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ABSTRACTS

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The role in behaviour of the non-specific thalamic system

It has been shown in cats with chronic implanted electrodes that by stimulating certain points of the non-specific thalamic system both of the two conditioned reflexes (alimentary and avoidance) set up beforehand in the same experimental apparatus can be activated, and when the conditioned reflexes are stable, the direction of this activation is determined by the actually active environmental stimuli. It has also been demonstrated that even the cessation of the electrical stimulation applied to these structures of motivating activity is by itself a conditioned reflexogenic factor.

When other points of the non-specific system of the thalamus are stimulated, effects opposite to those outlined above, notably an inhibition of both conditioned reflexes, will be brought about.

Correlations have been detected between the behavioural effects evoked by the electrical stimulation of certain points in the thalamus and the cortical electrical responses.

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The role of brain stem structures in the acoustic startle reaction

The effect of lesions of different brain stem structures on the elicitability of the acoustic startle reaction has been investigated in 78 rats.

It has been found that

(i) the acoustic startle reaction remains elicitable following bilateral lesion of the lateral and medial thalamus, the mesencephalic and pontine reticular formation, after bilateral lesion of the lateral mesencephalon, and after midcollicular decerebration;

(ii) the reaction is not elicitable when the lesion has destroyed the ventromedial reticular formation at the level of the medullopontine transition.

It is stated that the elements of the latter region are involved in the primary organization of the acoustic startle reaction and, at variance with the widely emphasized view, the primary role in its organization of the reticular activity system or the nucleus ruber is denied.

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The effect of spreading depression on avoidance conditioned reflex activity in the rat

The effect of cerebral cortical functional ablation has been studied on the development of the avoidance conditioned reflex, on its performance after it has become established and on its disinhibition after it has become extinguished. It has been found that under spreading depression no avoidance conditioned reflex can be set up, and such a reflex set up beforehand becomes inhibited; confirming thus some earlier data in the literature. If the unconditioned stimulus of the avoidance conditioned reflex had been presented following extinction and in the state of spreading depression, and the experimental animals were tested 24 hours later, the conditioned reflex reappeared, *i.e.* it had been disinhibited. The time necessary for the extinction of the reconditioned reflex was about the same as that required in the preceding control extinction period. The phenomenon observed suggests that spreading depression exerts no influence upon the natural drive component of the conditioned reflex, it merely inhibits the actual development of the temporary connection.

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Electrical stimulation of the cerebellum as a conditional signal

Chronic bipolar electrodes, suitable for both stimulation and recording, were implanted in cats. Cerebellar stimulation was employed as a conditioned stimulus (the response to which was controlled in cerebral cortical electrical activity), and this was reinforced by offering food, with the aim to determine whether the cerebellum had an essential role in the development of the temporary connection, or it acted merely as a motion-coordinating system for the arisal of the motor conditioned reflex. From the findings the conclusion has been drawn that a conditioned reflex to cerebellar stimulation can be set up only if the intensity of the stimulus reaches the threshold eliciting motion, in other words if it becomes a signal only secondarily.

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The role of the reticular formation in the development of elementary temporary connections in the mesencephalic animal

In cats decerebrated at high levels the possibility of elaborating temporary connections in the background of reticular formation stimulation has been studied over 2 to 3 days. As a temporary connection the respiratory response to direct electrical stimulation of the central stump of the vagus was set up, using pelvic stimulation as the conditioning stimulus. Before reinforcement, stimulation of the pelvic nerve did not influence the amplitude and frequency of breathing. After a certain number of reinforcements, however, a characteristic respiratory response was obtained on the isolated stimulation of the pelvic nerve. This phenomenon may be considered to be an elementary form of temporary connection, which can also be established in the mesencephalic animal. Without the stimulation of the reticular formation this temporary connection was established after 80 to 100 reinforcements, which in response to the stimulation of the reticular system of the brain stem it developed after 20 to 40 reinforcements, depending on the parameters of stimulation. The established elementary connection appeared to be more stable in the background of reticular formation stimulation than in the control group.

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Conditioned evoked potential in cats with implanted electrodes

Conditioned potentials have been evoked by electrical stimulation of the skin and by auditory stimulation in cats with implanted electrodes, delaying the reinforcing stimulation, with the aim of obtaining data supplementing the results of acute experiments concerning some elementary laws of the process of learning.

(i) After reinforcement a conditioned evoked potential appears in the cortical representation areas of both stimuli, according to the latent period of the reinforcing stimulus, while the response to the first stimulus is facilitated.

(ii) The connection thus established between the two stimuli persists for days, then it is extinguished and can be re-established by new reinforcements.

(iii) The conditioned evoked potential can be differentiated; it is evoked exclusively by the stimulus to which it has been set up.

From the results the conclusion has been drawn that a lasting, peculiar type of facilitation exists, furnishing the basis of the mentioned temporary connection.

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Reflex responses to hypoxia of young animals

In earlier experiments it has been shown that in adult animals the measure of hypothermia and the decrease of metabolic rate induced by hypoxia diminished if repeated hypoxia was associated reinforcement-like with the previous presentation of the same conditioned stimulus. This phenomenon is an early manifestation of a developing temporary connection. The conditioned reflex elicited by the presentation of the isolated neutral stimulus manifests itself with a response opposite to what is evoked by hypoxia, notably with an elevation of body temperature and oxygen consumption.

In the present experiments in rats and dogs 0 to 72 days of age the changes in the reduction of the metabolic rate and the conditioned reflex response to hypoxia have been studied.

It has been found that until the age of about 20 days the animals respond to repeated episodes of hypoxia with hardly any change in oxygen consumption, and the conditioned reflex manifests itself with a decrease of oxygen consumption, *i.e.* the change was of the same direction as in the case of the unconditioned response. At around 20 days of age oxygen consumption oscillates in response to the conditioned stimulus; it is often biphasic, first decreasing, then increasing. After 20 days of age the opposite conditioned reaction consisting in an increase of oxygen consumption is gaining preponderance, to become more and more marked with the advance of age.

From the results it is concluded that, parallel with the ontogenetical development of the nervous system, the organism's vegetative balance is ensured to an increasing extent by a higher, corrective central nervous regulation.

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Analysis of the various types of learning reactions in the rat by the use of drugs affecting behaviour

(i) In the jumping test (electrical shock of 110 V, ringing of a bell) the conditioned reflex of non-extinguishable character is not inhibited by sedatives, hypnotics, small doses of narcotic anaesthetics (morphine, 5 mg/kg) or single electroshocks. The hallucinogenics (LSD, mescaline) cause slight inhibition. Major tranquillizers (reserpine, 3 mg/kg, chlorpromazine, 10 mg/kg, tetrabenazine, 10 mg/kg) and massed electroshock (60 V, 20 mA, 10 shocks at 1-hour intervals) cause complete deconditioning.

(ii) In the modified jumping test (a plate of 45° C) the first escape is completely blocked by the central depressants, hallucinogenics, and massed electroshocks, and slightly by single electroshock. As a result, the animals die on the hot plate.

Whatever conditioned stimulus is applied under these experimental conditions, it is impossible to establish a conditioned reflex even if the unconditioned escape reaction is evoked many times daily throughout the life of the animal. On the other hand, a different type of learning develops. This can be demonstrated readily on the basis of the changes in the sensitivity to drugs affecting behaviour. It has been found namely that the animals escape the experimental situation once daily for 30 days, the reaction is not inhibited by sedatives, hypnotics, narcotic anaesthetics, hallucinogenic drugs or single or massed electroshocks, indicating that this type of learned reaction differs from the usual conditioning.

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The daily rhythm of performance of female textile workers

The employees working regularly on daytime shifts are classified into the same stereotype system, in spite of the fact that the forenoon and afternoon shifts are alternated weekly. Within the stereotype system the dynamics of the excitatory and inhibitory processes take effect in the sense that the beginning of the forenoon shift is followed by an improvement of performance, followed by a deterioration at a point of time depending on the strain imposed by the work and the environmental influences. In the next phase spontaneous improvement then again deterioration occur, *etc.* This undulation of performance does not cease when the shift is over.

Employees working always on night shifts belong to another stereotype. Their rhythm of performance does not fit into the pattern shown by the daytime workers, and they display changes in body temperature.

These changes in performance disposition are significant from the point of view of the system of work and rest, as well as from that of changing the shifts.

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Relationship between electrocorticographic pattern and single cell activity in the cerebral cortex of the cat

Superficial electrical phenomena from the cerebral cortex of the cat have been recorded and from the depth of the cortex single cell discharges were led off by means of micro-electrodes. It has been demonstrated that it is mainly in the first, superficial positive phase of the evoked and convulsive potentials that the neurones of the cortex are activated, while the cells showing spontaneous serial discharges (bursts) cease to be active during the surface negative phase of the convulsive potentials. Gamma-aminobutyric acid increased both the surface and the deep evoked potentials. The correlation of this with the single cell activity is under investigation. Data hitherto obtained indicate the presence of an inhibitory structure in the superior layers of the cortex.

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Changes of the evoked potentials in response to superficial cooling of the brain

According to the data in the literature the evoked potentials gradually diminish then disappear altogether when the brain is gradually cooled down.

Evoked potentials were recorded from the primary and secondary sensory projection cortical areas, in response to the electrical stimulation of the sciatic or splanchnic nerve. The area from which the records were being made was cooled superficially with a chilled fluid. Cerebral temperature was measured 2 to 3 mm deep with a thermoelectric thermometer.

The reduction by a few degrees of the temperature in the deeper layers of the cerebral cortex caused a significant temporary increase in the amplitude of the evoked potentials. After this process of excitation the evoked potentials

gradually diminished then disappeared even without a further reduction of the temperature, and often even when the temperature increased. They reappeared a few minutes later, and 8 to 10 minutes later the potentials could be evoked again, with the original amplitude. This indicates that even a fast cooling by a few degrees initiates a metabolic process, which leads to a temporary disappearance of the evoked potentials, without necessitating the induction of the lower temperatures reported on in the literature.

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Mathematical analysis of the electroencephalograms of neurotic rats

Continuing the studies reported at the 1963 meeting of the *Hungarian Physiological Society*, experiments have been carried out on 20 male white rats with silver electrodes implanted subdurally and in the hippocampus. Temporary neurosis was induced by conflicting the unconditioned drinking and defensive (escape) reflexes. Before and after the conflict situation EEG's were made. The methods used for evaluating the tracings were autocorrelation, cross correlation between the hippocampal and cortical activities, FOURIER (harmonic) analysis, dynamic averages, and the DROHOCKI index. Part of the calculations has been made by the use of M3 type electronic computer. The results thus obtained were compared with those yielded by the manual technique.

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New data concerning the reticular control of cerebral cortical evoked potentials

Previously it has been demonstrated in acute experiments on cats that stimulation of the brain stem reticular formation for different lengths of time evoked different changes in the configurations of the cerebral cortical responses to the stimulation of the sciatic and splanchnic nerves.

The present investigations had the aim of determining how these changes in configuration would be modified when the activity of the brain stem reticular formation was blocked with chlorpromazine. It has been shown that in response to the intravenous administration of 5 mg/kg of chlorpromazine the amplitude

of both phases of the cerebral cortical evoked potential decreased. At the same time, the changes in amplitude in response to stimulating the reticular formation for different lengths of time were the same in character and size as without chlorpromazine. This confirms the assumption that chlorpromazine eliminates the impulses running into the reticular formation, while the diffuse system of the brain stem remains capable of functioning under the effect of 5 mg/kg of chlorpromazine. The decrease in amplitude of the evoked potentials is presumably due to a diminution in reticular formation activity.

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Analysis of hippocampal electrical activity during processes of motivation

Hippocampal electrical activity has been studied in cats during conditioning as well as in response to stimulation applied to structures of different motivational character.

From the results conclusions have been drawn as to the role of the hippocampus in the control of the basic phases of motivational processes.

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The effect of convulsive agents on the gamma-aminobutyric acid content of the rat's cerebral cortex

The effect of several convulsive agents has been investigated on the gamma-aminobutyric acid (GABA) level of the rat's cerebral cortex in correlation with the ECoG pattern. GABA was determined by paper chromatography. In the case of local application, strychnine, d-tubocurarine, diminished the GABA content by 0—16 per cent while eliciting seizure potentials of a frequency of 1—2/sec. D-tubocurarine plus acetylcholine increased the GABA content with 13 per cent during rhythmic afterdischarges of a frequency of 8—10/sec. A correlation is assumed to exist between the appearance and frequency of the seizure potentials, and the changes in GABA level. In the case of the first three compounds, the potentials may be produced by limited changes in the local GABA level. The small changes in GABA content could be explained by the restricted area of application, and their failure to elicit

frequent discharges. D-tubocurarine plus acetylcholine, similarly to the effect of electroshock and spreading depression on the ischaemic cortex, may probably cause changes in pH in consequence of the increased metabolic rate and the circulatory strain, and in this way elevate the GABA production. It is supposed that the increased GABA content may protect the brain cells from irreversible exhaustion during such seizures.

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Electron-microscopic examination of synaptic structures in the cerebral ganglia of Anodonta cygnea L.

In the neuropil of the cerebral ganglia (CG) axo-axonic synapses, believed to be characteristic of molluscs, can be found. In addition, on the surface of a few nerve cells axo-somatic synapses are detectable. In the nerve endings, alongside the structures similar to the synaptic vesicles of vertebrates, large numbers of "dense-core" vesicles, 1000 to 1400 Å in size, are present. The two kinds of vesicle occur sometimes separately, but most often they fill in various proportions the inside of the nerve endings.

The presence of axo-somatic synapses suggests that the nervous system of the lamellibranchiates differs from that of other molluscs not only in gross and microscopic appearance, but also in finer structure.

Around some nerve cells, 8 to 14 layers of laminar glial cells and neurosecretory granules measuring a few microns can be observed; the latter structures vary from homogeneous, hyperdense forms to structures of the "myelin figure" type.

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Electron-microscopic studies of axo-axonic synapses

Contact surfaces of a specific synaptic structure between different axon terminals are shown from the spinal gelatinous substance, the lateral geniculate body, the thalamic pulvinar and the granulous layer of the cerebellar cortex. Although axon endings are frequently in close contact in other parts of the central gray matter such as the cerebral cortex, this by itself does not mean a functional connection and in such cases the usual morphological signs of the synapse are absent. By different degeneration and isolation experiments

it is illustrated that the axo-axonic synapses are not products of chance, but rigidly specific connections between certain types of neurones. The functional significance of the axo-axonic synapse is discussed with special reference to the phenomenon of presynaptic inhibition.

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Electrophysiological examination of unmyelinated sheath-decrementally conducting nerves

The fibres of the cerebrovisceral connectivum of *Anodonta cygnea* L. have been analysed by electrophysiological methods and the stimulation-dependent properties of the evoked action potentials, and the properties of the single components have been studied.

If adequate parameters are used, the action potential is composed of 4 to 5 components. The components differ according to velocity of conduction and amplitude. The strength-duration curve and the action potential depend on the distance travelled by the impulse. The curve obtained by plotting the voltage of stimulation against the amplitude of the components is S-shaped, and is different from the curve for amplitude *vs.* duration of stimulus. On serial stimulation, the components differed in frequency transfer and refractoriness.

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Investigation of the denervation supersensitivity on the cat's spinal neurones

The changes taking place in the activity of the cat's spinal neurones as a result of partial denervation have been investigated by the intracellular recording technique. Twenty-four to 96 hours after unilateral partial section of the dorsal roots of segment L_7, postsynaptic and spike potentials were evoked from the fibres that had remained intact, and they were compared with the reactions of the contralateral intact neurones.

On the operated side the duration of the excitatory postsynaptic potentials was prolonged, the slope of both the rising and falling phases became less steep. Their shape appeared to result from an interference of many waves, while synaptic potentials characteristic of monosynaptic transmission were

not observed. Their lack indicates that polysynaptic transmission had gained preponderance.

These phenomena are ascribed to a supersensitivity of the partially denervated neurones.

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Tonic expiratory vagal afferents from the pulmonary stretch receptors

From the cervical vagus of cats anaesthetized with chloralose, curarized and artificially respirated, respiratory afferents were isolated. Of all the fibres examined 23.5 per cent were afferents active not only during inflation, but also during the respiratory interval. The measure of this interval activity depends on the duration, volume and frequency of inflation. Long-lasting, high-volume or frequent inflation causes an "inhibition" of the activity of these fibres, they do not function for a certain time during the respiratory interval. The O_2 or CO_2 content of blood plays no role in the maintenance of respiratory interval activity. An insufficient emptying of the lungs does not explain the respiratory interval activity. The activity of the fibres can be influenced in the case of a pneumothorax just as with an intact thorax. As the fibres cease to act when the air is withdrawn from the lungs, their receptors are presumably stretch receptors of extremely low threshold value.

On the basis of the investigations, the vagal afferents are classified into two groups: (i) afferent fibres functioning exclusively on inflation (36.8 per cent), which function in phases; and (ii) tonic afferent fibres functioning during the respiratory interval too. The physiological significance of the tonic afferent vagal fibres lies in that they facilitate the inhibitory action on the inspiratory centre of the phasic *(Hering-Breuer)* stretch receptors.

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Decrease of volume in connection with muscle activity

The study by ABBOTT and BASKIN (1962) contains data relative to the decrease of volume in connection with muscle activity that differ from certain observations published by us. In our opinion the total duration of the volume decrease associated with shortening without tension is 10 msec; while that with tension is much longer (crystallization). In 1938, E. FISCHER described

an increase of volume, without detailing his method. ABBOTT, working with tied-down muscle and recording the meniscus movements writes about an initial increase of volume and a decrease of longer duration. We used ABBOTT's method, and found only two instances of increase of volume (on the first two stimulations in one experiment) of a total of 518 stimulations. The duration of the volume decrease is under 10 msec.

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The effect of decamethonium on impulse conduction in the skeletal muscle of the frog

The experiments were carried out on frog *(Rana esculenta)* sartorius muscle preparations containing 100 to 200 fibres each. The muscle preparation was stimulated directly at its distal end, by square pulses, and the action potentials were recorded extracellularly from the aneural pelvic end. Decamethonium was used at concentrations of from 10^{-6} M to 10^{-2} M.

It has been found that decamethonium increased 3 to 5-fold the stimulation threshold of the muscle. The time required for the development of this effect decreased on increasing the concentration. At low decamethonium concentrations, the stimulation threshold increased 3- to 5-fold; this level was not surpassed after considerably protracted incubation.

As its concentration increased, decamethonium exerted not only the above effect, but reduced more markedly the amplitude of the action potentials. The action potentials were irreversibly inhibited in 5 minutes at a 10^{-2} M concentration of decamethonium.

The muscle mechanograms showed changes going parallel with those of the action potentials.

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Sodium movements in frog's sartorius muscle

It has been known for some time that strophanthidin can block the outward movement of Na from muscle [1]. More recently, it has also been shown in freshly isolated frog's sartorius muscle that about 50% of the tagged Na efflux can be blocked by removal of external Na [2]. In the experiments to be described, the aim was to determine whether or not the mechanisms in-

volved in these two effects are distinguishable from one another. For these experiments, the Na efflux was measured by following the loss of ^{22}Na from isolated sartorius muscle into inactive solutions after it had been loaded with ^{22}Na by soaking for two hours without stimulation in *Ringer*'s fluid made with ^{22}Na.

On the average, 47 % of the resting Na efflux was inhibited by 3×10^{-5} M strophanthidin, in freshly isolated sartorius muscle [3]. This inhibition of Na efflux by strophanthidin was adequately described by an equation of the type $i = \frac{I}{I + K_i}$, where i is the fraction of the total strophanthidin-sensitive efflux (*i.e.* one half of the total efflux) which is inhibited by strophanthidin at a molar concentration of I and $K_i = 1.8 \times 10^{-6}$ M. The remainder of the Na efflux was largely dependent on the external Na and was drastically reduced when lithium or choline replaced Na in the external medium. Thus the total Na efflux in sartorii was reduced by 87 % when the muscles were exposed to Na-free solutions containing 3×10^{-5} M strophanthidin [3]. When sartorii were exposed to Na-free solutions without strophanthidin, the Na efflux was reduced by 37 % after an initial small and transient increase in the efflux. Thus, whatever the details are in the mechanisms responsible for the outward movement of tagged Na, there seem to be two types of mechanisms which can function independently of each other. Addition of strophanthidin blocks one type while the removal of external Na blocks the other. Between them, they can account for the major fraction of the Na efflux.

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2. Keynes, R. D. and Swan, R. C.: J. Physiol., *147*:591 (1959).
3. Horowicz, P., Taylor J. W. & Rienstra, D.: In preparation (1965).

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Reversible loss of irritability in K- and Ca-free "Ringer"-solution

A *Ringer*'s solution lacking in potassium and calcium was perfused through the hind leg preparation of a frog. Stimulated directly or indirectly, the gastrocnemius muscle after a certain perfusion period, ceased to show an action current and shortening. On changing over the perfusion fluid to normal *Ringer*'s solution, after a few minutes the muscle re-started to produce spikes and contractions. This ceasing and re-starting of the same gastrocnemius to display irritability, could be repeatedly brought about by changing over the perfusion fluid. At the end of those experiments in which the gastrocnemii

perfused without potassium and calcium were incinerated, the muscles showed a roughly normal potassium content. The current opinion concerning Na—K-migration as the basic process of excitation, furthermore the role in excitation of Ca and other trace elements have been discussed.

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Effect of tertiary and quaternary nitrogen compounds on the potassium contraction of tonic and tetanic muscles

There is evidence in the literature to indicate that in *Ringer*'s solutions of low K^+ and high Na^+ concentration the K^+ content of the frog muscle decreases, the Na^+ content increases. The change in intracellular ionic concentration is accompanied by an increase of the resting potential (hyperpolarization). In earlier experiments, carried out under identical conditions, physostigmine, prostigmine, DFP and d-tubocurarine inhibited, while decamethonium increased Na^+ uptake and K^+ loss. In the present series it was investigated how the contraction evoked by K^+-depolarization was influenced by the above compounds.

It has been found that physostigmine, at a concentration of 1 mM, diminished by 40 to 50 per cent the K^+-contraction of tetanic muscles, and by 20 to 25 per cent that of tonic muscles. Decamethonium at low concentrations (0.001 to 0.1 mM), caused the tonic muscles to contract. Their contraction was increasing in intensity with the increase of concentration, while at higher concentrations (1.0 to 10 mM) of the drug the intensity of contraction decreased with the increase of concentration. High concentrations of decamethonium definitely inhibited K^+-contraction. In tetanic muscles it induced no contraction, only caused marked inhibition.

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The effect of heat on the cholinesterase activity of actomyosin

It has been investigated whether the presence of actin would modify the ultracentrifugal homogeneity and the distribution of cholinesterase activity of the fractions obtained from myosin solution by heat treatment.

Pure actomyosin was prepared from striated muscles of the rabbit, by removing the sarcoplasmic proteins and *Ivanov*'s fraction "T". The actomyosin thus obtained had a cholinesterase activity of from 15 to 30 μg acetylcholine/mg protein/hour.

On exposure to 53° C at pH 5.0 to 8.0 for 5 min the cholinesterase active fraction of the highest specific activity could be liberated from actomyosin at pH 6.0 to 6.2.

In subsequent experiments heat treatment was carried out at pH 6.0 to 6.2. The liberated fraction (S) was separated by dialysis into a fraction P precipitated at 0.05 μ, and a fraction D which had remained in solution. Cholinesterase activity was enriched in fraction P.

The properties of the cholinesterase active fraction obtained from trypsin digested actomyosin by heat treatment undergo significant changes, insofar as in such cases the cholinesterase activity becomes enriched not in the P, but in the D fraction.

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The effects of cholinesterase inhibitory and receptor blocking agents on the Ca^{++} uptake of the vesicular relaxation system

The vesicular relaxation system was prepared according to NAGAI *et al.* (1960). 0.1 mg of protein from the fraction was applied to a cellulose column, then 5 ml of an incubating solution containing ^{45}Ca ($CaCl_2$, 0.00012 M; KCl, 0.055 M; $MgCl_2$, 0.005 M; potassium oxalate, 0.005 M; ATP-Na, 0.005 M; phosphate buffer, 0.01 M; pH = 6.8) and 8 ml of a Ca^{++}-free incubating fluid. The specific activity of the ^{45}Ca stock solution (0.17 g $CaCl_2$/ml, pH = 5) was 1.26 mC. After evaporation the activity of the fluid which had passed through the column was determined, and from the decrease in the impulse count Ca^{++} uptake was computed. The impulse count obtained without the application of the fraction, or without the use of ATP served as the control. It was found that the Ca^{++} uptake of the fractions prepared ranged from 8 to 14 μM Ca^{++}/mg protein.

Ca^{++} uptake by the vesicular relaxation system was inhibited by 1×10^{-3} M of d-tubocurarine completely, by 1×10^{-2} M of physostigmine to 70 to 80 per cent, and by 1×10^{-3} M of neostigmine to 60 to 70 per cent.

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Immunochemical studies of the proteins of denervated muscle

Immunochemical changes of the gastrocnemius muscle were studied after unilateral sciatic and femoral nerve resection in albino rats by the immuno-electrophoretic method of GRABER and WILLIAMS and by the double immune diffusion technique of OUCHTERLONY and BJÖRKLUND.

The extract of the denervated muscle gave with immune sera of rabbits inoculated with denervated rat muscle a new precipitation band, which is absent in normal muscle extract. It has been shown by the double immune diffusion method that the new precipitation band does not extend over into any band of normal muscle extract, *i.e.* it is an immunologically different protein. Following the absorption of immune serum with normal rat muscle extract, only the antigen of the denervated muscle gave a precipitation band. Thus, a protein of new antigenic activity is demonstrable in denervated muscle.

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Effect of fasting on the carbohydrate metabolism of tetanic and tonic muscles

In previous studies it has been shown that the so-called tonic and tetanic muscles, the skeletal muscles possessing anti-gravitational and locomotor functions, differed in carbohydrate metabolism. In the present investigations the role played by the two types of muscle in carbohydrate metabolism of the body as a whole, especially how fasting affected carbohydrate metabolism of the tonic and the tetanic muscles has been studied. The glycogen content of the tetanic muscle was found to decrease on fasting while on fasting for 1 day or 2 days the glycogen content of tonic muscles either did not change or was slightly increased. Thus, in response to fasting the difference in glycogen content between the two types of muscle diminished.

Beside the changes taking place in glycogen content, on fasting a certain accumulation of lactic acid took place in tetanic muscles while from the tonic muscles the normal amount of lactic acid disappeared almost completely.

The finding may be of some importance in studies concerned with the role of the two types of muscle in systemic carbohydrate metabolism.

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The influence of pantothenic acid and pyridoxine on the consequences of experimental cerebral lymphoedema

The various sequelae of experimental cerebral lymphoedema (changes in EEG, susceptibility to convulsions, barbiturate sensitivity, glycolysis, *etc.)* can be influenced by treatment with pantothenic acid and pyridoxine.

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Prevention by vitamin-E of the nervous lesions caused by triorthocresylphosphate

In previous subacute experiments it has been demonstrated that triorthocresylphosphate (TOCP) rapidly induced functional changes in central nervous activity. The EEG showed an increase then a marked decrease in the frequency of electrical activity, and in conditioned frequency of electrical activity, and in conditioned reflex experiments a rapid impairment of the established temporary connections could be noted.

As vitamin-E is known favourably to influence TOCP intoxication, it has been investigated how the drug would influence the nervous changes. EEG studies were carried out in cats subjected to treatment with 7 mg/100 g of vitamin-E before, simultaneously with, and for longer periods after poisoning with TOCP.

Previous treatment produced the best results. It significantly diminished the EEG and conditioned reflex disturbances. The protective effect of vitamin E, administered simultaneously with or after TOCP poisoning was much less marked and shorter in duration.

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Effect of alpha-methyl-DOPA on the pharmacological and biochemical actions of reserpine

400 mg/kg of alpha-methyl-DOPA (MD) inhibited the convulsion facilitating action of reserpine (2.5 mg/kg) both in the mouse and the rat. MD did

not influence the anaesthesia-potentiating and motility-reducing effects of reserpine. Pretreatment with MD inhibited the noradrenaline level decreasing action of reserpine, while the serotonin level decreased in animals pretreated with MD. The sedative effects of reserpine might be brought into correlation with the decrease of the serotonin level, while its convulsant action appears to be correlated with the lowering of the noradrenaline level.

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Effect of reserpine on the behaviour of aggregated mice and on the cerebral amine level following pretreatment with monoamino oxidase inhibitor

Reserpine is known to cause excitation following pretreatment with monoamino oxidase (MAO) inhibitors. In the present experiments it has been shown that the degree of excitation depends to a great extent on the fact as to whether the mice are kept one by one or in groups in glass containers of identical size. Aggregated mice are significantly more excited than isolated mice and the same phenomenon is observable as in the case of amphetamine, *viz.* in aggregated mice the toxic dose is about 10 times less than in isolated mice. Following pretreatment with 50 mg/kg of nialamide the LD_{50} of reserpine is 3.7 mg/kg in aggregated mice while in isolated mice 50 mg/kg kills 10 to 30 per cent of the animals. Aggregated mice die 1.5 to 2 hours after the administration of reserpine. The serotonin content of the brain at the time of death is double that measured in the survivors killed at the same time.

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Some effects on the nervous system of mescaline and its dimethoxy analogue

According to the investigations of A. J. FRIEDHOF and W. WINKLE, 2,4-dimethoxy-phenylethylamine (DM) occurs in considerable amounts in the urine of schizophrenics. As the compound may be considered to be a structural analogue of mescaline, it seemed worth while to investigate how it acted on the nervous system.

The effect of the compound has been studied on the metabolic rate and body temperature in the cat, and on the orientation reflex, stereotypy and on pain in the mouse.

It was found that, administered intraperitoneally in doses of 50 mg/kg, DM increased the metabolic rate and the body temperature less markedly and for a shorter time than did mescaline.

When administered subcutaneously in doses of from 60 to 120 mg/kg, it induced in mice stereotypy less markedly than mescaline. Unlike mescaline, DM did not enhance orientation reflex activity and had no analgesic effect in subtoxic doses, either.

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Analysis of the monoamine oxidase (MAO) inhibitor effect of phenyl-isopropyl-methyl-propinylamine (E-250), a new psychic energizer

E-250, structurally related to amphetamine, is a strong MAO inhibitor and psychic energizer, causing in rats a slight increase in motility and metabolic rate, and a fall in blood pressure.

MAO activity has been measured manometrically in homogenates and mitochondrial preparations of rat brain and liver, using tyramine as a substrate.

The inhibitory effect of E-250 has been compared with that of Nialamide. Inhibition of MAO activity *in vitro* is practically complete at a concentration of 10^{-5} M with both compounds.

One hour after the subcutaneous injection of 25 mg/kg E-250 a complete inhibition of cerebral and hepatic MAO was observed. The same pretreatment with nialamide completely inhibited the hepatic MAO but affected the cerebral enzyme only slightly. Nialamide is about 5 times less active than E-250 on cerebral MAO.

Enzyme-kinetic studies led to the conclusion that E-250 is a competitive irreversible MAO inhibitor and inhibits more electively and potently cerebral than hepatic MAO.

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Changes in cerebral blood flow and electrical activity in response to the intravenous administration of pentetrazole and strychnine

In 28 rabbits the temperature, blood flow and electrical activity of different cortical areas, mesencephalon, hypothalamus, thalamus and hippocampus, as well as systemic blood pressure, ECG and respiration were recorded simultaneously. It has been shown that (i) cerebral blood flow may be altered by such low doses of strychnine and pentetrazole, which do not influence electrical activity; (ii) there is no consistent correlation between the changes in systemic blood pressure, ECG and respiration, on the one hand, and those appearing in cerebral blood flow and electrical activity on the other; (iii) pentetrazole injected in subconvulsive doses increased the rate of blood flow in three quarters of the animals in the cortex, and in about half of them also subcortically; in the rest it reduced flow (in the cortex in one animal only); (iv) injected in subconvulsive doses, strychnine increased the flow in the subcortical centres in four-fifths of the animals, while it increased cortical flow in one-third only; (v) the effects of pentetrazole differed from those of strychnine, when employed in convulsive doses, in that pentetrazole enhanced cortical flow and reduced mesencephalic flow whereas strychnine increased the mesencephalic and reduced the cortical blood flow; (vi) the development of electroshock convulsions was preceded by an increase of flow in the cortex when pentetrazole was used, and in the mesencephalon when strychnine was injected; (vii) the cessation of the electrical convulsions was preceded by a decrease of flow; (viii) after the cessation of the pentetrazole convulsion, flow normalized first in the subcortical areas then in the cortex, while in the case of strychnine treatment the reverse of this happened: cortical flow was normalized before the normalization of the flow in the subcortical centres; (ix) during the convulsions temperature increased by several decimal degrees centigrade at every point of the brain.

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Distribution of Na in blood and cerebrospinal fluid

In previous investigations the changes in cation composition of the cerebrospinal fluid were studied in response to the simultaneous intravenous infusion of K, Ca and Mg salts, and the remarkable distribution of Mg has been pointed out. In the present investigations the distribution of Na on the two sides of the blood-CSF barrier has been studied in response to infusion of K, Ca and Mg salts.

Total molarity of plasma and CSF showed hardly any change during the experiments. Plasma K, Ca and Mg concentrations increased by a total of 11 mEq/kg H_2O, while the increase in the concentration of the same cations was less than 1 mEq/kg H_2O in the CSF. In response to the infusion, the plasma Na level decreased by 11 mEq/kg H_2O, while no change in the Na level resulted in the CSF.

Although the K, Ca and Mg levels in the CSF increased merely slightly and did not follow the changes in plasma concentrations, in the case of K and Mg relationship was linear. The Ca concentration of the CSF was practically unchanged. The plasma values calculated on the basis of the *Donnan equilibrium* and the Na levels estimated in the CSF were in good agreement. It is suggested that the distribution of Na may be based on the membrane equilibrium.

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Technique and use of intracerebral impedance measurement

A transistorized impedance measuring system has been developed. The measurements are made with a high-frequency current of μA order of magnitude ($\Omega = 2 \cdot 10^5$), which is non-stimulating and has no noxious effects.

By this method it is made possible to control the actual position of the electrodes in the course of stereotaxic operation, because the different components of the brain (gray and white matter and cerebrospinal fluid) have different impedances.

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Interactions of heart function, respiration and cerebral electrical activity in experimental pulmonary oedema

According to earlier investigations, pulmonary oedema induced by NH_4Cl is preceded and accompanied by marked EEG alterations (spike activity, changes in amplitude and frequency), convulsions, bradypnoea and bradycardia. To determine whether the convulsions and the excessive decrease of respiratory rate would be responsible for the pathological changes in cerebral electrical activity, the bradycardia and the ECG alterations, the motor nerve endings were blocked with tubocurarine in rats. The physiological respiratory rate was maintained by artificial breathing through an intratracheal cannula.

The control of convulsions and bradypnoea afforded substantial protection against the bradycardia; as opposed to the lasting and excessive decrease of heart rate in the control animals, there was no bradycardia, or it lasted a few seconds only, in the curarized and artificially respirated rats. The pathological changes in cerebral activity constitute a primary phenomenon absolutely independent of the changes in respiration, heart rate and the convulsions, appearing before pulmonary oedema. The inhibition of convulsions by curarization and artificial respiration did not protect against pulmonary oedema induced by NH_4Cl, but prevented the respiratory paralysis. They afforded, however, no protection against the cardiac repolarization disturbance.

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Reflexion in spiroergometry of the autonomic regulation connected with muscle activity

At the 1963 meeting of the *Hungarian Physiological Society* it has been reported that following controlled physical activity a negative phase in cardiac frequency developed. This counter-regulatory phenomenon was ascribed to trophotropic dominance and was correlated with the degree of physical fitness. In further investigations it could be demonstrated by spiroergometry that on performing a certain type of physical work the regulatory phenomena mentioned were followed by a counter-regulatory phase manifesting itself with changes in oxygen consumption and CO_2 production. Analysis of the autonomic

reactions in the single periods of the work (state of readiness, running up activity, ergostasis, restitution) has revealed that in subjects showing an economical regulation the trophotropic dominance in restitution was marked, while in the other subjects it was slight or absent. Thus, the counter-regulatory phenomenon may be considered an overcompensation, creating in the organism conditions more favourable from the point of view of performance than those prevailing before muscle work.

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Immune diffusion studies of smooth muscle extracts

Investigations have been carried out to find out whether the smooth muscle contained specific protein components different from those in other tissues, first of all in striated muscle. Homogenates from different smooth muscles of the dog were extracted with 0.154 M KCl solution. The supernatant obtained after centrifugation was examined as a solution of myogen, the sediment extracted with *Weber*'s solution as a solution of structure protein. By a similar procedure, extracts were prepared from striated muscles and parenchymal organs. With the extracts rabbits were immunized, the antigens were brought together with pure or absorbed immune sera.

It has been shown that the "anti-smooth muscle myogen" immune serum contains two components, while that against smooth muscle structural protein, one specific antigenic component. The potential role of these antigenic components in smooth muscle activity has been discussed.

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The humoral regulation of saliva secretion in the rat

The conditioned and unconditioned reflex control of salivation is well known. BEZNÁK was the first to show that salivation increased in response to humoral effects. There are no data, however, relative to an inhibitory mechanism. Such a mechanism might be expected to come into play when the food leaves the stomach and enters the duodenum. The entry of the food into the duodenum liberates several parahormones from the intestinal mucosa. Of these, enterogastrone markedly reduces gastric secretion.

It has been shown that intraduodenally administered olive oil strongly suppresses the pilocarpine-induced salivation, while it does not influence the

sialic acid, Na and K concentrations of the saliva. It may be surmised that the duodenal parahormones activated by the oil are responsible for the effect.

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Effect of hyperoxia on gastric hydrochloric acid secretion in the rat

In previous papers it has been reported that the development of the *Shay ulcer* was completely inhibited by hypoxia and strongly promoted by the inhalation of pure oxygen. In this intensive ulcerogenic action of hyperoxia an important role has been attributed to the increase of gastric secretion caused by oxygen.

In the present experiments male albino rats, weighing 180 to 220 g, were used. The animals were fasted for 48 hours, allowed water *ad libitum*, then *Shay*'s operation was performed under ether anaesthesia. After operation the rats were divided into three groups. The first group was exposed for 6 hours to flowing 100 per cent oxygen at 260 mm Hg pressure, the second for six hours to 100 per cent oxygen at 310 mm Hg pressure, the third group served as control. After six hours the animals were killed by exsanguination, and were examined for volume, free HCl content and total acidity of the gastric juice.

According to the results obtained, hyperoxia definitely increased gastric hydrochloric acid secretion.

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Factors influencing the Ca-sensitivity of the isolated frog heart

At a concentration of 5 mg/ml, heparin diminishes the contractions of the isolated frog heart. This effect is completely blocked by doubling the Ca concentration of the *Ringer*'s solution. Heparin applied at the above concentration to the *Stannius II.* preparation arrests the heart; in this case doubling of the Ca concentration of the *Ringer*'s solution is ineffective, thus the sensitivity to Ca of the isolated ventricle is reduced. The sensitivity of the ventricle to Ca is restored by adrenaline (10^{-6}) and caffeine (10^{-4}), while serotonin (10^{-5}), ephedrine (10^{-5}) and insulin (4 U/ml) are ineffective. The sensitivity to Ca of the whole heart is diminished by acetylcholine (10^{-6}),

d-tubocurarine (10^{-5}), hexamethonium (2.5×10^{-3}) and ergotamine (10^{-5}), *i.e.* following the administration of these drugs the effect of heparin is not counterbalanced by the doubling of Ca concentration. Under the experimental conditions employed the sensitivity to Ca of the heart was increased by sympathomimetic agents, and was diminished by sympatholytic drugs. It is remarkable that those sympathomimetic drugs were active, which are capable of activating phosphorylase.

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The role of catecholamines in myocardial hypoxia

The hypoxic ECG changes caused by vasopressin depend on the catecholamine content of the heart muscle. Pretreatment with amine oxidase inhibitors phenelsine, 50 to 100 mg/kg intraperitoneally enhances, pretreatment with reserpine (7.5 mg/kg/48 hrs, subcutaneously) diminishes the effect of vasopressin. The reduced sensitivity can be increased by the administration of catecholamines (200 μg/kg of adrenaline or noradrenaline or isopropyl-noradrenaline, subcutaneously). However, in the normal rat even high doses of catecholamines (2 mg/kg adrenaline, noradrenaline or isopropyl-noradrenaline and 10 mg/kg isopropyl-noradrenaline intraperitoneally) fail to enhance the vasopressin effect.

Changes of the catecholamine level have no influence on the direct vasoconstrictor and negative inotropic actions of vasopressin. (i) In rats deprived of their central nervous system previous reserpine treatment did not alter the pressor effect of vasopressin. (ii) In the guinea pig *Langendorff* heart the vasoconstrictor effect of vasopressin was not diminished by reserpine pretreatment (5 mg/kg/48 hours) *in vivo* and was not enhanced by the administration of a monoamine oxidase inhibitor (phenelsine 50 mg/kg intraperitoneally, 6 hours prior to killing the animal). (iii) As determined on the isolated auricle of the guinea pig, pretreatment with reserpine *in vivo* did not influence the direct heart muscle weakening action of vasopressin.

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Estimation of the action and resting potentials of the isolated frog heart by the use of a tape recorder

To study the mode of action of the active cell membrane factor (celluline), discovered at the Institute of Pharmacology, an intracellular method has been developed for measuring the bioelectric activity of cardiac cells. The complex apparatus is composed of a ball-joint micromanipulator, an universal square pulse generator ("Biostim"), a cathode follower preamplifier ("Akciometer") operated from the mains, a recording oscilloscope, a frequency modulated converter serving the tape recording and play-back from the tape recorder ("Biorecor"), and of a tape recorder.

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Studies on the mode of action of celluline by an intracellular technique

On the basis of studies of the action potentials of the isolated frog heart adapted to high potassium concentration (functioning with endogenous celluline) and of that functioning in the presence of high potassium concentration under the influence of exogenous celluline the hypothesis has been formed that celluline acted in the first phase of cellular activity by increasing the permeability to sodium of the cell membrane. In the present experiments it has been demonstrated that in an ionic milieu of normal composition celluline increases the overshoot of the action potential of the isolated frog heart, as well as the rate of rise of the action potential; these findings lend strong support to the above outlined hypothesis.

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Studies of the mechanism of the cardiac rhythm disturbance caused by ACh and catecholamines in His' bundle sectioned animals

The differences presumably existing in the interaction of adrenergic and cholinergic mediators have been studied in the atria and ventricles, respectively. We examined the disturbances of rhythm caused by adrenaline, noradrenaline

and acetylcholine after dividing *His*' bundle in anaesthetized dogs with the vagi intact, after vagotomy, and after vagotomy and atropine treatment.

The results obtained may be outlined as follows.

(i) The acetylcholine mechanism seems to have an exclusive role in evoking auricular fibrillation.

(ii) The direct effect of catecholamines plays a significant role in ventricular ectopic impulse formation. The catecholamines are capable of evoking ventricular extrasystolia even after the peripheral action of ACh has been eliminated.

(iii) The ventricular ectopic impulse formation in response to catecholamines increases after vagotomy and decreases after atropinization. On this basis it has been assumed that ventricular impulse formation is also under vagal influence, but unlike in the atria, in the ventricles the vagal impulses diminish the tendency to ectopic impulse formation.

(iv) No direct relationship could be demonstrated between the dysrhythmic and pressor activities of the catecholamines.

The evidence obtained substantiates the view that the autonomic nervous interactions differ significantly at the atrial and ventricular levels.

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Report on a new vasoactive substance regulating the metabolic adaptation of the coronaries

It has been shown earlier that abolition of the coronary constrictor tone leads to a cessation of the metabolic dilatation of the coronaries ("coronary rigidity"). From the experimental evidence obtained it has been concluded that this "rigidity" of the coronaries was due to the loss of some regulatory substance, which under normal conditions allows the coronaries to adapt their lumen to the increase of cardiac metabolism. By abolishing the coronary constrictor tone by surgical or pharmacological means, coronary rigidity was induced in dogs. During the evolution of coronary rigidity the existence of a substance could be demonstrated in the serum of the coronary sinus blood. The administration of this substance to a test dog caused its previously extinguished hyperaemic reactions to reappear, *i.e.* the rigidity to disappear. The control sera produced no such effect. In those experiments, in which for some reason coronary rigidity could not be induced in the donor dog, the sinus blood did not contain this active substance. A close correlation was found to exist between the appearance of the active substance in the sinus blood of the donor animal and the exact time of the disappearance of its reactive

hyperaemic responses. The fact that the serum heated to 10° C did not lose its ability to restore reactive hyperaemia clearly indicates that the substance is not a protein. This substance enhanced the hyperaemic responses of the non-rigid canine coronaries as well; it exerted a positive inotropic effect on the frog heart treated with Dibenamine. It caused coronary constriction and increased the reactive hyperaemia and abolished rigidity in the isolated rat heart. The substance restarted the isolated heart of the rat arrested by DPN or CN. This newly discovered substance is not identical with any of the known vasoactive agents. It may be assumed that in the case of human angina pectoris the pathological condition of the coronaries is due to a deficiency or lack of this substance.

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Coronary reflexes in the unanaesthetized dog

The elicitability of coronary reflexes depends to a great extent upon the kind and depth of anaesthesia. To avoid the difficulties involved, a method has been developed to evoke these reflexes in chronic experiments on unanaesthetized animals. In the course of aseptic operations polyethylene cannulae were inserted into the descending aorta and the right atrium, and a nylon thread was passed under the terminal part of the coronary sinus and led out from the chest through a rigid plastic tube. By pulling the thread the sinus could be occluded and thereby the receptors of the coronary sinus reflex and of the coronary depressor reflex could be stimulated simultaneously. This procedure elicited two opposite reactions: (i) hypotension and bradycardia, (ii) prolonged hypertension and tachycardia. The behaviour of the animal was characterized in the first instance by slight initial excitation followed by lasting lassitude, while intense restlessness set in in the second case. While either type of response may have developed in the same animal, usually one of them predominated. Neither type of reaction was accompanied by ECG changes indicative of myocardial hypoxia or dysrhythmia. Following the pericardial injection of procaine both the pressor and the depressor reactions failed to occur; a small dose of an anaesthetic agent was only effective in extinguishing the pressor response. It is assumed that the prevailing state of the pressor-depressor equilibrium significantly modifies the character of the coronary reflexes.

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The effect of temporary ramus descendens compression on coronary circulation and cardiac metabolism in acute dog experiments

The close correlation between O_2-saturation of arterial blood and coronary blood flow has been shown by several authors. In the present experiments the effect on coronary blood flow of transitory circumscribed myocardial hypoxia has been studied in dogs pretreated with morphine (2 mg/kg), and anaesthetized with sodium hexobarbital (30 mg/kg intravenously). Coronary sinus blood flow was estimated before clamping the descending ramus of the left coronary artery, during the clamping lasting 1 minute, and immediately following release of the clamp. The results were as follows.

(i) Coronary blood flow was reduced to 75.1 ± 16.6 per cent of the normal during clamping, and after release it increased to 137.4 ± 14.9 per cent.

(ii) This increase of coronary flow is not reflex in origin, since it fails to appear if the coronary receptors are paralysed with cocaine or if the heart is denervated.

(iii) From the increased myocardial lactic acid output during clamping it is concluded that lactic acid, too, has a role in the increase of coronary blood flow following temporary hypoxia.

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Relief of coronary spasm in unanaesthetized rabbits

ECG changes were induced in unanaesthetized rabbits by the intravenous injection of 0.5 to 2 U/kg of pituitrin, and the possibility of testing drugs capable of relieving the coronary spasm so induced has been studied with the aim of obtaining reliable rapid and pharmacologically useful information as to myocardial blood flow and oxygenation in the unanaesthetized animal.

It has been found that acute pretreatment with high, nearly toxic doses of classical coronary dilators only influenced the ECG changes (elevation of ST and T) induced by pituitrin. This occurred also on the synchronous administration of pituitrin and the coronary dilator agent in question. In contrast, in the phase of lasting T elevation caused by pituitrin even low doses of the coronary dilators appreciably diminished the ECG changes. After the acute vasodilator action had ceased, the T wave rose again, since the action

of pituitrin persisted longer. Thus, for the purpose of studying the ability of relieving coronary spasm, the "suspending procedure" seems to be the most sensitive, while the methods of "acute prevention" and "synchronous administration" are less efficient. On the basis of the evidence obtained, the correlations between the ECG changes caused by pituitrin and myocardial hypoxia and ischaemia, respectively, have been discussed.

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Effect of MAO inhibitors on coronary blood flow

After the introduction of iproniazide several MAO inhibitors have been shown to relieve the complaints of angina pectoris patients.

In acute experiments on dogs with opened thorax, under positive pressure breathing the effect on coronary blood flow of phenyl-isopropyl-methyl-propinylamine (E-250) has been studied and compared with that of nialamide. It has been found that

(i) administered intravenously, E-250 in doses of 0.1, 0.5 and 1.0 mg/kg increased coronary sinus blood flow by 19.5, 34.8 and 38.5 per cent, respectively. The effect developed immediately after administration and was over in about 15 to 20 minutes;

(ii) the increase of coronary flow was accompanied by hypotension and a slight increase in pulse rate;

(iii) therapeutic (1 to 5 mg/kg) doses of nialamide exerted no significant influence on coronary blood flow.

On the basis of the results it seems that the prompt increase of coronary blood flow by E-250 is not due to MAO inhibition, but to some direct or reflex vascular effect.

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The mechanism of noradrenaline potentiation by imipramine

In previous studies it has been shown that imipramine possessed a relatively potent antiarrhythmic activity. The experiments aimed at the elucidation of the underlying mechanism indicated the significant role of the cholinergic excitatory state. In the present studies the role of the cholinergic effects in the potentiation of noradrenaline by imipramine has been analysed. In dogs, imipramine enhanced the arrhythmic response elicited by high doses

of noradrenaline, while it inhibited the development of arrhythmia in vagotomized or atropine pretreated animals. Cocaine enhanced arrhythmia in both cases. In decerebrated and atropine-pretreated cats neostigmine and physostigmine enhanced the pressor effect of noradrenaline while *Win* 4981, 3,6 bis (3-diethylaminopropoxy)-pyridazine-bis-methiodide kindly supplied by the *Winthrop Co. Ltd.*, and curare inhibited the noradrenaline-potentiating effects of both imipramine and the cholinesterase blocking agents mentioned.

The results suggest the role of cholinergic mechanisms in the noradrenaline-potentiating effect of imipramine and that the sensitivity of the sympathetic receptor is significantly influenced by the actual parasympathetic tone.

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Mode of action of antiarrhythmic drugs

In earlier investigations (SZEKERES and VAUGHAN-WILLIAMS) the effect on the intracellularly recorded action potentials of five drugs, known to induce arrhythmia but different in chemical structure (quinidine, procaine, papaverine, dibenamine, procaine amide), was studied on the isolated rabbit atrium preparation. It was found that the action against ventricular fibrillation was based mainly on their influence upon the process of depolarization. In therapeutic concentrations, these agents did not influence repolarization. Since those experiments were carried out in isolated hearts and it was not possible to study directly the refractory periods, in the present experiments the action of these drugs on the refractory period, excitability and conduction of the artificially driven heart of anaesthetized cats was determined *in situ*. Simultaneously, the action of the drugs on the atrial and ventricular fibrillation thresholds was estimated. The most conspicuous finding was that in doses similar to the therapeutical ones these drugs did not influence the total refractory period, and only slightly the absolute refractory period, although they significantly elevated the atrial and ventricular fibrillation threshold, and considerably increased diastolic thresholds.

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Effect of corticosteroids on cardiac output and vascular resistance in dogs following blood loss

At last year's Meeting of the *Hungarian Physiological Society* the effect of a water-soluble corticosteroid analogue in haemorrhagic shock of the dog has been reported. Administration of the steroid in the oligaemic phase was followed by a significant rise in blood pressure. To find the explanation for this phenomenon, in the present experiments we have studied the changes brought about by the drug in cardiac output and peripheral vascular resistance.

Forty dogs under light pentobarbital anaesthesia were bled by the "reservoir technique". (Average initial cardiac output: 2.62 litres/min, 0.95 fiducial limits: $\pm$ 0.32 litres/min. Average blood loss by the end of bleeding 43.1 ml/kg.) After haemorrhage the cardiac output dropped significantly, as compared with the initial value, and peripheral resistance increased. Then a group of 14 dogs was treated with placebo (10 ml of 5 per cent glucose), another group of 15 dogs with the water-soluble corticoid analogue [(11 beta-, 17alpha-dihydroxy-3,20-dioxo 21-N/N′-methylpiperazinyl) 1,4 pregnadiene HCl, 15 mg/kg], and a third group of 11 dogs with aldosterone. In the second group cardiac output increased, while in the other two it did not change significantly. After the blood withdrawn had been reinfused, cardiac output increased, and peripheral resistance decreased in every group.

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Circulatory compensating mechanisms after haemorrhage in dogs with sympathetic nervous blockade

Beta adrenergic blockade was induced in dogs with phenoxybenzamine. By isotope and dye-dilution methods circulating blood (erythrocyte and plasma) volume, cardiac output and peripheral vascular resistance were estimated, further the total amount of circulating proteins, the oxygen contents of arterial and mixed venous blood, the pH of blood and the haematocrit. Following haemorrhage of different extent measured the amount of fluid and protein entering the circulation from the extravasal space, the total body haematocrit, the volume of sludged erythrocytes as well as the tissular oxygen extraction were determined. By analysing the experimental data, quantitative relationships have been demonstrated between the changes of the single parameters. The results were compared with those obtained in normal animals.

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Sympathetic activity in haemorrhagic shock

In cats anaesthetized with chloralose-urethane and immobilized with gallanine triethiodide the action potentials of the sympathetic nerves running to the kidney and heart have been recorded in different stages of haemorrhagic shock. Beside the basic activity, the effects of sciatic stimulation, adrenaline and asphyxia have also been studied.

During bleeding the basal activity was usually increased. Following re-transfusion sympathetic activity persisted until death in both the renal and cardiac fibres.

The normal effect of sciatic stimulation consisted in a reflex response followed by a silent period. In some cases no response to sciatic stimulation was obtained by the end of the oligaemic period, but the response reappeared following retransfusion. In the terminal phase of shock basal activity was marked, but no response was obtained on sciatic stimulation. The pressor effect of adrenaline inhibited sympathetic activity in shock. Asphyxia definitely increased sympathetic activity, even in the terminal phase.

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Local blood flow and oxygen tension of brain tissue in haemorrhagic shock

In previous investigations it was shown that irreversible shock was accompanied by a characteristic nervous lesion, insofar as in such cases the spontaneous cerebral electrical activity of the brain ceased.

To clarify the underlying mechanism, the microcirculation and local oxygen tension of brain tissue in the hypothalamic and cortical regions was determined in different stages of shock.

As preliminary investigations had shown phenoxybenzamine treatment to prevent the development of cerebral bioelectrical disturbances, the studies were extended to animals pretreated with phenoxybenzamine.

It has been found that in the control group with haemorrhagic shock blood flow decreased to 50—70 per cent of the initial level. In the oligaemic period oxygen tension in the brain decreased to 20 per cent. Following retransfusion, hypothalamic and cortical circulation returned to normal for a while, but oxygen tension remained at a low level. This observation indicates that

cerebral oxygen requirement is greatly increased in shock. In the animals pretreated with phenoxybenzamine the circulatory changes did not differ from those found in the control shock group, but oxygen tension decreased to a much lesser extent in the oligaemic phase and it became normal immediately after retransfusion.

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Myocardial blood flow in haemorrhagic shock with and without phenoxybenzamine treatment as determined by the "heated thermocouple" method

In recent years, increasing importance has again been attributed to cardiac lesions in the development of irreversible shock.

In the present experiments haemorrhagic shock was induced in dogs anaesthetized with chloralose and myocardial blood flow was studied by the "heated thermocouple" method of HENSEL and RUEF, based on the measurement of heat conductivity. As phenoxybenzamine is known to exert a protective effect, the studies were extended to animals pretreated with phenoxybenzamine.

It has been found that in response to phenoxybenzamine pretreatment arterial blood pressure decreased and myocardial blood flow increased. In the control shock group the flow decreased significantly, while vascular resistance only slightly, during the oligaemic periods. In the animals pretreated with phenoxybenzamine myocardial blood flow did not drop below the initial level, in spite of the hypotension, while resistance showed a marked decrease.

The results have allowed some new conclusions as to the mechanism and therapy of haemorrhagic and cardiogenic shock.

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Criteria of the thermistor method for studying tissue blood flow

Model and animal experiments have been carried out to standardize the physical and physiological conditions of estimating tissue blood flow by the thermistor technique. The heated-cold thermistor couple linked to one measuring bridge was found to be in every respect more advantageous than the generally used devices operating with separate heated and cold thermistors.

When tissue blood flow is measured by thermistors or thermocouples, in order to ensure reproducible results the following criteria should be adhered to.

(i) The measuring systems should have identical thermometer sensitivities, deviating by not more than 0.01° C.

(ii) The same measure of over-heating should be used in every experiment.

(iii) When the compensatory method is used (heated and cold thermistors connected to the same bridge) tissue blood flow may be recorded independently of oscillations of the absolute temperature.

(iv) When the heated and the cold thermistors are not in the same structure, or are not near enough to each other, the changes in tissue temperature caused by a given intervention should be determined before measuring the blood flow by unheated thermistors. Then the thermistor is heated at the point of measurement, the experiment is repeated, and net flow is computed by comparing the two curves.

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Pharmacological properties of alpha-methyl-m-tyramine (Pulsoton) and metaraminol

When injected subcutaneously, the LD_{50} of alpha-methyl-m-tyramine (α-MMTyr) is 17.1 mg/kg in isolated mice and 565 mg/kg in aggregated mice. As examined by means of KOMLÓS' water-displacement motimeter, 5 to 20 mg/kg doses of α-MMTyr cause marked excitation in aggregated mice but no such effect can be observed in mice kept in individual cages. Group toxicity and group motility are inhibited by 0.02 to 0.2 mg/kg doeses of reserpine. In acute experiments, α-MMTyr inhibits in anaesthetized cats the carotid sinus reflex, the pressor effect of tyramine and amphetamine, and gives rise to orthostatic hypotension. Cocaine has no influence on the pressor effect of the compound, but when applied locally it inhibits the lasting contraction of the nictitating membrane caused by α-MMTyr.

As suggested by several authors, in the organism α-MMTyr is converted through beta-hydroxylation to metaraminol. In many of its effects, metaraminol is different from α-MMTyr: no tachyphylaxis develops to its pressor effect, cocaine enhances its effects on blood pressure and on the nictitating membrane, and it does not inhibit the pressor response to amphetamine.

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The effect of renal sheathing on the granulated cells of the juxtaglomerular apparatus

One kidney or both kidneys had been wrapped in rubber capsules and the juxtaglomerular granulated cell index was studied in the sheathed and intact kidney at different points of time after the intervention.

Following unilateral sheathing the index gradually decreased from 12 hours till the 10th day in the intact kidney, while in the sheathed kidney the index did not exceed the average.

On the 10th day following bilateral sheathing there was marked hypertension, and the index showed a non-significant decrease.

The decrease of the index is attributed to the elevation of intraarterial renal pressure, which in turn develops to compensate the elevated intrarenal pressure.

Unlike in hypertension due to renal arterial vasoconstriction and accompanied by an increase in the number of granulated cells, in experimental hypertension induced by renal sheathing or in the clinical forms analogous to this state no decisive role may be ascribed to the increased (renin?) secretion of the granulated cells.

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Relationship between the pressor effect of renal extracts and their juxtaglomerular granulated cell content

Renal extracts different in juxtaglomerular granulated cell content were tested for pressor effect in rats sensitized to renin by bilateral nephrectomy. There was no significant difference in pressor effect between the extracts from adult rats containing a moderate amount of granules, from newborn rats containing no granules, and the mouse kidney extracts much higher in granule content than the rat's kidney. This proves, at variance with the view put forward by HARTROFT and others, that no direct relationship exists between the granulated cell content and the pressor effect, so that (i) either the granules of these cells are not identical with renin, or its precursor, or else, (ii) the renin produced by the granulated cells has no primary role in the maintenance of blood pressure under physiological conditions.

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Investigation into the pathomechanism of renal hypertension

The slightly modified operation developed by LŐRINC and GORÁCZ for inducing renal hypertension in the rat elevates in cats and dogs blood pressure by 40 to 95 mm Hg in 3 to 6 days. Administered intraperitoneally, the aqueous extract prepared from 20—50 g/kg dog kidney and purified by semi-saturation with alcohol does not lower blood pressure significantly until after the 10th to 14th postoperative days. 14 to 21 days following operation the extract lowers blood pressure by 30 to 50 mm Hg for 2 to 4 hours in rats, cats and dogs. Likewise, the kidney extracts lower blood pressure after 14 days in rats with renal hypertension induced by GROLLMANN's method. According to MUIRHEAD *et al.* the renal extracts do not block the renin effect, but afford protection against the hypertension which develops on nephrectomy. According to our data, renal hypertension cannot be influenced until the 10th to 14th days in the manner induced by renin, but after 14 to 21 days it can be influenced with renal extract, similarly to renoprive hypertension.

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The effect of regular muscular activity on factors involved in the pathogenesis of experimental cardiopathy

The effect of muscle activity was studied on the factors playing a role in the pathogenicity of the cardiopathogenic diet S-65. The blood cholesterol level of rats fed the cardiopathogenic diet and forced to swim daily was significantly lower than that of rats fed the diet only. The control animals and the animals forced to swim showed comparable values. It is known from the literature that the blood lipid level is lowered by exercise. It has been found that this is valid in chronic experiments, too, and may have a role to play under pathological conditions.

Swimming and the diet induced the same changes in the serum protein pattern (decrease of albumin, increase of globulin). In the swimming groups the gamma globulin level was higher than in the control and dietary groups.

At this stage, histological examination reveals only slight cardiac changes in some animals fed the cardiopathogenic diet.

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The effect of a magnesium rich diet on experimental vascular changes

In earlier studies it was found that a diet rich in Mg exerted a protective effect in experimental hypertension. The changes of the collagen crosslinks arising in the rat aorta in response to D_2 hypervitaminosis and to feeding diets high in vitamin D_2 and Mg have been studied by VERZÁR's method. In the control group the tension resulting from thermic contraction was 7.5 ± 1.1 g, in the animals fed a diet rich in D_2 vitamin this value was 9.3 ± 0.8, while in the group fed a $D_2 + MgCl_2$ rich diet, 7.7 ± 0.7 g, comparable to that obtained for the controls. The difference was significant statistically.

In the second group the Ca content of the aorta and the changes of the vascular wall thickness: lumen ratio in the coronary branches were studied. In the control group the aorta contained 0.5 per cent Ca. In response to feeding the cardiopathogenic diet this value increased to 1 per cent. In the animals fed a cardiopathogenic diet rich in Mg, the aorta contained 0.45 per cent of Ca, *i.e.* an amount similar to that found in the controls. The vascular wall: lumen ratio values were: 2.5 in the control group, 5.2 in the cardiopathogenic group, and 2.1 in the group fed the cardiopathogenic diet rich in Mg.

The experimental vascular changes induced by D_2 hypervitaminosis and the cardio-vasopathogenic diet can be effectively prevented by feeding a diet rich in Mg.

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The protective action of "Tromcardin" against the cardiopathogenic diet in the rat

The effects of Ca, Mg, K and Na asparaginate have been studied in rats fed a normal diet and in rats fed a cardiopathogenic diet. K and Mg asparaginate prevented the cardiopathogenic diet from elevating blood pressure and from increasing the cold pressor reflex, while Ca and Na asparaginate made the effects of the diet more severe. If injected daily, "Tromcardin" (K-, Mg-asparaginate) likewise inhibited the effects of the cardiopathogenic diet. The findings suggest that it is the K and Mg ions in the first place that may be held responsible for the protective action, while the asparaginate plays a subordinate role.

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Absorption of clearance substance from the renal pelvis

The absorption of various clearance substances from the renal pelvis has been studied in anaesthetized dogs with acute pyelectasis and experimental hydronephrosis. In both experimental groups solutions containing inulin, creatinine and PAH were injected at medium pressure into the left renal pelvis, the outflow was blocked and the intrapelvic pressure was measured. Simultaneously the concentrations of the clearance substances in blood and their amounts eliminated by the right kidney were estimated.

It is obvious that the clearance substances found in the blood or eliminated by the right kidney had originated exclusively from the left renal pelvis. The results indicate that the clearance substances are absorbed to a significant extent from the renal pelvis in acute pyelectasis and in hydronephrosis alike. The fact that the clearance substances of different physicochemical properties were absorbed at the same rate excludes the possibility of pelvitubular absorption and is indicative of a pelviovenous and/or pelvilymphatic reflex.

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Effect of papaverine on renal PAH excretion

It has been observed that the extraction of PAH was markedly diminished under the effect of papaverine. In the present studies made on isolated dog kidneys by the method recommended by JOSEPHSON *et al.* it has been found that in the presence of a diffuse tubular lesion, irrespective of whether at the low plasma PAH concentration the extraction of PAH was normal or less than normal, even a moderate increase of the plasma PAH level caused the PAH extraction to decrease. However, when focal lesions were present, E_{PAH} decreased only if the plasma PAH level had considerably increased.

(i) E_{PAH} was low (mean, 0.66) in the control periods already.

(ii) E_{PAH} did not change up to a plasma PAH concentration of about 15 mg per 100 ml. When the level was higher, E_{PAH} began to fall steeply.

(iii) The mean Tm_{PAH} value in the control periods was 12 mg/min/100 g kidney.

(iv) Under the effect of papaverine, E_{PAH} decreased to 0.28;

(v) and remained at that level up to a plasma PAH concentration of about 15 mg per 100 ml.

(vi) During the papaverine effect the mean Tm_{PAH} value was 6.5 mg/min/100 g kidney.

From the results it has been concluded that papaverine does not bring about a diffuse tubular lesion, the shape of the curve was similar to that characteristic of focal lesions. The reversibility of the process points to a correlation between the "focal" lesion and a change in the distribution of renal blood flow.

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Renal autoregulation in mannitol diuresis

In the kidney *in situ* no autoregulation is demonstrable in response to the infusion of 10 per cent mannitol for 30 minutes. In the kidney deprived of its nerves and placed on the neck of another dog (isolated kidney) the flow curve does not increase linearly in response to the increase of pressure.

The increase of intrarenal pressure resulting from ureteric occlusion causes no change in RBF in kidney with intact nerve supply, while it reduces it by about 50 per cent in isolated kidneys.

No autoregulation is observable during ureteric occlusion in the kidney *in situ*, and the pressure and flow curves are similar to those recorded from isolated kidneys prior to occluding the ureters.

The phenomenon is explained by the fact that the renal nerves may alter renal vascular resistance, when there is an increase in intrarenal pressure.

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The effect of angiotensin on renal circulation

It has been observed that the infusion of angiotensin II, at a rate of 0.1 to 1.0 μg/minute was followed by intense vasoconstriction in the kidney. The directly measured renal blood flow decreased by about 40 per cent both in kidneys with intact nervous supply and in isolated kidneys deprived of their nerves. As related to the control values, in the kidneys *in situ* C_{PAH} and C_{creat} decreased by 25 per cent while E_{PAH} and E_{creat} increased by 15 per cent and 30 per cent, respectively.

In the isolated kidneys C_{PAH} and C_{creat} decreased by 10 per cent, E_{PAH} and E_{creat} increased by about 30 per cent. All these indicate that there may

exist in the kidney such pathways which avert the blood from the functioning parts, and it is these that angiotensin causes to constrict in the first place. On injecting angiotensin into the renal artery, the animal's blood pressure drops; the hypotension cannot be ascribed to the technique of operation.

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Estimation of blood flow in the renal medulla

Medullary blood flow has a decisive part in maintaining the osmotic concentration in the renal medulla and thus of the secreted urine; this explains the many efforts for its estimation. In the present experiments SAPIRSTEIN's method was used for estimating renal cortical and medullary blood flow in the dog under hydropenic and hydraemic conditions. It has been found that

(i) blood flow decreases gradually from the medullary-cortical junction toward the papilla, that significantly enhances the activity of the counter-current system;

(ii) in hydropenia only 8.5 per cent of the total RBF passes through the medulla and only 1.5 per cent through the papilla;

(iii) in hydraemia total renal blood flow increases, accompanied by an increase in medullary flow, and 14.5 per cent of the total RBF passes through the medulla, *i.e.* approximately three times the amount found in hydropenia. The increased medullary flow may neutralize the increase of concentration induced by the counterflow system.

The change in the distribution of renal blood flow in hydropenia and hydraemia may be correlated with the vascular effect of ADH.

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The effect of an acute increase of cardiac output on the cerebral and extremital blood flow

In response to an acute increase of cardiac output (induced by a rapid infusion of physiological NaCl solution, 10 ml/kg) in the dog the blood flow in the internal carotid and the vertebral artery increased to a smaller extent, while that in the femoral artery increased excessively as determined by means of a floating rotameter).

According to clinical experiments, the acute increase of cardiac output on the infusion of 5 ml/kg of saline significantly increased cerebral and extremital blood flow. Oxygen and glucose uptake by the cerebral and extremital tissues increased, cerebral vascular resistance decreased slightly, extremital vascular resistance diminished markedly. The cerebral fraction of cardiac output decreased slightly while the extremital fraction of cardiac output increased (determined by venous isotope dilution methods).

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Blood circulation in the regenerative rat liver

The factors inducing regeneration following partial hepatectomy are not clearly known. Beside the humoral factors believed to be responsible for the effect, eventual quantitative shifts in hepatic blood supply may also play a role in the process. To elucidate the problem, hepatic circulation has been studied in different stages of regeneration.

Perfusion experiments on isolated liver preparations have shown no significant difference in perfusion flow per unit liver weight between regenerating and control livers. The pressure curves of regenerating livers did not differ from those of normal ones.

Our data indicate that cellular regeneration runs parallel with circulatory regeneration, and that the newly formed liver tissue has the same type of vascularization, both quantitatively and qualitatively, as the original one.

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The effect of agents influencing circulation on pancreatic blood flow

The effect of certain agents influencing systemic circulation — adrenaline, histamine, dehydrocholic acid — on the blood flow in the pancreas was assessed on the basis of measuring pancreatic blood flow and determining the changes taking place in it. The experiments were made on dogs under chloralose anaesthesia. Blood flow was determined by SAPIRSTEIN's ^{86}Rb method, the changes in flow were recorded by means of a heated thermocouple inserted into the pancreas. In response to the intravenous administra-

tion of dehydrocholic acid pancreatic blood flow (126.1 ml/100 g/mm) significantly increased. Whereas on the intravenous injection of 10 per cent dehydrocholic acid and intravenous histamine pancreatic blood flow increased to the double of the control value, the intravenous injection of 50 μg of adrenaline was without such influence. The increase of pancreatic blood flow is not due to a change in blood pressure. According to the results obtained, dehydrocholic acid and histamine induce considerable vasodilatation in the pancreas.

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Electrical recording of respiration in freely moving animals

A method has been developed for recording electrically the breathing of cats, without interfering with the movements of the animal and with a simultaneous recording of bioelectrical activities. On the basis of comparative studies, the advantages and shortcomings are discussed of the methods for recording respiration by the use of thermistors and thermocouples, as well as by techniques based on the measurement of impedance, suitable also for the determination of quantitative changes.

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The role of serotonin in experimental dumping syndrome

It has been shown earlier that in the dog the intravenous infusion of serotonin influenced the regulation of blood pressure in the way observable in the experimental dumping syndrome.

The azo dyes administered intravenously stain the enterochromaffin cells of the intestinal mucosa. The combination between dye and serotonin takes place also *in vitro*. Following the intravenous administration of 5-chloro-o-toluidine the dumping syndrome cannot be induced by the intraduodenal infusion of a hypertonic solution or of oil. This observation lends support to the view that serotonin plays a role in the dumping syndrome.

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Effect of semistarvation on the thermoregulation of the developing organism

Newborn rats were divided into two groups. The normal controls were given sufficient amounts of food, while the other group was maintained on a low-calorie diet. As a result a difference in body weight amounting to 31—44 per cent arose between the two groups. Until the age of 260 days chemical thermoregulation was examined in several experimental periods, at ambient temperatures of 35° C, 30° C, 20° C (cool) and between 3° and 5° C (cold).

(i) While in the control group body temperature was maintained on exposure to cold on the 16th—17th days, in the partially fasted animals thermoregulation became satisfactory on the 24th—25th days only.

(ii) Until the age of 2 to 3 months colon temperature and oxygen consumption of the fasted animals were significantly lower at indifferent and 20° C temperatures than in the normally fed group. At 109 to 141 days the difference in heat production still persisted, while colon temperature showed no significant difference any longer.

(iii) At the age of from 216 to 245 days, in spite of the considerable (44 per cent) difference in weight, at both 20° C and 3° to 5° C the increase of heat production and thermoregulation were identical in the two groups.

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On the Kyungrak system

In 1961, KIM BONG HAN, a Korean author described a fourth system existing beside the neuroendocrine, circulatory and lymphatic systems, correlating the effect of acupuncture, with that fourth system. The order of magnitude of the fourth system make it understandable why its discovery came so late; in view of the small number and size of its members it can hardly be recognized by the common methods of examination. They can be found in the "dead space" dimension between gross and microscopic examination. The most conspicuous elements of the system are the so-called *Bong Han corpuscles*.

Microchemical studies of preparations from newborn and adult animals in the "dead-space dimension" seemed to point to the existence of the fourth system.

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Mechanism of hyperoxic pulmonary oedema

According to data in the literature, experimental animals develop pulmonary oedema in response to inhalation of O_2 of high CO_2 content. The development of pulmonary oedema under such conditions is ascribed to the noxious effect of CO_2. In previous experiments we failed to induce pulmonary oedema in dogs by making them to inhale for 3 hours air containing 10 to 30 per cent CO_2 at atmospheric pressure. Some authors suggest that tissue hypercapnia is responsible also for the development of hyperoxic pulmonary oedema.

It seemed worth while to investigate the relationship between tissue hypercapnia and the pulmonary oedema developing in response to the inhalation of pure O_2. Normal rats, as well as rats pretreated with phenoxybenzamine were exposed for various periods to high-pressure O_2 and subsequently the CO_2 content of brain, liver and muscle, the survival time, as well as the gross and histologic appearance of the lungs were studied.

Inhalation of high-pressure O_2 was found to induce pulmonary oedema but its development was preceded by tissue hypercapnia. The severity of pulmonary oedema and that of tissue hypercapnia varied in proportion to the pressure and the duration of exposure. Phenoxybenzamine pretreatment slightly prolonged survival, increased the severity of pulmonary oedema and ameliorated tissue hypercapnia.

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The effects of excitation and physical work on the control of circulation

When young people are subjected to medical examination which at first usually causes some excitement, diastolic pressure is low and the pulse amplitude widens downward both after rest and the work the subject is made to perform for assessing the adaptability of circulation. When the examinations are repeated, diastolic pressure increases at rest and the fall in diastolic pressure following the exercise is slighter.

The pulse amplitude is widened downward and diastolic pressure decreases also when the subject is passing an exciting examination or after loading following the moderate exercise. In such cases the *Korotkov* sound is often and

in some of the test subjects repeatedly unchanged after the cuff of the sphygmomanometer has been deflated.

Work and sports are frequently accompanied by excitement and prolonged strain. In such instances the vasodilatation, presumably connected with the effort, may surpass the compensatory possibilities of the vascular bed already on moderate strain and even in young subjects. In certain individuals this may restrict the energy supply to muscles and promote the development of a vasoregulatory disturbance, which is most often the cause of faintness during sports.

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Electron-microscopical identification of the catecholamine substances of the adrenal medulla

After a general ultrastructural analysis of adrenal medullary secretion in different mammalian species, the identification of the secretory granules is discussed.

In some cells of the adrenal medulla of the frog *Rana esculenta* and of the grass snake, *Natrix natrix*, adrenaline-containing secretory granules 1000 Å in diameter, while in other cells granules containing noradrenaline and 3000 Å in diameter can be detected. In the rat, mouse and dog the two different-sized granules occur in the same cells of the adrenal medulla.

That the secretory granules containing adrenaline differ from those containing noradrenaline in size and specific gravity, is proved also by ultracentrifugal fractionation. The granule fraction of the dog's adrenal medullar homogenate sedimenting at 3000 g/30 min showed a noradrenaline content of 80 per cent, while the sediment obtained at 24,000 g/30 min showed an adrenaline content of 96 per cent. The adrenaline activity of the small granules is supported also by the evidence obtained by insulin loading experiments carried out in rats.

Beside the above two types of granule, a third type has also been observed, granules 0.5 to 1.5 microns in size, possessing a fine internal structure and delimited by a membrane. On the basis of ultracentrifugal fractionation and chemical determination, these structures are believed to be precursor granules containing dopamine.

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Electron-microscopic studies of the medial eminence in the rat

The ultrastructure of the layers (ependyma, hypendyma, fibrous layer and palisade layer) of the medial eminence is described. The surface of the brain is covered by a basal membrane. The endothelium of the portal vascular loops penetrating into the medial eminence, like that of the blood vessels transporting large volumes of fluid, is very thin and fenestrated. In the palisade layer, especially near the vascular loops, nerve fibre endings occur in large numbers. The endings are characterized by two types of vesicle: (i) vesicles of small size, with light contents, similar in order of magnitude to the synaptic vesicles; (ii) larger vesicles, similar to the neurosecretory vesicles, containing denser material. In the lateral and anterior parts of the medial eminence there are few nerve endings, and they give way to glial and ependymal soles. In this area and in the hypendyma the vascular epithelium is not fenestrated. These ultrastructural properties support the view that in the area of the medial eminence a substantial transport of substances is taking place between blood vessels and nerve endings.

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The electron-microscopic structure of the pituitary transplanted into the anterior chamber of the eye

Homologous adenohypophysis transplanted into the anterior chamber of the eye of male albino rats was examined 50 days following transplantation and later. The transplanted organ underwent significant structural and cellular changes, but every normal type of cell was demonstrable by electron-microscopy. In the transplants the cell ratio underwent a change, elements containing granules characteristic of the acidophilic mammotropic cells gained preponderance. It had been shown earlier by functional studies that the transplanted hypophyses secreted luteotrophin. The pituitary cells, especially near the blood vessels, possess well-developed and regular endoplasmic reticulum characteristic of active function, and often contain maturing granules. The results appear to indicate that *Golgi*'s apparatus, too, has a role in the production of the secretory granules.

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Effect of TSH administration on the ultrastructure of the thyroid gland of decapitated chick embryos

In previous electron microscopic studies it has been shown that at about the 11th day of incubation a large quantity of ergastoplasm of the lamellar type develops in the thyroid gland of the chick embryo, in response to the TSH secretion starting at that time. This does not happen in decapitated embryos. To prove that TSH acts directly, 14-day old decapitated embryos were treated with TSH, in response to which ergastoplasm similar to the normal developed, just as it happened in the case of decapitated, hypophysis-transplanted embryos of similar age. The developmental stages of the ergastoplasm have also been investigated, as well as the earliest manifestations of the TSH effect at different intervals following the administration of TSH.

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Electron-microscopic studies of the secretory activity of the parathyroid gland

Results obtained in the frog, *Rana esculenta*, are discussed. The secretory product is accumulated in secretory granules in the state of normofunction and hyperfunction alike. The form of appearance of the secretory granules depends on their genesis and on the functional state of the gland.

In the course of granulogenesis the first change is the appearance of large numbers of empty vesicles in *Golgi*'s apparatus. These vesicles then gradually separate themselves from *Golgi*'s apparatus, fine granular elements condensate around, and penetrate into, the empty vesicles. In the next phase lamellar elements appear in the granule; they are apparently ergastoplasmic in nature. The internal homogeneity of the mature secretory granules is a result of a dissolution of the above elements.

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Hypophysiotrophic area and adenohypophysial function

The adenohypophysial tissue implanted into the basal medial part of the hypothalamus of hypophysectomized albino rats retains its normal histological structure, as well as its adrenocorticotrophic, gonadotrophic and

thyrotrophic activities. That hypothalamic area was therefore termed "hypophysiotropic area". In the present experiments the area in question was isolated from other parts of the brain and the functional capacity of the adenohypophysis connected with the isolated hypophysiotrophic area was tested by examining the lipid pattern, compensatory hypertrophy, and ascorbic acid depletion of the adrenals, the corticosterone content of adrenal venous blood, the histological structure of the thyroid, the value of the T/S ratio, the reaction to thiouracyl, the histological structure of the ovary, its compensatory hypertrophy, as well as the sequence of events in the vaginal cycle. The experimental results have shown that the isolated hypophysiotrophic area is capable of maintaining the trophic function especially the thyrotrophic and adrenocorticotrophic functions, of the adenohypophysis.

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Effect of acute and chronic cortisone administration on the stress-induced activation of pituitary-adrenal function

The effect of acute and chronic elevation of plasma corticosteroid level by the administration of a single high dose of cortisone or by prolonged cortisone treatment has been studied on the stress-induced activation of adrenocortical function in cats and dogs. The activation of adrenocortical secretion reached the same values in formalin or epinephrine-stressed cats with an increased plasma corticosteroid level as in control stressed animals, although adrenocortical secretion in the non-stressed animals had significantly diminished under the effect of the applied cortisone doses.

Prolonged cortisone treatment depressed the resting corticosteroid output and prevented the epinephrine-induced adrenocortical activation. The adrenal responsiveness to exogenous ACTH was also diminished in treated animals.

The results indicate that the stress-induced activation of the pituitary-adrenal system is independent of the plasma corticosteroid level in acute conditions, while a chronic elevation of plasma corticosteroid level results in an inhibition of the stress-response by different mechanisms.

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On the mechanism of the hypothalamic control of the pituitary-thyroid system

In experiments on male albino rats it has been investigated how bilateral electrocoagulation of certain hypothalamic areas influenced oxygen consumption, ^{32}P uptake and TSH secretion of the anterior pituitary. Oxygen consumption and ^{32}P uptake were studied *in vitro*.

It has been found that electrocoagulation in the anterior hypothalamus damaging the paraventricular nucleus significantly reduced oxygen consumption and ^{32}P uptake of anterior pituitary slices.

In accordance with earlier observations, the lesion significantly reduced TSH secretion.

The present results have confirmed that the rate of TSH secretion is correlated with the oxygen consumption and ^{32}P uptake of the anterior pituitary.

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The effect of thalamic stimulation on pituitary-thyroid activity

In male albino rats with chronic deep electrodes the effect of stimulation of different thalamic areas on pituitary-thyroid function have been investigated. The results were as follows.

Stimulation with the electrode placed medially and dorsally in the anterior part of the thalamus led to a significant increase of ^{131}I uptake.

In contrast, ^{131}I uptake was reduced on stimulation of the lateral thalamus.

When stimulation was applied with the electrode placed epithalamically, touching the nucleus habenulae, the rate of ^{131}I uptake depended on the frequency of the stimulus. On stimulation at 50 c/s, ^{131}I uptake decreased, while on stimulation at a frequency of 15 c/s, the ^{131}I uptake increased significantly.

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Prednisolone elimination in stress

The mechanism of two earlier observations have been analysed by the estimation of steroid elimination. (i) Following short-term ACTH administration acute neurogenic stimulation makes the blood corticosterone level to increase to a greater extent than it does in the controls. After prolonged administration, however, the direction of the effect is reversed. In this period the adrenals are not depleted. (ii) Following ACTH treatment for 10 days the corticosterone content of peripheral blood is normal, although the adrenals of such rats synthetize more corticosterone *in vitro* and the reactivity of the animals changes as if adrenal cortical hyperfunction were present (anti-phlogistic effect, decrease of sensitivity to histamine).

In the present investigations it has been demonstrated that following acute neurogenic stimulation prednisolone is eliminated at a reduced rate. This effect is observed after intraperitoneal and intravenous ACTH administration alike. The difference between the control group and the stimulated one becomes significant after 30 minutes. The effect is even more marked following short-term, low-dose ACTH treatment. In the animals treated with ACTH for 10 days the rate of prednisolone elimination is significantly increased. The results are discussed from the point of view of the two above outlined phenomena.

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Effect of cervical sympathectomy on the increase induced by chronic stress in the hormone content of the neurohypophysis in the rat

It has been observed that removal of the superior cervical ganglion lowered the oxytocin content of the neurohypophysis in the rat. At the 1963 Meeting of the *Hungarian Physiological Society* it has been shown that total exhaustion induced daily significantly increased the hormone content of the neurohypophysis and that this increase was prevented by previous superior cervical ganglionectomy. Other methods of reducing the posterior pituitary hormone content, for example ovariectomy and chronic oxytocin treatment, had no significant influence on the effect. The results raise the possibility of a vascularizing effect exerted by the cervical sympathetic trunk on the posterior lobe of the pituitary.

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The effect of ACTH on the excretion of 5-OH indole acetic acid (5-HIAA) in the rat

5-HIAA, a degradation product of serotonin and other indole derivatives, is excreted in urine. From the changes in its excreted amount indirect conclusions as to serotonin metabolism may be drawn. It has been investigated whether ACTH would influence the urinary excretion of 5-HIAA.

Albino rats of either sex, weighing 80 to 125 g, were used. From urine collected for 20 to 22 hours 5-HIAA was determined by UDENFRIEND's spectrophotometrical method, at 540 mμ. ACTH was injected in a dose of 4 U/100 g intramuscularly immediately before beginning to collect urine.

As compared to the resting value, 5-HIAA excretion was significantly increased following the administration of ACTH. The controls were treated with the solvent; here no change in 5-HIAA excretion resulted.

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Regeneration of the adrenal cortex following enucleation, on the basis of the incorporation of the radioactivity of ^{3}H-progesterone into different corticosteroids

SHEPPARD has shown that by the zona glomerulosa the radioactivity of ^{14}C-progesterone was built in mainly in 18-OH-corticosterone and aldosterone, while by the zona fasciculata and reticularis into 18-OH-DOC and corticosterone. In the present investigation it has been studied, into which steroids the regenerating adrenal tissue would build in the radioactivity of ^{3}H-progesterone, in order to obtain information as to the cytogenesis of the regenerating cells and the pathogenesis of the consecutive hypertension (SKELTON). Although according to the data in the literature the regeneration starts out from the zona glomerulosa cells which persist after enucleation, it has been found that after a short initial period in the regenerating adrenal tissue only the function of the internal zones persisted while that characteristic of the zona glomerulosa had ceased. The activity was mainly built into 18-OH-DOC and corticosterone, hardly any was incorporated into 18-OH-corticosterone. The regenerating tissue builds no activity into aldosterone (!). In the activity curve the appearance of a substance intermediate in polarity between aldosterone and 18-OH-DOC was observed. It is believed that a correlation

may exist between the obtained result and certain pathological changes: the pathological effects influence the physiological process of adrenal transformation (for example, following treatment with formalin the function of the zona glomerulosa gains preponderance).

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Incorporation of ^{3}H-progesterone activity into aldosterone, corticosterone and 18-OH-corticosteroids in the rat during pregnancy immediately following delivery and in the newborn state

The possibilities offered by ^{3}H-progesterone allow insight into the biosynthesis of corticosteroids under various physiological conditions. It has been investigated in rats during pregnancy immediately after delivery, and in the newborn period how surviving adrenal slices incorporated into corticosteroids the radioactivity of ^{3}H-progesterone. In pregnant rats no significant differences were noted, although 18-OH corticosterone activities showed a tendency to increase. In newborns 18-OH-DOC activity decreased slightly ($0.1 > p > 0.05$) and corticosterone activity markedly ($p < 0.01$). In earlier investigations it has been shown that the adrenals of the newborn rat synthetize less corticosterone from progesterone than do the adrenals of the controls. Immediately after delivery 18-OH-corticosterone activity decreased slightly ($0.1 > p > 0.05$), corticosterone activity decreased moderately ($p < 0.05$), aldosterone activity decreased markedly ($p < 0.01$). Immediately after delivery the decrease of incorporated activity was particularly marked, as compared with the results obtained for pregnant rats. A final elucidation of the differences in biosynthesis is expected from studies involving the use of other labelled precursors.

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The combined effects of stress and prednisolone administration on adrenocortical steroid production

By analysing the suppression of adrenal activity by corticosteroids it has been shown that while in proportion to the dose employed prednisolone pretreatment diminishes the ACTH-sensitivity of corticosterone biosynthesis

in vitro and the exposure to stress alone does not enhance it significantly when stress and prednisolone are applied simultaneously *in vivo*, the responsiveness of the adrenal cortex to ACTH is increased and this increase is proportionate to the dose of prednisolone. No such correlation could be demonstrated in the changes of adrenal weight. The stressor effects applied did not differ qualitatively. The results obtained by the use of prednisolone and cold and ethanol as non-specific stimulants are discussed, on the basis of measuring corticosterone biosynthesis *in vitro*.

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The effect of 6-alpha-methyl-17-alpha-acetoxy-progesterone (MAP) on adrenal steroidogenesis

According to data in the literature, MAP, an orally active synthetic progesterone, causes adrenocortical atrophy. It has been investigated in which parameters of adrenocortical function are changes brought about by MAP. It has been found that after 6 days of pretreatment with MAP surviving adrenals produced the same quantity of corticosterone in response to ACTH as without such pretreatment. At the same time, the corticosterone content of the adrenals preincubated without ACTH decreased in proportion to the applied dose of MAP. Added to the adrenals *in vitro*, MAP did not influence the steroidogenesis evoked by ACTH. The present results, compared with those obtained earlier, appear to indicate that the sensitivity to ACTH *in vitro* and *in vivo* are running parallel, while the basal steroid content of the adrenal is divergent. Accordingly the various steroids inhibiting adrenal activity differ from one another in the mode of action.

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Correlation between morphology and function of the adrenals

It has been investigated whether the changes obtained by kariometric statistical methods and by the measurement of layer thickness would correspond with the changes in steroid secretion induced by agents of known mode of action.

The experiments were made in two groups.

(i) ACTH, hydrocortisone, DOCA, spironolactone, formalin or heparin were administered daily for 8 days and the adrenals were examined 30 minutes after the last injection.

(ii) ACTH, hydrocortisone, aldosterone or formalin were administered on a single occasion and the adrenals were examined 30 minutes after the injection.

In the first group the nuclear volume in the zona fasciculata was significantly increased by ACTH, and decreased by hydrocortisone. In response to DOCA, the nuclei in the zona glomerulosa decreased significantly in size, while spironolactone caused them to increase. Formalin increased nuclear volume in the zona glomerulosa and the zona fasciculata alike. Heparin reduced nuclear volume in the zona glomerulosa.

The karyometric changes in this group went parallel with the changes in function.

In the second group significant changes in nuclear volume, corresponding to the hormonal effects, were noted. Formalin, which gave rise to a significant corticoid secretion, produced no appreciable changes in nuclear volume in any of the zones.

Measurement of layer thickness proved less suitable than the karyometric method for the demonstration of changes in function.

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Determination of steroids from normal human blood

A method has been developed for the simultaneous determination of cortisol, dehydroepiandrosterone and androsterone from 10 ml of human plasma.

Determination of cortisol was carried out by the method of BONDY and WEISZ (VECSEI) except that paper chromatography was made in PECHET's system. For quantitation, tetrazolium blue was used. The sensitivity of the method is 0.5 μg/10 ml of plasma.

After the determination of cortisol, the proteins were precipitated by equal volumes of acetone and ethanol in the same sample, the aqueous phase evaporated to 1/10 volume and hydrolysed by the method used for the hydrolysis and extraction of urinary 17-ketosteroids. The dry residue was then purified by thin-layer chromatography (Kieselgel G, solvent system benzene: ethanol = 97 : 3), the zone corresponding to 17-ketosteroids was removed, extracted, evaporated to dryness, separated by paper chromatography (solvent

system propylene glycol/ligroin : benzene : methanol = 130 : 60 : 10) and estimated by ZIMMERMANN's reaction. The sensitivity of this method is 1—2 μg/10 ml of plasma.

The reliability and accuracy of the method was assessed and the data were summarized.

From the estimation of the three steroids in the plasma of normal humans a wide range of individual levels became apparent: cortisol 6.3—17.5 (mean 11.6), dehydroepiandrosterone 21.3—79.0 (mean 46.7) and androsterone 14.0—46.0 (mean 25.4) μg per 100 ml.

The method allowed to gain some information concerning the adsorption of steroids on erythrocytes. Practically 50 per cent of the free cortisol was found to be adsorbed on the cell surface; this was not the case with 17-keto-steroid-esters.

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Effect of ACTH and TSH on adrenal and thyroid blood flow

The effects of ACTH and TSH on adrenal and thyroid blood flow have been investigated in dogs. The changes in flow were recorded continuously by means of heated thermocouples inserted into the glands. The changes were recorded by means of a *Fluvograph*. To facilitate comparison, the ^{86}Rb extraction method of SAPIRSTEIN was used.

It was shown in acute experiments that even when injected repeatedly by the intravenous route, ACTH (3, 10, 40 I. U.) increased adrenal blood flow. Adrenal blood flow was increased even after corticoid secretion had ceased to increase. In the other organs used for comparison (kidney, thyroid) ACTH did not influence blood flow. By means of thermocouples fixed in the adrenal it could be shown in alert animals that after operation small doses (1 I. U.) of ACTH sufficed to cause a significant increase in adrenal blood flow. The method has proved suitable for use in studies concerned with the relationships between adrenal secretory activity and blood supply in the alert animal.

The results achieved by means of ^{86}Rb corresponded with those obtained by the thermocouple method.

In acute experiments TSH produced no change in thyroid blood flow, as determined by the above two methods.

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Correlations between adrenal blood flow and corticoid secretion

The informations influencing corticosteroid secretion reach the adrenal cortex mainly by the blood stream. The role of circulatory changes in the regulation of adrenal function is, however, unclear.

In dogs anaesthetized with pentobarbital the effect of acute hypophysectomy on corticoid secretion, adrenal blood flow, rate of blood flow per minute in the abdominal aorta at the level of the diaphragm and below the origin of the renal artery, as well as on arterial blood pressure has been examined.

It has been found that the excessive decrease of hydrocortisone and corticosterone secretion was not accompanied by a decrease in the rate of adrenal blood flow. Arterial blood pressure dropped in every case, thus adrenal vascular resistance was significantly diminished. There was no change in the rate of blood flow per minute in the abdominal viscera and the hind part of the body. Adrenal blood flow increased even when abdominal aortic blood flow decreased.

In response to 0.5 U/min oxytocin adrenal blood flow increased in both the normal and the hypophysectomized animals. Corticosteroid secretion did not increase in either case. In response to oxytocin infusion, abdominal blood flow tended to increase prior to hypophysectomy, and tended to decrease after hypophysectomy.

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The role of the adrenal cortex in calcium absorption

Absorption of sodium from the small intestine is known to be greatly enhanced by mineralo- and glycocorticoids alike. There are, however, no data on how these hormones influence calcium absorption *in vivo*.

Using ^{45}Ca according to KERTAI and LUDÁNY, calcium absorption from the small intestine has been studied. It has been found that previous bilateral adrenalectomy significantly reduced the rate of Ca absorption. In the adrenalectomized animals prednisolone administration increased Ca resorption. Aldosterone treatment was ineffective in adrenalectomized animals, while in sham-operated animals it diminished the absorption of Ca.

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Dynamical study of iodine metabolism with double $^{125}I - ^{131}I$ labelling

Studies of the intermediate products of iodine metabolism yield evidence permitting insight into the dynamics of iodine incorporation. For this purpose, investigations were carried out with double labelling, treating rats with inorganic ^{125}I and ^{131}I at a predetermined interval. Thereby the isotope which reached the hormonal phase served as a basis for reference in the case of initial iodine uptake by the individual and the other members of the experimental series. The changes in thyroid and gastric wall activities were examined by radio-paperchromatography combined with autography, in the light of the model scheme relative to iodide transport. The paradoxical distribution of inactive and radioactive iodine in the gastric wall was remarkable.

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The effect of anabolic steroids administered in newborn age on the function and morphology of the reproductive organs in the female rat

There are data in the literature indicating that sexual dysfunction develops in rodents following testosterone treatment in newborn age. The disturbance consists in an ovulatory constant oestrus, accompanied by sterility and changes in sexual behaviour. In view of the fact that the anabolic steroids have more or less marked androgenic side effects, and that they are employed extensively in the treatment of newborns and premature infants, it seemed worth while to investigate how treatment with these compounds in newborn age would influence the ovarian cycle, the morphology of the reproductive organs and the fertility of female rats.

The compounds tested were 19-nortestosterone phenyl-propionate, delta-1-dehydro-17-alpha-methyl-testosterone and testosterone propionate. Doses of from 30 to 1500 μg of each drug were injected subcutaneously, on one occasion, at 5 days of age. Depending on the compound and the dose, persisting oestrus, changes in sexual behaviour, sterility, cystic changes in the ovaries and an absence of corpora lutea have been observed. The phenomenon went parallel with the androgenic side effect of the preparations tested.

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Disturbances of pregnancy, labour and lactation in "hypothalamic obesity"

It is known that destruction of the medial hypothalamic area leads to hyperphagia and thus to pathological obesity. Depending on the location and extent of the lesion, excessive obesity may result without interference with the sexual cycle. To characterize the neuroendocrine system of such animals, the course of gestation, labour and lactation has been studied.

It has been found that even in the case of "hypothalamic obesity" the females continue to copulate, but the number of those becoming pregnant (31 per cent) is much less than in the control group (95 per cent). Of the 11 extremely obese rats 2 could not deliver and died, while in the remaining 9 animals labour was difficult and prolonged. Seventy-five of the newborns were born dead. Other rats with slight obesity, or subjected to operation during pregnancy and becoming extremely obese later, delivered normally. It had therefore to be surmised that the abnormal parturition in the case of the excessively obese rats could be ascribed to mechanical, somatic causes, rather than to endocrine disorders.

Maternal instinct could be observed in every rat after delivery, but most of them could not lactate. From this it was concluded that in the hypothalamus there is an area, or there are pathways near the satiety centre, the intactness of which is essential for lactation. In the case of normally lactating rats lesions inflicted to similar areas interfere with, or stop, lactation.

It has also been demonstrated that pregnancy does not modify the development of obesity and the obese state.

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The role of gonadotropic hormone in the control of the serum glycoprotein level in the rat

The changes in total serum protein, protein-bound hexose and sialic acid concentration, as well as the roles of the adrenal and the pituitary have been studied in orchiectomized and control rats, as well as in rats treated with gestagen (Lyenoestrol, Organon). It has been found that orchiectomy and the inhibition of gonadotropin secretion equally elevate the serum glycoprotein level. This effect requires the presence of intact adrenal function.

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Oxygen uptake by different segments of the oviduct and the effect of calcium ion on oxygen uptake

It is expectable that in the hen the oviduct, corresponding with its task, will become activated when egg production begins. The changes of oxygen uptake accompanying the different stages of oviduct activity have therefore been investigated. Considering that the uterus is involved in the production of the egg-shell and in calcium metabolism, the influence of the Ca ion on the oxygen uptake by the different parts of the uterus was also subjected to investigation.

In sexually immature hens the correlation between the weight of the body and that of the oviduct is characterized by a high correlation coefficient ($r = 0.71$; regression: $Y = 2.645 + 3.504\ x$, where Y is the weight of the oviduct in grams, x the body weight in kilograms).

Oxygen uptake by the uterus is the highest, $Q_{O_2} = 3.70$, when there is an egg in the magnum, and significantly lower in hens which have yet not produced eggs.

The correlation coefficient between the weight of the oviduct and the Q_{O_2} of the uterus was high ($r = 0.94$) when the magnum contained egg ($Y = 2.8645 + 0.0061\ x$, where Y is the oxygen uptake by the uterus and x the weight of the oviduct in grams).

Changes in calcium concentration of the medium did not significantly modify oxygen uptake by the uterus, while exerting a significant influence on oxygen uptake by the other parts of the oviduct.

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The role of the gonads in the sensitivity of male guinea pigs to serotonin and histamine aerosol

The biogenic amines (for instance histamine, serotonin, *etc.*) are well known to have an important role in the events taking place in certain (*e.g.* allergic) pathological conditions.

It seemed therefore worth while to investigate how the resistance to serotonin and histamine would be influenced by the gonads, by treatment with gonadotropic hormone and with the nor-steroid inhibiting gonadotropic hormone secretion by the anterior-pituitary, and whether the resistance thus

developing to histamine went parallel with the changes in the serotonin resistance of the animals.

The results of the experiments involving male guinea pigs indicate that testosterone or oestradiol treatment diminished the resistance to shock released by serotonin or histamine inhalation, while bilateral orchiectomy and epididymectomy, and also treatment with exogenous chorionic gonadotrophin, enhanced the resistance to histamine and serotonin.

The resistance to histamine and serotonin aerosol diminished following substitution testosterone treatment or in response to treatment with the nor-steroid inhibiting gonadotropic hormone secretion by the anterior pituitary in the castrated animals.

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Metabolic activity of the kidneys

It has been shown that in the rat the kidneys take up glucose if its concentration in arterial blood exceeds 90 mg/100 ml. With levels lower than 90 mg/100 ml the kidneys release glucose into the blood stream. Renal glucose uptake is increased by the direct action of insulin, and decreased by adrenaline. The uptake of lactic acid, too, depends on its concentration in blood, but there is no correlation between glucose and lactic acid uptake.

A similar correlation was found in the dog. Glucose and lactic acid uptake and also free fatty acid uptake depends on the blood concentration of the substances. In agreement with the results of HOHENLEITNER and SPITZER the present experiments had the purpose to confirm the free fatty acid uptake in the rat and to compare the mutual relationship in the uptake of the above substrata.

It was found that as in the dog free fatty acids and fatty acid esters are taken up also in rats in dependence on the arterial blood concentrations.

An inverse relation has been found between the uptake of free fatty acids and glucose. In most instances, when glucose is taken up, free fatty acids are released and *vice versa*. On the grounds of these results it is assumed that (i) the kidney participates in the homeostasis of energetic metabolism. (ii) The energetical needs of the kidneys are supplied by glucose or lipids according to their blood concentrations.

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Changes in histamine liberation in response to treatment with dried thyroid and thiamazole

The effect on local histamine release of dried thyroid and thiamazole has been studied. Rats were treated orally with dried thyroid and methothyrine for 3, 6 and 9 days, and on the day following the last treatment local histamine release was determined by the HALPERN-BRIOT method. The animals of the control group received physiological saline for the same lengths of time.

To eliminate the effects of adrenocortical hormones, adrenalectomized rats were also treated in the same manner and for the same periods, and then tested for histamine release.

In the group treated with dried thyroid for 3 days, local histamine liberation was markedly increased, while in the groups treated for 6 and 9 days it was inhibited.

In the rats treated with thiamazole for 3 days showed an inhibition of histamine liberation, which increased further in the groups treated for 6 and 9 days.

The increase of local histamine liberation in the adrenalectomized control group was considerably enhanced by dried thyroid as well as thiamazole.

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The effect of thymectomy, adrenalectomy and corticoid treatment on the serum heparin level in the rat

The effect of thymectomy, adrenalectomy and treatment with adrenocortical hormones on the serum heparin level has been studied in thymectomized and in sham-operated rats.

A total of 190 male *Wistar* rats, weighing 100 $\pm$ 10 g were used. Treatment with hydrocortisone (5 mg/100 g intramuscularly), DOCA (1 mg/100 g intramuscularly) and physiologic saline, respectively, was begun 48 hours after thymectomy, adrenalectomy and sham operation. On the 10th day, 60 minutes after the last injection the animals were decapitated. The serum heparin level was determined on the basis of thrombin inactivation.

On the 10th day after thymectomy the serum heparin level was 9.6 ± ± 0.3/ml, as compared with the 16.6 ± 0.3 value obtained for the controls, while after bilateral adrenalectomy it rose to 20.6 ± 0.4/ml. The increase of the serum heparin level after adrenalectomy did not take place in the thymectomized rats. In the normal control rats hydrocortisone treatment significantly reduced the serum heparin level, whereas DOCA treatment had no effect on it. In thymectomized animals, as compared with the controls, hydrocortisone administration caused a slight, DOCA treatment a marked, elevation of the serum heparin level.

The investigations have supplied further evidence as to the role played by the thymus in acid mucopolysaccharide metabolism.

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Effect of RES-blocking agents on hepatic dye excretion

The activity of the RES is best reflected by the dye clearance techniques. The dyes which disappear from the blood stream by way of the bile must necessarily pass through the endothelial and parenchymal cells of the hepatic sinuses, thus when the parenchyma is intact, the rate of clearance depends exclusively on the function of the reticulo-endothelial cells of the liver. This can be studied independently from the other parts of the RES by measuring the dye concentration in the bile. To obtain bile at any point of time, the common duct was intubated in alert rats, by a technique elaborated earlier.

In the present experiments 66 male rats weighing 400 g were used. Ten days after operation the curves for the excretion in the bile of three different dyes injected intravenously have been studied. In response to medium doses of 12 different RES-blocking agents these normal curves showed no substantial change, dye excretion was inhibited by large doses only. When, however, the blocking agent was administered daily and thus the RES was filled up, dye excretion decreased significantly.

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Pharmacological investigations concerning the therapeutical use of thebaine

The hexobarbitural anaesthesia potentiating and analgesic actions of thebaine in white mice, and its effect on diuresis in rabbits have been studied,

It has been found that thebaine potentiated anaesthesia more potently than the same dose of morphine, while its analgesic action was less potent than that of morphine.

These effects of thebaine were markedly potentiated by chlorpromazine.

Thebaine caused no decrease of diuresis, not even when administered together with chlorpromazine, a significant difference from the case of morphine.

On the basis of the above findings the use of thebaine in anaesthesiology might be taken into consideration.

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The influence of panthotenic acid on capillary resistance

The first part of the experiments was carried out on the de-furred back of 23 rats of either sex, weighing 120 to 150 g. Capillary resistance was determined by means of BORBÉLY's apparatus. The rats selected for the experiments showed the appearance of petechiae in 1 minute in response to suction at a constant negative pressure of 250 mm Hg. After the CR values had been determined, the rats were treated with panthotenic acid (5 mg/kg intraperitoneally). Three and six hours after this treatment capillary resistance was again determined. The study was considered complete when no petechiae were formed after the lapse of 5 minutes. Capillary resistance significantly increased in 19 of the 23 treated animals, no petechiae were visible after 5 minutes. Slight rises were found in the remaining 4 animals, too.

In the second part of the experiments the persistence of the effect was studied in 18 rats. A significant prolongation was noted in 11 animals even on the 5th day following treatment with panthotenic acid. Another three animals showed a slight protraction of the effect.

Tests made in 16 small children have likewise shown that panthotenic acid increases capillary resistance.

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The effect of beta-receptor inhibitors on the carbohydrate metabolism of the liver

It has been demonstrated that at a concentration of 700 μg per 100 ml the beta-receptor blocking agent dichloroisoproterenol (DCI) causes a practi-

cally total inhibition of the sugar output by the isolated liver perfused with sugar-free *Tyrode*'s solution. Chloropropamide caused 60 per cent inhibition. As compared with the control, the beta-receptor stimulator isoproterenol (2 μg per 100 ml) significantly increased sugar output by the liver. DCI and chloropropamide (200 mg per 100 ml) completely blocked this effect. Dibenamine (20 μg/ml), too, had an inhibitory effect.

The correlation between adrenergic receptors and hepatic carbohydrate metabolism has been analysed. It is remarkable that the oral antidiabetic chloropropamide should inhibit the sugar output and decrease the liver-glycogen level induced by isoproterenol.

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Analysis of changes in the activation energy of succinate dehydrogenase under the influence of some antitumour agents

The changes of activation energy of succinate dehydrogenase have been studied under the action of certain antitumour agents.

It could be shown that

(i) a cytostatic effect does not necessarily involve changes in the activation energy of the enzyme; while

(ii) substances capable of exerting an inhibitory effect lead to a decrease of activation energy of the same magnitude; and

(iii) inhibition only occurs at physiological and near-physiological temperatures.

The relationship between enzyme inhibition and the decrease of activation energy has been discussed on the basis of the recent concept of enzyme-substrate combination in compliance with the process of alkylation taking place at the molecular level.

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A method for studying bone marrow cells occurring in small numbers

The bone marrow, which contains cells of different kind and maturity, is a heterogenous system. The properties of the single types of cell are difficult

to examine even by morphological and cytochemical methods, therefore a method of isolation based on the different sedimentation velocities of the cells has been developed.

DAVIDSON's method for enriching the white and red blood cell fractions of peripheral blood has been modified. Bone marrow is suspended in the animal's own plasma and centrifuged in a plastic tube. If prior to centrifugation the percentage distribution of cells has been determined in bone marrow smears, the quantity of bone marrow is sufficient and the length of the tube is adequate, the section of the tube containing the type of cell sought for can be cut out with a high degree of probability.

Under the experimental conditions employed the method was found to be well suited for the enrichment of the single cell types. In the smears made of such fractions the cells are morphologically intact and suitable for use in cytochemical tests. The sections of the tube contain sufficient quantities of cells for making certain biochemical tests.

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Autoradiographic examination of substances influencing mitotic activity of the bone marrow

Substances influencing the mitotic activity of bone marrow cells have been studied experimentally. Mitotic activity was estimated on the basis of the incorporation rates of ^{14}C-thymin or formiate *in vitro*. Distribution of the incorporated activity among the different cell types was determined by quantitative autoradiography.

It has been found that in the myeloid elements of bone marrow incubated in serum obtained from leucopenic rabbits the activity increased at the myeloblastic level already, and was significantly higher throughout the entire myeloid series, as compared with the cells incubated in control serum. Activity decreased in the entire myeoloid series on incubation with sera obtained at the maximum of leucocytosis.

As opposed to the data in the literature, in our system erythropoietin had no influence on the mitotic activity of the myeloid series.

Likewise, at a concentration of 200 μg/ml MENKIN's leucocytosis promoting factor was ineffective.

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Further studies concerning the existence of a factor regulating myelopoiesis

In earlier investigations it has been shown that leucopenic rabbit serum contained a factor influencing the mitosis of myeloid cells *in vitro*.

Further investigations have shown the presence of this factor in the sera of control animals at a concentration constant but lower than in leucopenic sera. The quantity of the stimulating substance is increased not only during the leucopenic state preceding leucocytosis, but also during leucocytosis of longer duration (such sera increase the formation of DNA in the bone marrow myeloid elements *in vitro*).

At the peak of short leucocytosis the amount of the circulating stimulating substance decreases by an average of 30 per cent, as compared with the control sera.

The substance is bound by live granulocytes and bone marrow cells, but not by lymphocytes, ascites tumour cells or dead granulocytes.

On the basis of the evidence obtained it is surmised that the substance is a humoral factor regulating the mitotic activity of bone marrow myeloid elements also under physiological conditions.

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The role of the plasmin system in white thrombus formation

Thrombocyte aggregation has been studied in native and streptokinase-treated euglobulin rich in platelets. It has been found that the platelets do not disintegrate on diluting the plasma with distilled water and acidification, but separate from the plasma together with the euglobulin. These thrombocytes can be re-suspended by dissolution of the euglobulin. It has also been demonstrated that the platelets contain an activator beside the proactivator. In model experiments a correlation has been demonstrated between the reduction of plasminoplastin activity and thrombocyte aggregation. On the basis of the evidence obtained it is surmised that the plasmin system plays a role in white thrombus formation.

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The mechanism of the defibrination syndrome caused by snake venom

The disturbance of blood clotting caused by the venom of the Malayan viper is an excellent model experiment for studies of the pathogenesis of the "defibrination syndrome".

The effect of the venom of *Ancistrodon rhodostoma* on blood coagulation has been investigated in rabbits. The changes in coagulability have been determined by thromboelastography, by examining the generation of thrombin, as well as by the method of thrombin inactivation.

The results may be outlined as follows.

(i) Immediately following the injection of snake venom blood clotting increases.

(ii) The increased coagulability leads to a significant decrease of the circulating fibrinogen.

(iii) As a result, the coagulability of blood decreases (fibrination-defibrination syndrome).

(iv) A few minutes after the administration of the snake venom, fibrinolysis ceases, then it is greatly increased in the second hour.

The results obtained indicate that the primary phenomenon following injection of Malayan viper venom is an increase of thrombin activity. Fibrinolysis is merely a secondary, compensatory process, which leads to a lysis of the coagulated fibrin.

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Haemorrhagic lipaemia

Repeated bleeding experiments have been carried out on rabbits and guinea pigs, to obtain detailed information concerning the phenomenon of haemorrhagic lipaemia. By thin layer chromatography it has been demonstrated that it is first of all the triglyceride fraction of the serum lipid components that changes most markedly. By the end of the experiments most animals showed fatty degeneration of the liver. In rabbits, reinjection of the animals' own serum had no influence on the changes in the level and composition of lipids in the serum, or on the development of fatty degeneration of the liver. However, the injection of mixed, normal rabbit sera significantly diminished the increase of the serum fatty acid ester values in response to bleeding and inhibited the development of fatty degeneration in the liver.

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The effect of Phlogodym and didymium nitrate on endotoxin shock in the rat

At the 1963 Meeting of the *Hungarian Physiological Society* we reported that Phlogodym (a complex formed by neodymium with pyrocatechin disulphonic acid), synthetized and shown by JANCSÓ to have antiphlogistic and anticoagulant properties, significantly enhanced the severity of traumatic shock in the rat, causing at the same time a drastic fall to almost zero of the fibrinogen level. It has been shown that it was not an increased rate of fibrinolysis which was responsible for the disappearance of fibrinogen, because the latter was inhibited by heparin, an agent increasing fibrinolysis, and was not prevented by EACA, which inhibits fibrinolysis. The factor to be held responsible was an intravascular coagulation of blood, as a result of the production of fibrinogen B in excessive amounts in response to Phlogodym.

In the present experiments it has been shown that Phlogodym and didymium nitrate, which also contains neodymium, greatly increased the severity of endotoxin shock in the rat, and in the animals treated with Phlogodym and didymium nitrate the fibrinogen level dropped steeply in response to the endotoxin. According to recent data in the literature, endotoxin has a significant role in the genesis of shock. The results seem to support this view, because Phlogodym exerted similar effects in both traumatic and endotoxin shock. It may be surmised that in both cases the same eliciting factor or factors may be held responsible for the excessive fall of the fibrinogen level.

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The pathophysiology of LPS endotoxins

Employing the slit-lamp method of AMSLER and HUBE the effect of endotoxin on the permeability to fluorescein of the blood-aqueous barrier has been investigated. It has been demonstrated that LPS toxins prepared by WESTPHAL's method from different strains of *E. coli* increased significantly the capillary permeability. This increase of permeability has two peaks, one 30 minutes and the other 3 hours after the intraperitoneal injection of endotoxin. Hyperimmune serum produced in rabbits by the administration of endotoxin as well as antihistaminics prevented the increase in capillary permeability.

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Experimental endotoxin leucocytosis

According to KOMIYA and GORDON a leucocyte mobilizing factor is released in endotoxin-treated animals. To investigate the problem in more detail, experiments have been carried out in rabbits. *Salmonella typhi* endotoxin, purified according to BOIVIN and MESROBEANU, induces first leucopenia then leucocytosis. In the animals pretreated daily with endotoxin, the leucopenia tends to decrease, and ultimately only an early leucocytosis of short duration is observed. Dibenamine and spinal section have no influence on the reaction. In parabiotic rabbits the endotoxin injected into one rabbit evokes leucocytosis in the other, although no endotoxin has passed over into the partner. Thus, humoral factor must be responsible for the leucocytosis, while the nervous system has merely a minor role. In conclusion, the relationship between endotoxin and macromolecular leucocytosis is discussed.

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The effect of pyrogenic substances on the blood sugar level

The endotoxin of *Gram*-negative intestinal bacteria significantly increases the blood sugar level in the rabbit. The maximum increase is noted in the second to third hours, and the level is back again near the initial level in the fifth hour. This hyperglycaemic response has been studied in pyrogen-resistant rabbits, as well as in rabbits pretreated with Dibenamine, glutathione and cysteine. Dibenamine did not influence the hyperglycaemic reaction. If administered 2 minutes before the injection of endotoxin, glutathione inhibited the increase of the blood sugar level but was ineffective if administered 5 minutes after the endotoxin. The protective effect was exerted exclusively on the hyperglycaemic response, the febrile reaction and leucocytosis were unaffected. As the action of the endotoxin is analogous to that of alloxan, it is suggested that it might damage the pancreatic islet beta cells.

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The effect of polysaccharides not containing sulphur on fat metabolism

By the method of CSEH *et al.* water-soluble polysaccharides have been prepared from different microorganisms and tested for lipaemia-clearing activity. The changes in the lipase activity of serum lipoprotein and its fatty components (cholesterol, phospholipid, triglyceride, free fatty acids, beta-lipoprotein) have been studied. The antilipaemic effects of the high-molecular neutral polysaccharide obtained from the penicillin mycelium (PMP), dextran and inulin have been analysed in detail. It has been found that

(i) if administered intravenously to dogs, PMP clears up alimentary lipaemia to about the same extent as heparin, but its effect develops at a slower rate and is more durable. If administered intramuscularly, it significantly diminishes alimentary lipaemia; the clearing activity of dextran is weaker, and in the doses employed inulin is ineffective;

(ii) unlike heparin, even five times higher doses of these polysaccharides do not inhibit acute polyoxyalkylene lipaemia in the rat;

(iii) in the rat PMP injected subcutaneously in a dose of 10 mg/kg significantly diminished the subchronic alimentary lipaemia induced by the administration of cholesterol and sunflower oil. Even the 100 mg/kg dose was ineffective on oral administration.

The differences in effect between heparin and the neutral polysaccharides not containing sulphur are discussed.

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The glycoprotein content of lymph and its changes in response to stress

There seem to be no data in the literature on the glycoprotein content of lymph. In 15 normal rats the total protein content and the glycoprotein carbohydrate fractions have been estimated in blood and lymph. The blood values were in agreement with those obtained earlier and with the data in the literature. In the lymph, the glycoprotein content corresponded with the total protein concentration and was lower than in blood (total protein 6.83 mg per 100 ml; protein-bound sugar, 67.4 mg per 100 ml; hexosamine, 37.47 mg per 100 ml; sialic acid, 35.21 mg per 100 ml; fucose 5.9 mg per 100 ml).

The glycoprotein content of blood changes significantly in response to various effects. In further experiments muscle necrosis was induced in 15 rats and the blood and lymph were tested quantitatively for glycoproteins. In both blood and lymph the sialic acid, fucose, protein bound hexose, and hexosamine contents were found to increase in comparison with the controls.

According to these experiments, the elevation of the lymph glycoprotein level in response to stress runs parallel with the increase taking place in blood.

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Prevention of prednisolone-induced adrenal cortical atrophy by protracted hyperhydration

In previous experiments it was shown that on protracted hyperhydration adrenocortical function was increased and cortical hypertrophy resulted. In addition, the development of cortical atrophy in response to the combined administration of steroids and sodium was prevented. In the present investigations it has been studied whether protracted hyperhydration would prevent the development of the prednisolone-induced cortical atrophy.

Male rats were treated with 100 mg/100 g body weight of prednisolone daily for 5 days and part of these animals were subjected to protracted hyperhydration. There was also an untreated control group. The animals were sacrificed on the 6th day, the adrenals were weighed and examined histologically.

The changes in adrenal weight (mg/100 g body weight) and morphology indicated that in response to the above prednisolone treatment adrenal atrophy had developed and that this atrophy was prevented by protracted hyperhydration.

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