ACTA MORPHOLOGICA

ACADEMIAE SCIENTIARUM HUNGARICAE

REDIGIT
I. TÖRÖ

SUPPLEMENTUM IX

AKADÉMIAI KIADÓ
BUDAPEST
1960

PROCEEDINGS OF THE ANNUAL MEETING OF HUNGARIAN PATHOLOGISTS AND ANATOMISTS

Budapest, 1959

PLENARY SESSION

Anatomy and Pathology of the Neuroendocrin System

K. Farkas: President's Address

Ladies and Gentlemen,

in the life of scientific societies, of expert groups, a Congress represents an important moment. The results of the group's work over a whole year are submitted here. In addition, the subjects discussed and their mode of interpretation reflect the scientific policy and philosophy of the group.

The medical world looks forward with great expectation to every congress and it is perhaps no professional chauvinism when we say that this interest is intensified regarding the congress of pathologists. What makes us say that?

Surveying the history of medical science, it may be stated that every period's conception of the genesis of a disease — which is actually the aspect of that period's medical science — is best expressed by the advances in pathology.

From this point of view, it is with the main subject of the Congress that we have to deal with first. The innervation of the anterior pituitary lobe may strike us — considering the question mechanically — as an unduly specified subject; when we come to think, however, that the great influence which the pituitary exerts upon the organism depends upon its innervation, we may state that the choice of this subject comprises on the one hand an anatomical, on the other a functional problem involving the whole organism.

The question arises what has made the discussion of this subject timely within the compass of a congress. Briefly the answer is: ever since the identification of hormones, the examination of the endocrine and nervous systems has been at all times a matter of great interest. Particularly in our days, when biochemistry discriminates within the hormones supposed to be uniform such elementary substances which, as to their efficacy, exceed by far the allegedly uniform hormone. This circumstance, moreover the recent methods of morphology, impose upon us the task of carefully studying both the role and the origin of the new active agents. It is known that the suprarenal cortex, controlled by the pituitary, interferes with all the functions of the organism and basically changes the reactivity, the protection against

diseases. Accordingly, this system plays a part in every phase of pathogenesis.

Nowadays, when biochemical and morphological analysis have reached the stage where function and structure practically combine, every day a fresh opportunity arises for unifying our pathologenetical conceptions. The key organ in the synthetic conception is the pituitary gland, hence it is justified thoroughly to examine its role in relation to innervation and thus to clarify the influence of the nervous system upon the endocrine system, it being undeniable that, no matter how the pituitary be connected with hormonal circulation, the nervous system plays a decisive role in the building up of the connection.

Consequently, the choice of subject is fully justified, as it is also justified to deal with the question in the anatomical-pathological relation. Medical history bears witness to the fact that the theories which determine the character of an epoch's medical science have originated from pathologists, or from clinicians who were themselves eminent anatomists or pathologists. It can be laid down as a fact that a decisive change was brought about in medical science by the development of anatomy and pathology. The standard statements of the wayleading from the classical anatomy of VESALIUS to electron microscopy, the acme of morphology, have originated for the most part from pathologists. These statements have determined the development of medical science for decades or even centuries.

The greatest influence has been exerted by MORGAGNI's organo-pathology and VIRCHOW's cellular pathology. The statement which has proceeded from them, i. e. that the root of the disease is an organic lesion, is to-day considered out of date by many authors. Nevertheless, within our synthetic concepts, organo-pathology, the theory of localization have acquired a new meaning. Histochemistry, the new method of morphology, has proved that organo-pathology is valid also in relation to the elementary parts of the cell, so to say in relation to its molecular elements. What I have in mind is not that the pathologist judges the nature of the disease by the macroscopic or microscopic organic lesions, but that on the new methodological or ultrastructural basis it is proved daily that the local lesion, on whatever basis it may have originated, plays an important part in the history of the disease. It should also be taken into consideration that textbooks, both clinical and pathological, are basing their classifications on organic localization.

In the last decade a concentric attack was launched against organopathology and cellular pathology, with the slogan "away from the cell" and VIRCHOW's principles were rejected as a whole. In contradiction to the conception, "there are no generalized diseases" another extremistic conception has developed, according to which there existed only generalized diseases. Actually, in the course of all diseases there occurs a period when the

disease affects the whole organism, when the disease becomes generalized even in the ordinary sense. On the other hand, it must be admitted that the diseases — nearly without exception — manifest themselves in a certain organ, tissue or cell. The disorder of one organ stands in the focus during the course of most diseases. Although this sounds paradoxical, the exhaustive analysis of local lesions is most appropriate for confirming the general nature of the disease. It is only by the careful examination of the local lesions that the general nature of the disease can be established.

Considering that in the genesis of the diseases combined biological and pathological processes must be taken into account, both in local and general relation, this in itself precludes the possibility of the diseases being declared as of solely local or solely generalized nature. There certainly exist local pathological processes, but the basis of the local disturbance is frequently constituted by a generalized, for instance metabolic, disturbance. The conception now generally and rightly accepted is that in a certain situation every disease becomes the disease of the entire organism, affects the individual as a whole.

Investigation of the local pathogenetical factors is above all a task of pathology. As to the investigation of the generalized nature of the disease, this is in the first place a clinical problem. It stands to reason that now the principles and methodology both of pathological and clinical research considerably differ from those that prevailed when the local and generalized nature of diseases was differentiated for the first time. Histochemical und ultramicroscopical methods have brought morphology within close range of function, and more than once practically merged the two into one. On the level of histochemistry and ultrastructure, such an intimacy of function and structure comes to light, which moulds the so-called functional morphology into a living reality.

In accordance with this conception, the true nature of the diseases can be ascertained only through the local organic lesions, consequently through their pathology and general symptoms, hence by employing clinical and pathological methods.

The demand for a co-operation of theoretical and practical medical science for the explanation of pathogenetical problems is not of recent date. The study of medical history points clearly to the fact that a lasting pathological conception always came into being when the anatomical, pathological and clinical conceptions had been made to agree.

These efforts reach back to several centuries. The great physicians of the 19th century were all — so to say without exception — clinicians, anatomists and pathologists. Cytology and histology as well as experimental pathology constituted the foundation of theoretical medical science. Microbiology and microchemistry became associated with them in the second

half of the century. ROKITANSKY already energetically emphasized that the analysis of a lesion localized into an organ or tissue does not in itself solve the problem of the pathogenesis of the disease. LAENUNEC brought the clinical symptoms into connection with the pathoanatomical and pathohistological changes. The work of SEMMELWEIS and of his friends SKODA and HEBRA was prompted by the spiritual influence of their master, ROKITANSKY. All the periods of medical history teach us that really epochal conceptions in advance of their time could develop only when pathological anatomy and clinical science were closely co-operating.

In point of fact, it is this perception which fully justifies the choice of the main subject of our Congress because, although clinicians do not take part in our discussions, the manifest conception of our pathologists is to ascribe in addition to morphological research a major importance to the functional points of view. I believe that by investigating the connexion between pituitary gland and nervous system and the pathological analysis of the suprarenal cortex we stand for the conception that in the development of diseases — taking into account the great part played by the above-mentioned organs in the hormonal system and through that in the control of all physiological and pathological functions of the organism — the general aspects are quite as important as the local lesions.

In the spirit of these conceptions I declare the session open.

RELATOR

J. Szentágothai

(Department of Anatomy, University Medical School, Pécs)

Nervous Control of Anterior Pituitary Function

Attention is focussed in this review upon the histological aspects of the problem. Therefore, the following questions are treated with special care, whilst others of equal importance, with purely or predominantly functional bearing have been left unconsidered:

1. *The finer structure of the hypothalamus and its neuronal connections.*
2. *Neural connection between hypothalamus and anterior hypophysis and the innervation of the pituitary gland in general.*
3. *Vascular connections between hypothalamus and the hypophysis.*
4. *Neurosecretion and hypothalamo-hypophyseal transmission mechanisms.*
5. *Localization of endocrine functions in the hypothalamus.*

1. *The finer structure of the hypothalamus and its neuronal connections*

Understanding of hypothalamic functions is considerably impeded by lack of information concerning the mode of connection of hypothalamic

neurons amongst themselves and with afferent and efferent extrahypothalamic pathways. Since the classical investigations of CAJAL very little has been done in this field, progress almost exclusively being restricted to the phenomenon of neurosecretion in the magnocellular nuclei. — We are since many years in thorough need of a Golgi analysis of the hypothalamus.

The author shows by demonstration of some of his own Golgi and Golgi—Cox preparations of the hypothalamus that besides being secreting nerve cells the neurons of the magnocellular nuclei have a definite dendritic pattern and a fine intercellular terminal plexus with synapses on the surface of these neurons. Hypothalamic lesions, electric stimulation and recording of action potentials cannot be properly performed and their results correctly evaluated if the dendritic patterns, the abundant initial collaterals of neurits and the often highly-differentiated synaptic terminal structures of the different hypothalamic nuclei are not sufficiently considered.

More progress has been in the field of afferent hypothalamic pathways with the aid of modern silver methods suited for identification of degenerated axons and synapses. Unfortunately, the difficulties in evaluation of axonal degeneration in the hypothalamus have not been realized by several authors, MEYER, WALL, GLEES, KNOCHE) so that their positive findings must be questioned. Varicose swellings of terminal fibres and even "beaded" appearence very often occur in the the hypothalamus in completely normal material. The criticism by COWAN and POWEL (1956) of the above authors appears therefore fully justified.

The relator demonstrates with a number of photomicrographs taken from the literature and own material, that the BIELSCHOWSKY type methods especially also the GLEES method are not suited for degeneration studies in the hypothalamus. Reliable results are yielded in this part of the brain exclusively by the NAUTA methods. On the basis of the excellent investigations of NAUTA, WHITLOCK and NAUTA, ADEY, MERRILEES and SUNDERLAND and the unpublished findings of the author, a comprehensive diagram of afferent hypothalamic connections has been prepared and is demonstrated.

Direct fibre connections from the cerebral cortex to the hypothalamus must be extremely few, if any. Abundant direct connections from the amygdaloid complex, posterior part of the hippocampus and the thalamus have been demonstrated repeatedly. No direct connections from the retina can be traced to the hypothalamus. Opposing findings of different authors (KNOCHE) are considered erroneous.

The relator draws attention to direct connections from the mesencephalic reticular formation to the hypothalamus and especially abundant direct afferent connections from the anterior mesencephalic gray substance. These connections may play an important role in conveying impulses from the retina (over the anterior corpora quadrigemina), the cerebral cortex and

non specific spinal afferent systems to the hypothalamus. The probable significance of the latter connection is discussed with respect to recent findings of contralateral histological changes in the hypothalamus after unilateral adrenalectomy by HALÁSZ and SZENTÁGOTHAI.

The efferent connections of the hypothalamus are scarcely known anatomically and treated therefore only briefly.

2. *Neural Connections between Hypothalamus and Anterior Hypophysis and the Innervation of the Pituitary Gland in general*

The question of innervation of the anterior hypophysis is still highly controversial. A comparison of the illustrations of earlier authors claiming positive results (PINES, BROOKS and GERSH) with preparations in which reticular conjunctive tissue fibres have stained with silver, reveals that these results came about by misinterpretation of reticular elements as nervous fibres. Nevertheless, the observations of CAJAL had established that nerve fibres originating from the hypophyseal stalk enter the intermediate lobe and the pars tuberalis. No completely-convincing findings of nervous elements in the pars distalis have been reported until recently, so that the conclusion of HARRIS and GREEN, according to which the pars distalis practically lacks innervation, was fairly justified. The situation fundamentally changed with the investigations of METUZALS (1954—56), who in the duck, horse and the cat with the aid of the Bielschowsky—Gros impregnation method furnished definitive proof of a rather rich innervation of the anterior pituitary tissue. The excellent photomicrographs of METUZALS show beyond any doubt that there are two types of innervation. One type is the well-known sympathetic ground-plexus, which is entering the anterior hypophysis together with the blood vessels. The sympathetic ground-plexus is such a characteristic nervous formation and its nervous nature has been established so reliably in most tissues with vegetative innervation, and recently also with the aid of the electron microscope, that any mistake is practically impossible. The other type the so-called "secreto-motor end-plexus" consists of single fibres with characteristic fusiform enlargements, which get into close contact with the gland cells. These fibres could be traced back to their origin from larger fibres leaving the nervous hypophyseal stalk and entering first the pars tuberalis. On the basis of these new and absolutely convincing results the hypothesis of non-innervation of the pars distalis must be abandoned.

3. *Vascular Connections between Hypothalamus and Hypophysis*

The circulation of the pituitary gland has been the subject of many investigations in the last two decades. The relator considers it irrelevant to argue about the question how far the so-called "portal vessels" of the anterior

lobe can be considered true portal vessels. This completely depends on the length of the stalk. If the stalk is long and there is no broad bridge between the *pars tuberalis—median eminence*-complex and the *pars distalis*, — as it is the case in most rodents and in man, — the vessels emerging from the former join into larger trunks, to brake up only in the pars distalis into sinusoids. If, as in the cat or the dog, the pars distalis immediately originates from the median eminence, the number of vessels connecting the *pars tuberalis —median eminence* contact region with the pars distalis is large and they do not join generally into large trunks, so that one cannot speak of true portal vessels. The principle of blood circulation being in both cases the same, this is of course of no importance. — The predominant direction of blood flow, as established by a number of observations in the living animal, is from the *pars tuberalis—median eminence* contact region towards the *pars distalis.* Considering however the critical importance attributed to the portal circulation in the hypothalamo-hypophyseal transmission mechanisms, the relator thinks most descriptions of the hypophyseal circulation, especially those made by endocrinologists (GREEN, HARRIS), as somewhat oversimplified and too schematic. No or not sufficient attention has been paid to the following facts.

a) There are abundant connections between the median eminence capillary loops and the capillary net of the hypothalamus surrounding the infundibular recess.

b) Capillary loops are not restricted to the contact zone between pars tuberalis and median eminence as it appears in most illustrations. They are found in similar numbers in more distal parts of the hypophyseal stalk entering from the contact zone between neural stalk and intermediate lobe. — These capillary loops have no connections with the blood vessels of the anterior lobe. So the somewhat teleological inference, what for should the capillary loops entering the median eminence if not for the purpose to convey some substance from this to the pars distalis through the portal vessels, loses much of its appeal.

c) There are several observations in the living animal (TÖRÖK, WORTHINGTON) concerning changeability of direction of the blood flow in the median eminence region and evidence of blood flow from the pars distalis, in smaller veins of the posterior surface, towards the median eminence. — The relator has produced experimental evidence in cats that a small fraction of the blood from the median sectors of the pars distalis may be drain towards the hypothalamic capillary network.

These and several other observations seem to indicate that the highly-logical conclusions drawn from the present oversimplified concepts on hypophyseal circulation will appear far less obvious if the complexity of the whole mechanism will be appreciated and better understood. When the possibility

of drainage of venous blood from the pars distalis towards the hypothalamic capillaries is taken into account, immediately the possibility arises that humoral signals of the anterior lobe may act on the hypothalamus. This possibility was tested experimentally (HALÁSZ and SZENTÁGOTHAI) by homoplastic implantation of anterior pituitary tissue into the hypothalamus. A significant depression of adrenocorticotropic activity was experienced which was never found in numerous control groups with implantation of other tissues into the same site, or of anterior pituitary tissue in extrahypothalamic parts of the brain. Thus the possibility of a "short circuit" feed-back control of pituitary function, by direct action of substances liberated by the pituitary upon nervous elements of the hypothalamus must seriously be taken into consideration.

4. *Neurosecretion and Hypothalamo. Hypophyseal Transmission Mechanisms*

From a discussion of the controversial observations concerning the possible role of the neurosecretory substances produced by the magnocellular hypothalamic nuclei as hypothalamo-hypophyseal transmitter, the relator arrives at a negative conclusion, far more evidence speaking against than in favour of such a role. — More attention will probably be paid in the next future to other kinds of neurosecretory phenomena observed in several hypothalamic nuclei. It will, of course, not suffice to detect simple histological signs indicative of some secretory process. Only close correlation of the phases of intensity of such secretory processes with activation of one or another of the trophic functions of the anterior pituitary will furnish useful histological evidence in favour of a mechanism of this kind.

Concerning the very existence of a neurohumoral hypothalamo-hypophyseal transmission mechanism, the relator is somewhat sceptic, because of the following reasons. *a)* Recent definite proof of a rich innervation of the pars distalis (paragraph 2) considerably reduces the necessity of such an assumption. *b)* As seen from paragraph 3 the hypophyseal circulation is not so simple as to suggest automatically or forcibly this explanation. *c)* The complete correspondence between results of pituitary stalk interruption (HALÁSZ; see report at this meeting) with those of gradual hypophysectomy by GANONG and HUME is strongly in favour of the assumption that interruption of the pituitary stalk results simply in a pan-hypopituitarism because of a breakdown of the circulation. No far-reaching conclusions concerning hypothalamo-hypophyseal transmission can therefore be drawn from experiments with interruption of the pituitary stalk. *d)* The meagre as well as inconsistent and especially not sufficiently-specific results gained from experiments with hypothalamic extracts are rather discouraging.

5. *Localization of Endocrine Functions in the Hypothalamus*

First the difficulties in evaluation of the results of hypothalamic lesion or stimulation experiments are discussed. Especially in case of lesions involving the neighbourhood of the median eminence, neural and vascular effects cannot properly be separated. But even if impairment of the vascular supply can safely be excluded, one can never be certain whether in any lesion or stimulation the effect was brought about by stimulation or interruption of a pathway running merely through the respective region, or whether the effect is really due to a cell group localized there.

Nevertheless, some characteristic endocrine functional localizations in the hypothalamus are now fairly well established. It has been known since the early forties (DEY, HILLARP) that lesions of the region ventral from the paraventricular nuclei impairs luteinization. Therefore a nervous center for LH-mobilization is generally localized into this region. The closer investigation of this effect (FLERKÓ), however, revealed that the explanation is not so simple. Lesion of this region impairs the inhibitory influence of elevated blood oestrogen level upon FSH-secretion. The existence of an inhibitory nervous mechanism of FSH-secretion in the anterior hypothalamus follows also from the experiments of DONOVAN and VAN DER WERFF TEN BOSCH. This region seems to be specifically sensitive to direct oestrogenic action (FLERKÓ and SZENTÁGOTHAI). Lack of luteinization after lesions in this region cannot simply be due to destruction of a hypothetic luteinizing centre, since arteficial depression of oestrogen production, in animals by resection of the ovaries or their implantation into the spleen, immediately leads to luteinization (FLERKÓ and BÁRDOS; see report at this meeting). — Thyrotrophic functions on the basis of the findings of GREER and HALMI—BOGDANOVE are generally localized between the suprachiasmatic nuclei and the median eminence. In a series of experiments MESS has adduced evidence in favour of the role of the habenular nuclei in the controll of TSH-secretion. —

Localization of adrenocorticotrophic functions is still very uncertain. Impairment of the compensatory hypertrophy occurs almost after lesions of any localization not only within the hypothalamus but of a large field involving parts of the thalamus and septal regions (MOLL). The specificity of this effect of hypothalamic lesions must therefore be questioned.

The relator presents the results of a completely different mode of approach to this problem by histometric means. Advantage is taken from the fact that nuclear size is fairly constant in the different hypothalamic cell groups of male animals when kept under strictly constant environmental conditions. In female animals the oestric cycle induces considerable cyclic changes of nuclear size in several hypothalamic nuclei. In cases of simple interference with endocrine functions like castration, thyroidectomy,

adrenalectomy, thiouracil-, cortisone-, oestrogen-, thyroxine-, ACTH-treatment, stress etc., characteristic nuclear size changes occur which can exactly be evaluated with karyometric methods. Since a change in the functional state of neurons is well-known to bring about nuclear size changes, these results can be exploited for localization of functions. From a vast material of such karyometric investigations a map of nuclear size changes has been assembled giving a localization of functional changes of different hypothalamic nerve cell groups in the case of interference with endocrine functions. Some hypothalamic nuclei are completely or largely irresponsive, like the suprachiasmatic and the supraoptic nuclei. In others like the paraventricular nuclei almost all kinds of interference with endocrine functions induce some change, so that the effect does not seem to be specific. In a group of nuclei, however, the nuclear changes seem clearly to be indicative of localized functional changes. Interference with gonadotrophic functions results in marked nuclear size changes in the anterior hypothalamic nucleus, a region completely irresponsive to other endocrine effects. Experiments resulting in a change of adrenocorticotrophic function show effects on the nuclear size in several especially posterior hypothalamic nuclei, but the most markedly in the ventromedial nuclei. Interference with thyroid function results besides smaller nuclear size changes in different cell groups, in spectacular effects upon the habenular nuclei.

These results are to some extent in fair accordance with the localization results of the lesion experiments mentioned above. On the other hand they also indicate that topic localization of distinct functions, whether endocrine or other, cannot be carried very far in the hypothalamus. It would be quite impossible — and also in sharp contradiction with modern concepts of neural functions — to try to find a distinct cell group in charge of the control of any specific function. Considering also the histological structure and the interneuronal connections of the hypothalamus, the existence of a mozaic of distinct functions in the hypothalamus appears to be extremely improbable, just as it does not exist in the cortex. It is far more probable that like in the cerebral and cerebellar cortex the same neural elements are involved in an infinite number of different combinations i. e. patterns of excitation and inhibition constantly changing according to the varying afferent information patterns (neuronal and humoral), and distributing accordingly through its efferent channels whole patterns of neural and chemical (neurosecretory) signals controlling the function of nearly all internal organs.

DISCUSSION

B. Flerkó and **Vera Bárdos**

(Department of Anatomy, University Medical School, Pécs)

On the Anterior Hypothalamic LH-releasing Mechanism

In albino rats with bilaterally-placed electrolytic lesions between the optic chiasm and paraventricular nuclei, having constant vaginal oestrus and no corpora lutea in the ovaries, luteinization could be induced (1) by unilateral ovariectomy and hemiresection of the other; (2) by grafting of the half of one ovary after bilatery ovariectomy into the renal capsule or (3) into the spleen. — While under experimental conditions (1) and (2) the degree of luteinization (with preponderance of thecal elements) has been found to be in reciprocal relation to the size of the remaining or grafted ovarian tissue, intrasplenic ovarian grafts (3) contained a large number of corpora lutea. Ovarian tissue in all the three experimental groups contained also more or less cystically-dilated follicles. Luteinization in groups (1) and (2) was mostly thecal luteinization in the walls of cystic follicles.

Formation of corpora lutea could, accordingly, be induced in rats with anterior hypothalamic lesions by diminution of the oestrogen level in the blood. Luteinization was most pronounced in the intralineally-grafted animals in which reduction of oestrogen-producing tissue has been combined with practically quantitative oestrogen inactivation by the liver. — The possible mechanisms of luteinization induced by decrease of the oestrogen level in rats with anterior hypothalamic lesions are discussed with respect to an "LH-mobilizing center" assumed in the anterior part of the hypothalamus.

B. Halász

(Department of Anatomy, University Medical School, Pécs)

Pituitary-Adrenal System after Hypophyseal Stalk Lesion

The histological structure of the adenohypophysis, adrenals, thyroids and gonads was studied after pituitary stalk lesion. The lesion was complete in 15 and incomplete in 16 cases. In the first group gonads, adrenals and thyroids were heavily atrophied, though this was not of the degree experienced after hypophysectomy. The adenohypophysis was completely degranulated after total stalk lesion. In case of partial lesion there was no atrophy of endocrine glands in 6 animals, atrophy of the gonads in 2, of gonad and thyroid in 5, and atrophy of gonad, thyroid and adrenal in 3 cases. Thyroid atrophy without gonadal, and adrenal atrophy without gonadal and thyroid atrophy has never been found. Among the animals lacking adrenal atrophy nuclear volume in the fasciculate zone was augmented in 6 cases, indicative of an increased level of ACTH-secretion. The findings are in complete correspondence with the results of W. F. Ganong and D. V. Hume (Endocrinology *59*, 292. 1956) concerning endocrine gland atrophy after graded hypophysectomy. — This correspondence supports the view that endocrine effects of hypophyseal stalk lesion are brought about simply by panhypopituitarism due to impairment of hypophyseal circulation.

A. Donhoffer and **J. Szentágothai**

(Department of Anatomy, University Medical School, Pécs)

Argyrophil Neurosecretion in the Hypothalamus

After perfusion with formol-pyridine in the hypothalamus of the cat (and also of the dog) in Gros—Bielschowsky-stained preparations strange rows of argyrophil droplets were noticed, looking very much like secondarily-degenerated axons. On more thorough examination, however, it became clear that these droplets appear first as argyrophil granules in the cytoplasma of nerve cells in the ventromedial nucleus. The granules are probably carried into the axons by the axial stream of neurons. —

After bilateral adrenalectomy the number of argyrophil droplets shows a spectacular increase, reaching its maximum on the 3rd postoperative day. Thyroidectomy or castration does not bring about any change in the argyrophil granules. — The Gömöri positive neurosecretory substance of the magnocellular nuclei and Herring bodies are not stained with silver after formol-pyridine fixation, and the argyrophil droplets described here do not stain with GÖMÖRI's chrome-haematoxylin. —

The possible significance of these argyrophil granules is discussed with special reference to the hypothetic corticotrophine-releasing factor.

B. Mess and **J. Hámori**

(Department of Anatomy, University Medical School, Pécs)

Bioassay of Somatotropic Hormone by P^{32} Radioautography

The sensitivity of the tibia test of EVANS et al. is not sufficient for determining the STH content of a single rat hypophysis, and needing hypophysectomized rats, it is also cumbersome, especially in large experimental series.

In the present experiments litter mate newborn rats were used, since the proximal epiphyseal cartilage of the tibia begins to store significant quantity of P^{32} only from the 10—14th day after birth. Half of the material with STH to be assayed is injected subcutaneously on the 2nd, the other half and simultaneously 2 μC P^{32}/g body weight on the 3rd day. 24 hours later the right tibia is fixed, decalcinated, embedded in polywax and sagittally cut into 20 μ sections. The radioautographs are prepared either with stripping film or with the coating technique of KOLOUŠEK. The reduced silver granula are counted with the aid of a 5×5 mm rectangular ocular diaphragm. The number of reduced silver granula calculated from five visual fields is considered characteristic of the quantity of injected STH.

The sensitivity of our method is between 15—200 μg purified STH (Esthropan, Hoechst), i. e. 2—3 times more sensitive than the classical tibia test. The regression curve calculated from the data of Esthropan titration is linear. Assay of the STH content of 0.5, 1.0 and 2.0 rat hypophyses gives also a linear regression curve, so the method is suitable for determining the STH content of half a rat hypophysis, even if it should be lower than normal.

An example for the application of the method is presented. The inner part of the bovine hypophysis, the so called "medulla" consists mainly of basophilic cells, while the outher part, the "cortex", contains mainly eosinophilic cells. The bioassay described above shows that the "cortex" has twice as great an STH-activity than the "medulla".

J. Baló

(1st Department of Pathological Anatomy and Experimental Cancer Research, University Medical School, Budapest)

Sequels of Pituitary Cysts

COLLIN, ROUSSY and MOSINGER believed that the product of the pituitary gland streams toward the brain. E. and B. SCHARRER, W. BARGMANN, KORPÁSSY and his co-workers claim the neurosecretion of the hypothalamic ganglion cell groups to pass toward the posterior pituitary lobe. However it may be, the fact remains indubitable that cysts developing in the pituitary gland interfere with the function of the hypothalamus—hypophysis-system.

In the authors's necropsy material 29 cases of pituitary cysts were observed. 11 of these were situated in the anterior lobe, 12 between the two lobes, 3 cysts in the posterior lobe, and 3 cysts extended over the entire organ. 18 cysts contained colloid. 6 cysts were lined by ciliated epithelium, 5 cysts had no proper wall.

Pituitary cysts may be associated with nanosomia, sclerodermia, hypophyseal cachexia, diffuse cerebral sclerosis, tuberous sclerosis, further with increased pancreotropic, thyreotropic, gonadotropic or adrenotropic function. The sequels of these hyperfunctions are : Langerhans'islet cell adenoma, exophthalmic goiter, macroorchia, or adrenocortical tumour, respectively.

J. Kövi

(Ist Department of Pathological Anatomy and Experimental Cancer Research, University Medical School, Budapest)

Effect of Yttrium^{90} on the Human Hypophysis

In cases of breast cancer with metastases, Yttrium^{90} placed into the hypophysis resulted in the destruction of 90 to 95 per cent of the anterior lobe. In the adenohypophysis 4 zones could be distinguished, according to their distance from the radioactive substance

1. *Zone of complete radionecrosis* characterized by a lack of nuclear staining by swelling of the cytoplasm, indistinct cell borders, and hardly-visible outlines of glandular structure.

2. *Zone of necrobiosis.* The majority of cells are destroyed. In some of them, dark, pycnotic nuclei are seen within a scanty agranular cytoplasm. The destroyed cells are surrounded by a few necrosing neutrophil leucocytes and a considerable number of foam cells containing fat droplets.

3. *Zone of repair.* This is of varying extent and is not invariably found between the necrosed and the intact zone. Septa of varying width formed from the connective tissue of the capsule and the vascular adventitia surround some small groups of well-staining and destroyed cells at the border of the necrobiotic zone.

4. *Marginal intact zone*, made up of 8 to 10 or more cell layers. The cells stain well and are probably undamaged and functioning.

B. Aros, B. Vigh

(Department of Histology and Embriology, University Medical School, Budapest)

Histology of the Neurohormonal Apparatus in Invertebrates

180 sexually mature earthworms have been examined. They were collected in the winter, at a temperature from —3° C to —12° C, and were killed either immediately, or later by decapitation, or by putting the animals anaesthesized with ether or chloroform into the fixing fluid. Paraffin sections were stained with paraldehyde-fuchsin and Gömöri's chromhaematoxylin method.

During winter sleep, a great number of hypersecretorial cells were found in the cerebral ganglion. At the same time, some cell groups of the subpharingeal ganglion displayed only a minimal secretory activity.

After winter sleep, most of the cells showed a medium secretory activity and besides these, the so-called transitional cells also occurred.

M. Ertl, B. Aros

(Department of Histology and Embriology, University Medical School, Budapest)

Hypothalamic Changes in Renal Hypertension

If increased amounts of pressor substances are present in the circulation on account of either increased production or reduced excretion, ischaemia of renal cortex will ensure with consequential hypertension. This final result can be brought about experimentally by narrowing the renal artery or wrapping up the kidney.

Experiments were carried out on 50 albino rats weighing from 150 to 250 g each. First parabiosis was produced, then a renal operation was performed. In this way hypertension resulted in both animals. They were sacrificed by decapitation at a blood pressure of 150 and 200 mmHg, respectively. The brain was fixed in Bouin's fluid embedded in methylbensoate celloidine, cut in the frontal plane serially in sections 5 micra thick and stained with Gömöri's haematoxylin-phloxin.

The following changes were revealed in the supraoptic and paraventricular nuclei:

1. At a blood pressure of from 150 to 160 mm, neurosecretion was accumulated in the nuclei, retention came about.

2. At a blood pressure of from 180 to 200 mm, the ganglion cells were enlarged, the plasma contained no secretory granules, enhanced neurosecretion had to be assumed.

3. The posterior lobe of the pituitary was free of secretion in both cases.

It is believed that the changes of neurosecretion were related to the experimentally-induced renal hypertension.

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Diabetes Insipidus Associated with Paraproteinosis, Diffuse Myelomatosis, Regressive Changes in the Hypothalamus, Chromophob Adenoma and Basophilia in the Pituitary

In a woman 57 years of age who has been suffering from diabetes insipidus for $1^1/_2$ years, paraproteinosis and diffuse plasmocytosis appeared one month before death. Post mortem there were regressive changes in the hypothalamus, mainly in the area of the special nuclear group, further chromophobe adenomas and basophilia in the anterior pituitary lobe.

Taking into account some similar observations and the experimental results of SAKURAI and WUHRMANN, the present case supports the presumption that the functions of the supraoptic and paraventricular nuclei influencing haemopoiesis, protein and fluid balance, are closely interrelated.

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New Data to the Effect of Experimental Diencephalic Lesions on Pituitary Function

By means of WYSS' high frequency electrocoagulator, bilateral lesions were placed in the anterior, middle, and posterior parts of the hypothalamus of female Wistar rats in a stereotaxic apparatus. As to the effect of these lesions on pituitary function, the following observations were made.

1. The neurosecretory material of the neurohypophysis diminishes or disappears only if the anterior hypothalamus has been destroyed. This phenomenon is a further evidence of the proximodistal transport of secretion products. At the same time, the theory of "production of secretion by neuron decomposition" is refuted by this observation.

2. Corticotrophic function, at least that influencing the weight of the adrenal glands, depends on the structural integrity of the anterior and posterior hypothalamus. Of the lesions of the posterior hypothalamus, those affecting the supramammillar portion of the posterior area are most significant.

3. Data in the literature and the above experiments have shown that the gonadotrophic function of the anterior lobe is controlled by a limited area seated above the posterior part of the chiasma in the anterior hypothalamus.

4. The pars intermedia probably receives fibres, apart from the nucleus paraventricularis, from the posterior portion of the ventromedial and dorsomedial nuclei, its volume being diminished after the injury of these areas.

4. The disturbance of adrenocorticotrophic and gonadotrophic functions due to lesions damaging the neurosecretory function can be elicited also by such hypothalamic lesions that do not interfere with neurosecretion.

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Morphology of Endocrine Renal Function, and its Hypophyseo-Hypothalamic Relationships

In albino rats the pituitary stalk and the tuber cinereum were lesioned and the cells of epitheloid character to be found in the wall of the vas afferens (JGC) were examined. These cells are free of fibrils, their cyptoplasm is granulated. According to the literature, the number of these cells and the extent of their granulation are inversely proportional to the serum sodium level, whilst a direct proportion exists between their granulation index and the thickness of the zona glomerulosa of the adrenal cortex. The JGC index representing also the extent of granulation was calculated by a semiquantitative method, on the basis of 850 glomeruli examined in both kidneys of each animal.

In the first series, killed 24 days after placing the lesion, 2 of 9 rats served as controls; their index was 14.9 on the average. Out of 7 operated animals, in 4 the pituitary stalk had not been completely destroyed; their index was 13.45 (average). In cases with complete lesion the average index was 29.

Similar results were obtained in the second series where the animals were killed 9 days after placing the lesion. The control index was 8.26; in the animals with incomplete lesion it was 9.5; in those with complete lesion 21.63.

In each animal the hypothalamus, hypophysis, adrenal glands, thyroid, and the gonads were also examined. After total destruction of the pituitary stalk these were atrophy and low lipid content in the zona fasciculata and reticularis, while the glomerulosa was broadened and markedly sudanophilic.

It has been reported that adrenalectomy or a diet poor in salt result in a higher JGC index and the broadening of the zona glomerulosa. Under such conditions hyponatraemia proved to be the primary factor. This was wery probably the case in our experimen*s, as seen from the high JGC index and the histology of the adrenal glands, although the serum sodium level was not estimated. Since, according to HARTROFT, hypophysectomy has little influence on the JGC index, the morphological changes and the significant increase of the JGC index in our experiments had to be ascribed to the lesion of the pituitary stalk and the tuber cinereum. The effect of the lesion on the index may have been exerted indirectly, through the zona glomerulosa; nevertheless, the possibility that the two effects are simultaneous but independent, cannot be excluded.

The experiments, apart from illustration the hypothalamic control of the zona glomerulosa and the juxtaglomerular granulated cells, have pointed to the probable role of the substance produced by the juxtaglomerular cells in the interrelation of zona glomerulosa and hypothalamus.

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Examination of the Granulated Cells of the Juxtaglomerular Apparatus

The granulated cells of the juxtaglomerular apparatus were studied by histochemical methods. The purpose of the examinations being merely to gain some preliminary information, of the methods demonstrating proteins, fats and carbohydrates only those yielding general information were applied.

It has been shown that the granules of the juxtaglomerular apparatus consist of protein, carbohydrate, and lipid constituents. As to the closer nature of protein and lipid components, no data have been obtained. The carbohydrate is assumed to be a mucoprotein or a glycoprotein.

L. Megyeri

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Cystic Changes in the Epiphysis

In 4 of 30 unselected cases the pineal body was enlarged. This was due to a solitary cyst in 3 cases, to multiple cysts in one case. Of the change in question, termed cystic hydrops by CARR, 34 cases have been reported in the literature.

26 pineal glands were of normal size. Of these, 7 contained a cyst and 2 exhibited a multiple cystic change. The latter changes frequently mentioned in the literature, are presumably due to dysontogenetic processes.

K. Lapis, L. Vekerdi

(Oncopathological Research Institute, Budapest)

Development of Experimental Thyroid Tumours

Morphologic, histochemical, autoradiographic (I^{131}), and biochemical examinations were carried out in various stages of experimental thyroid cancer induced in rats kept on a iodine poor diet (D) by the administration of 2-acetyl-aminofluorene (2-AAF) and 4-methyl-2-thiouracil (B). The effect of these individual factors was also examined.

1 hour prior to killing them the rats were given 50 mikrocuries. I^{131} intravenously. The thyroid was then taken out, weighed and worked up for histology and biochemistry.

D alone caused moderate hyperplasia. D+B resulted in extensive diffuse hyperplasia. Thyroid activity was according to the autoradiography greatly-reduced and more diffuse than focal.

2-AAF alone produced tissue lesion but hardly influenced function. None of the individual factors induced a tumour during the 400 days of observation, if they were administered separately. Combined treatment (D+2—AAF+B) brought about adenomas in all animals in about 250 days.

The following stages could be distinguished morphologically in the induced tumours. (i) Aspecific tissue damage (due to 2-AAF). (ii) Diffuse hyperplasia (due to lasting TSH overproduction caused by B). (iii) Multiple microadenomas. (iv) Papillary adenomas and cystadenomas.

None of the animals receiving the combined treatment had developed a malignant tumour within 400 days. On the other hand, the adenomas had lost their hormone dependence, as seen from the fact that regression could be achieved neither by discontinuing B treatment nor by the administration of high thyroxine doses. No I^{131} was incorporated by the adenomas, though they contained colloid. This colloid was obviously different from that present in normal thyroids.

L. Vekerdi, K. Lapis

(Oncopathological Research Institute, Budapest)

Functional Examinations during the Growth of Experimental Thyroid Tumours in Rats

After the intravenous injection of 50 microcuries of I^{131}, the amount incorporated by thyroid proteins and inorganic iodine were separated by radio-paper-chromatography. The changes were examined in the thyroids of rats treated with acetaminofluorene, methylthiouracyl, resp. both.

The ratio of the two fractions seemed to be charachteristic of thyroid function. Acetaminofluorene brought about marked morphologic alterations, but had hardly any influence on the ratio of the two I^{131} fractions. Methylthiouracyl diminished the incorporation of I^{131}, thus, the inorganic fraction increased. As seen, acetaminofluorene exerted more of a morphologic effect, whereas the functional effect of methylthiouracyl was stronger. Little, if any, I^{131} was incorporated by the adenomas developing in the course of combined treatment.

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Changes of the Blood Mucopolysaccharide Level in Hypo- and Hyperthyreosis, and in Diseases Attended by Tissue Destruction

In some diseases attended by tissue destruction the authors found in agreement with data in the literature a considerable elevated mucopolysaccharide (hexosamine) level in blood. The elevation amounted in tuberculosis and cancerous patients to 50 per cent of the normal average 83 mg per 100 ml. In tuberculosis, and in C_3H mouse cancer the local production of mucopolysaccharides and their transport through lymph vessels was demonstrated into the veins, which fact has clarified the mechanism of rise in the blood level.

Parallel with the restitution from tuberculosis, the hexosamine level becomes normal or subnormal. The question arises, which of the organs or (neuroendocrine) apparatuses influences the mucopolysaccharide content of serum. There being data on the increased hexosamine level in myxoedema, the thyroid may be taken into consideration. The colloid of thyroid stains with PAS. Therefore, 15 patients with hyperthyreosis were examined for the blood hexosamine level. The average difference was 17 per cent. In some of these patients, thyroid hyperfunction was alight.

In animals, cold and heat stress did not yield equivocal results. In 6 dogs, thyroidectomy resulted within 4 to 6 weeks in an increase of the hexosamine level by 43 per cent. Thiouracil gave rise to an increase of 31 per cent, thyroxine to a drop of about 30 per cent. The elevation due to thyroidectomy or thiouracil treatment was counteracted by thyroxine, even subnormal values could be attained.

These examinations have shown that the mucopolysaccharide level of blood is controlled partly by the thyroid, its hyperfunction leads to the decrease, its hypofunction to the increase of the blood mucopolysaccharide level. Tissue destruction results in a pathologic elevation of the mucopolysaccharide level in blood.

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Leprechaunism

British authors in 1954 and 1955 reported on a new endocrine syndrome, and termed it leprechaunism after the dwarfs in Irish folk-tales. After the 4 cases reported in the literature the authors have observed a fifth case. The basis of the condition is the early maturation of ovarian follicles and their cystic transformation, accompanied by the overproduction of oestrogen. As a sequel, somatic development ceases, body and organs are undersized, except the ovary which may attain 20 times its normal size. Oestrogen overproduction leads to a hyperplasia of the breasts, the external genital organs, and Langerhans' islets. Excretion of 17-ketosteroids is augmented. Insulin overproduction results in increased liver glycogen content. The iron content of the liver is also increased. Renal tubules are dilated and filled with lime casts. The production of pituitary growth hormone is inhibited. Therefore, the growth of shaft bones lags behind that of the small bones of hands and feet. Atrophy of subcutaneous tissue may ensue (emaciation). The hair is long, the face is hairy and oldish. The head is large, especially the skull. The eyes are large, protruding, lying wide apart. The nose is clubby, with a deep-root and patent alae. The lips are thick, the mandible hypoplastic, pointed.

Three symdromes are related to leprechaunism. TURNER's syndrome is its opposite (ovarian agenesy, with hypoplasic external genital organs, scanty hair, excessive excretion of gonadotropin, decrease of 17-ketosteroids). — HUTCHINSON—GILFORD's disease (progeria) exhibits much resemblance to leprechaunism, being characterized by the cessation of development, oldish face, large cerebral skull, hypoplasic mandible, subdermal atrophy. As compared with leprechaunism, progeria is non-familial, does not set on before the 1st year, its further signs are alopecia, a beak-like nose, hypoplasia of breasts, and missing ear lobules.

Leprechaunism shows the greatest resemblance to STEIN—LEVENTHAL's syndrome, which is also characterized by the small-cystic transformation of ovarian follicles, hyperoestrinism and male-type hypertrophy of hairs. The differences are due to the fact that STEIN—LEVENTHAL's syndrome arises in the adult, while leprechaunism during intrauterine life or in infancy. Therefore, endocrine dysfunction is more varied in leprechaunism coming about in a developing organism. Despite this, leprechaunism may be considered the intrauterine or infantile variety of STEIN—LEVENTHAL's syndrome.

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Endocrine Relationships of Partial Myxoedema

In thyreotoxicosis, especially while it is being treated, certain symptoms pointing to a peculiar endocrine dysfunction may appear. These are (in the order of frequency) exophthalmus due to ophthalmoplegia, pretibial myxoedema, clubbed (drumstick) fingers, acromegaloid face, mild diabetes. The simultaneity of these symptoms is not fortuitous. Except for diabetes, all may be due to the multiple, partial, circumscribed, myxomatous transformation of connective tissue. The common factor may be related to some little known effects of TSH and STH. With both hormones may be associated certain little known principles giving rise to a myxomatous transformation of connective tissue in some areas (orbita, pretibial region, acra), and to diabetes. These factors act particularly in case of a thyreo-hypophyseal imbalance, e. g. during the treatment of thyreotoxicosis. In such cases, complex endocrine dysfunction may lead to partial or complete development of the above syndrome.

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Thyroid Changes in Old Age

40 thyroid glands originating from subjects over 60 years of age were examined post mortem. Several parts of even gland stained with H.-E., van GIESON's, AZAN, KRAUS' colloid stain, and ANDERSON's stain for the demonstration of secretion to examine the capsule, the septa, cortical substance, width of acini, amount and histochemical characteristics of secretory granules, conditions of secretion, interfollicular cells, colloid absorption and orientation colloidophagia, degenerative changes, proliferation phenomena, genesis and type of goitre, etc.

All the data were statistically evaluated from 40 points of view. The results have shown that after the 6th decade the thyroids undergo involution associated with the deposition of colloid and hyalin, and hypofunction. After the 7th decade, small islets displaying secretion or hyperfunction appear in the inactive gland. Malignancy was found in three cases. The type of colloid can be determined from its staining by the above-mentioned five dyes.

RELATOR

J. Soós

The Adrenogenital Syndrome

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The pathological basis of the adrenogenital syndrome is furnished by an overproduction of adrogenic substances by the adrenal cortex. It is difficult to sum up the clinical observations and to evaluate biological data; the pathological changes are simple: hypertrophy of the cortex and tumour.

It is often difficult or impossible to differentiate the condition from other changes not associated with increased hormone output.

The term adrenogenital syndrome is unfortunate, giving the impression of the adrenal medulla being involved, since its product is called adrenaline. Attempts are being made to find a better name for the condition; TRAPEZNIKOVA has suggested the term suprarenogenital syndrome.

The syndrome has a peculiar character, first because it varies according to the time of onset, it being different in the prenatal, prepubertal and menopausal phases, and second, because it comprises apparently heterogeneous symptoms. This is why the many syndromes, based on virilism, hirsutism, genital changes and eventually feminism, have come into existence.

At first KERMANUER (1924) the genital changes were considered to be morphological, developmental ones; the opposite extragenital sexual characters were correlated with the gonadal glands. GOLDSCHMIDT introduced the concept of intersexuality; it was only later that the adrenal cortical changes in pseudohermaphroditism were recognized and hormonal disorders were thought of. According to the present view, masculine pseudohermaphroditism is not due directly to hormonal changes, although some evidence seems to indicate that this may be so, because the adrenal cortex may produce not only corticoandrogenic, but also corticooestrogenic agents.

Further studies on the feminine pseudohermaphroditism have then revealed that in the course of development quantitative and qualitative shifts may take place in the adrenal cortex, that may cause intersexuality even in the absence of tumour.

The interpretation of the syndrome is further complicated by its many connexions with sexuality. The sex characteristics are a property of the organism which manifests itself also in the structure of the nuclei of every cell. These nuclear appendages, first described in 1949 by BARR and BERTRAM, then simultaneously by WIEDEMANN—TOLKDORF and ROMATOVSKY, then DAVIDSON—SMITH, are such reliable signs of sexuality, that they make it possible exactly to determine the sex in cases of pseudohermaphroditism or intersexuality.

The development of the condition and its evaluation are rendered difficult by the fact that the complex of hypercorticalism is difficult to be taken apart, then being an overproduction of steroids in every case. According to JORES, hormones produced are not in the physiological proportions required for harmonic action. In the case of pathological overproduction the usually unidirectional and unequivocal nature of the disease is missing. The different states of overproduction of single hormones are responsible for the preponderance of one feature over the other in the various syndromes and for the variable forms of appearance of the adrenogenital syndrome. Although clinically syndromes have been isolated corresponding to the three groups

of steroids *(Table I)*, ultimately we shall find among the symptoms following the overproduction of mineralo- and glycocorticoids, or androgenic hormones phenomena and changes suggesting overproduction of the others.

Table I

Syndromes of Adrenal Hyperfunction

	Conn's syndrome	*Cushing's syndrome*	*Adrenogenital syndrome*
	Overproduction of		
	aldosterone	cortisol	androgens
Effect:	Na retention K loss hypertension alkalosis	glyconeogenesis protein-CHO-fat	protein synthesis sexual characteristics
Symptoms :	hypokalaemia hypernatraemia alkalosis hypertension tetany polyuria	reduced glucose tolerance diabetes mellitus adiposity of trunk moon face osteoporosis striae polycythaemia leucocytosis eosinopenia lymphopenia hypertension hypokalaemia alkalosis acne amenorrhoea	hirsutism virilism acne muscles well-developed precocious skeletal development feminine pseudo-hermaphroditism amenorrhoea precocious pseudopuberty
In the urine:	aldosterone	17-hydroxycorticoid formaldehydrogenic steroid 17-ketogenic steroid	17-ketosteroid

It seems that in the biology of cortical function a principle of uniformity of function takes effect. This is made possible by the fact that ACTH is a common stimulator of the production of the above-mentioned hormones, but undoubtedly first of all of glycocorticoids. Another evidence in favour of this view is the fact that a diminished hormone output results in the development of one disease, Addison's syndrome.

The evidence obtained as to the function of the foetal cortex has greatly contributed to our knowledge of cortical function. The development and presence of the cortex in the foetus prove by themselves that it is an essential feature of foetal life. If it had no role to play, it would not appear, because the permanent cortex could have developed even without this intermediary form. The presence of the foetal cortex suggests that it either complements the activity of the maternal cortex, or has a function of its own. Unfortunately, the hormones active there cannot be assayed by histochemical reactions and the signs of cortical activity have to be studied by other methods. Indirect

signs are, the relation of the size and volume of the embryo's cortex to the body weight, and its specific gravity. CASTALDI's formula: adrenal volume in ml divided by the body weight in g and multiplied by 100, is intended to reflect the changing relations. Although the adrenals increase in size during intrauterine life, they lag behind body weight.

The change in the weight of the foetal cortex is a result of the growth of the volume of the inner zone. DHOM—ROSS and WIDAK proved the activity of the inner zone in the early phase of development by nuclear variation studies. Many authors have made use of the accumulation and excretion of various substances. It has been shown that cholesterol and periodic acid positivity appear in the inner zone of the adrenal cortex of the 25 mm or smaller embryo.

On the other hand, GLOSS and STAEMMLER claim that the materials accumulated originate from the maternal organism and thus act as depots. BORSTER and VINES; GROLLMANN; BACHMANN; ROTTER; BOTELLA and LLUSIA think that the cortex of the young embryo is the site of sexual hormone production, in view of the presence of androstene and dehydroepiandrosterone in the cortex of 9—14 week old embryos.

Such a function of the cortex is proved also by the following data. Hydrocortisone has been demonstrated in the tissues of 9 to 17 week old embryos, the corticosteroid content in the embryonic cortex increases with pregnancy and in it can be found $^2/_5$ of the progesterone content of the corpus luteum, and that the umbilical venous blood contains 3 to 5 times as much 17-ketosteroid as the maternal blood. In 1939, TOBIN showed a shift in cellular elements in the hypophysis following adrenalectomy in 17 day old rat foetuses. JAKAITS and WELS implanted cortisone subcutaneously into 14-day foetuses and found an arrest of growth of the adrenal cortex, a thinning of the inner and a thickening of the outer zone; at the same time, the distribution of lipoids was also disturbed. An evidence of the foetal cortex being active is the appearance of fuchsinophilic granules in from 9 to 21 weeks in male, and in from 11 to 15 weeks in female embryos, as shown by VINES, who believed these granules to be identical with androgenic hormone and suggested that the embryonic cortex would produce male sexual hormone. He thought that pseudohermaphroditism would result from a prolongation of the production of this hormone in female embryos.

The next observation apparently proving the existence of embryonic cortical activity is the so-called androgenic or "*x*" zone, demonstrable in the 8-week embryo already. It has been reported to appear as early as at 3 weeks in embryos of either sex. There is a marked sexual difference in the fourth week. This zone regresses slowly; the grade of regression visible in the male at 40 days is comparable to that seen in the female between the 100th and 200th day. Thus, the zone is characteristically active in some phases only

and constitutes the major part of the cortex before birth. Its involution proceeds rapidly after birth. There is no androgenic zone in anencephals, this being responsible for the small size of their adrenals. Some workers refuse to accept the view that the "*x*" zone would have a function of its own, pointing out that it could not be demonstrated in most species. In contrast with this, VAAL showed that the male offsprings of pregnant mice treated with testosterone propionate during pregnancy exhibited malformations and degeneration of the "*x*" zone. In the female offsprings malformations of the urogenital apparatus, and particularly of the clitoris were noted.

After these variable changes of the embryonic cortex the final metamorphosis is seen after birth. This rearrangement was described as early as 1911. It consists first of all of an involution of the inner part of the foetal cortex. This occurs in every case, indicating that this process composed of degeneration and regeneration is a physiological one. In the course of degeneration the inner zone is broken down, and regeneration starts from the cells of the outer zone. There is an intensive cell activity in the inner zone, indicating that this zone has significant function during foetal life. ROTTER has offered an explanation for the postfoetal disappearance of the inner zone. According to him, before birth the inner zone is under the control of the placentar gonadotrophic hormone; this control ceases after birth and as a result the inner zone disappears. A new hormone, the pituitary corticotrophic hormone comes then into play, protecting of course not the disintegrating zone, but the outer one, which is still capable of regeneration.

TONUTTI has put forward a transformation theory to explain the sequence of events in the adrenal cortex. This theory strives to shed light on the adrenal dynamics. There are two fields of transformation; in one of them progressive, in the other regressive changes are taking place. The former is associated with hypertrophy of the organ, with an increase of function, of the amount of lipoids deposited and with a widening of the zona fasciculata. The regressive transformation causes a diminution of volume, hypofunction, functional exhaustion, lipoid depletion and a thinning of the zona fasciculata. The transformation, notably the progressive one, is controlled by ACTH. In response to cortisone administration or to hypophysectomy the picture of regressive transformation develops. Thus, transformation means adaptability of the cortex, which changes according to WHETTUR impulses inducing hyper- or hypofunction reach the cortex and to some extent according to the need of forming secretes by the parenchyma, which correspondingly grows or decreases in size.

Morphological changes characteristic of pathological cortical activity have been described by some authors. BIDELHART and DIETRICH reported that in response to toxin hyperaemia, oedema, cellular infiltration and destruction of parenchymal cells resulted.

In my studies in this direction I have found the destruction of the parenchyma to be followed by a peculiar reaction of reticulum cells. Once masses of round cells, then elements reminiscent of bone marrow cells are produced. There were no such changes in the adrenal cortex of normal infants who had died suddenly, but there were present in every adult I have examined and also in pigs after previous massive immunization. I have pointed out that such changes are the result of noxious and stressor effects. At that time SELYE's theory that various effects produce identical aspecific changes was not known. Thus, it is unjustified to look for special toxins in such investigations and to call the changes encountered specific ones.

The ACTH formed during stress stimulates the activity of the cortex, to which the cells of the cortex respond by diaprasia. The cortical cells give off lipoids, cholesterol and ascorbic acid, which, together with the biologically active steroid, enter the blood stream. During diaprasia the sudanophilic substances disappear, while during resistance the process is reversed, with the constituents passing from the blood into the adrenal cortex. This process is called enchosis. Should a disturbance affect these processes, according to BACHMANN, the morphokinetical reaction of TONUTTI will develop.

From those elaborated above follows that the older view, according to which there is a direct correlation between the adrenal cortex, and the gonads, and this is governing the changes of the cortex, sexual maturation, involution, etc., should be rejected. Any correlation of such nature depends on the production outflow and quantitative changes of the corticotrophic hormone. TONUTTI's view should be accepted and the changes in the cortex and the shifts in the sexual sphere should be interpreted on the basis of the stress mechanism.

In addition to the problems of development and morphology, those connected with the origin, metabolism and evaluation of the steroids form a second group in the problematics of the adrenogenital syndrome. The question arises, which of the compounds with a hormone-like activity are the genuine hormones of the adrenal cortex and which are their precursors or metabolites? Analysis of the cortical venous blood has shown that of the hormones leaving the adrenal 70 per cent is cortisol, 15 per cent corticosterone, 1 per cent aldosterone, and 14 per cent 11-OH-androstenediol and as yet undifferentiated steroids. Cortexone and cortisone have not been found in the blood, thus they cannot be considered to be genuine hormones.

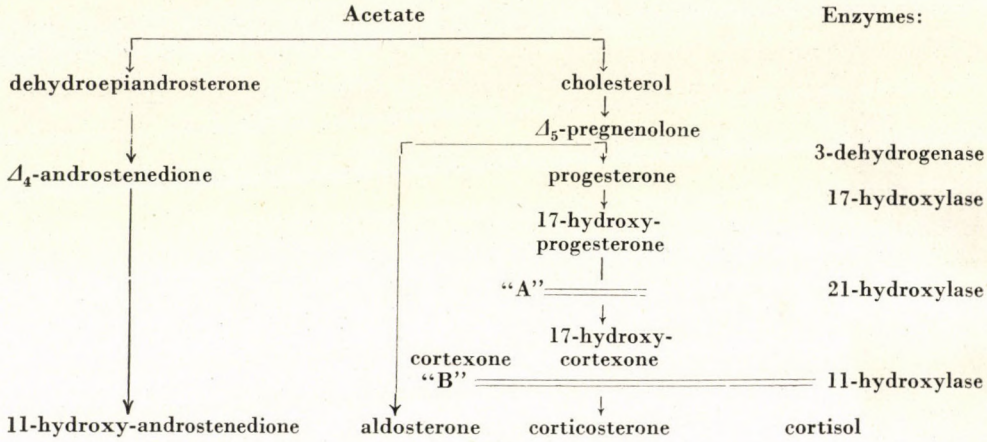
Genuine hormones are formed in two ways *(Table II)*. In one mechanism androstenedione is synthesised under ACTH control through progesterone formation, in the other through unidentified grades and epiandrosterone formation. Meanwhile, enzyme actions take effect.

The hormone "androgen N" acts on the protein/nitrogen metabolism. Many such compounds of androgenic action have been demonstrated in the

cortex: 17-hydroxyprogesterone, Δ_4-androstene-3,-17-dione, androstene-3,-11-diol-17-one; progesterone and oestrogenic agents have also been demonstrated.

Table II

Origin of Adrenal Cortical Hormones



Congenital Adrenogenital Syndrome. Disturbance of Steroid Synthesis at "A" and "B"

Block "A"	*Block "B"*
(Commonest form of congenital adrenogenital syndrome)	(Congenital adrenogenital syndrome with hypertension)
C_{21} steroids: mainly pregnanetriol	C_{21} steroids: mainly tetrahydrocortexone and tetrahydro-S
C_{19} steroids: 17-ketosteroids, chiefly the 11-oxy form, increased	C_{19} steroids: 17-ketosteroids increased, but 11-oxy-17-ketosteroid is absent

According to ZIMMERMANN, these are intermediary and metabolized products originating from the labile corticosteroids, which in turn are similar in chemical structure to the androgens, and thus to testosterone.

Such androgenic compounds are produced apart from the cortex in the testicles, ovaries and placenta. They are difficult to be differentiated on the basis of their origin, in spite of cortical androgen being known not to prevent the changes caused by castration. A differentiation is rendered difficult also by the fact that these agents are metabolized in the same way and are excreted by the same route. The substances thus demonstrated are not all cortical androgens. On the contrary, it is possible that they are metabolites of cortisol, as similar compounds originating from cortisol are known to appear in the urine.

Also, when the testicular hormones are metabolized, androsterone, epiandrosterone, ethylanolone are formed and appear in the urine.

In the case of the congenital adrenogenital syndrome it is an important question whether or not the embryonic testicle produces androgenic hormones.

In the early phase the gonads are bisexual. This raises the problem, whether a gonad anlage can differentiate by itself, or else, does it need an external hormonal effect to achieve differentiation? Transplantation experiments have shown the female gonad anlage to be different from the male one. As early as 1917, F. R. LILLIE studied experimentally the sexual transformation. He united chorionic anlages of cows, creating thereby a common circulation. No disorder resulted when the twins were of the same sex. When they were of different sex, in the female the gonadal cortex atrophied and development started in the testicular direction. This masculinization of the female partner has been explained by an action of the substance produced by the testicle of the male one, if the foetuses were not longer than 32 mm.

Foetal castration experiments also prove that the foetal testicle has a strong stimulating action on the basic sexual organs. This action is abolished by castration and in a genetically male foetus uterus, vagina and tuba may develop. Such an effect will occur, however, only in the early phase of embryonic growth.

*

In the foregoing I have pointed out the role in the genesis of the adrenogenital syndrome of the androgenic substances formed during the transformation and production of glycocorticoids. Their action is different in the male and the female, before and after birth, in acquired or congenital disease, when the onset is before or after puberty or in the menopause.

The genuine hormones are glyco-mineralo corticoids and the aldosterone, which are supplemented by the androgens, oestrogens and gestagens produced from them or together with them in variable proportions.

In normal conditions hyperfunction leads to the production of cortisol and androgens, in the first place. In pathological conditions there are three possibilities:

1. Cortisol preponderates in the hyperproduction.

2. An agent normally not present is produced. Such substances are mainly ones with androgenic or oestrogenic activity. Aldosterone, too, may be produced in excess.

3. A combination of 1. and 2.

From the resulting clinical signs and symptoms those indicative of virilism are often overemphasized. Virilism may appear in 3 forms:

1. As the masculine form of the secondary sex characteristics.

2. The secondary female sex characteristics are absent or show a regressive tendency.

3. Only the clitoris is hypertrophied.

This is the triad developing in response to testosterone treatment, to overdosage or overproduction of androgens, as in the adrenogenital syndrome or in cases of ovarian tumours producing certain kinds of androgen, accompanied by an increased, urinary output of 17-ketosteroid.

Hirsutism is another misused term, understood to mean masculine-type distribution of hair in females. If it is not associated with other symptoms and signs of the androgenic syndrome, as it often happens, the urinary 17-ketosteroid output will be only slightly increased. Hirsutism alone does not establish the diagnosis, because it is often a constitutional anomaly, or a symptom of Cushing's disease or of the Stein—Leventhal syndrome. Hypertrichosis must not be mistaken for hirsutism, because the former is not of hormonal origin, but a peculiar reaction form of the hair follicle, a result of a congenital ectodermal disorder, which is never part of the adrenogenital syndrome.

Mention should be made also of the conditions facultatively associated with the congenital adrenogenital syndrome. These are: 1. the salt depletion, 2. the hypertensive and 3. the hyperglycaemic syndromes.

The adrenogenital syndrome characteristically occurs in siblings, but not in the parents and relatives. In the affected siblings always the same genital change is repeated, just like the above-mentioned 3 facultative syndromes. From this follows that both the adrenogenital syndrome and the facultative associative conditions are genetic in nature.

These syndromes indicate, further, that the basis of the adrenogenital syndrome is furnished not by an overproduction of independent androgens, but by a defective synthesis of glycocorticoids, as a primary disturbance in cortical function. This view is supported by the fact that cortisol and its metabolites are present in blood and urine at a reduced level; a decrease of the cortisol level increases ACTH output, which, just because of the primary defect or the adrenal cortex, does not initiate an increased production of cortisol (or at least of full-value cortisol), but causes the adrenal cortex to respond with an overproduction of androgens. This increased androgen-oestrogensteroid interferes with the secretion of gonadotrophin, and as a result the gonads never reach functional maturity.

In *Table II* an attempt is made to illustrate the correlations, by combining the scheme of EGERLEIN and BONGIOVANNI with the steroid-synthesis scheme of HECHTER.

It is visible in Table II that there are two vulnerable areas in the process of steroid synthesis: block A and block B. One is between 17-hydroxyprogesterone and 17-hydroxycortexone, the other between the latter and cortisol, when at the same time a disturbance arises also between cortexone and corticosterone. Ultimately, it is the synthesis of cortisol that proves to be defective in both cases, and this should be considered to be the primary one. From this should be deduced the congenital adrenogenital syndrome and its

hypertensive form should be interpreted on this basis. This view is supported also by the clinical experience that in every one of these syndromes cortisol brings improvement, while ACTH causes deterioration.

In the case of block A pregnanetriol and 11-oxy-17-ketosteroid, in the case of block B tetrahydrocortexone and tetrahydro-S are accumulated. The accumulation of these substances, however, cannot be considered to be the cause of the accompanying syndromes. All that it implies is that cortisol synthesis is defective, the precursors are broken down before they could reach their final chemical form; the cause is a deficiency of cortisol itself.

The salt depletion syndrome is a peculiar accompanying condition of the congenital adrenogenital syndrome. In this syndrome the same disturbance of the electrolyte household appears as is so well-known in Addison's disease. The syndrome is often mistaken for pyloric stenosis, although a simple X-ray examination suffices for differentiation, because in the adrenogenital syndrome the stomach empties normally. Nevertheless, data in the literature indicate that the pathogenesis of the syndrome is not wholly elucidated. An overproduction of steroids is suspected as being responsible for the loss of salts. WETTSTEIN, DESSAULLER and NEHER have isolated a sodium diuretic factor, the role of which in the genesis of the salt depletion syndrome is accepted by PRADER, too.

In the background of the other accompanying syndrome, the hypertensive syndrome, there is a deficiency of cortisol, as seen in *Table II* in the case of block B.

Likewise, primary cortisol deficiency is responsible for the hypoglycaemic syndrome, in which a marked hypersensitivity to insulin is common.

*

In those outlined above I have tried to sum up what we know of the propedeutics of congenital adrenogenital syndrome at the embryological, histological, biological and chemical levels. In possession of these data I refer to the table by SOFFER, GABRIOLET, JAILER and JACOBS, showing the forms of the adrenogenital syndrome. The syndrome may be congenital and acquired; the latter includes cases with the onset before or after puberty. In each form the manifestations vary according to sex.

The tabulated evidence indicates that in every one of its forms of appearance the acquired adrenogenital syndrome is complicated by Cushing's syndrome. It is also clear that in the congenital vases there is hyperplasia of the adrenal cortex, while in the cases with the onset before puberty hyperplasia of the cotrex is rare, and tumour is more common, as opposed to the cases beginning after puberty, in which tumour is rare and hyperplasia is common.

In the salt depletion syndrome the hypertrophic cortex changes colour: it is pale grey in infants and brown in older children and adults.

Before concluding our discussion of the congenital adrenogenital syndrome, a few words must be said about the commonly-known change that occur in the ovaries, testes, hypophysis and epiphysis.

In the ovaries the number of follicles decreases with age, disappearing around 30.

In the testis the germinal epithelium develops only to the stage of primary spermatocyte formation.

In the hypophysis the most marked changes are found when the patients survived the salt depletion syndrome and reached infancy or childhood. In such cases the number of mucoid cells increases. These cells stain intensely with the over-acidified resorcin-fuchsin stain described by me. This stain was used by ROMEIS for the differentiation of the pituitary cells, for which the periodic acid Schiff reaction is also a reliable method.

There is no proof as to the correlation with the epiphysis. A correlation between the epiphysis and adrenals was denied by LEHMANN and DEMMEL, then by DENN, HATOG, JAGER and HEIL, on grounds of evidence obtained in extirpation experiments. In 1937 KUP described a case of cancer of the adrenal cortex associated with precocious puberty. He believed the tumour to have suppressed the antagonistic epiphysis, while the adenophypophysis gained preponderance. His view has not been accepted.

There are shifts in the growth of the individual suffering from adrenogenital syndrome. In the first year of life growth is normal. At the age of from 3 to 10 years the patient is big for his age; we then speak about adrenogenital gigantism. Over 13 years the patients are small for their age this is the adrenogenital dwarfism. These individuals when fully developed usually reach not more than 135 to 150 cm. The secondary sex characteristics manifest themselves in the precocious appearance of pubic hairs of the male type, often with beard growth and in adult females with baldness. Testicular development is rudimentary, because the overproduction of androgens inhibits gonadotrophin production. Thus, hypogonadotrophic hypogonadism develops.

If the testis is still big, it may contain a tumour of adrenocortical tissue. The clinical picture vill indicate not a true but pseudopuberty, in wich the urinary androgen and 17-ketosteroid output is increased, while in the former it is normal.

One of the differences between the congenital and prepubertal adrenogenital syndromes is that the latter occurs not only in girls, but also in boys; a farther difference is the normal findings in the early phase of extrauterine life.

In prepubertal adrenogenital syndrome adenoma or carcinoma is often present.

The syndrome, which begins in adults, has a separate place. It is associated with feminisation in man and with virilisation in woman. While the latter is common the former is an infrequent occurrence. At any rate, the adreno-

genital syndrome occurring in females should be differentiated from androgen-producing arrhenoblastomata, idiopathic hirsutism and the Stein—Leventhal syndrome. The urinary output of 17-ketosteroids is increased in the adrenogenital syndrome and in cases of ovarian tumour only.

Thus, in the pathogenesis of the adrenogenital syndrome importance should be attributed to the facts that the foetal adrenals have differing structure from, serve other purposes and have other biological roles then the permanent adrenals. The very presence of the foetal cortex proves that it has a special part to play; it has a tendency not only to make organs to be formed, but also to build up itself. The former produces the pathological shifts observable in the congenital adrenogenital syndrome. It is also important that the adrenal cortex does not produce directly androgens, but substances similar in activity to certain components of testosterone and oestrone may arise in the course of the synthesis and breakdown of cortical steroids, that may to some extent substitute testosterone or oestrone. The pathologically-affected adrenal produces an excess of such agents and this is responsible for the acquired adrenogenital syndrome.

DISCUSSION

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(1st Department of Pathological Anatomy and Experimental Cancer Research, University Medical School, Budapest)

The Pathological Anatomy of Congenital Adrenogenital Syndrome

The least frequent type of congenital adrenogenital syndrome is that attended by hypertension. The histological pattern of this rare form is reported. In a 22-month old child, pseudohermaphroditismus femininus externus was observed, with a penis-like clitoris and well-developed pubic hairs. Blood pressure was 149/105 mm Hg. In the cells of the oral mucosa, female sex chromatin was found. The child died of bronchopneumonia. Necropsy revealed enlarged adrenal glands weighing 13 and 14 g, respectively. Histologically, hypertrophy of the zona reticularis, and hyperplasia of the zona glomerulosa were conspicuous. In the anterior pituitary lobe, an increase of the eosinophil and ampophil cells, and reduction of the acidophils and chromophobic cells were present. In the ovaries numerous mature follicles and luteinization of the internal theca cells could be seen.

If the congenital adrenogenital syndrome is uncomplicated, and associated with loss of salts, atrophy of the zona glomerulosa is the usual finding. If, however, the syndrome is attended by hypertension, the zona glomerulosa undergoes hypertrophy, as observed in three cases examined by biopsy, and one by necropsy. Clinical observations and the histologic pattern admit the conclusion that the hypertension is provoked by the hypertrophy of the zona glomerulosa in which 11-desoxycorticosterone is produced.

The clinical and morphological study of similar cases may contribute to a better understanding of the role of the adrenal cortex, and of endocrine relationships.

I. Fodor

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Morphology of the Adrenal Zones

After removal of one adrenal gland of rats, the hyperplasia ensuing in the other adrenal was studied by administering colchicine to demonstrate mitotic activity. No limited germinative zone was found. Mitoses were present in the capsule, the zona glomerulosa and

fasciculata, at their junction, and in the subcapsular layer. The majority of mitoses were found in the outher cortex, wherefore a special role is ascribed to the cells of this layer extending from the capsule to about the inner third of the fasciculate zone.

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(1st Department of Paediatrics, and 2nd Department of Pathology, University Medical School, Budapest)

Adrenal Haemorrhage after Cortisone Treatment of Animals in Insulin Shock

In the course of examinations related of the effect of intravenous insulin administration, 64 rabbits of about 3 kg weight that had succumbed to insulin shock were examined. Six of the animals had been treated with cortisone, the other rabbits had not been pretreated. In 6 animals unilateral haemorrhage and necrosis of the adrenal gland was revealed; 4 of them had been pretreated with cortisone, 2 received insulin only.

It is believed that the functional state of the adrenal gland may to some extent account for haemorrhage and necrosis. Attention is called to the danger represented by insulin if administered after cortisone therapy.

K. Farkas

(State Institute of Rheumatology and Balneology, Budapest)

Changes in the Adrenal Gland Following Cortisone Treatment

The therapeutic application of substances produced in the adrenal cortex may lead to such changes in the adrenals, and through the backfeed mechanism in the pituitary-diencephalon system, which exert a general effect and may have a role in the development of numerous diseases. Corticoids beside their advantageous effect often exert a damaging, not infrequently fatal, action. An increasing number of observations points to the serious injury of the adrenals and the hypophysis by prolonged administration of cortical hormones.

In the last year, 5 pertinent cases were observed. Three of bronchial asthma and one each of rheumatoid arthritis and disseminated lupus erythematosus. Prior to death, they all had been treated with high doses of cortisone. In the latter lupus erythematosus patient vascular changes attributable to a lack of steroid hormones were present. The rheumatoid arthritis has turned in sepsis, presumably in consequence of cortisone overdosage.

Cortisone treatment brings about a histologic pattern in the adrenals resembling that occurring after the breakdown of the anterior pituitary lobe.

F. Biliczki, Éva Horváth

(Department of Pathology, University Medical School, Szeged)

Effect of Endocrine Factors on the Histochemical Picture of Normal and Regenerating Liver

In earlier experiments in rats cortisone was found to retard the regeneration following partial hepatectomy and to inhibit the action of the humoral factor stimulating regeneration. On the other hand, bilateral adrenalectomy increased mitotic activity in the intact liver.

In recent histo- and biochemical investigations carried out on partially hepatectomized and on bilaterally adrenalectomized rats authors found that:

1. 10 mg cortisone administered immediately after the partial hepatectomy, subcutaneously, inhibited the increase of alkaline phosphatase activity usually accompanying the restoration of liver tissue, and, on the other hand, helped to normalize the activity of succinic dehydrogenase which had been reduced after the hepatectomy.

2. Bilateral adrenalectomy (as determined three days after operation) enhanced the activity of succinic dehydrogenase and alkaline phosphatase im liver tissue. Alkaline phosphatase activity was practically confined to the swollen, round Kupffer-cells.

3. According to biochemical determinations beside the increase of alkaline phosphatase indicating an increased protein synthesis the mucoprotein level and the a_1-globulin ratio of serum showed a significant rise, as well. These changes could not be observed in hepatectomized rats treated with cortisone, i. e. in animals of reduced regenerative capacity.

On the strength of these findings it may be suggested that the restoration of liver tissue may — either directly or indirectly, perhaps through the stimulating serumfactor — be influenced by the corticosteroid level of blood.

P. Weisz[1], I. Purjesz, L. Ritter

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Correlations between Aldosteron Formation in Vitro and Morphology under Chronic Effects

In earlier studies the corticosterone level in the suprarenal vein of rats was examined, in the so-called stage of resistance of the general adaptation syndrome, i. e. in the stage of reaction to chronic effects. This has been considered a hyperfunctional state. Following the chronic application of formalin, cold, or adrenalin the corticosterone (glycocorticoid) content of the blood of the suprarenal vein was never increased, and often even reduced, despite the hyperfunctional morphologic pattern (adrenal weight and histologic signs).

In the present experiments not the venous blood, but the steroid production of the adrenal gland was examined in vitro. Under these conditions the production of aldosterone could also be observed. The rats were treated daily with 0,5 ml/100 g of 2 per cent formalin subdermally, for 5 or 10 days. One day after treatment had ended the rats were sacrificed by decapitation, the adrenal glands were removed, weighed, and partly worked up for histology, partly incubated for 2 hours at 38° C in a Krebs—Ringer-bicarbonate solution through with a constant stream of 95 per cent O_2 and 5 per cent CO_2 was passed. 200 mg/100 ml glucose but no ACTH, was added to the medium. Morphologic conditions were charasteritic of the stage of resistance of weight, signs of hyperfunction in sections stained with sudan or unstained and examined in polarized light, broadening of the cortex, increased LIPID content in the zona fasciculata, missing chromophobe zone, were noted. After incubation the medium was extracted, the extract was purified, allowed to wander in a system of benzene-methanol-water (2 : 1 : 1) then the individual steroids were developed by terazolium-blue and estimated by photometry. Aldosteron was identified in some cases by "soda-fluorescence", and comparison with standard compound. Aldosterone production in vitro was considerably enhanced more than the double the original amount was formed, the amount of corticosterone was normal or slightly reduced. Thus, the morphologic pattern of hyperfunction was in harmony only with aldosterone production, whil the corticosterone did not support the morphologic picture. In some experiments, corticosterone was estimated also in peripheral blood by paper chromatography with a silica gel column for purification but no increase was observed by this approach either.

The findings paint to the necessity of furthers detailed hormonal analysis of the general adaptation syndrome.

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Phaeochromocytoma

The cases of phaeochromocytoma found in the last 5 years material of the Institute were studied. The incidence was comparatively high, 0.25 per cent in the unselected necropsy material. On the basis of three typical cases, the following conclusions seem admissible.

(i) Clinical diagnosis of the tumour is improving. All the cases had been recognized before death.

(ii) Diagnosis has one firm basis: the examination of biocatalisators. First, the pressor substance has to be assayed biologically. The examination of enzymes may also contribute to diagnosis (negativity of alkaline phosphatase, positivity of 5-nucleotidase).

(iii) The typical histologic pattern of phaechromocytoma is debattable.

(iv) Correct morphologic conclusions can exclusively be drawn from fresh material.

(v) Regarding Points (ii) to (iv) some criteria should be strictly observed. Several cases reported in the literature do not seem to have been phaeochromocytomas.

(vi) The great amount of pressor substance produced by the tumour leads beside the lasting hypertension and its sequels to hormonal imbalance, especially trough the hyperfunction of the adrenal cortex, and the exhaustion of the islet apparatus in the pancreas.

(vii) For the often fatal outcome after succesful operations the above outlined hormonal conditions are presumably responsible.

I. Gy. Fazekas

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Role of Endocrine Factors in Hypersensitivity to Ethanol

The cause of ethanol hypersensitivity has not been clarified. In the adult, 6 to 8 g/kg, in children 3 g/kg is the lethal dose (ELBEL). Four lethal cases of hypersensitivity are reported.

1. A 4-year old boy died after drinking 400 ml of wine (10 per cent ethanol, lethal dose 1.97 g/kg).

2. A chondrodystrophic dwarf (24 years of age, 119 cm tall, 43 kg) died 6 hours after drinking 1200 ml of wine (lethal dose 2.2 g/kg). His adrenals weighed 5.86 g (i. e. 4.27 g) (42 per cent less than normal) (Low adrenal weight is a well-known feature in chondrodystrophy!) and he had a persisting thymus weighing 30 g.

3. A 20-year-old woman, 144 cm tall, 41 kg, wanted to induce abortion in the 2nd month; she introduced mallow root into her womb and drank 1000 ml of wine. She died within 4 hrs. The lethal dose calculated from the alcohol content of her blood was 3.4 g/kg. Her pituitary gland weighed 0.6 g, the thyroid: 21.6 g, the thymus 35 g, the two adrenals 8 g, which means a 27 per cent hypoplasia.

4. A girl aged 4.5 years and weighing 15 kg died 12 hours after the consumption (on an empty stomach) of 50 ml of 52 per cent rum. Here, 1.37 g/kg was the lethal dose. The adrenals exhibited a hypoplasia of 35 per cent, and signs of hypofunction. The thyroid was hyperplastic (245 per cent) and hyperfunctioning, the thymus hyperplastic (222 per cent) and hyperfunctioning. In the adenohypophysis, a numerical increase and enlargement of the eosinophil cells, their mitotic activity and riches in granules, with a decrease of basophils with poor chromatin content of nuclei and sparse granulation, were seen.

Adrenocortical hypofunction, hyperfunction of thymus and thyroid, with a subsequent decrease in the alcohol dehydrogenase activity in liver may be responsible for the hypersensitivity to ethanol and the necrotic foci found in the liver. In similar cases a favourable effect may be expected from the administration of corticosteroids and alcohol dehydrogenase at due time.

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Effect of Phosphorus on Chondral Ossification

Phosphorus has a prominent role in chondral ossification. Many controversial data have been reported on the significance of phosphate esters, mainly on the basis of experiments in vitro. Recently, the significance of glucose-1-phosphate, glucose-6-phosphate and ATP in calcification has been emphasized, as well as the role of mucopolysaccharides. Therefore, the action of phosphate esters was examined in vivo, by morphological methods.

Young rats of nearly equal, 50 g weight, and older ones of about 120 g weight were treated daily with GIP, G6P and ATP. The controls were treated with glucose+phosphate or were left untreated. The animals were sacrificed after 1, 2, 3 or 4 weeks, respectively. The proximal epiphyseal cartilage of the tibia was worked up for histology (H.-E. and Azan stain) and for histochemical examination (RITTER—OLESON, toluidine blue, with hyaluronidase pretreatment and acetylation).

Results

1. In young and older animals, chondral ossification of the epiphyseal cartilage was accelerated andor prolonged by phosphate esters.

2. ATP was the most effective compound. In young animals, the calcification zone developed earlier, the new bone attained earlier the cartilage. In older animals, ATP prolonged the activity of epiphyseal cartilage.

3. GIP and G6P were also effective. Histology in these experiments in vivo revealed much less difference in the efficacy of phosphate esters than the biochemical evaluation of experiments in vitro.

4. Chondral ossification displayed a certain periodicity. Broadening of the zone of proliferation, hypertrophy of the maturation zone swelling of cells, evacuation followed each other, then a new period began.

5. The accelerating effect of phosphate esters on ossification was shown also by the histochemical specimens.

6. According to the histochemical findings, phosphate esters affect the mucopolysaccharides of cartilage and it is through them that they exert an effect.

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Respiratory Metabolism of Regenerating Articular Surfaces, with Special Regard to Cartilage Formation

Half-joint was prepared in dogs by the method of KROMPECHER and PUKY. The femoral surface of the left knee joint was removed with a few mms of spongiosa. In the course of regeneration, the respiration of the new tissue was examined by WARBURG's method in the stages characteristic of cartilage formation (on the 7th, 20th, 26th, 33rd and 70 th postoperative days). Examinations were carried out in 4 groups: (1) in the presence of atmospheric oxygen; (2) with subsequent addition of methylene-blue; (3) with subsequent addition of glucose; (4) in nitrogen atmosphere. It has been found that in the presence of atmospheric oxygen the respiratory capacity of the granulation tissue growing on the articular surface gradually increased until the 33rd postoperative day, then a rapid decrease followed until the 70th day. (At 7 days, 255 microliter O_2 (hr) g dry substance; at 33 days, 864 microliter O_2 (hr) g dry substance; 70 days, 386 microliter O_2 (hr) g dry substance). If methylene-blue was added to the system which had worked in the presence of oxygen for 2 hrs., respiration greatly increased. The increase, as compared with the system working without methylene-blue, amounted to 21% on the 7th day, 25% on the 33rd day, 54% on the 70th day. If glucose was added 2 hrs. later, no marked change ensued. In nitrogen atmosphere, the granulation tissue producing no cartilage displays anaerobic glycolysis throughout the whole period of observation.

On the other hand, granulation tissue giving rise to cartilage formation exhibited after intensive initial anaerobic glycolysis decreasing values when cartilage production was in progress. (7th day, 778 microliter CO_2 (hr) g dry substance; 20th day, 1782; 26th day, 1667; 33rd day, 1534; 70th day, 1222.)

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Periosteal Decomposition of Bone in the Development of Paranasal Sinuses

In the development of paranasal sinuses, two parts may be distinguished: *a)* the paleosinus appearing as a pouch of the epithelium lining the nasal cavity, and situated in the perinasal loose tissue; *b)* the neosinus developing later by absorption of cranial bone parts and growing into those bones. The development mechanism of the paleosinus is well-known.

The authors studied the development of the neosinus. The experiments of KROMPECHER have shown that the periosteum is capable not only of forming osseous tissue, but also to decompose it, if normal physiologic stimuli are missing. Histologically, osteoblastic and osteoclastic periosteum can be distinguished.

The sphenoidal sinuses of individuals aged from prematurity to 30 years, were examined. The examinations have shown that the ingrowth of the sinus into the sphenoidal bone results from decomposing periosteal activity. Osteoclasts are seated on the part facing the depth of cavity, hereby denoting the direction of growth. As to the question, which is the factor directly giving rise to the growth into the bone, the role of dentition and mastication could be demonstrated in agreement with data in the literature. Intense development of the sphenoidal sinus coincides with dentition. Paranasal sinuses appear in areas on which no mechanical action is exerted, between load carrying trajectoria.

I. Nagy

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Cell Counts in Vegetative Ganglia Innervating Salivary Glands of Man

In previous studies the histotopography of the sublingual ganglion was examined by reconstruction and in the sublingual nerve and its branches nonally 15 ganglia were found, with a total length of nearly 2 cm.

As to the cell counts in the vegetative ganglia innervating salivary glands, the smallest of these, the sublingual gland, is innervated by 8000 to 9000 the submandibular by 3000 to 4000, the parotis (the largest of them) by 1400 to 1600 ganglion cells.

It has been concluded that serous salivary glands are innervated by less ganglion cells than mixed glands, and by much less ganglion cells than mucinous glands.

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Localization of Lead-Reactive Substance in Various Tissues

Motor endplates in the subneural apparatus can be demonstrated by the method of SÁVAY and CSILLIK. Fresh tissue samples are incubated in lead nitrate for 30 to 120 minutes, then frozen sections are made and treated with sodium sulfide. Smooth muscule gives an even lead reaction. In some cells, however, the lead reactive substance is markedly accumulated. In the heart, a strong reaction is given by Eberth's lines. An elective lead reaction was observed in the synaptic area in the ciliary ganglion of the hen. In nerve fibres, lead reactive structures made up of granules arranged in two regular rows were found at each Ranvier's node (mitochondria?). A positive reaction was yielded in the kidney by the brush border in the convoluted tubules and by the basal striation; in the liver by the cell nuclei, the wall of intrahepatic capillaries, and under proper conditions by the mitochondria; in the small intestine, by the cuticula of epithelial cells. A relationship is presumed to exist between the reaction to lead and phosphatase activity.

B. Csillik

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Relation of Subneural Apparatus to the Postsynaptic Membrane

The claim that the subneural apparatus possessing cholinesterase activity within myoneural synapses is identical with the postsynaptic membrane, was examined by histochemical and histophysical methods.

In frogs, the lamella-like "organites" of the postsynaptic membrane treated with lead nitrate, and examined in polarized light exhibited a monaxial positive double refraction. The analysis of the type of double refraction allows the conclusion that these lamellae are built up from micellar submicrons of longitudinal orientation, the polypeptide chains of which are likewise longitudinally oriented, whilst the intramicellar lipid molecules lie at a rectangle to this structure.

The lamellae of the subneural apparatus possessing cholinesterase activity and a similar microscopic arrangement, and the lamellae becoming double refringent after lead treatment, are not identical, but the former fill the spaces between the latter. Lasting supramaximal stimuli result in that the double refraction of the lamellae of the postsynaptic membrane changes its type, inasmuch as within the unchanged micellar submicrons the intramicellar (molecular) organization undergoes a considerable change, affecting the orientation of both the polypeptide chains and the lipids. On the other hand, lasting stimulation does not affect the cholinesterase activity of the subneural apparatus.

The conclusion seems admissible that the chiolinesterase active subneural apparatus is not identical with the postsynaptic membrane, they being two different, well-defined structures. It is assumed that the two structures act together in the synaptic transmission of stimuli.

I. Schneider, B. Csillik

(Department of Anatomy and Embryology, University Medical School, Szeged)

Innervation of Tonic and Tetanic Muscles

The "small nerve system" studied by KUFFLER plays a prominent part in the innervation of the tonic muscles (reacting with lasting contraction) of amphibia, whereas tetanic muscles (quick and short response) are innervated by the "large nerve system".

The subneural apparatuses of both muscle types were examined by histochemical methods. The subneural apparatuses of the "tetanic portion" and those of the "tonic portion" (Sommerkampf's Tonusbündel) of the frog's iliofibular muscle display characteristic morphologic differences. A method was devised for the simultaneous representation of subneural apparatus and myelin sheath and it has been found that the nerve fibres passing to the subneural apparatus are thinner in the tonic portion than in the tetanic one. These results confirm KUFFLER's observations in respect of the two nerve systems. The other claim of KUFFLER that the entire surface of tonic muscle fibres is covered by innervating nerve fibres, has not been confirmed.

Ilona T. Tomity, B. Csillik

(Department of Anatomy and Embryology, University Medical School, Szeged)

Role of Neurotrophism in the Maintenance of Myelin Sheath Organization

Fresh unfixed sciatic nerve was dissected in isotonic salt solution, and the double refraction of its fibres was examined. Numerical relationships were found between the calibre of fibre and the value of double refringency of this myelin sheath. Freezing of nerve fibres with CO_2-snow resulted in a significant weakening of double refringency. This observation is in harmony with the electron microscopic findings of FERNANDEZ—MORÁN, revealing a breakdown of the lamellar structure of the myelin sheath after extreme cooling; and with those of

MUNGER who examined pancreatic tissue by polarization optic methods and stated that the double refraction of frozen cells was considerably reduced.

A further observation was that freezing of the sciatic nerve *in vivo* is followed in 6 to 8 hrs. by the gradual but complete restitution of double refringency. At the same time, conductivity is also restored.

In a third experimental series the sciatic nerve frozen *in vivo* was cut and the double refraction of the myelin sheath was examined 2 to 8 hours later, proximally and distally to the site of division. In the proximal part, double refraction was gradually restituted in 6 to 8 hours. In the distal stump, double refraction persisted at the low value caused by freezing. As shown by the controls, cutting the nerve without freezing it does not impair double refraction in the distal stump, i. e. WALLER's degeneration does not yet manifest itself at this time.

K. Jobst

(Department of Pathology, University Medical School, Pécs)

Analysis of the Different Degradation Products of Deoxyribonucleic Acid

The degradation products of the deoxyribonucleic acid molecule produced by treatment with acids of varying concentration were examined by paper chromatography and electrophoresis. These examinations confirmed the conclusions drawn from earlier quantitative histochemical and polarisation-optical observations on the structural transformation of the DNA molecule.

B. Vigh, B. Aros

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Blood Circulation in the Thymus

The thymus gland of guinea-pigs and rats was examined, with different methods: injection with India ink, routin histological technique and dissection under micromanipulator.

In the thymus of the guinea-pig, the vessels entering the organ gradually divide into minor branches in the interlobar septa, befor they would enter the parenchyma. The arteries passing through the medulla give off capillaries during gradual division; at the cortico-medullary junction they bifurcate and continue in the cortex as radially arranged capillaries — the cortical capillaries collect into thick veins on the surface. The veins of the medulla leave the organ at the entrance of arteries. According to the above findings, the double venous system described by EBNER (1860, 1902) seem to exist also in the guinea-pig.

In rats, conditions are different. Arteries enter into the thymus near the hilus. There is no perilobular venous system, or it is made up of very thin vessels. Cortical capillaries exhibit a net-like, rather than radial, arrangement.

The findings of RENAUT (1897) and MONROY (1940), that the capillaries would enter from the surface of the cortex into its interior, has not been confirmed, either in guinea-pigs or in rats. As shown by our examinations, in both animals circulation takes place toward the cortex.

L. Holczinger

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Histochemical Demonstration of Free Fatty Acids

The method is based on the fact that free fatty acids in tissues form salts with metals.

Fatty acids of analytical purity, phospholipids, mono- and triglycerides, amino acids dropped upon paper strips, unfixed frozen sections of various animal organs, and sections of lungs in which fat embolism had been induced by intravenous fat injection were examined.

The specimens were kept in 0.005 per cent copper acetate or 1 per cent nickel sulphate for some hours. Metal in excess was removed by treatment with EDTA for 20 sec. Bound nickel was demonstrated by alcoholic dimethylhlyoxime solution, bound copper by 0,1 per cent aqueous rubeanic acid, whereby red or greenish black precipitate, respectively, had been formed.

The nickel-dimethylglyoxime precipitate being made up of needle-like crystals, the localization of fatty acids did not always succeed. The copper-rubeanic acid precipitate, however, seems to lend intself for histochemical examinations.

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Microtopography of Intrarenal Arteriovenous Anastomoses

According to clearance studies dehydration, arterial hypoxia, haemorrhagic and traumatic shock bring about a reduction of renal circulation. In the literature this phenomenon has been ascribed to the contraction of renal vessels. Direct measurements, however, have revealed that the renal fraction of the minute volume does not decrease. The question was therefore raised in which way does renal circulation take place, when renal failure increasing to anuria is associated with an undiminished renal fraction. In our opinion part of the blood passing through the kidneys reaches the renal venis through shunts, without passing through the parenchyma.

Morphologic evidence to support this assumption has been presented by the polyvinylchloride corrosion technique. Owing to its viscosity, a 5 per cent solution of polyvinylichloride cannot enter the capillaries. The kidneys of dogs were removed under chloralose anaesthesia, and the renal artery was immediately filled with polyvinylchloride solution. In the corrosion specimens, beside the arteries, veins were also found to be filled, especially when preceding examination of the animals pointed to the presence of shunts. By stereomicroscopic preparation, arteriovenous anastomoses were demonstrated in these cases. Similar anastomoses do not appear in normal kidneys injected post mortem. Venous filling had accordingly to be due to retrograde circulation, through arteriovenous anastomoses.

Such anastomoses were found at the cortico-medullary junction (juxtaglomerular and aglomerular recta system), between interlobular arteries and stellate veins (venous system in the cortex corticis).

B. Zolnai

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Topography of the Vertebral Artery and the System of Vertebral Veins

Necropsies and corrosion preparations have shown that in man the suboccipital section of the vertebral artery lying on the posterior arch of the atlas is surrounded by an abundant venous network. Earlier controversial results had been obtained in regard of the number and topography of veins. These were now examined in corrosion specimens and thick histologic cross sections from both adults and foetuses.

The findings were as follows:

1. The suboccipital section of the vertebral artery is surrounded by an abundant venous network, which with respect to its structure should be termed a sinus rather than a plexus.

2. This suboccipital sinus, though varying in extent, was invariably present.

3. The suboccipital sinus bears much resemblance to the cavernous sinus and especially in the foetus is better developed than the latter. In the sulcus of the vertebral artery, it is not the artery which lies directly upon the bone, but the suboccipital sinus.

4. The vertebral artery attains the posterior atlanto-occipital membrane not at a rectangle, but tangentially. This membrane is made up of several coats, between which venous sinuses are present.

5. The suboccipital sinus owing to its situation and broadness represents an essential communication between the intracranial sinuses, occipital veins, the jugular vein, the exterior veins of the cranial basis and the veins of the spine.

These anastomoses have a practical importance and their circulation will be further, studied with special regard to the interrelations of arteries and veins.

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Contributions to the Pathology of the Stein—Leventhal Syndrome (Virilization Associated with Polycystic Ovaries)

The therapy suggested by STEIN to be followed in the syndrome named after STEIN and LEVENTHAL, the excision of wedge shaped piece from the ovaries, was carried out in 45 cases. In the excised specimens beside a numerical increase of cells in the external and internal theca, the occurrence of paralutein cell groups in the loosened stroma, the appearance of many atretic follicles, a characteristic structure of collagen fibres in the thickened capsule and typical vascular alterations were observed. In association with ovarian hyperthecosis no mature yellow body can be found and in accordance with this fact, the uterine mucosa in the phase of proliferation or shows hyperplasia, but no secretory phase occurs.

The observations seemed to favour the view that the syndrome in question is associated with the decrease, or absence of the luteo-mammotropic hormone of the pituitary gland, so that hyperthecosis must be taken for an endocrine disturbance. The polycystic ovaries occurring in this syndrome have to be sharply distinguished from the cystic degeneration of the ovary, on base of gross and microscopic signs.

Hyperthecosis ovarii has been revealed also in cows suffering from sterility or lactation disturbances. Authors observed familially occuring female hermaphroditism associated with hyperthecosis ovarii in brothers.

Wedge excision according to STEIN had no favorable effect in the cases under discussion. Experiments with hormone therapy are in progress.

I. Kiss

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The Role of Hyperfolliculinism in the Endosteal Ossification of Phalanges (Acroosteosclerosis)

In 35 per cent of patiens suffering from endometrial (glandular cystic) hyperplasia, X-ray revealed endosteal hyperostosis on the 3rd, 4th, and 5th end phalanges of the hands. This diffuse and patchy sclerosis extended to the compacta and the marrow space.

Only women in the 4th and 5th decade are affected by the condition. Beside the uterine mucosa, vaginal scrapings too reveal an increased oestrogen production.

Acroosteosclerosis is thought to be induced by endocrine neurovascular factors. As to its localisation, it occurs in the area supplied by the terminal branches of the ulnar artery. Enhancement of ossification may be due to an anomalous androgen-oestrogen relation.

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Relationships of Follicle Hormone Activity, Diphenylamine Reaction, and Enzymatic Changes in the Endometrium, in Cases of Endometrial Hyperplasia

In 144 cases of endometrial hyperplasia, follicle hormone production was examined in vaginal smears by staining according to Papanicolaou stain, the diphenylamin reaction of serum by a modification of the macro-method of AYALA et al., the alkaline phosphatase activity of uterine mucosa by GÖMÖRI's method, formazane deposition pointing to dehydrogenase activity by SELIGMAN—RUTENBURG's procedure. The PAS reaction was also performed.

Hyperfolliculinaemia was found in 104 patients. The diphenylamine test was increased in 115 patients. Alkaline phosphatase was present in 46 cases with normal distribution and intensity, in 98 specimens only in patches, within the epithelium of the mucosa. Formazane deposition was normal in 23 cases while 121 cases displayed a weaker reaction. Positive reaction occurred mainly in the capillary endothelium, in the basement membrane and some parts of the cervical mucosa. The PAS reaction was considerably stronger than normal in the basement membrane and the stroma fibres in 103 cases. The elevated diphenylamine values and the PAS positivity are closely related to each other, as seen from the examinations with 2×2 contingency tables (P 0.001). The difference in the serum test averages between PAS positive and PAS negative cases was statistically significant by the "t" test (P 0.01).

Thus, phosphatase activity was like in cases of in cancer, but tumour growth, unlike hyperplasia, is attended by extensive formazane deposition. In contrast to the findings of other authors, in on cases phosphatase activity did not run parallel with the follicle hormone level. No correlation was found between oestrogen effect and formazane deposition either. It is assumed that the diphenylamine and PAS reactions are based on the presence of identical or very similar substance, because PAS positivity is belived to be due to such substances as are indispensable for a positive diphenylamine test.

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Rare Endocrine Conditions Related to Sexual Developmental Disorders

Two cases are reported. 1. A 20-year-old female with primary amenorrhoea, missing oestrogen activity, infantile body constitution, missing pubic and axillary hairs. Turner's syndrome was diagnosed. Genetically the patient was a female. Explorative laparotomy revealed an infantile uterus and Fallopian tubes and thin tissue bundles in the place of the ovaries in which no ovarian tissue, but mesonephrogenic tubular elements and groups of large pale cells (adrenal germs or hilar cells?) embedded in fibrous connective tissue were found histologically. — 2. A 15-year-old female with a general masculine appearence, had never had menstruation, has a strinkingly enlarged, penis-like clitoris, othervise normal external genitalia, pubic hair and vagina which ended blindly. Genetically the patient was a female. By diagnostic laparotomy neither gonads nor genitalia were found. In both inguinal canals a hazelnut-sized testicle was present which revealed histologically no evidence of spermatogenesis, in the interstitium Leydig's cell groups were found. This very rare pathologic condition corresponds essentially to the Ovarian dysgenesis with vestigial medullary development described by Grumbach et al. It is of special interest that presence of testicles is in accordance with the absence of elements developing from the Müllerian ducts, whilst at the same time feminization of the sinus urogenitalis could be observed.

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Endocrine Relationships of Sex Chromatins

In rats of different sex and age, the sex chromatins of leucocytes were examined by KOSENOW's method. Androgen and progesterone treatment performed after castration resulted in a change of the incidence of the form C of leucocytes. The number of these forms is progressively increased in infantile rats. At maturation their characteristic incidence is 5 to 6 per cent in females, 12 per cent is males. Androgen treatment of newborn male animals accelerated maturation of the forms C. In female rats the increased incidence of the form C was followed by the appearance of a male sex chromatin pattern.

Follicle hormon had no such effect. In male animals large doses of progesterone resulted in a decrease in the number of form C and in the appearence of a female chromatin pattern. The percentage of forms A and B and the sex chromatin structure in the skin were unaffected by this hormone treatment. It is concluded that, in contrast to the forms A and B, the form C cannot be regarded as a real sex chromatin body.

L. Virág, L. Kádas

(Department of Pathology, County Hospital, Szombathely)

Neuroendocrine Apparatus and Heparinocytes : Heparinocytes and Blood Clotting

In the rat mesentery, numerical and qualitative changes of heparinocytes were examined along with the changes in blood clotting, by GERENDÁS' thrombin inactivation method.

Adrenalin caused a destruction of heparinocytes and thus a prolongation of clotting time. Histamine also led to the destruction of heparinocytes, but coagulation time remained unchanged. If adrenalin administration had been preceded by antihistamine treatment, neither cell destruction nor prolongation of clotting occurred. Heparin administration resulted in the prolongation of clotting time, though cells were not destroyd, whereas the simultaneous administration of heparin and histamine caused the the destruction of heparinocytes without influencing coagulation.

Under hexobarbital anaesthesia, neither adrenalin nor histamine-induced cell destruction or prolongation of clotting time. If, howewer, ACTH was additionally administered, cell destruction ensued and clotting was retarded.

The following conclusions have been drawn:

(i) Heparinocytes contain heparin.

(ii) The hormones of the pituitary-adrenocortical system destroy the heparinocytes; the heparin of the latter enters into the circulation and retardates blood clotting.

(iii) This effect of heparin is counteracted by histamine.

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Neuroendocrine System and Heparinocytes: Heparinocytes and Blood Clotting in Cases of Sudden Death

Clotting conditions were followed in coagulogrammes in cases of sudden death (suffocation, nunchal shot) in dogs and rabbits. After clotting the blood again became fluid on fibrinolysis, heparinocytes disintegrate and the blood heparin level increases.

If sudden death had been induced under hexobarbital anaestesia, clotting ensued, but no fibrinolysis occurred. The blood heparin level did not increase in spite of a breakdown of heparinocytes.

The conclusion has been drawn that for the fibrinolysis setting in 4 to 6 hours after sudden death due to mechanical factors, the hormones of the pituitary-adrenocortical system are responsible in a way that the liberation of heparin leads to fibrinolysin activation.

Anna Vécsei

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Vascular Changes in the Retina Associated with Diabetes Mellitus

Retinopathy is one of the late complications of diabetes. Small haemorrhages in the eye-grounds are well-known to occur in diabetic patients; recently it has been demonstrated that these changes correspond to minute aneurysms.

The eye bulbus from individuals who had suffered from diabetes for 2 to 41 years have been examined. In some of them intercapillary glomerulosclerosis was present in the kidney. The purpose of the present examinations was to establish the sites of aneurysm within the retina, and the alterations induced by them.

Smaller aneurysms were lodged in the nerve fibres and ganglion layer. When growing, they push wide apart the inner granular layer then the other layers, but cause no disturbance of sight. In contrast, blood or exudate escaping the aneurysm does not oaserve the tissue

limits, whereby even in the case of small aneurysms, it may destroy the retinal tissues and attains the cones and the vitreous. At these sites the organized exudate brings about irreversible changes. This is the cause why with the prolongation of survival of diabetic patients there has been a market increase in he frequency of diabetes-induced blindness.

P. Rutkai

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Kimmelstiel—Wilson's Syndrome

Histologic changes characteristic of Kimmelstiel—Wilson's syndrome were found post mortem in 30 of 68 diabetics who had died of various causes.

Clinical data have shown that the syndrome occurs with long-standing diabetes. In the examined cases, diabetes had been present for 16.6 years, on an average. All the symptoms (albuminuria, oedema, hypertension, typical changes in the eye-grounds) were rarely present at the same time, so that the diagnosis can be established with certainty only on the basis of renal histology.

After the description of the individual forms it is emphasized that nodular, diffuse, and exudative glomerular changes are frequently associated in the microscopic sections. A combination of the diffuse and the nodular forms was the most frequent.

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Function and Histology of the Liver in Diabetes Mellitus

In 65 unselected cases of diabetes, liver biopsy (with Vim-Silverman's needle) and functional examinations (thymol test, serum bilirubin, urobilinogen excretion, total serum protein, albumin: globulin quotient) were performed. The patients were divided in two groups: stable and labile type of diabetes. Pathologic liver function was observed in 66 per cent. Histologically, pathologic changes (fatty degeneration, inflammation, fibrosis and cirrhosis) were found in 77 per cent with fatty degeneration the most frequent, 53 per cent. Inflammation and cirrhosis or fibrosis were invariably associated with pathologic liver function, whilst in half the cases of fatty degeneration functional tests were negative. Thus, fatty degeneration cannot be recognized without histology.

Fatty degeneration occurred with stable diabetes more frequently than with the labile type. This sign may be one of the features distinguishing the two types. Obesity, too, is a condition favouring fatty degeneration in the liver. — No correlation was found between morphologic changes and the good or poor control of diabetes. — A high serum cholesterol level (over 250 mr per cent) was more frequently associated with morphologic changes, especially fatty degeneration. This fact may be regarded as a sign of the relationship between fatty degeneration of the liver and the disorders of lipid metabolism in diabetes.

Considerable vacuole formation i. e. the presence of glycogen in the nuclei (with a frequency exceeding 10 per cent) was revealed in 18 patients. This finding was apparently unrelated to disturbed function, type of diabetes, its control, and general histologic pattern. Therefore, none of these examinations admit conclusions regarding nuclear glycogen formation.

P. Kapp

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Osteopetrosis in Fowls

Osteopetrosis was observed in three cases of a stock. Their erythrocyte count was slightly reduced. Blood calcium and phosphor were normal. The alkaline phosphatase activity was 51, 76, and 71 Bodansky units in the above mentioned the cases. The bones of wings and legs were thickened, curved. The cortical layers were homogeneous and compact,

the marrow spaces were contracted. Histologically, transformation of the compacta was observed, a new structure arose characterized by a mosaic pattern on the new trabecules. Transformation of the cortex was accompanied by extensive periosteal bony formation. Enchondral ossification was disturbed only in one of the three fowls. This seemed to be due to rickets. Residual cartilagenous islets were not seen. In one hen and one cock parathyroid hyperplasia were present. In the second cock hyperplasia of the testicela was observed. No other change was observed.

The examinations could not disclose the aetiology. Parathyroid hyperplasia was considered a secondary process. No sign of leucosis was revealed, wherefore the assumption of some authors stating that osteopetrosis is related to leucosis has not been adopted. The fact that the disease occurs only in certain stocks, and frequently in the offsperings of diseased fowls, admits the conclusion to the role of recessive hereditary factors.

A resemblance of osteopetrosis and ALBERS—SCHÖNBERG's disease was postulated by some authors. The present observations, however, point to a relation to Paget's osteitis chronica deformans.

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Enzymatic Decomposition of Collagen Fibres

Collagen-mucoproteinase (CMP-ase) was isolated by preparation from a purified elastase enzyme complex.

In CMP-ase dissolved in m/40 veronal acetate buffer of pH 7.4 (1 mg per ml) fresh, unfixed collagen fibres from the tail of a 6 months old rat were incubated.

The fibres treated in this way were examined under a dark-field microscope. The fibres placed on a hollow slide responded at room temperature to the addition of one drop of a 40 per cent aqueous KI solution with contraction. Subsequently, they underwent solution.

Collagen fibres were placed upon a plane slide, under a coverslip, and the effect of weights of 20 to 75 g, placed on the coverslip, was observed. If both ends of the fibres were fixed, contractions invariably resulted in tear.

Fibres pretreated with hyaluronidase behaved like untreated controls, the above changes did not appear.

From the above observations and detailed biochemical examinations the conclusion has been drawn that CMP-ase brings into solution the complex substance accountable for the stability of collagen fibres. The substance has been termed mucoid$_2$.

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Histochemical and Biochemical Examination of Acute Hepatic Lesions Induced by Tannic Acid

Authors found that a single sublethal dose of tannic acid (250 mg/kg, subcutaneously) results in severe lesions of liver parenchyma in rats (swelling of cells, pyknosis, hydropic degeneration, acinocentral necrosis). These structural alterations are accompanied by pronounced histochemical and biochemical changes.

Histochemical alterations (decrease of liver glycogen, of succinic dehydrogenase and lipase activity, of protein content) appeared in 30 to 60 min. after the administration of tannic acid, but after one week, the histochemical picture returned to nearly normal. Strikingly, no increase in the stainable fat content of the liver occurred at any time after tannic acid poisoning.

Tannic acid intoxication is associated with an increase in the free amino acid content of the liver. According to paperchromatography, in addition to the amino acids found in normal liver methionine, norvaline, leucine, tyrosine and aspartic acid appeared after tannic acid injection. The occurrence of these phenomenon is explained by the simultaneous

action of two factors, viz. a failure of deamination due to liver damage, and cell destruction in the necrotic areas.

Considerable changes occur in the distribution of serum proteins: decrease in albumin, pronounced increase of α_1 and a great increase of α_2 globulin. These changes may be due to an specific stress effect and/or the lesion of the liver parenchyma.

The changes induced by tannic acid cannot all be interpreted by the hepatotoxic effect of the compound. Other systems (endocrine, reticular) may also partake in this.

K. Kovács, A. Tiszai and J. Kovács

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Liver Biopsy in Haematologic Diseases

Liver biopsy (with Vim-Silverman's needle) was done in 50 patients suffering from different haematological diseases, in order to establish the diagnostic value of the procedure.

Liver biopsy has been a valuable in a variety of conditions, for instance for differentiating myeloid metaplasia from true myelosis, further in the diagnosis of aleukaemic lymphadenosis, systemic treticuloses, congestive splenomegaly, Vaquez-Osler's disease, hyperglobulinaemic purpura. In some of the cases a disease of the haemopoitetic apparatus had been assumed but liver biopsy revealed some different process.

Caution is recommended at the ecaluation of the biopsy findings. Only distinctly positive findings are of diagnostic value, no disease can be ruled out on the basis of a negative biopsy finding.

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Formation of Kosugi's Granuloid in the Epithelium of Renal Tubules

In human and animal shock-kidneys, the presence of roundish, structureless bodies was observed, which in freshly fixed material often filled the lumen of tubules and Bowman's capsules. They were identical with the granuloids described by KOSUGI in 1927. These granules have been considered artefacts by many authors, while others have claimed that they are formed before death. The present experiments proved the intravital origin of the granules. In rats, unilateral ligature of the ureter was in 8 to 16 hours followed by the appearance of the bodies in the main tubules of the obstructed kidney, while in the other kidney they did not occur. In the aspirated content of the renal pelvis no granuloids were demonstrated. 24 hours after the ligature had been taken off, the granuloids were still present in the main tubules. Their extensive formation was observed also after experimental alloxan shock.

The granuloids measuring on the average 8.3 micra in diameter, amorphous, mostly homogeneous, but occasionally with a delicate foamy structure. They contained no alkaline phosphatase, their derivation from the brush border seemed unlikely. The protein nature of the substance was proved by DANIELLI'S tetrazonium reaction. As to their appearance together with shock-induced real changes, it is believed that they are due to hypoxia induced by the failure of renal circulation. As glomerular filtration decreases, granuloids accumulate in the tubules, fall into pieces which coalesce and are concentrated to form numerous casts. Haemoglobin or myoglobin is probably only one of the constituents of casts. The view of BAKER and DODDS claiming that anuria and uremia are due partly the obstruction of tubules by casts has been refuted by many authors. The recent examinations of SHIMAMINE, and the fact that the tubules and Bowman'S capsules are considerably dilated in such cases, speak in favour of the opinions that urinary flow is impeded. In this way, the granuloids may have a role, though not primarily or exclusively, in the development of shock-induced renal lesions.

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Morphology of Vascular Obstructions in Patients with Cancer

12 cases in which cancer was associated with thrombosis were examined post mortem. In 3 of them, cancer started from the stomach and in 2 of these a muciparous tumor was found. In the other cases the cancer was situated in the breast (2), the urinary bladder (2), prostate (1), uterus (1), rectum (1), gall bladder (1), liver (1).

Obstruction occurred in the pulmonary artery in 7 cases and in the coronaries in 4 cases (only one of the latter had been recognized before death). In 3 cases the portal vein and a renal vein were thrombosed, with occlusion of the hepatic vein, the lienal vein, the vena cava inferior, the vena iliaca communis, the femoral and the cubital vein. In one case, recent suprarenal haemorrhage was found. Thrombosis of small vessels was frequent as well as organized thrombi. The conclusion is that thrombosis may occur at any time in the course of cancer.

Gy. Romhányi

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Polarization-Optical Examination of the Submicroscopic Structure of Endoplasmic Reticulum (Ergastoplasm)

In unstained specimens of the epithelium of pancreatic acini and liver cells, ergastoplasm displays a weak anisotropy wherefore a polarization-optical analysis of its complex structure cannot be achieved. However, intense double refraction could be elicited by ferricyanide treatment following staining with rivanol, or toluidine blue. In accordance with electronmicroscopic findings, this may be taken as a sign of the presence in the cytoplasm of submicroscopic ribonucleoproteid structures of lamellar orientation, containing transversally oriented lipids.

The lipids are of acid character and inhibit ribonuclease acticity and play a role in the oriented binding of some dyes, since after their extraction no toluidine-induced anisotropy can be demonstrated, despite unchanged basophilia.

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Polarization-Optical Examination of Osteolathyrism

Osteolathyrism was induced in rats weighing from 90 to 100 g by the administration of aminoaceto nitrile (daily 10 mg subcutaneously for 21 days). Polarization-optical methods (metachromatic staining at different pH values) revealed diminished incorporation of acid mucopolysaccharides in pathologic cartilage. For the quantitative evaluation of metachromasia, the negative double refraction maesured at a wave length of 640 mmicron was used. At the same time, the incorporation of collagen fibres into the new osteoid tissue was disturbed. This alteration was indicated by a reduction in the phenol reaction, being characteristic of the collagen fibril system.

Changes in the structure of collagen fibres were revealed by several other observations. The temperature of heat-contraction is lower in collagen fibres affected by lathyrism, these collagen fibres are easier to extract, the extract contains more tropocollagen, which differs from normal tropocollagen in gelification properties.

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Cytomorphology of Ectopic Pregnancy, and its Teratologic Relationships

It has been shown by other authors and by our own experiments that in the early stage of development the gradient of partial oxygen pressure is the directing factor of the development, and any anomalous gradient results in a developmental anomaly.

Ectopic pregnancy has been studied as one of the extreme forms of disturbed nidation, out of 40 000 biopsies, 1099 referred to Fallopian tubes. Tubal pregnancy was found in 473 cases; in 15 cases ovarian, retrouterine, intramural, or tuboovarian pregnancy was present. Tubal pregnancy was associated with tuberculous salpingitis in three cases, with simultaneous intrauterine pregnancy in one case. In a further case, dysgerminoma of the ovary was accompanied by ectopic pregnancy. Of the 488 ectopic pregnancies observed, cytomorphologic conclusions were drawn only from 121 cases, that were fixed while still fresh in triacid-picric acid and stained with tuchechtgelb or fluorochrome. Several samples were examined under the phase contrast microscope.

In ectopic pregnancies beyond the 3rd month, slight basal nidation was observed, mainly in the well vascularized mesosalpinx. The missing foetal vascularization of chorionic villi, the high number of fibrinoid margins, and the predominance of primary villi, were histologic signs of a poor blood supply. Other structural changes could also be regarded as histologic equivalents of tissue hypoxia, such as the numerical increase of mitochondria in the villi displaying no mesenchymal organization in their palisade-like arrangement at some places. The fact that, in the villi possessing mesenchymal organization, the cells of the narrow cytotrophoblast coat are rich in plasma but free of mitochondria, was evaluated in the same sense, as well as the sticking together of the brush borders of syncytial cells, and the reduction of intervillous space.

The early developmental anomalies revealed in the precent study favour the view that hypoxia had exerted its damaging effect between the zygote stage and that of early pharyngeal cleft. The structural anomalies occurring with the presented malformations (phocomelia, cerebral dysplasia, microphthalmia, archiencephalia, craniorachischisis, pygepagus made up of 2 or 3 somites) may be considered morphologie equivalents of disturbed nidation in ectopic pregnancy.

Éva Gáti

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Enzyme-Histochemical Examination of Ehrlich Ascites Tumour during Chemotherapy

Experimental resistence to the mustard derivative Degranol was induced by subtherapeutic doses in EHRLICH's ascites tumour. After the administration of half lethal dose, the sensitive and resistant tumour cells were stained with Feulgen's stain, methyl green pyronine and gallocyanin. Of enzymes, succinate-dehydrogenase, cytochrome-oxydase, peroxydase, alkaline and acid phosphatase, and aspecific esterase, were demonstrated.

The findings admit the conclusion that it is the activity of the respiratory enzymes bound to mitochondrial function which is inhibited by Degranol, though the nucleic acid balance was also affected by the drug, inasmuch as a decrease occurred in the amount of RNA. With the development of resistence to the drug; multinucleated giant cells appeared in which the activity of all the examined enzymes was increased. The stability of the colour intensity brought about by gallocyanin was interpreted as a sign of unimpaired nucleic acid balance.

Forensic Medicine

E. Somogyi, J. Irányi, B. Orovecz

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Contributions to the Problem of Suicide by Electric Current

In the last decade, 10 cases of suicide committed or attempted by means of electric energy were observed by the Ambulance Corps Budapest, and the Department Forensic Medicine. In agreement with great statistics, electric shock is the least frequent means of suicide in this country. All victims were men, like in the vast majority of cases reported abroad. Thus, this mode of suicide is typical, though not specific of men. Lay people chose a long-distance transmission line, because public opinion holds that only high voltage represents a life-danger. In some cases the purpose for touching the cable was not suicide but to elicit a psychic reaction of another person. Lethality was 88 per cent. The causes were incurable disease, fear of punishment, love, psychosis. Psychic infection played often a role in the selection of the instrument.

Three types of artificial electrotrauma occurred: 1. Three individuals climbed up the pylon to touch the wire with both hands. Unconsciousness ensued immediately; further, extensive burns and secondary injuries were found, such as, fracture of cranial basis, femur or the pelvis, rupture of lungs or kidneys. 2. Three persons bound one end of a long wire to their wrist and threw the other end supplied with a weight across the cable. Long exposure time was the characteristic feature in these cases. 3. Four persons put a wire around their body and connected its ends with the mains through a wall-socket. The lasting action of the current inevitably resulted in death.

Necropsy revealed the well-known features of electrotrauma. If the role of current was questionable, diagnosis was based on the histologic examination of the suspicious skin area, dermal metalisation, digital and palmar prints found on metal objects. A further problem was the distinction between accident, suicide, and murder. This was performed on the basis of necropsy findings, examination on the scene, history, preparations for the action, farewell letter, etc. Evidences should be evaluated with criticism, and the possibility of murder should always be taken into consideration.

L. Harsányi

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Severe Lesion of the Nervous System Due to a Wrong Connection during Anaesthesia

In a case intratracheal anasthesia, wrong connection committed in the initial phase resulted in that the patient received N_2O only, without O_2, for 5 minutes. After the detection of the mistake, O_2 inhalation was applied. The condition of the patient became seemingly normal, and the operation could be finished. After the operation the patient remained unconscious, convulsions occured repreatedly on the following days. From the 8th postoperative day the patient had fever, and died on the 12th day with the symptoms of circulatory failure.

Necropsy revealed catarrhal tracheo-bronchitis, bronchopneumonia, signs of circulatory failure, and gross and microscopic changes in the brain: gross emollition in the left lenticular nucleus, microscopic emollition foci in the motor and the occipital cortex, in the stem ganglia, atrophy in the Ammon's horn, severe regressive changes along with general

oedema of the brain and the lesion of myelin sheaths. In the cerebellum severe regressive changes were displayed by Purkinje's cells, of which only one third was present.

It is recommended that the technique of intratracheal anaesthesia, or the apparatus, be modified to prevent wrong connections.

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and Department of Forensic Medicine, University Medical School, Budapest)

Air Embolism after Diagnostic and Therapeutic Air Insufflations

Insufflation of air into cavities or tissue spaces for the purposes of X-ray diagnosis or therapy is a rare cause of embolism. Five lethal cases are reported. One was due to pneumoperitoneum, one to perirenal insufflation, one to abdominal insufflation through Douglas' cavity. In the latter case the air insufflated into Douglas' cavity had elevated the peritoneum and entered the retroperitoneal space instead of the abdominal cavity. Beside these three cases in which insufflation was performed for diagnostic purposes there were two cases of therapeutic pneumoperitoneum. In both of them the cannula was introduced on the right side, above the umbilical level. Both cases ended fatally. In one of them the air embolism ensued immediately after the introduction of the needle, before the onset of insufflation. It is believed that in this case death was caused by the residual air that had remained from a previous insufflation, in a way that while introducing the cannula the inferior epigastric vein was injured and intraabdominal pressure made the air enter the gaping vein.

Attention is called to the dangers of air insufflation. The procedure being dangerous, it should not be applied without very carefully considering its indication. If a pneumoperitoneum must be brought about, the cannula should be introduced in the midline, where there is the least possibility for injuring a vein.

E. Somogyi, L. Komáromy

(Department of Forensic Medicine, University Medical School, Budapest)

Cranial Injuries in 1958

The data of 172 necropsies (126 men and 46 women) have been worked up and beside the usual points of view the question was examined whether the clinical management of the injured was conform to modern demands.

Most (113) of the cranial injuries had been suffered in a traffic accident. 49 per cent of the injured died immediately or during transport to the hospital. The vast majority of this group had suffered several injuries. In the group of those who died in the hospital, the number of persons with a single injury and those with several injuries was nearly equal.

About one third of those admitted to a hospital died on the day of the accident. The lethality on the next day was half of that of the first day. The decrease of lethality with time was continuous. Out of 87 admitted cases 37 were operated on and 30 were tracheotomized. 10 of 30 operations failed to solve the condition which had given cause to the operation. In 12 of the 50 non-operated cases necropsy disclosed such changes which could have been solved by surgery.

Gy. Dallos

(Hungarian Army Medical Corps)

Subendocardial Haemorrhages Associated with Bullet Wounds of the Skull

The study of 157 individuals shot through the head has shown that the frequency of subendocardial haemorrhages continuously increases with the time elapsing from injury to death. The site of the injury has no essential role. In all cases also without gross changes

hyperaemia and microscopic extravasations were always found in histologic sections. Statistical data, histologic findings, and the character of cranial wounds, allowed to conclude to the significant role of shock in the genesis of subendocardial haemorrhages.

B. Rengei

(Department of Forensic Medicine, University Medical School, Szeged)

Comparative Examinations to Distinguish Human and Animal Blood by Precipitation and Proteolytic Methods

Animal blood, whether from living or dead animals, whether soon or late after death, independently of the dilution of the sample, did not yield a positive reaction with the precipitation and proteolytic methods. Negative reactions were obtained with dried animal blood, and blood which had been exposed to various physical effects. Human blood, however, reacted to both methods, even if the blood spots had stood at room temperature for $1^1/_2$ years. If the blood had been preserved at 56° C, a positive reaction was obtained with both methods for 8 months. It made difference if the blood drop had fallen on wood, iron, nickel, etc. As to the sensitivity of the reactions, any amount of blood containing 0.03 μ g protein was readily demonstrated. The conclusion is drawn that the proteolytic method represents a reliable means for the distinction of human and animal blood.

O. Kozáry

(Department of Forensic Medicine, University Medical School, Szeged)

Carbon Monoxide Intoxication of Hardly-Detectable Origin

After a review of the cases of carbon monoxide poisoning that had occurred in Szeged, a case examined post mortem is reported. Two girls, about 15 years of age had suffered carbon monoxide poisoning while taking a shower in a small room. One of the girls died in a hospital where botulism was assumed as the cause of death because the gas water-heater was seemingly faultless. Necropsy, however, disclosed carbon monoxide poisoning, and this was confirmed by spectroscopy.

The question was raised how the accident ensued since before the shower had been used by many people without any harm. Examination revealed that the gas heater had no flue pipe and the room which had no ventilation whatever was so small that the carbon monoxide gradually accumulated to a toxic concentration. Thus, time factor had a prominent part in the accident and when the air of the room was analysed under the same conditions that had prevailed at the time of the intoxications after a critical time a sudden increase of the carbon monoxide level up to a lethal concentration was revealed.

L. Veress, B. Rengei

(Department of Forensic Medicine, University Medical School, Szeged)

Glutamic acid—Oxalo-acetic-acid Transaminase Activity of Serum in Experimental Nicotine Poisoning

In rabbits, transaminase activity of the serum was examined in experimental subacute nicotine poisoning, in order to establish the liver damaging effect of this substance. The animals was given 20 mg nicotine per kg body weight for 8 days subcutaneously. During treatment transaminase activity rose to 15 to 20 times of the initial value, to return gradually to normal after treatment had ceased. At the same time liver function tests and serum protein fractions remained normal. In sections made of the liver, moderate centrolobular fat accumulation was seen.

Some rabbits were given a single lethal dose of nicotine. The enzymatic activity of the serum was significantly elevated even as late as 24 hrs. after death.

It is concluded that the increase of serum transaminase activity may be used — under certain conditions — to confirm the diagnosis of nicotine poisoning.

K. Zsigmond, J. Nagy

(Department of Forensic Medicine, University Medical School, Debrecen)

Method for the Quick Determination of Carbon Monoxide in Blood

A blood sample of 0.2 ml is haemolyzed, oxyhaemoglobin is precipitated by acetate buffer (pH 4.19) at 55° C, and the CO-haemoglobin remaining in solution is estimated by colorimetry, against the original blood dilution the haemoglobin content of which is regarded as 100 per cent.

By preparing different dilutions of the original blood the colorimeter becomes superfluous. Thus, no special instrument is needed and the examination can be carried out during necropsy.

The results were compared with those obtained by WENNESLAND's method. In most cases the differences were within the limits of error. In some cases lower values were obtained, probably because CO-Hb dissociated during the dilution of blood and CO-loss ensued. The differences did not exceed 10 per cent in these cases either.

Z. Nagy, Klára Zsigmond, J. Nagy

(Department of Forensic Medicine, University Medical School, Debrecen)

Spectrumanalysis in Forensic Medicine

In a case of zinc phosphide poisoning, the poisoning agent was revelated by spectrumanalysis. The organs to be examined were treated with nitric acid and hydrogen peroxide, neutralized with sodium bicarbonate, and the dried residue was examined.

On account of its simplicity, quickness, and sensitivity, spectrumanalysis lends itself for the demonstration of poisoning metals, especially if more than one must be taken into consideration.

The procedure and the fields of its application in forensic medicine have been discussed in detail.

S. Ökrös

(Department of Forensic Medicine, University Medical School, Budapest)

Pre- and Postmortal Changes following Myocardial Injury

The changes were examined in human, swine and dogs hearts. Animal experiments were needed to study the result of injuries occurring in the first minutes after death.

Death occurred in all cases in a few minutes after injury, owing to blood loss. All sections were stained with H.-E., Mallory's stain and impregnated with metal salts.

The most severe alterations were found in the environment of the injury. The cut ends of muscle fibres were swollen, homogenized, basophilic, chromaffin. After silver impregnation, they were sharply different from the uninjured fibres. Impregnation allowed to distinguish four zones in the injured bundles. In the zone of torn myofibrils, the fibrils were swollen, rounded, and clubbed. The interruption of the continuity occurred in the isotropic section. Next came the zone of elongation, then that of tetanic ring-shaped contraction which was intensely metalaffin. Then a short elongation zone, and zone of weaker contractions

followed, finally a very short elongations zone of contiguous with intact areas. At the site of insertion similar though considerably milder changes were seen, like a mirror image of those described.

Following myocardial injury in the first phase of intermediar life, hardly any swelling of the injured muscle fibres seated in the wall of the wound was observed in the experimental animals. Silver impregnation resulted in a slightly black colour, though the myofibrils were not fragmented.

L. Takácsy

(Department of Forensic Medicine, University Medical School, Budapest)

Electron microscopic Ultrastructure of Myocardial Capillaries

Samples taken from the subepicardial muscle layer of rats, left ventricle were fixed with osmic acid, embedded in butyl-methylacrylate, cut with F. JUNG's ultramicrotome, and photographed with an electromagnetic electron microscope type WF.

The capillaries appeared as oval structures of varying length, depending on the angle the section formed with the vessel, and the blood content. Capillaries do not perforate the sarcolemma, and they do not enter between the myofibrils. Between the fibril and the capillary, intact sarcolemma is seen. Their basic elements are the endothelial cells. The nucleus of these cells is varying in shape, has sharp contours, a nuclear membrane, it contains osmophilic granules and in its environment there are numerous plasmosomes. The cytosplasm is limited by a 300 to 350 Å thick smooth external membrane, and on the inner side by a wavy 100 to 150 Å thick internal membrane. The unevenness of the latter is a factor increasing the surface, whereby parietal blood flow is retarded. The 300 to 400 Å thick cytoplasm contains numerous vacuoles, cavities, and plasmosomes. The parietal spaces, probably serving the physiologic permeation of celle and fluid, are clearly visible.

The myocardial capillaries form a living protoplasmic system of very intricate structure, the actual condition of which plays a prominent role in metabolism and function.

P. Antoni, I. Kelemen

(Department of Forensic Medicine, University Medical School, Debrecen)

Morphologic Changes of Spermia in Mixed Saliva

In saliva, spermia disintegrate in a very short time. The greater is the relative amount of saliva, the quicker and more complete the disintegration. Therefore if spermia are to be demonstrated in saliva the sample should be taken as soon as possible. The effect of saliva is not uniform, intact and thoroughly destroyed spermia being present in the same sample.

While in undiluted sperm this destruction takes place evenly, i. e. the whole tail begins to undergo destruction at the same time, in diluted sperm destruction of the tail begins at the middle part, independently of being saliva or physiologic salt solution the diluting medium. This different behaviour could not be explained on the basis of the present examinations. If sterilized saliva is used, destruction proceeds slowly, though the growth of bacteria is rather intense, it is therefore concluded that both bacteria and enzymes are taking part in the process of destruction.

J. Nagy, L. Pusztai

(Department of Forensic Medicine University Medical School, Debrecen)

Medicolegal and Criminological Microlaboratory

A plastic case measuring 38 : 28 : 25 cm has been designed in which all instruments and apparatuses employed in medicolegal and criminologic laboratory work have been collected. There is a separate compartment for holding bottles with acides and bases.

Instruments and apparatuses being fixed in the case, the microlaboratory is portable. This microlaboratory is considered useful in both forensic practice and teaching work.

L. Pusztai, J. Nagy

(Department of Forensic Medicine, University Medical School, Debrecen)

A Stand for Taking Criminologic Photographs, with Special Regard to Chemiluminescence Examinations

On a black background measuring 160 : 127 cm along the one diagonal, two rectangular figures are placed facing each other. These can be illuminated and adjusted to the size of the picture. Light is procured from behind, from a low voltage bulb. The shadowless illumination of the background is secured by four strong bulbs held by arms of proper lengtb. A series of three figure numbers can also fixed on the background to numerate the photographs. The object to be photographed is fixed by hooks to the frame of the background.

The apparatus is of particular adventage when used for chemiluminescence tests. The place of the luminescent blood spot can be drawn on the light photograph of the object by means of known identical points. The lighting rectangles can be fixed on the photographs taken in the dark and light; if they are superimposed the identical points will coincide.

The simple designation of identical points can be assured also by placing the lighting rectangles on the scence.

L. Pusztai, J. Nagy

(Department of Forensic Medicine, University Medical School, Debrecen)

A Plastic Case for Holding Sections

Storing of sections is still a problem. Their storage in a small place should be associated with simple registration and management.

To this end a case measuring 250 : 90 : 7 mm was made of a 1 mm thick plastic plate. The section holding unit consists of a chief plate bearing 8 slides on each side. Fixation of sides is assured by elastic plastic processes measuring 15 : 17 mm protruding from the bottom. Slides are separated from each other by plastic prisms. Each cell is 28 mm wide. The bottom part of the case is closed. The plastic processes keeping the slides in place exert such a pressure that the slides do not fall out even if the case is turned upside down.

The units can be placed into cases of ten. In this way, sections can be found within a very short time.

For special slides, units of appropriate size can be constructed.

Vl. Porubsky

(Department of Forensic Medicine, Komenský University, Bratislava)

Lesions by Oxidation Products in Small Rooms

Referring to a fatal accident in a bathroom, it is emphasized that such accidents may be caused by two factors. First, the oxidation product, e. g. carbon monoxide, may cause direct poisoning. Second, intense oxidation may result in the consumption of oxygen and the production of a great amount of carbon dioxide whereby suffocation may ensue. Following items should be given attention, if the expert has to prove suffocation due to oxygen deficiency.

1. Careful necropsy is to be carried out, to exclude collapse from any other cause.
2. CO-haemoglobin determination in blood, for the exclusion of CO-intoxication.
3. Reconstructive examination at the place of the accident, to establish the CO_2-congent of air and the partial O_2-tension.

In the author is view, careful examinations will reveal this kind of accident to be more frequent than usually assumed.

M. Vámosi

(Department of Forensic Medicine, Komenský University, Bratislava)

Distribution of Ethanol in the Brain

Theoretically, the estimation of alcohol in brain tissue has a fundamental significance in the statement that the subject was acting under the influence of alcohol. This problem was investigated and considerable differences were found in the alcohol content of the different parts of the brain. Similar differences were established in experimental animals (dogs and monkeys).

On the basis of these results, the author does not adopt the opinion of many medico-legal experts who contend that the simple estimation of the brain alcohol contents constitutes a reliable basis for the diagnosis of "alcoholic influence". Moreover, the estimation of the alcohol contents of a single brain part admits no conclusion as to the entire brain.

P. Schneider

(Department of Forensic Medicine, Komenský University, Bratislava)

Changes in Blood Supply and Oxygen Tension in the Brain under the Influence of Alcohol

The blood circulation and the oxygen supply of the central nervous system was examined in 150 experimental animals at a blood alcohol level exceeding 0,2 percent. In case of a high blood alcohol level, dilatation of cerebral vessels, retarded circulation, and reduced oxygen saturation of the blood were observed. All these facts interfere with the oxygen supply of the brain, whereby adaptation mechanisms deteriorate. For instance, acute blood loss was less tolerated by these animals, as compared with the controls. The conclusion is drawn that even slight acute blood loss is badly tolerated by subjects with a high alcohol concentration in their blood. In such cases, proper therapy should include early transfusion of blood.

L. Buris

(Department of Forensic Medicine, University Medical School, Debrecen)

Changes of the Urine Alcohol : Blood Alcohol Quotient in Experimental Alcohol-Barbiturate Poisoning

In dogs the ureters were cut, the proximal stumps were sutured to the abdominal skin, the distal stumps were ligated, to isolate the urinary bladder from the kindneys.

Then the bladder was filled with 50 ml of 1 to 2 per cent alcohol. From this, samples were taken at 1 hr. intervals and their alcohol content was estimated by Widmark's method. In two other series this procedure was preceded by alcohol and alcohol-barbiturate poisoning.

In non-poisoned animals, the alcohol content of the bladder decreased to zero in 3 hrs. After alcohol poisoning the disappearance of alcohol from the bladder took 6 to 8 hrs. and after alcohol-barbiturate intoxication there was still alcohol in the bladder in 24 hrs.

The conclusion has been drawn that the permeability of the bladder wall to alcohol is greatly impaired by preceding alcohol, till more by alcohol-barbiturate intoxication. Further, the fact that alcohol and alcohol-barbiturate poisoning of man is accompanied by an increase of the urinealcohol : blood-alcohol quotient, can be readily understood on the basis of the above results.

L. Nagy, J. Nagy, Klára Zsigmond

(Department of Forensic Medicine, University Medical School, Debrecen)

Excretion with Saliva and Expired Air of Small Oral Doses of Alcohol

Experiments were performed on 50 adult persons. Administration of 0.3 g/kg of alcohol by mouth resulted in some cases in a high blood alcohol level, and also the alcohol content of saliva was comparatively high. The curve of alcohol excretion in the saliva displayed a normal course in 80 per cent of the cases, and an irregular course in the rest. For the latter anomalous absorption conditions were made responsible.

The samples of saliva free of alcohol were kept for some days at room temperature or in a refrigerator betwen 1° C to 4° C. No increase of reducing substances or of substances interfering with Widmark's test was observed.

From the results it has been concluded that the examination of saliva for alcohol is a useful and reliable method of establishing alcohol consumption, if blood cannot be withdrawn.

The alcohol content in the expired air was qualitatively examined by means of J. NAGY's alcohol sound. A positive reaction was obtained if the concentration of alcohol in the saliva exceeded 0.01 per cent.

Klára Zsigmond

(Department of Forensic Medicine, University Medical School, Debrecen)

Rapid Tests for the Demonstration of Barbiturates

By means of the well-known cobalt nitrate test the demonstrability of the barbiturate compounds Veronal (Ac. diaehylbarb.), Veronal sodium (Na diaethylbarb.), Sevenal (Ac. phenylaethylbarb.), Hypnoval (Ac. cyklohexenyl-aethylbarb.), Hypnoval calcium (Calcium cyglohexenylaethylbarb.), Dorlotyn (Ac. isoamylaethylbarb.), Evipan (Ac. N-methyl cyklohexenylmethylbarb.), Evipan sodium (Natrium N-methyl cyklohexenylmethyl barb.) was examined.

The limit of demonstrability was found, under the given conditions, at 60 to 120 μg per ml. In aquaeous solutions, about 50 per cent of the dissolved quantity could be recovered by the chloroform method. Evipan is an exception, being hardly soluble in water. If the compounds had been thoroughly mixed with organ pulp, only 10 per cent were recovered by extraction with chloroform.

Considering that in case of lethal poisoning great amounts of barbiturates are ingested, the direct chloroform extraction of body fluids and organs should be performed despite the considerable lose of substance, because the recovered quantity does, as a rule suffice for a positive test.

J. Nagy

(Department of Forensic Medicine, University Medical School, Debrecen)

Changes in Plastic Threads Caused by Gunshot

Experiments were performed by shooting with a 7.62 mm army gun at wowen plastic materials from distances ranging between 0 and 300 cm and examining the changes in texture and threads. The material was partly melted. The mechanical action manifested itself with various changes in shape (elongation, brush forms, ets.) Melted parts formed, along with the products of gunpowder, a homogeneous mass. At the places of gunpowder impact, loss of substance was observed. Photomicrograms allow to conclude as to the distance from which the gun was fired.

L. Kiss

(Department of Forensic Medicine, University Medical School, Debrecen)

Comparative Examination of Fingerprints in Twins

The fingerprints of twins were compared with those of the parents in 20 families. On the basis of the methods and laws disclosed by ÖKRÖS the development of the figure-forming parts, and the distribution of the so-called parental minutiae were examined. As to development of figure types, and the percentages of identity of figures whith that of one of the parents, no difference was found in comparison with non-twin siblings. Similarly, parental minutiae, too, develop according to the law valid for siblings. The identity resp. difference of figures found on corresponding fingers occur neither more nor less frequently than in non-twin siblings.

Twins can be distinguished from each other on the basis of their fingerprints. The occurence of parental minutiae does not impede this identification and twins behave in this respect like normal siblings.

B. Korpássy: Chairman's Summary

Ladies and Gentlemen,

the flattering task of evaluating the work of this Congress before its dissolving by the President has, at the request of the Central Committee, devolved on me. Even the simple survey of the extremely rich programme, but still more the hearing of the two reports, of the 84 papers and of the often very animated discussions connected with them would confuse greater authorities than I am, and it is quite evident that a comprehensive and exhaustive evaluation of all the results presented at the Congress is an unsurmountable task. With your permission I shall content myself with outlining my impressions of a general character.

This year's Congress has been enriched by a new factor. The choice of the anatomy and pathology of the neuroendocrine system for the main subject was necessary and timely. Necessary because in this field the ten years' work of our investigations may be considered one of the successful achievements of Hungarian biological research, duly appreciated also abroad. And timely because the theories setting the hypothalamus into the centre of the endocrine system have given such unprecedented momentum to research that our clear sight has to some extent been clouded and a review of the facts — besides its incentive character — was to a certain degree expected to clarify the different points of view.

In my opinion, however, there was some discrepancy between the all-embracing character of the main subject and the number of reports. This year I had occasion to attend the Congress of German pathologists and could convince myself how fitting it was to have set 4 or 5 reports of 40 to 50 minutes each.

From among the relators the harder task fell to Professor SZENTÁGOTHAI. Only those who are familiar with the complex and extremely complicated character of the connections between pituitary and hypothalamus with the often diametrically-opposed results and interpretations which, on the one hand, follow from the very delicate methods applied, moreover from the inherent anatomical and physiological properties of the hypothalamus, and

on the other from the extremely rigid points of view of some of the authors — only those persons can properly appreciate the report of Professor SZENTÁGOTHAI. Compelled to toss between the Scylla and Charybdis of the data of the literature, Professor SZENTÁGOTHAI has found the way out and his report presents a true picture of the uncertainty, which to this fate still prevails in this field and of the situation, which after the appearance of new results varies — as might be said with some exaggeration — from day to day.

From among the lectures connected directly with his report, 4 papers of the members of his school, furthermore the researches of BACHRACH andd KORDON in Paris represent the recent results. The authors from Pécs have acquired an amazing assurance in this extraordinarily complex field and beside the time-tested old staff the appearance of gifted young workers may also be registered with pleasure.

The report of Professor Soós entitled "Adrenogenital syndrome" as well as that of Professor SZENTÁGOTHAI, exceeded by far the subject limited by the title. Before discussing the pathological relations, Professor Soós has very justly dealt with the timely problems of the physiology and biochemistry of the suprarenal cortex and condensed into illustrative tables the main points of the knowledge which, also in this domain, is continually broadening and developing. In this manner the participants of the Congress have obtained a comprehensive picture of the actual situation concerning the physiology and pathology of corticosteroid production. The interesting and substantial report of Professor Soós has been successfully complemented by the observations of J. JUHÁSZ on the pathology of the congenital adrenogenital syndrome.

I cannot fail to discuss the very lively discussions that followed the two reports. These discussions were one of the most outstanding moments of the Congress. The content of the contributions of the great number of members taking part in the discussions has shown a thorough knowledge of the literature, the critical acumen and, at the same time, the moderation of the Hungarian research workers concerned with neuroendocrinology, in other words, their complete altitude for international debates.

Listening to the papers immediately following the two reports, not only has a picture been obtained of the studies carried out in this field, but very essential human pathological observations have also been voiced and followed with keen interest. This great interest clearly proved that human observations are by no means of a lesser importance than experimental research. I should like to emphasize in this respect the importance of the observations of Professors BALÓ, FARKAS and FAZEKAS.

Studying the programme of the Congress and following its course with attention, the shadow beside the light cannot pass undetected. Personally, I considered the fact as most conspicuous and regrettable that although the Hungarian physiological and pathophysiological Institutes are so to say

without exception concerned in neuroendocrinological research — in fact it is the main subject of some of them — nevertheless, with the very estimable exception of the Pathophysiological Institute of Budapest — we regretted the absence of the representatives of these Institutes. At the same time, it has been gratifying to note the appearance and the contributions of several of our eminent clinicians. I believe, everybody agrees with me that the sharp separation of morphological and physiological pathology — whereupon this Congress threw a light — is not to the advantage of the development of Hungarian medical science.

In my opinion, Hungarian morphologists cannot bear the blame for this, as not only has our President stood up for the functional morphological view, but this Congress is a convincing evidence of this view being an incontestable reality. I believe that the setting up as early as possible of a Hungarian Neuroendocrinological Society might be the working plan which would assure the collaboration of all the investigators concerned with this branch of science.

I should like to mention briefly the meetings of the forensic medical and anatomical sections, though I must emphasize that I do not feel qualified for appreciating the lectures delivered there. Our present congress, like the earlier was actually composed of three congresses. The 22 papers given at the Section of Forensic Medicine raise the possibility of organizing in future an independent congress of forensic medicine. The lectures of our colleagues from Bratislava delivered at the meetings of the Section of Forensic Medicine were followed with great interest and have endowed our Congress international character. I am convinced that all of us have been happy to welcome our Czecho-Slovak colleagues and hope that the scientific and friendly relations between our countries will increase still further in the future.

The meeting of the Anatomical Section has unfortunately coincided with our conference dealing with the position of the pathological institutes. Referring to the work of that Section stress must be laid upon the ever increasing and successful unfolding of histochemichal researches, which warrant the further development of morphology in Hungary. Beside the papers by the Szeged authors, those from Debrecen were also noteworthy setting beside the classical morphological methods a fine example of the combined utilization of histochemical, biochemical and biological procedures.

Ladies and Gentlemen,

comparing the standard of our Congress of this year with the western congresses at which I had the opportunity of participating, I can definitely state that, in spite of our backwardness in regard to instruments, and of the great difficulties concerning the technical staff, the balance was not unfavourable for us. I must particularly emphasize the keen interest — the hall was nearly always overcrowded — and the lively spirit shown during the whole course of the Congress, which doubtlessly prove on the one hand that the

attractive power of morphological research in Hungary is not only undiminished but even shows an upward tendency, and on the other that Hungarian morphologists have quickly adapted themselves to the change in biological-medical conception, to the new aspect of pathology and have been able by utilizing up-to-date procedures to call into being, despite the subsisting difficulties, something new and of abiding value.

A kiadásért felel az Akadémiai Kiadó igazgatója — Műszaki szerkesztő: Farkas Sándor

A kézirat nyomdába érkezett: 1960. VI. 29. — Terjedelem: 5,25 (A/5) ív

1960.51646 — Akadémiai Nyomda, Budapest — Felelős vezető: Bernát György

INDEX

Forensic Medicine