Reserpine (a total of 7.5 mg/kg in two days) or guanethidine (30 mg/kg six hours before the experiment) significantly reduced the sensitivity to vasopressin: $ED_{50} = 7.0$ (5.46 — 8.88) and 5.8 (3.72 — 8.98) U/kg, respectively. In reserpine-pretreated animals strophantin (250 to 500 μg/kg 30 minutes before the injection of vasopressin) did not restore the diminished sensitivity to vasopressin.

Pretreatment with 50 mg/kg of phenelzine, a monoaminoxidase inhibitor, significantly increased the sensitivity to vasopressin: $ED_{50} = 0.50$ (0.33 — — 0.75) U/kg and suspended the effects of reserpine and guanethidine.

Epinephrine and norepinephrine administered intravenously (0.5 to 10.0 μg/kg) had no influence on the ECG tracings of the normal and the reserpine-pretreated animals. When, however, the animals treated with reserpine were administered 100 μg/kg of norepinephrine subcutaneously and 5 minutes later the usual dose of vasopressin sensitivity was restored to normal.

The results suggest a close correlation between the elicitability of hypoxia and the catecholamine content in heart muscle.

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Effect of imipramine (N-[3-dimethylamino-propyl]-iminodibenzyl-HCl) on impulse formation in the rat heart in vivo

In the nervous effect of imipramine both sedative and antidepressant components can be demonstrated. The effect of the drug on the electrocardiogram of rats anaesthetized with urethane has been studied under various states. Arrhythmia or fibrillation were elicited with aconitine (50 μg/kg, intravenously) and calcium chloride (120 mg/kg, intravenously). Bradycardia was induced by pretreatment with reserpine (2×5 mg/kg, subcutaneously), bretylium tosylate (2×40 mg/kg, subcutaneously) and guanethidine (2×20mg/kg, subcutaneously). We have determined, that

1. Imipramine in intravenous doses of 4 to 6 mg/kg inhibited the disturbance of rhythm caused by aconitine and calcium chloride.

2. The bradycardia elicited by pretreatment with reserpine could be antagonized in 65 per cent of the cases by the intravenous injection of 4 mg/kg of imipramine. The drug, however, had no influence on the bradycardia caused by bretylium tosylate and increased the negative chronotropic effect of guanethidine.

The data indicate that the opposing effects of imipramine on the nervous system can be demonstrated also in the opposing excitatory states of the heart.

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On the problems of regulation in experimental infarctoid cardiomyopathy

In the case of infarctoid cardiomyopathy, complex problems of regulation and correlation occur side by side. In the course of investigations into the effects of the cardiopathogenic diet S. 65. it has been found that changes are demonstrable in the central nervous system at the time the cardiac changes develop. In the cerebral blood vessels sclerosis, in the cerebral cortex, subcortical areas and the spinal cord microhaemorrhages, microemollitions, nerve cell degenerations are detectable. Cholinesterase activity decreases, and, correspondingly, an increase of acetylcholine can be demonstrated. The paper of GELENCSÉR and DÉSI will deal with nervous system involvement, those of CSALAY and SELMECI with the hormonal influences and changes connected with cardiopathy. New data will be presented by RIGÓ as to the role of potassium and magnesium.

The significance of lipids has been studied by the administration of increased amounts of fatty acids. Treatment with oleic, linoleic, lauric, palmitic, arachic and sebacic acids has shown that the protection against the components of the cardiovasopathogenic effect does not depend simply on the saturated or unsaturated nature of the fatty acids.

The significance in the changes in enzymatic and metabolic activities will be discussed by HARMOS. Vitamin E, too, plays a similar role. Tocopherol afforded protection in some measure against the development of infarctoid changes, and prevented the decrease in the nitrogen content of the aorta and the increase in the serum cholesterol-ester level. Thus, innumerable extra- and intracardiac processes are involved in infarctoid cardiopathy.

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Correlation between adrenal activity and experimental cardiopathy

In previous studies it has been shown that in rats fed on a cardiopathogenic diet the corticosterone content of adrenal venous blood and hormone synthesis by the adrenals were increased during the period preceding myocardial lesion. In the light of this evidence and of data in the literature concerning the correlation between experimental cardiopathy and adrenal activ-

ity, the role of the adrenals in the genesis of the cardiac lesion produced by the cardiopathogenic diet has been investigated.

Rats subjected to adrenalectomy and treated with prednisone developed in response to the cardiopathogenic diet grave liver lesion prior to the appearance of myocardial lesions. Chronic ACTH treatment caused aggravation of the cardiopathy and brought about hepatic lesions.

It has been shown that in the genesis of the heart muscle lesion which develops during chronic ACTH treatment equally important roles are played by the salt composition of the diet (rich in Na^+, Cl^-, PO_4^{3-}, deficient in K^+ and Mg^{2+}), as well as by the increased intake of protein fat and vitamin D_2. Similar observations have been made concerning the developemnt of the liver lesion. The glycogen content of the liver did not change in respnose to the cardiopathogenic diet, but it decreased on ACTH treatment. The vitamin E deficiency demonstrable in the animals maintained on the cardiopathogenic diet may have a role in the development of the liver lesion.

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The role of sex in the development of experimental cardiomyopathy

It has been studied whether the sex difference had a role in the development of dietary cardiomyopathy. Rats from the stock of the Institute, weighing 120 to 140 g, were used. There were three groups of 11 animals each, (i) males, (ii) females and (iii) castrated females. The duration of the experiment was 8 weeks.

During the experimental period the males and castrated females lost weight. Blood pressure increased in all three groups. The difference in the blood pressure increase was not significant between the single groups.

There were decisive differences in survival rate. By the end of the 8th week only 2 of the males, 1 castrated female and 10 females were alive. In the heart of the dead animals infarctoid changes and infarction were found. Thus, the development of dietary cardiomyopathy is decisively influenced by the sex differences and hormonal activity.

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Effect of magnesium on the changes of myocardial potassium content

In the infarctoid changes induced by means of a cardiopathogenic diet the K and Mg content of the heart muscle decreased. It is known from the literature that the administration of KCl and $MgCl_2$ is equally capable of preventing the cardiac infarctoid changes induced by various methods. The question is, in what way does Mg regulate the K content of heart muscle?

In one group of experimental animals infarctoid cardiac changes were produced by feeding a cardiopathogenic diet. It has been found that the K content of heart muscle decreased from 90 meq/1000 g to 70 meq/1000 g. In animals maintained on a cardiopathogenic + Mg rich diet the decrease of K did not take place and the infarctoid changes did not develop, either. To elucidate the phenomenon, the K content of the perfusing fluid (Boyle—Conway's solution) under the effect of different Mg concentrations was examined in the isolated frog's heart, suspended according to Straub. On increasing the concentration of Mg fivefold, the K content of the perfusing fluid was significantly lower than the control value. According to investigations involving the use of ^{42}KCl, the myocardial activity of the animals fed the high Mg diet was 20 per cent higher than that of the control group 3 hours following the intraperitoneal administration of the labelled K.

The results indicate that in a medium rich in Mg the K uptake by the heart muscle is increased and the K output decreased.

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Histochemistry of dietary cardiac lesions

To exert a dietary influence on cardiac metabolism, an atherogenic diet (S-60) and a cardiopathogenic diet (S-65) were fed. The succinic dehydrogenase, ATPase, alkaline phosphatase, and PAS reactions, the methylene blue extinction (at pH 2.62), and the SH content of the heart and the coronaries were studied.

Under the experimental conditions employed dietary factors produced profound metabolic changes in the heart and the coronaries. These were demonstrated histochemically earlier and more sensitively than by the usual histological techniques.

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Effect of cardiopathogenic diet on the thiopental anaesthesia

The duration of sleep induced by thiopental has been studied in rats maintained on a cardiopathogenic diet, as well as in rats fed half portions of a normal diet causing a similar loss of body weight. The animals maintained on the cardiopathogenic diet developed hypertension, while the semi-starving ones showed a slight decrease of blood pressure. As compared to the control group, the duration of sleep induced by thiopental gradually increased in both groups during the six weeks of the experimental period, but the increase was considerably greater in the cardiopathogenic diet group. In the third and sixth weeks of the experiment the duration of ether anaesthesia was practically unchanged. With the development of the dietary lesion the fall in body temperature and blood pressure became more and more marked, thus, not only the duration, but also the depth of anaesthesia increased. Lethal consequences occurred in the largest numbers during the sixth week of the cardiopatho genic diet. The results lend support to the previous evidence that thiopental anaesthesia is contraindicated by nutritional disturbances of the heart muscle.

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Central nervous lesions caused by cardiopathogenic diet

It has been investigated whether the cardiopathogenic diet S-65 would damage exclusively the heart muscle or disturbs also the central nervous regulation.

In 25 rats EEG and conditioned reflex studies have been made. Prior to and during feeding the cardiopathogenic diet the spontaneous EEG tracings, as well as the changes in the EEG response to electrical stimulation were examined daily by built-in electrodes.

From the 6th day onward the frequency of spontaneous activity began to increase, the amplitude decreased. Later, hypersynchronous activity of very fast frequency and high amplitude appeared from time to time. Gradually, the duration of desynchronization in response to stimulation increased and the

established conditioned reflex responses weakened. Histological changes could be demonstrated in the brain of the experimental animals.

Considering that the functional central nervous changes occurred during the first week of the experiment, whereas the myocardial lesion developed in the fifth week, increased central nervous excitability may probably have a role in the development of myocardial lesions.

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Adaptation to muscle activity of circulation control

The increase of heart frequency in response to graded muscular work and the time required for restitution depend on the ability to physical performance. It has been shown that with the normalization of the pulse rate after physical performance (the 250 and 500 mkg step test of NEMESSURI) a prolongation of the RR distances beyond the resting value occurs usually within one minute. This counterregulatory phenomenon is demonstrable not only in sportsmen, but sometimes also in schoolchildren, as early as 30 to 40 seconds after physical activity. In trained sportsmen this negative phase of the heart rate, that of trophotropic excitation, manifests itself in the second or third minute following performance and may depress the heart rate by as much as 5 to 10 min. below the resting value. The phenomenon is demonstrable, but does not become dominant, if the same sportsmen are not in good form. In such cases the duration of restitution, half to one minute long in good form, is substantially prolonged and also the increase in pulse rate significantly exceeds the values measured in good form.

The results tend to indicate that the dominance of the negative phase lasting one or two minutes or longer in the pulse rate response to physical effort may be interpreted as a sign of adaptation favourable from the point of view of performance.

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The regulation of energy metabolism

In an introductory lecture the problem has been discussed whether energy metabolism represents simply the sum of a number of more or less independently regulated entities, or whether, in addition, the existence of an integrative regulation of energy metabolism has to be postulated. The literature

on the metabolic rate of poikilothermic animals, the analysis of the hyperthermic increase in the metabolic rate, on the hypoxic decrease in heat production, and the changes in the ratio of shivering and non-shivering heat production in response to cold exposure, were interpreted to indicate the presence of an integrative mechanism regulating overall heat production in response to cold and also in some responses not concerned directly with thermoregulation.

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The role of the nervous system in the adaptation of oxygen consumption to hypoxia

In air containing 8 to 10 per cent O_2 the oxygen consumption of the rat drops, and at the same time the O_2 content of the air in the chamber increases for about 2 to 3 minutes, or in the closed chamber the pressure of the air increases. Thus, the partial O_2 pressures of the organism and the air become equilibrated and in that period true consumption cannot be measured by such a method. On reverting to air, an opposite change takes place, the hypoxic reaction does not change, or changes only slightly in repeated experiments. If, however, the experiments are begun with the presentation of an indifferent (optic) stimulus, O_2 uptake drops in the second or third hypoxic period already, and the organism responds in the third or fourth period of hypoxia with an immediate increase of O_2 consumption. In this case the conditioned reflex elicited by the indifferent stimulus manifested itself with an increase of O_2 uptake, but without the indifferent stimulus the organism responds to hypoxia in the same way as before the associations. Hypoxia without association temporarily extinguishes the established conditioned reflex. Hypoxia as a stimulus altering O_2 uptake, acts similarly to drugs having a peripheral site of action, the O_2 uptake increases in response to mild hypoxia, remains unchanged when hypoxia is of moderate severity and decreases when it is grave. The organism adapts itself rapidly to repeated hypoxias combined with indifferent stimuli. The differences in reaction of the different animal species and of the individual animals are determined by the phylo- and ontogenetical development of the nervous system, as well as by the acquired individual reactivity.

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Responses of energy metabolism in the newborn

The newborn rat fails to maintain body temperature in an environment of 30° C, although heat production rises well above that observed at an ambient temperature of 35° C. The fall in body temperature is not due to an inability to increase heat production further, since after exposure to hypoxia (12% O_2) oxygen consumption was considerably greater. Newborn rabbits fall into two groups. The first, comprising the great majority of the animals were capable of maintaining their body temperature in an ambient temperature of 20° C already on the first day of life, whereas the second group failed to do so despite an increase in heat production of the same magnitude. Although the latter group consisted of animals of smaller body weight, this was not the determining factor, since body temperature continued to fall in response to exposure to 20° C even after the body weight had surpassed the birth weight in the first group. Genetic differences appear to be the most plausible explanation. Like most mammals, the newborn rabbit responds to hypoxia in an environment of 20° C by a fall in body temperature and a reduction in heat production. This response of body temperature persisted throughout the investigated first three weeks of life, whereas the metabolic rate failed to respond to hypoxia after the 10th day of life even at ambient temperatures of 6° to 8° C.

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The effect of caloric and protein restriction on the heat production and body temperature in the rat

In rats maintained on a diet covering 1/3 of the caloric requirement and containing 3 per cent protein, heat production significantly decreased at every ambient temperature tested (35°, 30° and 20° C) when body weight had decreased by 10 to 20 per cent. Colonic temperature was unchanged at the indifferent and at the warm temperatures, but at 20° C the decrease of body temperature exceeded by far that found in the normal controls. Although at 20° C the increase of heat production was less and less with severity of inanition, it remained demonstrable until death ensued. The greater decrease of body temperature at an ambient temperature of 20° C was not due to an

inability of the animal further to increase heat production, because on exposure to lower temperatures heat production reached considerably higher levels. At 6° to 10° C colonic temperature was not lower than at 20° C, in some cases it was even 0.1° to 0.6° C higher, although the lowering of the ambient temperature from 30° to 20° C was followed by a significant fall (0.5 to 2.2° C). The changes in heat production and body temperature during starvation are due to alterations in the controlling mechanisms and cannot be ascribed to an inability to produce sufficient heat to maintain the body temperature.

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Localization of thermoregulatory heat production

In adult rats under light urethane anaesthesia continual recordings were made of the O_2 consumption, colonic, muscle and subcutaneous temperatures, electric activity of the lumbar and thigh muscles, on transfer from indifferent to cool temperature, at cool ambient temperature (19° to 21° C), as well as in the same environment during hypoxia (12 per cent O_2) and hypercapnia (6 per cent CO_2). The results indicate that *a)* there is no close correlation between the changes in electric muscular activity and the changes in heat production; *b)* the musculature is not the primary site of non-shivering heat production; and, *c)* a global control of heat production should be taken into account.

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Correlation between the gaseous iodine and "complex iodine" content of air and the energy metabolism of the rat

It has been shown [Acta physiol. hung. **14**, 7 (1958)] that close, but complex correlation exists between the gaseous iodine content of the vapour saturated air at 37° C and the energy metabolism of the rat. The complex nature of the correlation makes it impossible to hold the gaseous iodine content of the air exclusively responsible for the changes in the energy metabolism of the animal. In thyroidectomized rats a single directly proportionate correlation has been found between the gaseous iodine content of air and the oxygen consumption by the animal, from which it has been con-

cluded that the inversely proportionate correlation found in the normal animal alongside the directly proportionate one is brought about by the increased thyroid activity. This hypothesis has been confirmed by the ^{132}I uptake curve, which showed that the gaseous iodine content of air was inversely proportionate to the isotope uptake by the thyroid. Even in possession of these data we have been unable to explain the correlation betweenthe gaseous iodine content of continental air and the energy metabolism of the animal.

Climatochemical investigations of other nature have substantiated the view that besides the gaseous iodine, the air also contains "complex" iodine, not demonstrable by reactions requiring the binding of ions. It was remarkable that with the gaseous iodine content, the complex iodine content obtained after incinerations was 5 to 6 times higher in continental air than in marine air. In this case the energy metabolism of the animal dropped by about 30 per cent. Assuming that the gaseous iodine content of air directly increases tissue oxidation by some unknown mechanism, whereas at the same time the increase in the "complex" iodine content causes a diminution of thyroid activity, a fraction has been set up, with the numerator showing the gaseous iodine, and the denominator showing the "complex" iodine contents. Plotting the energy metabolism of the animal against this fraction, the complex correlation found in the normal animal is reduced to a single directly proportional correlation, which showing the character of a fraction function, converges asymptotically toward 0.

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The role of psychopharmacologic drugs in the analysis of the physiological mechanisms of higher nervous activity

The activation of the central nervous system and its influencing by pharmacological methods have been discussed. Two kinds of activation were differentiated, the non-specific activation systems, on the one hand, and the active focus, as specific activation, on the other, which, however merges in an inseparable synthesis with the function of the non-specific activation systems.

In non-specific activation the reticular formation of the brain stem, the non-specific thalamic nuclei, as well as the subthalamic and hypothalamic structures are involved simultaneously. All these structures probably combine to form a system, which as a whole plays a fundamentally important role in higher nervous activity, in the transformation of every afferent impulse,

in the determination of the biological value of the afferent impulse, in the proper adjustment of its effect on the cortex, corresponding to the requirement of the entire organism. It seems reasonable to look upon this system as a whole and to call it, as suggested by PENFIELD, the centrencephalic system. Through corticopetal and corticofugal projections, the centrencephalic system is in the closest correlation with the cortex.

The stimulation of the centrencephalic system of normal excitability results in characteristic behavioural and EEG responses in animals, and also its sensitivity to drugs is characteristic.

This normal excitability is characterized by the fact that if the EEG or the behavioural arousal reaction is evoked either with the afferent impulse or by the electrical stimulation of the single points of the centrencephalic system, it will be rapidly extinguished if the stimulus is applied repeatedly, in rapid succession. In appropriate doses, every central depressant drug is capable of inhibiting the behavioural and the EEG arousal reactions. In this respect the classical sedative and hypnotic drugs, *e.g.* the barbiturates, are just as effective as the minor or major tranquillizers.

A sudden qualitative change takes, however, place in the excitatory state of the central nervous system when the state of excitation, called drive by the psychologists, comes into existence. Drive is understood to mean the psychic excitation occurring when the animal, adapting itself in an infinitely plastic way to its environment, performs some important activity, for example seeking food or a sexual partner, etc. On the basis of our experiments conducted since 1951 we have arrived at the conclusion that in such cases there exists an excitatory focus of specific, dominant nature involving equally the centrencephalic system and the cortex, and having characteristic physiological properties. Such a focus of excitation has been termed by us the active focus (KNOLL *et al.* : Acta physiol. hung. **8,** 327, 347, 369 (1955); **9,** 99 (1956); **10,** 89 (1956); **12,** 69 (1957)).

In the presence of the active focus the orientative — searching reflex activity is significantly more intensive and lasting than it is in an animal whose central nervous system is in no such state of excitation. Thus, the active focus is not only demonstrable, but its state of excitation can be estimated quantitatively. If we allow a rat to move about freely in a large area divided into squares, and we measure the animal's movements partly by the number of the squares and partly by the size of the total area covered, the correlation is readily demonstrable. In the standard setup used in our experiments a rat with normal central nervous excitability passed through 25 squares in the first 10 minutes, 6 in the second and 3 in the third 10 minutes of the 30-minute period of observation, covering 10.2 per cent of the total area. When an alimentary active focus is created by means of a conditioned stimulus, *i.e.* if we temporarily bring into existence a specific activation

centre, a sudden qualitative change is noted in the animal's behaviour. The number of squares covered during the first ten minutes increases to an average of 86, in the second 10 minutes to 67, and in the third 60, and 78.6 per cent of the total area will be covered. If we create a so-called bell-glass searching active focus in the rat by means of a conditioned stimulus (in this case the animal is capable of finding a bell-glass in a place unknown to it), we see essentially the same correlation. The average number of covered squares during the first 10 minutes is 107, in the second 10 minutes 88, in the third 70, the total area covered, 86.4 per cent. This motor quality is characteristic of the presence of the active focus, and cannot be created or induced with any motility-increasing agent. For example, amphetamine greatly increases the number of squares covered, but the size of the area covered by the animal will be smaller than that covered by the controls even if large doses are employed. Moreover, treatment with 5 mg/kg of amphetamine results in an inhibition of the characteristic behaviour in the presence of both the alimentary and bell-glass-searching active foci, the size of the area the animal covers decreases to 11.6 per cent in the case of the alimentary active focus, and to 14.4 per cent in the presence of the bell-glass-searching active focus.

We have also shown that in the presence of the active focus the character of the EEG arousal reaction, too, changes in the rat. If we examine the EEG arousal reaction evoking effect of an auditory stimulus of ringing a bell, it will be found that after presenting it repeatedly, the stimulus will lose its ability to release EEG arousal. If the same stimulus is converted in the same rat to a conditioned signal and a conditioned reflex is elaborated, which possesses the classic properties, the effect of the stimulus on the central nervous system will not change, and if the ringing of the bell is repeated several times, its ability to evoke the EEG arousal reaction will be just as rapidly extinguished, as it used to be when it was merely an indifferent stimulus. When, however, under suitable experimental conditions the same auditory stimulus acquires the ability of creating an active focus in the central nervous system, a sudden qualitative change will take place in its effect to release the EEG arousal reaction. We have shown that in the same rat the ringing of a bell, after it had become the signal of the active focus, could permanently and in a not-extinguishable manner evoke the EEG arousal reaction (J. KNOLL: Acta biol. med. germ. Suppl. **1**, 9 (1961); KELEMEN *et al.* : Elektroenceph. clin. Neurophysiol. **13**, 745 (1961)).

The behavioural and EEG experiments have shown that the active focus plays the role of a specific activation centre. Presumably, the active focus may be considered a temporarily existing functional unit of neurone networks in a state of specific excitation, *i.e.* a centre in the dynamic sense of the word. In such a sense the active focus is an inseparable synthesis of centrencephalic (and probably primarily hypothalamic) and cortical elements

and in the development of the characteristic state of excitation unconditioned and conditioned stimuli may equally take part. In my opinion this active focus is the physiological basis of what psychology calls the drive. The drive is a description, the active focus is a physiological mechanism, and their relation is exactly the same as that between association and temporary connection.

In the presence of the active focus, thus in the presence of specific activation, the central nervous system shows a qualitatively altered pharmacological sensitivity. Experiments conducted in recent years have shown that in the presence of the active focus the centrencephalic system loses its ability to be inhibited by the classical sedative drugs and the minor tranquillizers, but it remains selectively sensitive to the major tranquillizers (KNOLL *et al.* : Arzneimitt. Forsch. **8**, 330 (1958); **9**, 633 (1959); Neuropsychopharmacol. **1**, 334 (1951); MTA V. Oszt. Közl. **11**, 145 (1960)). The major tranquillizers, for example reserpine and chlorpromazine, may be considered to be selective inhibitors of specific activation. Various groups of compounds can antagonize this effect, as every major tranquillizer can be acutely antagonized with the compounds of amphetamine-like activity, while the monoaminooxidase in hibitors antagonize the effect of the Rauwolfia alca ds only. The monoaminooxidase inhibitors are not effective, however, in acute experiments, they can inhibit only the depression induced by chronic reserpine administration, if given together with that drug. A new compound, phenyl-iso-propyl-methyl-propinyl-amine, has been synthesized, which possesses the properties characteristic of the amphetamine group, but inhibits monoaminooxidase *in vivo* about 200 times more potently than nialamide does. The compound effectively antagonizes the depressant action of the major tranquillizers on the specific activation of the central nervous system in acute and chronic experiments alike. Imipramine, belonging to the group of iminobenzyl derivatives, occupies a most peculiar position among the antidepressant agents. It does not influence the effect of phenothiazines, and antagonizes reserpine in chronic experiments only and in a small measure. However, in the untreated animal it increases the excitability of the central nervous system in the course of chronic administration, promotes the arisal of the active focus and under specific conditions its effect is readily demonstrable.

It has been pointed out that in the course of chronic treatment with small doses of reserpine the selective inhibition of the sites of junction between the classic afferent pathway system and the centrencephalic system may play a role in the depressant effect. Similar conclusions have been drawn concerning the phenothiazines (P. B. BRADLEY : Neuropsychopharmacol. **1**, 10 (1959)). The pharmacological analyses tend to create the impression that just as there are junctions of specific pharmacological sensitivity at the periphery, both interneuronally in the autonomic ganglia and between the

nerve endings and the effector cells, as on the neuromuscular junction, or on the sympathetic or parasympathetic end apparatuses, so there are also in the central nervous system interneuronal junctions of specific pharmacological sensitivity. Which that one of the most plausible of such sites of selective pharmacological sensitivity is the junction between the classic afferent pathway system and the centrencephalic system, that I propose to call sensory-reticular junction. This junction seems to be particularly sensitive to the effect of major tranquillizers and it is here that they are antagonized by most of the antidepressant drugs.

Certain drugs cause a remarkable dissociation between the EEG and the behavioural arousal reactions. For example, following the administration of eserine the EEG arousal reaction can be observed for a long time without a parallel behavioural response, and atropine produces just the reverse of this effect. I have suggested that in the interest of a finer analysis of drug effects it seems reasonable to employ autocorrelation analysis in the evaluation of the EEG (J. S. BARLOW : IRE Transactions on Medical Electronics 179 (1959)). The possibilities offered by this new procedure in physiological and pharmacological research have been illustrated with several examples.

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The role of humoral factors in the organization of behavioural processes

The problems dealt with may be summed up as follows.

1. The specific sensory pathways not only supply specific information to the structures of the brain stem and forebrain, but their elimination may also result in complex changes of behaviour ("sensory hunger" characterized by increased orientative activity, as well as "emotional deafferentation", characterized by a total lack of emotional reactions).

2. Psychopharmacological drugs inducing anaesthesia can dissociatiate the EEG activity and behaviour. This manifests itself also in the specific chemosensitivity of the brain stem structures. If injected into the area of the rostral thalamus, eserine causes cortical desynchronization (spindle formation, barbiturate spindle bursts), while if injected into the mesencephalic reticular formation it inhibits the slow EEG activity evoked by barbiturate and brings about desynchronization. Adrenaline increases the activities of both the synchronizing and desynchronizing systems. The adrenaline-sensitive intrareticular nervous structure is in connection with both the cholinergic synchronizing and the brain stem desynchronizing systems, but the direction of its

effect depends on the state of equilibrium in the functions of the two cholinergic systems. By means of Anokhin's microelectrode leads it has been shown that chlorpromazine is capable of inhibiting only certain, most probably adrenergic neurones in the reticular formation of the brain stem.

3. For influencing the daily motor activity in the rat relatively high doses of the tranquillizers are required. In their effect species differences play a significant role. In the conditioned reflex situation the goal-directed spontaneous motor activity, which in Pavlovian terminology corresponds to the intersignal reaction, can be inhibited by small doses of reserpine or chlorpromazine. Likewise, the goal-directed motor activity in the conditioned reflex situation is inhibited by 5 to 10 μg of reserpine, injected into the tegmental reticular formation. The central nervous organization and the processes playing a role in the goal-directed spontaneous motor activity accompanying conditioned reflexes are discussed in detail.

In stimulation experiments it has been found that stimulation with certain parameters of the medial forebrain bundle, septum and the reticular formation of the brain stem inhibits the goal-directed motor activity, but has no influence on the developed conditioned reflex. The data obtained by stimulation and by methods involving injection through microcannulas outline the form of a structural correlation, which includes the archicortex, septum, medial forebrain and brain stem reticular formation, and this system plays a role of fundamental importance in the organization of the processes of internal inhibition. This nervous mechanism is sensitive to humoral factors at various levels and forms the basis of the sites of action of different psychopharmacologic drugs.

4. The daily motor activity observable under normal conditions, the goal-directed spontaneous motor activity appearing in the conditioned reflex situation, as well as the conditioned reflex motor activity appearing in the temporary connexion, have many common components as regards structural organization, but the effects of psychopharmacologic drugs and hormones indicate that the humoral factors are primarily acting on the nervous organization of the spontaneous goal-directed motor activity, that may be considered to characterize motivation.

5. Among the neuroendocrine correlations, the nervous organization of the stress mechanism has been discussed in more detail. It has been pointed out that the structures, whose stimulation increases the internal inhibition in the Pavlovian conditioned reflex situation, inhibit the pituitary-adrenocortical activation in response to stress and decrease the corticosteroid concentration of adrenal venous blood. As to the central nervous effects of corticoids, it has been shown that in the cat, dog and monkey hydrocortisone and cortisone, but not corticosterone, increased the extinction of the alimentary and defensive reflexes, which suggests an activation of internal inhibitory processes, but this

does not take place in the rat. This species is commonly known not to secrete polar corticosteroids, such as hydrocortisone or cortisone. Electrophysiological and endocrinological observations indicate that the adrenocortical steroids act in the first place upon those structures of the central nervous system, that take part in the organization of the above mentioned processes of internal inhibition. At the same time, these structures, so for example certain representation of the archicortex, septum, lateral hypothalamus and the reticular formation of the brain stem, inhibit the nervous integration of the stress mechanism. Electrophysiological observations have shown that the organization of the sexual behaviour reactions is bound to these structures. According to the data of SAWYER, PORTER and CRITCHLOW a characteristic change in electrical activity may be observed in the lateral hypothalamus, as due to the permissive action of the sexual steroids.

The complex behavioural reactions involved in the organization of the brain stem and limbic structures and the influence exerted upon them by humoral factors unequivocally indicate that this nervous organization possesses extensive and selective chemosensitivity. While in lower species psychopharmacologic drugs are influencing exclusively the spontaneous motor activity, in higher species the effect manifests itself in the first place in the goal-directed motor activity, which appears in the conditioned reflex situation and which is characterizing motivation. The evolutional development in the action of hormonal and neuropharmacologic agents harmonizes well with the suggestion made by SECHENOV, that psychic activity corresponds to an "uncompleted motor act".

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Evoked potentials in the strychninized cerebral cortex of the cat

The potentials evoked by an auditory stimulus, as well as the spontaneous strychnine potentials have been studied on the gyrus ectosylvius of cats anaesthetized with chloralose. It has been found that in the evoked potentials appearing on the previously strychninized cortex a so-called trigger component, corresponding to the specific evoked potential, can be recognized. By changing the parameters of stimulation this potential can be separated from the strychnine potential evoked by it, which is essentially a discharge similar in shape to the spontaneous strychnine spike. The 1 per cent eserine-acetylcholine left to act on the cortex for 30 to 60 minutes proved to be ineffective on the evoked potentials, but at the same time it broke up the strychnine

spikes, facilitated their elicitation, and shortened the duration of their refractory period. One per cent GABA, applied superficially on the cortex, greatly augmented the evoked potentials, reversed the polarity of the strychnine spikes recorded from the surface, while the strychnine spikes recorded from the depth of the cortex retained their original reversed polarity.

On the basis of the above observations it is thought that the neuronal substrate of the specific evoked potentials differs from that of the strychnine effect, and some problems of the neuronal organization of the cortex, as well as the mode of action of GABA and of strychnine have been discussed.

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The mescaline-antagonizing effect of some ergot alkaloids in correlation with their antiserotonin activity

The effects of D-lysergic acid diethylamide (LSD-25), 2-bromo-lysergic acid diethylamide (BOL-148), methysergyl (Deseryl, UML-491) and dihydroergotamine (DHE) on mescaline stereotypia and excitation have been studied in mice. The former has been determined by means of an oscillometer connected to a counter operating with differential capsule, the latter by activity measurement according to DEWS by means of a photocell.

Inhibition of the scratch reflex evoked by mescaline was strongest in the case of LSD-25, which caused 42.7 per cent and 65.5 per cent inhibition in intraperitoneal doses of 25 and 50 μg/kg, respectively. Bromo-LSD and dihydroergotamine were less potent. The effect of methysergyl was the weakest.

The stimulating effect of mescaline (100 mg/kg subcutaneously) was completely blocked by 30 minutes pretreatment with the above doses of LSD. Similar inhibition was caused by the 200 μg/kg intraperitoneal dose of bromo-LSD. In such doses methysergyl and dihydroergotamine were ineffective.

In the next step the peripheral antiserotonin activity of the compounds was examined. The inhibition of paw oedema was estimated in rats anaesthetized with 100 mg/kg Butethal injected intraperitoneally. The most potent was methysergyl of which 100 μg/kg subcutaneously caused 73.4 per cent inhibition, while LSD and bromo-LSD were less potent. In the 400 μg-kg subcutaneous dose dihydroergotamine was ineffective.

The results indicate that the intensive antimescaline effect of LSD and bromo-LSD cannot be explained by the peripheral antiserotonin effect of these compounds.

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The central nervous effects of cholinolytic compounds

The central effects of nearly 60, mostly newly synthesized tropine esters, as well as a few parasympatholytic compounds of other types have been analyzed.

A simple method has been developed for the measurement of the inhibitory effect exerted on the cholinergic receptors of the central nervous system.

Among the central effects of cholinolytic drugs the analgesic one merits most attention. Quantitatively, the effect is most marked as tested by the hot plate method, in which certain compounds show an activity orders of magnitude higher than that of morphine. It is likely that this is not or not only an analgesic effect, but part of some more complex central nervous (*e.g.* hallucinogenic) effect.

Besides the "analgesic effect", the cholinolytics possess mild central stimulatory, antitremorin and electroshock activating activity, which do not run parallel.

The optimal structural conditions required for the central cholinolytic activity are described and it is suggested that in the central nervous system there may be cholinergic receptors of several types greatly different in the fine structure of the active surface.

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Effect of tranquillizers on the activity of higher and lower nervous structures

Some clinical and experimental observations correlated with the application of tranquillizers are discussed.

1. Clinical and experimental investigations followed since 1956 showed that tranquillizers (phenothiazine derivatives and alkaloids), develop clinical anaesthesia, with deep sleep, retrograde amnesia, and at the same time hypersynchronous, only slightly slowed activity in the EEG, instead of the usual slow activity. The electrophysiological evaluation of clinical anaesthesia appears in a different light in possession of the experience obtained with the use of tranquillizers.

2. EEG studies of the nervous effects of the corticoids supply information concerning the organization of stimulatory and inhibitory processes. It has been shown that the tranquillizers, *e.g.* meprobamate, diminished the cortical activity accelerated by hydrocortisone. At the same time, the electrical cortical activity slowed down by meprobamate is accelerated by hydrocortisone.

3. The site of action of the tranquillizers has been extensively studied. From observations in connexion with hemispherectomies it has been concluded that the electrical activity lead off from deeper cerebral structures during neuroplegic action showed the same pattern as the activity of cortical structures. In response to tranquillizers the subcortical structures seem to behave in the same way as the cortical ones.

4. The question arose, how the lower nervous structures react to tranquillizers. The results obtained by KATONA and WOLLEMANN in invertebrates, from hydrozoa to cephalopodes, have indicated, that the tranquillizers reversibly suspend the activity of even the most primitive nervous structures, without affecting the vital functions of the experimental objects.

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The convulsions facilitating effect of reserpine

It is known that reserpine significantly increases the susceptibility to seizures brought about both by electrical stimulation and pentetrazole. In this study the effect of reserpine on insulin-induced hypoglycaemic convulsions was examined. After giving 5 mg/kg reserpine to mice insulin brings about convulsions in such low doses (2 to 3 U/kg) in 100 per cent of the animals which dose produces seizures at the most in 10 per cent of the control group. The fall of the blood sugar level shows no difference between the reserpine-treated and insulin-treated groups. The dose of insulin employed had no influence on the brain glycogen level, and this did not decrease in the animals treated also with reserpine, *i.e.* in those showing convulsions. Iproniazid (100 mg/kg) inhibited the convulsions facilitating effect of reserpine, but did not influence the fall in blood sugar or the glycogen content of the brain.

The experiments indicate that changes in the amine level of the brain play a decisive role in the tendency to convulsions, thus hypoglycaemia or a decrease in the brain glycogen level alone cannot be held responsible for the convulsant action of insulin.

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The effect of guanethidine on the noradrenaline level of the brain and its pharmacological significance

The antihypertensive drug guanethidine significantly reduces the noradrenaline level of the rat's brain. Three hours after the subcutaneous administration of 5 mg/kg, the noradrenaline level is reduced by 60 per cent. After 6 hours the decrease amounts to 22 per cent only. At the lowest noradrenaline level the behaviour of the animals resembles the effect of reserpine in that sedation, myosis, defecation are observable. Guanethidine has no influence on the spontaneous motility of mice (as measured by means of Knoll motimeter), but significantly reduces the locomotor excitation caused by amphetamine, whereas reserpine decreases spontaneous motility, but has no influence on the excitation caused by amphetamine. Guanethidine diminishes also the metabolic rate-increasing effect of amphetamine. Pretreatment with iproniazide prevents guanethidine from lowering noradrenaline level. It seems therefore that the decrease of noradrenaline level is due to depletion, though an interference in noradrenaline synthesis cannot be ruled out with certainty either. It has been found namely that 50 mg/kg of DOPA (the precursor of noradrenaline) increases the metabolic rate of rats by 80 per cent, and guanethidine abolishes this effect.

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Attempt at the statistical recording of human higher nervous activity

The dynamics of higher nervous activity has been investigated in university students under physiological conditions as well as pharmacological influences. Two tests were used. The first was a motor conditioned reflex with verbal reinforcement, the rhythmic stopping of the moving hand of the HIPP's chronoscope at given points. The delay and/or precipitancy of this reaction was measured in milliseconds. The second test was the so called "zero and cross" game played by two persons. The number of steps made by each of the persons was recorded. Both tests were applied repeatedly, the game-test 30 times, the motor conditioned reaction 75 times in each trial. The frequency of occurrence of the different latency-times and step-numbers was represented in diagrams. The frequency diagrams of the latency-times

were reproducible in 75 per cent of all persons tested. In 25 per cent the diagrams were not reproducible. The step-number frequency diagrams were also reproducible. Chlorpromazine, amphetamine, meprobamate, caffeine did not significantly alter the shape of the diagrams in a single maximal therapeutic dose, although the psychic effect of the drugs was characteristic in every case.

It has been concluded that *a)* the shape of the frequency diagrams is characteristic of the individual; *b)* on this ground two types of higher nervous activity can be distinguished, a stable type which compensates well environmental influences; and an unstable one which compensates poorly, producing diagrams of variable shape. The remarkable agreement between the results of the two different tests is considered a manifestation of the mechanism of psychic homeostasis.

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Biochemical studies concerning the neurophysiological effects of phenothiazines

The mechanism by which the phenothiazines inhibit dehydrogenase activity has been studied. Recent results suggest that the oxidized intermediary compound of chlorpromazine (free radical) produced during incubation with PGAD (3-phosphoglyceraldehyde-dehydrogenase) re-oxidizes DPNH (reduced diphosphopyridine nucleotide). The absorption maximum at 510 mμ of the irradiated intermediary chlorpromazine compound disappears in response to DPNH or $Na_2S_2O_4$, and the maximum of DPNH decreases at 340 mμ.

The intermediary compound could be demonstrated in the rat's brain following the administration of chlorpromazine.

Critical analysis of the data in the literature in the light of the present results indicates that since the biochemically demonstrable inhibition of an enzyme or enzyme system reflects only one site of action, this allows no far-reaching conclusions as to the site of action of the complex neurophysiological effect. In spite of that, biochemical studies may supply valuable information concerning the metabolism of psychopharmacologic drugs and the collected data may facilitate a better understanding of the mode of action.

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