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SZEGED, SEPTEMBER 1—4, 1971

ABSTRACTS

AKADÉMIAI KIADÓ, BUDAPEST
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ANDROGENS

1.

Transformation in vitro of (4-^{14} C) dehydroepiandrosterone by normal human skin slices

I. FAREDIN, I. TÓTH and M. JULESZ

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Abdominal skin slices obtained from normal female and male patients were incubated with [4-^{14} C] dehydroepiandrosterone in Krebs—Ringer-phosphate-buffer at 37 °C for 5 hours. Metabolic products of [4-^{14} C] dehydroepiandrosterone were identified by the reverse isotopic dilution technique. It was found that both female and male skins transformed [4-^{14} C] dehydroepiandrosterone into 7α-hydroxydehydroepiandrosterone, 7β-hydroxydehydroepiandrosterone, 7-ketodehydroepiandrosterone, androst-4-ene-3,17-dione, 5α-androstane-3,17-dione, androsterone, androst-5-ene-3β, 17β-diol, testosterone and dehydroepiandrosterone sulphate. We proved through the steroids identified that both normal female and male skin contain 7α-hydroxylase, 7-hydroxysteroid dehydrogenase, Δ^5-3β-hydroxysteroid dehydrogenase, Δ^4-5α-reductase, 3α-hydroxysteroid dehydrogenase, 17β-hydroxysteroid dehydrogenase and Δ^5-3β-hydroxysteroid sulphokinase activity.

2.

Correlation between dehydroepiandrosterone sulphate, androsterone sulphate level in human plasma and their content in axillary sweat

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Amounts of dehydroepiandrosterone sulphate (DHA-S), androsterone sulphate (A-S) and their ratio were determined both in plasma and axillary sweat, from the men and the women. It was found that a certain relation was between DHA-S, A-S content in axillary sweat, and their concentration in plasma. Namely, it was showed that the increase of DHA-S and A-S concentration in plasma under ACTH treatment was accompanied by their increase in sweat. But, this latter increase varied individually, indicating that several other factors — without steroid level in plasma — influence the excretion of 17-ketosteroid sulphates in human axillary sweat.

3.

Dehydroepiandrosterone and androstenedione in early human placental tissue

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A reliable and practical method was worked out for the determination of dehydroepiandrosterone sulphate, dehydroepiandrosterone and androstenedione, by the direct isotope dilution technique, in early human placental tissue. The method was controlled by recovery experiments and specific activity measurements. Dehydroepiandrosterone sulphate, if present, was below the range of sensitivity of the Zimmermann colour reaction. Data concerning the concentration of dehydroepiandrosterone and androstenedione in 60 different placental tissue samples obtained from healthy 11—12-week-pregnant women are presented. An attempt was made to correlate the concentration of androstenedione to that of dehydroepiandrosterone. It is suggested that the regression line, thus obtained, would be a new approach for the presentation of the 3β-hydroxysteroid dehydrogenase activity in the placenta at that stage of gestation.

4.

Comparative study of the physiological effects of methylandrostenediol (Madiol) and some neurotropic substance

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The effect of methylandrostenediol (madiol), pilocarpine and atropine upon the growth of albino rats was studied. At the same time the mobilization of fatty acids, the energetic metabolism and the modifications of ionic concentration of the blood were investigated. The results showed that madiol and the other investigated substances exert different influences upon the biochemical and physiological mechanisms accounting for the growth of the organism.

5.

The response of the sebaceous glands to androgenic steroids

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Androgens stimulate the sebaceous glands, but their action is influenced by the pituitary. The response in rats has been measured in two ways: from changes in the hair fat levels and from the incidence of mitoses in the sebaceous glands. Testosterone, 5-alpha-dihydrotestosterone and, to a lesser extent androstenedione all increase both sebum production and the incidence of sebaceous mitoses in castrated rats. After hypophysectomy, however, testosterone and testosterone-propionate failed to produce significant increases in sebum production, though they has some effect on sebaceous mitosis. On the other hand, 5-alpha-dihydrotestosterone and androstenedione significantly increased both sebum production and mitosis. The response of hypophysectomized-castrated rats to testosterone has been restored with preparations of growth hormone, prolactin and thyrotrophic hormone. It is concluded that androgens have at least two points of action on the sebaceous glands, on mitosis and on intracellular synthesis, and that pituitary hormones influence steroid transformation and hence the responses of the sebaceous glands to different steroids.

6.

Study on metabolism of androgens and glucocorticoids in disorders associated with abnormal weight loss

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and First Department of Medicine, Semmelweis University Medical School,
Budapest, Hungary

The androgen and glucocorticoid metabolism have been studied in disorders characterized by an abnormal loss of weight as a common symptom. The excretory rate of individual 17-oxosteroids and 17-OH-corticosteroids has been determined under basal conditions. The pituitary-adrenal function has been tested by the determination of steroids following the administration of metopirone or exogenous corticotrophin. In cases of abnormal weight reduction a decrease in the excretory rate of androgen and glucocorticoid metabolites has been found before, as well as after, the stimulation of pituitary or adrenal function.

7.

Metabolism of various androgens on a cellular level in target tissues of male rats and in prostatic tissue of patients with benign prostatic hypertrophy (BPH)

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Immature normal or castrated male rats were intravenously injected with either 120 μCi ^{3}H-testosterone, ^{3}H-5α-dihydrotestosterone or ^{3}H-androsta-3,17-dione. 30 min later the animals were sacrificed and after homogenization of the respective organs total radioactivity was measured in all samples. Isolation and identification of the various metabolites in the ventral prostate lobes, the seminal vesicles and the blood were performed as previously published. In experiments with human beings 30 min before prostatectomy 400 μCi ^{3}H-testosterone were intravenously injected. Samples of blood, peripheral muscle, prostate and BPH were taken. Methods used for counting total radioactivity and for isolation and purification of the various compounds were the same as in the animal experiments. From the results the following conclusions could be drawn: 1. The 17-hydroxy pathway is preferred in target tissues of human males and male rats. 2. The interconversion rate depends upon the predominant cellular type of a given tissue. 3. In BPH the amount of 5α-dihydrotestosterone exceeds significantly the values found in normal prostatic tissue of both species. 4. In both species blood levels do not reflect androgen metabolism in target tissues.

8.

The effect of norandrostenolon-phenylpropionate on the sleeping time of rats with hepatic injury

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It has been noted that the activity of the drug metabolising enzymes increases in the liver of normal rats by treatment with certain steroids, especially with spironolactone and norbolethone. This phenomenon, which can be seen also by other agents (e.g. phenobarbitone) is concerned with the induction of microsomal enzymes. The reduction of sleeping time by hexobarbitone is a generally used in vivo indicator of the microsomal enzyme induction. In our recent investigations we have seen that the pathologically long sleeping time of rats with hepatic lesion caused by thioacetamide treatment can be significantly shortened by premedication with nor-androstenolon-phenylpropionat. The same effect was noticed by animals intoxicated with copper. Our results show that the microsomal enzymes can be induced also in cases of liver injury. This view is supported by our clinical experiences in liver diseases.

9.

Determination of testosterone and the individual 17-oxosteroids in human urine by a combined paper, thin-layer and gas-chromatographic method

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A method is presented for the determination of testosterone in urine of female and male subjects. The procedure is suitable for the simultaneous measurement of dehydroepiandrosterone, etiocholanolone, androsterone, 11-OH-etiocholanolone, 11--OH-androsterone and 11-keto-etiocholanolone levels from the same urine sample. After the hydrolysis of steroids and benzene extraction, testosterone, epitestosterone and the 17-oxosteroids were separated by paper chromatography. Testosterone was eluted from the paper and the 17-oxosteroids determined by an in situ Zimmermann-reaction and spectrophotometry. Testosterone was acetylated and the acetate purified by thin-layer chromatography. The zone corresponding to testosterone-acetate was eluted and chromatographed in a Pye-Unicam Series 104 analytical gas-chromatograph for an accurate measurement of the steroid level. Testosterone 4-C 14 tracer for correction of losses, a combined marker-system to check mobility of steroids on paper and chromatoplate and pregnadienolone-acetate as internal standard for gas-chromatography were used for accurate measurements. The results of control experiments, values for normal human subjects and for patients with typical endocrinopathies obtained by the method are presented.

10.

Dehydroepiandrosterone and dehydroepiandrosterone-sulphate dynamics in human subjects under physiological conditions

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and Fourth Medical Department, Postgraduate Medical School, Budapest, Hungary

The secretion rate, production rate, the rates of interconversion and irreversible metabolism of dehydroepiandrosterone and dehydroepiandrosterone-sulphate, and the rates of entry into the urine of various metabolites have been studied according to the "urinary method" of Gurpide et al. following simultaneous injection of dehydroepiandrosterone-4-C14 and dehydroepiandrosterone-7-H3-sulphate tracers as a single dose. The parameters have been compared with those calculated according to the "blood method" proposed by Tait. A comparison has been made, further, between the results of the two-compartment analysis with isotopes and those obtained by studying the urinary and blood levels of steroids the subjects being loaded with

a large amount of dehydroepiandrosterone or dehydroepiandrosterone-sulphate. The levels and cumulative specific activity of the steroids in urine and blood have been determined according to the method of Fehér. The results obtained for normal human individuals in steady-state conditions are presented and discussed.

11.

Dehydroepiandrosterone and dehydroepiandrosterone-sulphate dynamics in patients with obesity

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The secretion rate, production rate, the rates of interconversion and irreversible metabolism of dehydroepiandrosterone and dehydroepiandrosterone-sulphate, and the rates of entry into the urine of various metabolites have been studied in patients with simple obesity under normal-calory diet after simultaneous injection of dehydroepiandrosterone-4-C14 and dehydroepiandrosterone-7-H3-sulphate tracers as a single dose. The parameters determined by measuring the cumulative specific activity of dehydroepiandrosterone and the parent sulphate and the change of radioactivity of the metabolites in urine have been compared with parameters determined by measuring the level and radioactivity of steroids in blood. In other experiments, patients have been given dehydroepiandrosterone or dehydroepiandrosterone-sulphate in large amounts and the levels of steroids in urine and blood have been determined. Results obtained for patients with obesity and changes related to the characteristics of steroid dynamics in normal individuals are discussed.

12.

Dehydroepiandrosterone, androsterone and 17-OH-corticosteroid level in blood of female subjects before and after corticotrophin administration

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Alterations in the level of dehydroepiandrosterone-, androsterone-sulphate and that of unconjugated 17-OH-corticosteroids have been studied before and following administration of corticotrophin to patients with menstrual disorders without any

evidence of other endocrinopathy. The 17-oxosteroids were determined by a combined thin-layer and paper chromatographic method with spectrophotometry for evaluation, and corticosteroid values were measured in plasma by a spectrofluorimetric procedure. Blood samples were obtained before and one, two, three, four and six hours after the stimulation of adrenals. Results revealed a similar increase of the plasma level of corticosteroids and dehydroepiandrosterone-sulphate with the exception of a relative decrease in the three-hours' level of dehydroepiandrosterone-sulphate which was not seen in the case of corticosteroids. However, the decrease observed was in close correlation with a sharp increase in androsterone--sulphate values.

13.

Diurnal variation of dehydroepiandrosterone, androsterone and 17-OH-corticosteroid levels in blood of female subjects

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Although the daily variations of the corticosteroid levels in blood effected by changes in pituitary corticotrophin release are well established, published evidence as regards the diurnal variations of the level of 17-oxosteroid-sulphates is still contradictory in certain respects. In the present study, dehydroepiandrosterone- and androsterone-sulphate have been measured in plasma of female subjects with menstrual disorders without signs of other endocrinopathy. Blood samples were obtained 8 hours in the morning, 12 hours at noon and 8 hours in the evening. The changes observed for the 17-oxosteroid levels were compared with those of unconjugated 17-OH-corticosteroids. The results are presented and discussed in the context of previous findings.

14.

Excretion of total 17-ketosteroids and of 17-ketosteroid fractions in mastopathia fibrocystica and in malignant neoplasm of breast

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Excretion of 17-ketosteroids, including total amount, androsterone, dehydroepiandrosterone and etiocholanolone, was examined in 150 patients forming two groups, 1) mastopathia fibrocystica, 2) breast cancer. The results, compared to the normal

values derived from the literature, are summed up as follows: In mastopathia fibrocystica, total excretion of 17-ketosteroids as well as excretion of dehydroepiandrosterone and of androsterone, are significantly reduced. In breast cancer neither the excretion of total 17-ketosteroids nor that of dehydroepiandrosterone, androsterone or etiocholanolone, are significantly reduced. An increase in the excretion of etiocholanolone was demonstrable in a number of cases of the breast cancer group. Under normal conditions, excretion of this fraction decreases beyond the age of 40 to half its original value. Absence of this finding in 28 out of the 73 breast cancer patients may be connected with the production of the tumour. Total excretion of 17-ketosteroids, including the fractions studied, were significantly reduced after oophorectomy.

15.

Clinical observations in pubertas praecox and pseudopubertas praecox

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Certain clinical aspects of the authors' clinical observations relevant to the subject are summed up in the following: 1) In opposition to published evidence, in true pubertas praecox (girls 5 to 7 years of age throughout) long-term massive-dose therapy with chloromadinone resulted in a tendency to remission of the secondary sex characters and in a suppression of growth intensity to the prepuberal rate. 2) A case of pseudopubertas praecox produced in a six year old boy by a feminizing adrenocortical adenoma weighing a few grams is described. To the authors' knowledge there are scarcely 10 published cases of this kind, the primary process being of malignant character in one half of the material. Thus far, the case under review seems to be of benign nature. The acceleration of skeletal maturation has been of greater intensity and the growth rate of minor degree than under otherwise similar conditions resulting from excessive androgen incretion. 3) A Leydig-cell adenoma causing intensive virilization in a six year old boy within a few months is described. During the two years after semicastration the boy's growth rate descreased to minimal levels. No consecutive hormonal activity of the contralateral testicle ensued which, however, has been repeatedly described in case of ectopic adrenal elements.

16.

Function tests, androgen excretion and free steroids in adrenal venous blood in patients with hirsutism

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In 1966 we reported upon steroid concentrations in adrenal venous blood from women with and without hirsutism. In patients with hirsutism we found remarkably high androgen concentrations in adrenal venous plasma. Similar studies in the last years produced no uniform results. Therefore, in the present study, in addition to adrenocortical function tests and free steroid concentrations in adrenal venous plasma, the excretion of testosterone and androstenedione were also measured in patients with hirsutism. No relationship was found between distribution and/or intensity of hirsutism on one hand, and the measured parameters, on the other. Although none of the patients exhibited clinical symptoms typical of adrenogenital syndrome, a latent adrenocortical insufficiency was evident in a few cases.

17.

Value of combined adrenal stimulation and suppression and of ovarial stimulation tests in the diagnosis of hyperthecosis (Stein—Leventhal syndrome)

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In the diagnosis of ovarian hyperthecosis the combined adrenal stimulation--suppression test (ACTH, dexamethasone) and the ovarian stimulation test (dexamethasone, choriogonadotropine) described by Netter and later by Lloyd were believed of practical value. From theoretical aspects it was found necessary to reevaluate these methods. Sixteen patients with the mean age of 24,2 years were investigated. They were selected on the basis of the following features: hirsutism, menstrual disorders, sterility. The tests were performed according to Lloyd. Urinary 17-corticosteroids and 17-OH-corticosteroids were measured. In all patients perirenal insufflation as well as laparoscopy was performed. In case of abnormal findings, ovarian biopsy and histology were also done. The diagnosis of the Stein—Leventhal syndrome which was based solely on histological evidence, was made in ten patients, one patient had adrenal adenoma. The hirsutism of the remaining 5 patients was believed to be idiopathic. As to the laboratory results the mean values agreed well with the histological diagnosis and were in accordance with the data given by Netter and Lloyd. However the scatter of the individual values was remarkable, thus, the diagnosis of the Stein—Leventhal syndome should never be based on the laboratory tests alone.

18.

Estrogen secretion of the ovaries in the Stein-Leventhal syndrome

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Histochemical study of polycystic ovaries removed from 50 patients with Stein—Leventhal syndrome revealed a prevalence of dystrophic processes in these ovaries. In the theca cells and in the paralutein cells deposits of birefringent lipids were demonstrable. Endometrial histology, as well as the cytology of serial vaginal smears and the excretion rate of estrogens in these patients are connected with hyperplasia of the theca interna and with the distribution and histochemical pattern of lipids, pointing to a fairly sustained estrogen secretion. The etiology of the morphologic changes in these ovaries is discussed.

19.

Treatment of female hirsutism with oral contraceptives

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18 women (age: 17—42 years) with hirsutism of different degree was treated for average 18 months with oral contraceptives (Infecundin, Bisecurin, Orgametril + Mikrofollin). Two of them had high urinary 17-ketosteroid output, one of them had a mild elevation in the steroid excretion. The urinary 17-ketosteroid and ketogenic steroid output of the others were normal. Under treatment with oral contraceptives the high urinary steroid excretion decreased to normal values. The hirsutism was reduced in 10 cases — in 5 cases the regression was complete. In 8 patients the application of contraceptive steroids had no effect on hirsutism. Data are discussed.

20.

The influence of antiandrogens (cyproterone acetate and chlormadinone acetate) on sexual behaviour and fertility in rats

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Cyproterone acetate and chlormadinone acetate — highly effective progestines which are also well known as antiandrogens — produced complete sterility in intact male rats without any impairment of sexual behaviour. Both compounds were even

capable of inducing sexual activity in prepuberally castrated males that had not exhibited any mating behaviour in adulthood before treatment. These findings are at variance with the reports on an inhibition of sexual activity by cyproterone acetate in man. On the other hand, both substances showed distinct antiandrogenic and antigonadotrophic activities. Thus, male hypogonadism associated with maintenance of sexual activity was produced by cyproterone acetate or chlormadinone acetate in rats. Substances of this kind appear to be of interest for further investigations with regard to the development of compounds inhibiting spermatogenesis within the problem of fertility control.

21.

Studies on the adrenocortical function in hirsute women treated with StC 407[R] (6-dehydro-16-methylene cortison) and Cyproterone acetate[R]

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The function of the adrenal cortex was investigated in 5 patients with simple hirsutism and in 2 with Cushing's-syndrome during long-term treatment with StC 407[R] assumed to have a peripheral and/or central effect on the hypothalamo-pituitary--adrenal axis. Plasma cortisol level, its nyctohemeral rhythm, responses to insulin--induced hypoglycaemia, dexamethasone suppression and glucose loading tests, lastly the rebound phenomenon at the end of the treatment were determined. Evidences on the glycocorticoid like action of StC 407 and on its tendency to restitute the normal nyctohemeral rhythm have been obtained; the observed changes in the morning basal values and in the suppressing action of dexamethasone must be judged with caution. Simultaneously the urinary content of 17-ketosteroid- and 17OH corticosteroid fractions as well as plasma DEA- and androsterone sulphate levels have been analyzed. Clinically the patients' hirsutism improved considerably. In the second phase of the trial Cyproterone acetate[R], acting on androgen receptors was administered. The clinical and biochemical effects of the two types of anti-hirsutism treatment could be confronted and their relevancy to adrenocortical function evaluated.

22.

Treatment of masculinovoblastoma with Cyproterone acetate

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The authors report a case of a 65 years old women with extremely rare masculinizing ovary tumour. The tumour of right ovary was removed and the histological examination revealed a typical masculinovoblastoma. One year after the operation severe virilisation and high fever was observed. Clinical examinations showed a lot of metastases in the liver, an increase of sexual steroid hormone excretion. The function of adrenal cortex was normal. After the removal of a large hepatic metastasis, the hormone content of the daily urine became normal. Three months later both the clinical symptoms and the increase of urinary sexual steroid excretion proved a further progression of the disease. At that time the antiandrogenic Cyproteron acetate was given (100 mg/day) for a month and the 24 hours'excretion of sexual steroids were measured at a weeks interval. During the treatment with Cyproteron acetate the total 17-ketosteroids and their fractions were reduced almost to normal level, the virilisation was markedly decreased and the "endocrine" fever disappeared. In our opinion the Cyproteron acetate seems to be a useful preparate in the treatment of masculinovoblastoma with metastases.

23.

Familial hypogonadism

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Three siblings (20—18—14 years old) were examined. All of them had a reduction in the amount of body hair and beard growth (no axillar and public hair at all), an abnormally small phallus and testes of hazel-nut size. Normal heights with long arms and feet and hypo-aplastic prostates were noticed. The epiphyseal closure was delayed in all of them. In the biopsy specimens of the testes germinal aplasia was found in two of the siblings and only epididymal tissue was seen in the third. The androgens in the urine both of adrenal or testicular origin were decreased. Following HCG-loading the androgens decreased further but the estrogenic hormones increased. The maternal chromosomal pattern was normal. A large *Y* chromosome was found in the father of the siblings and this was noticed in all of the children. In addition, in the oldest child XY/XO mosaicism, in the 18 year old XY/XXY mosaicism was found. It was postulated that the short arms of the Y chromosome were abnormal and this fact caused an error of the development of the testes and a diminution of the androgen metabolism too.

ESTROGENS

24.

Mechanisms of estrogen action in female puberty

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There is consistent experimental evidence that precocious and probably also natural puberty are induced in female rats by a hypothalamic action of estrogen. On the other hand, Döcke and Dörner (1965) found that the anterior pituitary is the main site of estrogen action in the "Hohlweg effect", i.e. in the induction of corpus luteum formation in immature female rats. To clear up this apparent discrepancy, and to check if the "Hohlweg effect" takes part in the process of natural puberty, estradiol benzoate and progesterone were implanted at different times into the hypothalamus and the adenohypophysis of prebuperal female rats. The following conclusions were drawn from the results: 1. The induction of pubertas praecox and the "Hohlweg effect" depend on different mechanisms of estrogen action. 2. The "Hohlweg effect" is not equivalent to estrogen-induced pubertas praecox. 3. In natural puberty, estrogen acts first on the hypothalamus, inducing in this way an increased gonadotrophin release that causes growth of ovarian follicles and vaginal opening. The elevated estrogen level in blood, resulting from the increasing secretion of hormone by the maturing ovarian follicles, induces then the first puberal ovulation by mainly acting on the anterior pituitary. The "Hohlweg effect" may thus be essential to the completion of natural puberty in female rats.

25.

Competitive antagonism between placentotrophin (PCTH), actinomycine-D (D) and methotrexate (MTX). In vitro experiments

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The biological effect of placentotropin, a hormone of pituitary origin, identified and separated in the laboratory of the Department of Gynaecology and Obstetrics, Medical University, Pécs, is the stimulation of the trophoblastic HCG synthesis both in vivo and in vitro. The existence of PCTH is the first proof of an endocrine correlation between the ventral lobe of the pituitary and the placenta.

The effect of D., MTX and Endoxan on the PCTH-stimulated HCG biosynthesis was investigated in model experiments using trophoblastic tissue obtained by legal termination of pregnancies. It was shown, that 60 μg of D failed to inhibit the stimulative effect of 4 Trophoblast Units (T.U.) of PCTH. On the other hand, far larger amounts of PCTH (60 T.U.) were required to neutralize the negative (HCG depress-

sing) effect of 3 mg MTX. These observations suggest the existence of a competitive antagonism between PCTH and the antimetabolites (D, MTX). On the basis of these investigations, the effect of PCTH on HCG synthesis might be explained by stimulation of the synthesis of messenger- and ribosomal RNA, tetrahydrofolic acid and DNA in the trophoblastic tissue. Endoxan had no inhibitory effect on HCG synthesis induced by PTCH in these experiments.

26.

Proceedings in the detection of human chorionic gonadotropin and pregnancy-specific protein body of blood stains

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For a period of three month mark of blood of pregnant women were tried on textiles containing washing agents and abortifacients were examined. In weekly intervals the marks of blood were eluted and the eluted substance was tested for the presence of chorionic gonadotropin with the hemagglutination inhibition test. Another samples were tested for the presence of pregnancy-specific protein body by starch gel electrophoresis. The result: the marks of blood on textiles containing abortifacients and washing agents showed a positive pregnancy test between two and eight weeks, dependent on the agent. Separation of blood stains by starch gel electrophoresis allowed to reveal a protein fraction localized immediately before the transferrins in the β_1 region of the electropherogram. Its identity with transferrin and coeruloplasmin could be ruled out.

27.

A comparative study of estrogenic potential („estrogenicity") of various synthetic compounds

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Induced estrogenic effects must be considered under two aspects: firstly — evaluation of development and peak of induced hormonal effect, secondly — duration of estrogenic activity. A review of current literature shows that comparative research on the estrogenic potential of various synthetic compounds is poorly documented. Moreover, the criteria of evaluation are inaccurate and inconsistent, making a comparison of the published results difficult. Among the large group of amenorrheic and postmenopausal estrogen-deficient women, small homogenous tests-groups of patients with similar pretreatment cytohormonal pattern of vaginal smear were

selected and treated by a uniform technique of 10-day medication. Three numerical cytologic indices of estrogen activity were employed. The induced therapeutic estrogenic effects were measured by the shift of the Maturation Index (MI) to the right and increase of the Superficial Cell Index (SCI) and of the so-called Maturation Value (MV). The relative potency of various steroidal and non-steroidal compounds are tabulated, in relation to the estrogen effect induced by 0,1 mg of Mestranol and 1.0 mg of Stilboestrol, respectively.

28.

Cervical secretion and activity of sexual steroids

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1280 samples of cervical mucus aspirated from the cervical canal by means of a special instrument were weighed. The quantities of cervical discharge thus obtained were found to rise parallel with the predominance of estrogen-activity. In the normal menstrual cycle the amount reached its peak value (162 ± 17□) at midcycle, it being significantly higher than those of the postmenstrual (48 ± 6□) and of the premenstrual (18 ± 3□) periods. In the Infecundin- and Bisecurin-groups the quantities of secretions did not vary significantly in the course of the cycle. At midcycle the amount in the Bisecurin-group (33 ± 6□) was significantly lower than that in the Infecundin-group (70 ± 13□). The amount in the estrogen-group (125 ± 18□) was about twice higher than that in the progestogen-group (64 ± 12□). According to the above results the determination of the quantities of cervical secretions taken from the cervical canal may reveal the activity of the steroids in the female genital tract.

□ = milligrams of fresh cervical mucus.

29.

Determination of mucoid hexosamine, sialic acid and hexose in the menstrual discharge, as a method for evaluating the effect of sexual steroids on endometrium

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The preliminary results of measurements of mucoid-bound hexosamine, sialic acid and hexose in the menstrual discharge are reported. 78 healthy women with ovulatory, anovulatory cycles, all taking progestogen, estrogen or their combination

forms (Infecundin, Bisecurin) for contraceptive purposes were investigated. On the evidence of 255 measurements, the levels of hexosamine, sialic acid and hexose were found to rise parallel with the prevalence of progestagen effect, response of hexosamine being, however the most specific. The amount of hexosamine in the menstrual mucus in the ovulatory group (126 ± 8□) was significantly higher than that in the anovulatory one (14 ± 5□), but on its part, significantly lower than that in the progestogen-treated group (233 ± 25□), which was also many times higher than that in the estrogen-group (11□). The amount in the Infecundin-group (35 ± 3□) was significantly lower than that in the Bisecurin-group (288 ± 22□). The origin of menstrual mucus from the endometrial glands having been pointed out by the authors in an earlier communication, the mucoid-bound hexosamine, sialic acid and hexose demonstrable in the "endometrial mucus" on the evidence of the present study may be regarded as characteristic of a progestagen effect. In conclusion, measurement of hexosamine, sialic acid or hexose in the menstrual mucus is proposed as a practical test for the evaluation of endometrial function in case of impossibility of diagnostic abrasion (metrorrhagia, presence of intrauterine contraceptive device etc.).

□ = micrograms of hexosamine per 100 milligrams of fresh mucous menstrual discharge

30.

The estrogen content of postmenopausal ovaries

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The steroid hormone content of pre- and postmenopausal ovaries were examined in a comparative study by means of gas-chromatography. The postmenopausal ovaries were found to contain estrogens in detectable amounts still 30 years after the onset of menopause. The estrogen content showed a gradual decrease in connection with the postmenopausal age as compared to the pre-menopausal values, but there was no absolutely inactive ovary in the material investigated. The results give food for speculations on the, presumably significant, part of postmenopausal ovarian estrogens in the maintenance of hormonal homeostasis in this period of life.

31.

Endocrinologic and cytogenetic aspects of dysgenetic gonadal tumors

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The occurrence of dysgenetic gonadal tumors was studied in 80 patients with primary amenorrhea and gonadal malformations. 15 tumors were discovered by exploratory laparotomy. Of 26 cases of Turner's syndrome only 2 cases of gonadal tumors were found — one gonadoblastoma (gonocytoma III) and one interstitioma. Of 42 cases of isolated gonadal dysgenesis (pure or mixed form without somatic malformation) — 13 tumors were found — gonocytomas I, II or III (dysgerminoma and gonadoblastoma) in 12 cases and — Brenner's tumor in one. Among the 12 cases with ovarian dysplasia — no gonadal tumor was detected. Dysgenetic tumors were found in association with 1) abnormal somato-sexual development in patients brought up as women, with primary amenorrhea and some signs of masculinization; 2) negative sex chromatin pattern and the presence of the Y chromosome in the karyotype, contrasting with feminine genitals. The presence of sex chromosome Y seems to play a particular role in tumorigenesis. Generally, no tumor was discovered among the patients with 45, X 45, X/46, XX or 46, XX karyotype, and with complete sexual immaturity. The author concludes that persistent germ cells from the embryonic stage, within malformed testicular elements in subjects with hormonal imbalance, namely a persistence of high gonadotrophin levels, play an important pathogenetic role.

32.

Divergent effects of hormone therapy in amenorrheic patients with different constitution

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Patients with amenorrhea and atrophy of endometrium received estrogens for 21 days and subsequently estrogen-gestagen injections for three days. Therapy was continued for three months. During therapy, vaginal cytology reflecting maximum estrogenic effect and the histological finding of curettage material, after withdrawal of steroids, the appearance, duration and degree of bleeding were studied. According to the observations, significant changes could be seen in the above parameters caused by hormone treatment in patients with constitutional differences.

33.

A study of medical treatment of benign prostatic hypertrophy with synthetic progestogens

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20 patients in stage I. of benign prostatic hyperplasia were given synthetic progestogens (Hormofort, Orgametril) in three courses, each of 8 weeks' duration. The clinical parameters (subjective symptoms, palpation finding, amount of residual urine, uroflow, urethrocystography for the measurement of the prostate to evaluate any changes in size) were found to improve significantly in the course of treatment as regards the urinary symptoms and bladder function. Parallel with the clinical response, a decrease in estradiol + estriol + estrone and a slight drop in 17-KS were demonstrable. No clinical and laboratory changes under placebo treatment (10 patients) were noted. No gynecomastia and no decrease in libido or potency were observed. The favorable response to progestogen-treatment in benign prostatic hyperplasia is attributed to the marked anti-estrogenic, anabolic and a slight androgenic actions of these compounds.

ALDOSTERONE

34.

The effect of potassium ions in vitro upon steroid biosynthesis by the adrenals of sodium depleted, repleted and loaded rats

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Quartered adrenals of rats kept on a sodium-deficient, normal or high sodium diet for 7 to 14 days were incubated for 4 hours in a modified Krebs—Ringer-bicarbonate-glucose solution. The potassium level of the medium was 4,7 and 8.3 mEq/1, resp. The elevation of potassium level stimulated both aldosterone and corticosterone production rate by adrenals of sodium-repleted animals. Sodium loading in vivo abolished the stimulation of aldosterone by potassium ions in vitro. Potassium ions failed to increase corticosterone production by adrenals of sodium-depleted rats. No difference was found between the adrenal response in vitro of male and female animals. The observed alterations in the adrenal responsiveness may be explained by the following hypothesis. Potassium ions augment corticosterone synthesis in the glomerulosa cells only. A part of corticosterone is converted to aldosterone while another part of it diffuses into the incubation medium. Hence, both hormones display an increased production rate. The conversion of corticosterone to aldosterone is inhibited by previous sodium loading. In such a case potassium ions fail to increase aldosterone production rate but elicit an increased release of corticosterone into the medium. Sodium depletion is followed by an accelerated conversion of corticosterone to aldosterone. Potassium increases corticosterone synthesis, which in turn may by further converted to aldosterone, resulting in increased aldosterone and maintained corticosterone release into the medium.

35.

Effect of growth hormone on aldosterone production in hypophysectomized sodium-deficient rats

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Treatment of chronic hypophysectomized, sodium deficient rats with somatotrophin in combination with ACTH restored the aldosterone hypersecretory response of the adrenals to sodium deprivation. Somatotrophin being without any direct effect on aldosterone production of the adrenal, it was assumed that growth hormone might affect aldosterone secretion by an influence on the kidney, probably on renin secretion. Body weight is reduced by sodium deficient diet as well as after hypophysectomy. ACTH-treatment did not alter the decrease in body weight, administration

of growth hormone, however, caused a distinct increase. In these experiments no significant change on blood pressure was observed. The sodium deficiency enhanced the plasma renin activity of both unaffected and hypophysectomized animals. Treatment with STH, ACTH, separately as well as in combination did not change plasma renin activity. The rate of aldosterone production by adrenals taken from 54 hours hypophysectomized rats that had been treated with ACTH, and had been subjected to dietary sodium restriction for 2 weeks was depressed 6 h after nephrectomy. In these animals, the administration of growth hormone restored in the presence of ACTH the aldosterone secretory response to sodium deficiency. These results are interpreted in assuming that the action of growth hormone in maintaining the aldosterone secretory response to sodium restriction is not mediated by the kidneys.

36.

Studies of adrenal sensitivity to the direct effect of angiotensin

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It is proved that the renin-angiotensin system plays an important role in the regulation of aldosterone secretion. However, an increase in aldosterone production in response to the in vitro direct effects on adrenals was found by us only in animals being under changed physiological and pathological conditions. Such effects include the state of hyperaldosteronism in ground squirrels with sodium deficiency in the food, aortic constriction in rats weighing more than 180 gm, the inferior vena cava constriction above the liver in dogs with ascites development. An increased renin production by kidneys was found in these experiments. The direct effect of angiotensin on adrenals has been found as well without any hyperaldosteronism in young rats (weighing less than 180 gm) with aortic constriction. This fact arouse the question about the role of the growth hormone in the origin of increased adrenal sensitivity to angiotensin. Moreover, the aldosterone-producing tissue reaction to angiotensin appeared in adrenals of intact dogs with increase in potassium concentration of 1.4 mEq/l in incubation medium. Thus, the aldosterone-producing effect of angiotensin is conditioned by the presence of some potentiating factors such as an increase in the renin release, the effect of hypophyseal hormones, a change of sodium/potassium ratio in the medium and possibly other factors increasing the sensitivity of adrenals to the effect of regulatory factors.

37.

Renin secretion in Addison's disease

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The changes in plasma renin activity were examined in different conditions connected with hypocorticalism including adaequate substitution, poor substitution and Addisonian crises. The measurements of plasma renin activity were performed at bed rest, after orthostasis and after sodium depletion as also in response to an acute sodium load. The plasma renin activity showed a slight elevation in the stage of compensation. In this state the stimulation by orthostasis or by sodium depletion caused a more considerable elevation in the plasma renin activity than in normal patients. High sodium intake caused a less marked supression in plasma renin activity than that found in normal subjects. The studies revealed a considerable elevation of plasma renin activity in the under-substituted periods of the disease and its extreme rise in response to the stimulation test. The Addisonian crises were accompanied by excessively high plasma renin levels.

38.

Simultaneous measurement of aldosterone excretion and secretion rate using doubly labelled (3H and 14C)-D-aldosterone

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A relatively simple method has been elaborated and used in serial clinical examinations for the simultaneous measurement of aldosterone excretion and secretion rate. The method was the following: from urine collected for 48 hours following injection of approximately 3—4 μC of ^{3}H-d-aldosterone the total amount of free aldosterone plus that liberated from the acid-labile fraction was determined. For the correction of the amount lost ^{14}C-d-aldosterone was used. The most important steps of aldosterone isolation were: Following isolation in three different paper-chromatographic systems, acetylation with acetic acid anhydride was applied in order to enhance the specificity of the method. The obtained aldosterone diacetate, which can in this form readily be separated from the other steroids appearing mostly as mono-acetates, was then purified in two further paper-chromatographic systems, until the ^{3}H/^{14}C ratio became constant. Aldosterone excretion, i.e. its absolute amount in μg was established making use of the micro-Chen method. The loss occurring during measurement was calculated by correction of the ^{14}C-labelled aldosterone.

On the basis of the usual formula, aldosterone secretion rate was calculated after having established the specific activity of aldosterone. The above method is simple and expedient because "cold" acetic acid anhydride is used for acetylation and aldosterone excretion and secretion rate are established at the same time.

39.

Inhibition of mineralocorticoid secretion by aminoglutethimide and its clinical usefulness

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Aminoglutethimide (Elipten CIBA) (AG) was shown to be a potent inhibitor of the early steps of corticosteroid biosynthesis. Our present work refers to the effect of AG on adrenal mineralocorticoid secretion and its usefulness in the treatment of clinical conditions associated with mineralocorticoid excess. In control subjects AG (1000 mg/day) produced an evident decrease in aldosterone secretion rate (ASR), from 142 ± 10 to 31 ± 8 µg/day ($p < 0{,}01$) which was associated with an increase in plasma renin activity (PRA) from 9 ± 1 to 21 ± 5 recumbent and from 22 ± 4 to 43 ± 7 ng/L/min upright. DOC and 18-hydroxy-DOC secretion rates decreased only if AG was given simultaneously with Dexamethasone (2 mg/day) to suppress the compensatory increase in ACTH. AG inhibited ASR not only in controls but also in the patients with hyperaldosteronism. In 4 patients with primary hyperaldosteronism the decrease in ASR, fall of the blood pressure and increase in the urinary Na/K were not accompanied by an increase in suppressed PRA. Thirty two out of 37 edematous patients with secondary hyperaldosteronism responded to the AG administration with a significant sodium diuresis secondary to a decreased tubular reabsorption of sodium. During AG administration their aldosterone excretion fell from 19 ± 2 to 6 ± 1 µg/day ($p < 0{,}001$) and PRA rose from 28 ± 3 to 61 ± 7 ng/L/min. In 2 of 5 patients resistant to combined treatment with AG and Lasix, sodium diuresis could be achieved by additional administration of Triamcinolone. In patients with uncomplicated essential hypertension AG did not influence the high blood pressure in spite of a decrease in urinary aldosterone and an increase of Na/K ratio. On the other hand, in patients with renovascular hypertension and increased aldosterone excretion administration of AG alone, or in combination with Dexamethasone in 2 other patients with mineralocorticoid-dependent hypertension led to a distinct fall of blood pressure. AG may be an advantageous contribution to the treatment of mineralocorticoid excess.

40.

Anorexia and vomiting leading to severe aldosteronism in a psychopathic patient with complete recovery

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A 12-year-old girl with a psychopathic personality developed anorexia nervosa. From the age of 16, she experienced recurrent periods of vomiting without manifest electrolyte disturbances. At the age of 20, she was in a state of cachexia and developed intractable vomiting with severe hypokalemic, hypochloremic alkalosis and secondary aldosteronism. Medical treatment combined with psychotherapy resulted in permanent recovery. Body weight increased from 25 kg to 49 kg. All biochemical alterations disappeared. All this was associated with conspicuous changes in personality. The results and problems of this special type of aldosteronism developing on the basis of psychic disorders are discussed in the light of the literature.

ACTH
ADRENOCORTICAL SYSTEM

41.

Isolated rat adrenal cells as a sensitive system for the study of drugs affecting corticosteroid synthesis

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It has been demonstrated that isolated rat adrenal cells show a more sensitive response to ACTH in comparison to quartered adrenal glands. Accordingly, the adrenal cell system gives the opportunity to determine minute amounts of ACTH and it might be a good system to study the effect of substances affecting corticosteroid synthesis in vitro. In our department the method was set up according to Swallow and Sayers. This method includes isolation of adrenal cells by trypsine treatment and addition of trypsine inhibitor prior to incubation with ACTH. Since the yield of cells, basal corticosterone production and degree of sensitivity to ACTH appeared to depend on minor variations in the procedure, the intensity of stirring, the incubation medium and the effect of an additional pre-incubation were studied to obtain optimal conditions. In our hands, addition of ACTH to the incubation medium increased the corticosterone production over a range from 3—300 micro Units/ml ACTH activity could be determined in 0.2 ml plasma samples of adrenalectomized rats. Using this system, the effects of two drugs which are known to inhibit corticosteroid synthesis, i.e. metopirone and aminoglutethimide, were studied in vitro. Both drugs caused a dose-dependent inhibition of corticosterone production in cells which were stimulated by ACTH. Significant inhibitions were obtained by 10^{-7} Mol metopirone and 10^{-8} Mol aminoglutethimide. The metopirone-induced inhibition was counteracted by adding equivalent doses of deoxycorticosterone to the incubation medium.

42.

Interference with feedback inhibition of adrenocorticotropin release by protein binding of corticosterone

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It had been shown previously that twenty-four hours after the last injection of prolonged ACTH treatment certain stressor agents as histamine and formalin failed to cause elevation of the plasma corticosterone concentration in rats. It had been assumed by the authors that the inhibition of stress reaction was due — at least partly — to the feedback action of the high corticosterone concentration produced by the last ACTH injection. To test this hypothesis to rats treated with

ACTH for fourteen days they administered plasma with high corticosterone-binding globulin content (CBG), simultaneously with the last two ACTH injections. Twenty-four hours later formalin which elicited no rise of plasma corticosterone level of the ACTH-treated rats caused significant elevation of plasma corticosterone concentration in the animals treated with ACTH plus CBG. On the other hand, stress reaction after histamine injection was inhibited in both ACTH-treated groups regardless of the administration of CBG. It is concluded that the inhibition of stress reaction after prolonged ACTH treatment is due to the feedback effect of high corticosterone concentration and the feedback action of corticosterone is impaired by the corticosterone being bound to CBG. The reasons why histamine failed to cause elevation of plasma corticosterone level in rats treated with ACTH plus CBG are discussed.

43.

Effect of ACTH on ovarian estrogen and progesterone secretion in dogs pretreated with HCG

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In earlier work it had been shown that in dogs in metoestrus or anoestrus ACTH increased ovarian blood flow but left estrogen secretion unaffected. It remained to establish whether ACTH intensifies estrogen secretion in animals pretreated with HCG. To this end, dogs were given daily dose of 100 IU/kg b. wt. of HCG for 5 days. On the sixth day, the ovarian vein was cannulated under chloralose-urethane anaestesia, and estrogen and progesterone in the outflowing blood were determined (ng/min). It was found that during a 10 minute intravenous infusion of 0,5 μg/kg/min of Synacthen (β 1—24 ACTH), estrogen secretion was significantly increased but returned to starting value one hour after termination of the infusion. The one hour's Synacthen infusion increased the ovarian blood flow and estrogen secretion, and kept it at this level. Blood flow took 60 minutes and estrogen secretion 30 minutes to return to starting value after termination of the infusion. ACTH intensified progesterone secretion during the one-hour infusion but this effect passed off before the end of infusion. Unlike ACTH, HCG increased progesterone secretion instantaneously, and both blood flow and estrogen secretion one hour later. When preceded by cycloheximide ACTH increased ovarian blood flow as well as estrogen secretion but HCG after cycloheximide had no effect.

44.

Interaction of ACTH, GH and Prolactin-splanchnomegalic effects

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Abstract not received.

45.

The role of growth hormone in morphological and secretory dimorphism of the adrenal glands in the rat

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Abstract not received.

46.

Pituitary-adrenal function of grouped and isolated rats

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Grouping of 10 rats was followed by a pronounced stimulation of the pituitary-adrenal system. Within the first week, the corticosteroid concentration in blood stabilized at a level twice above the average winter hormone level in the blood of the isolated rats. The subsequent corticosterone concentrations were essentially independent of the time of observation (up to 25 weeks). Clear distinctions were noticed in the responses of the pituitary-adrenal system of the isolated and grouped animals to various influences, particularly in respect of the seasonal variations of the corticosterone concentration in blood: in isolated rats the corticosteroid levels were considerably higher in spring than in winter whereas in grouped rats the opposite was true. A pronounced depression of the reserve capacity of the adrenal cortex of grouped animals was observed in summer. The response of the pituitary-adrenal system of grouped rats to ACTH and formalin injection was appreciably weaker then that of isolated animals.

47.

Secretion of steroids and its connection with other humoral changes in the trained organism

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In previous experiments the changes of plasma steroid levels and the interacting factors were investigated in rats trained by regular swimming, and in athletes. Other humoral effects, particularly the resistance against biogenic amines, were studied as well. In this mechanism a factor was found which was transferable by the serum, its effect being demonstrable in the recipient animal too. In the present investigation the resting plasma steroid level was found to be higher in the 3rd week of regular swimming while in the 6th week it was either, at, or lower than, the control levels. 4 weeks after a 12 week swimming program the values of the test animals were lower than those of the controls. While histamine-resistance was demonstrable as early as by the 9th day of swimming, decline in serotonin-sensitivity did not become significant before the 6th week. This was the period when the serum factor, which was produced in response to the training stimulus, became effective, too. The serum factor affected neither the influence of swimming on plasma steroid concentration, nor the in vitro synthesis of steroids. These humoral changes may be interpreted to some extent by changes occurring in glucocorticoid secretion, however a direct connexion between steroids and the serum factor could not be demonstrated as yet.

48.

Determination of corticosterone in biological material by means of gas-chromatography

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Abstract not received.

49.

Differential diagnosis of adrenocortical insufficiency by an intravenous one-hour ACTH test

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In a study comprizing 86 patients with adrenal hypofunction (101 tests) an intravenous one-hour ACTH test has proved to be effective in the differential diagnosis of adrenocortical insufficiency. From the fasting patient venous blood was withdrawn between 8.30 and 9.30 a.m. and through the same needle 25 IU of a natural or synthetic ACTH preparation were slowly injected. 60 minutes later a second blood sample was collected. Unconjugated 11-hydroxycorticosteroids were determined in the plasma using a fluorometric technique described by Stahl and Doerner. In 50 control persons the plasma corticosteroid level increased during one hour following ACTH application from 9.8 ± 2.9 to 25.5 ± 5.1 µg/100 ml. In severe adrenocortical hypofunction of various origins the basal plasma concentration of 11-hydroxycorticosteroids was found below the normal values. Contrary to the response in secondary adrenal hypofunction, no significant rise following ACTH injection was found in 29 tests in patients with primary adrenocortical insufficiency (2.7 ± 1.5 µg/100 ml before, 2.9 ± 1.6 µg/100 ml after ACTH). In untreated panhypopituitarism (27 tests) the plasma corticosteroids increased from 3.6 ± 1.7 to 13.0 ± 4.3 µg/100 ml. Patients with pituitary diseases and only questionably impaired adrenal function showed mean values of 7.3 ± 2.3 µg/100 ml before, and of 18.0 ± 5.8 µg/100 ml following ACTH (21 tests). A good response was obtained in functional adrenocortical insufficiency without any organic lesion of endocrine glands. In this group (15 tests) the corticosteroids increased from 5.7 ± 1.7 to 23.6 ± 8.0 µg/100 ml. Variable degrees of suppression of the corticosteroid levels and variable responses to ACTH were observed in some prednisone-treated patients. The intravenous one-hour test with fluorometric determination of plasma corticosteroids seems to be the most simple and reliable test for adrenocortical reserve, being fully adequate to requirements of clinical, including outpatient, practice. In spite of the simplicity of the procedure, adaequate differentiation between primary and secondary adrenal hypofunction is possible in nearly all cases.

50.

Importance of plasma cortisol level and cortisol secretion determination in various forms of Cushing's disease

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Three different forms of Cushing's disease due to pituitary-adrenocortical hyperfunction have been separated, on the basis of clinical observation of 120 cases. In the first group the "formes frustes" of the disease in the second, its forms of major severity have been included. The third group comprizes the "oligosymptomatic" type marked by hypertension due to adrenocortical hyperfunction. Fluorometric measurement of plasma "cortisol" level was found to be a test providing rapid information in the above groups. Cortisol level was, however, found to be in the normal range in certain oligosymptomatic cases. A far more elaborate specific procedure for the diagnosis of Cushing's disease is the study of cortisol secretion making use of the cortisol secretion rate technique. As according to this method changes in secretion occurring in the course of 24 hours are observed, it is not suitable for rapid testing. Nevertheless, it is of great value in diagnosing primarily the oligosymptomatic form of Cushing's disease, in which increased cortisol secretion could be observed upon loading, despite the normal plasma cortisol level. Determination of both plasma cortisol level and cortisol secretion is a valuable diagnostic means in various forms of Cushing's disease. However, owing to frequent discrepancy between clinical symptoms and laboratory data, a simultaneous assay of free, biologically active, not protein-bound cortisol seems to be necessary. Differences in sensitivity between the various cortisol receptors should be taken into consideration even in this case.

51.

Clinical course and steroid excretion in adrenal carcinoma

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4 cases of clinically diagnosed adrenal carcinoma are presented. In the entire series comprizing one male and three females the clinical finding was characteristic of a mixed type ot hypercortisolism and of an enhanced androgen production, as reflected by excessive acne in the male patient. Terminal tumour cachexia was absent in all of the cases. Surgical intervention could be performed in 3 cases, yielding tumors up to 500 g in weight, which in 1 case encircled the kidney with the result of ureterostenosis and hydronephrosis. Treatment with o, p'-DDD could be imposed

in 2 cases only, since one of the patients acquired skin allergy and another died very soon. Renal excretion of dehydroepiandrosterone (DHEA) served as one of the parameters of treatment efficiency. In a 24 year old female it reflected the patient's state in connection with explorative and curative application of ACTH, furthermore with dexamethasone, o, p'-DDD, 3 types of cytostatics, and with surgery; and here the fluctuations of tetrahydrocortexolone excretion were still more impressive. Corresponding, but more marked, findings in respect of DHEA were obtained in the 24 year old male, where excretion, even under basal conditions, was as high as 164 mg/24 h. Cytostatics, particularly cyclophosphamide, exhibited stronger actions than did o, p'-DDD.

52.

Long-term treatment of Cushing's syndrome with aminoglutethimide (Elipten^{R}- CIBA)

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Aminoglutethimide (Elipten^{R} CIBA) has been shown to be a potent inhibitor of adrenal steroidogenesis. The effects of a three years, treatment by Aminoglutethimide have been studied in three patients suffering from ACTH-dependent hypercortisolism of Cushing's type. Aminoglutethimide was used in two patients where the recurrent Cushing's syndrome developed following subtotal adrenalectomy, the third patient did not undergo surgery. In two patients the treatment was started with 1000 mg of Aminoglutethimide daily but later the dose was decreased to 750 mg. In the third patient the dose of 750 mg was used from the beginning. In all three patients a sustained suppression of adrenocortical function was achieved and resulted in good clinical and laboratory remission, only the hirsutism and the osteoporosis were not affected. The urinary 17-hydroxycorticoids and to a lesser extent even the urinary 17-ketosteroids decreased to normal or subnormal levels. The remission lasted throughout the administration of Aminoglutethimide. After the treatment was discontinued a gradual return of clinical and laboratory signs of hypercortisolism was observed. The cortical stimulation by Synacthen produced an intense response in urinary as well as in plasma 17-hydroxycorticoids soon after Aminoglutethimide had been withdrawn while the basal values were still normal. The only exception was observed in one patient where after three years of treatment adrenocortical insufficiency developed and has been persisting for 26 months after withdrawal of Aminoglutethimide. No side effects of Aminoglutethimide were noted and only a slight decrease of radioiodine uptake by the thyroid was found. There were no alterations in blood count, liver function tests or cholesterol and total lipid levels. Aminoglutethimide represents a valuable contribution to our therapeutical possibilities even in ACTH-dependent hypercortisolism, particularly in mild forms of the disease or in relapses following subtotal adrenalectomy.

53.

ACTH-adrenocortical function in primary hypothyroidism

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It is well known that in patients with primary hypothyroidism, the excretion of adrenocortical hormone metabolites is reduced; plasma hydrocortisone level and its change induced by different stresses are normal. The urinary excretion of total-17-ketosteroids, total-17α-hydroxycorticosteroids, pregnanetriol and their changes were measured during the administration of metyrapone (Metopiron, CIBA) and synthetic ACTH preparation (Synacthen Depot, CIBA) in nine untreated, primary hypothyroid patients. The plasma cortisol level was also determined before and after the administration of ACTH (Synacthen, CIBA) and synthetic Lysine-vasopressin (Sandoz). A reduced amount of steroid metabolites was found in the urine of primary hypothyroid patients. The hormone excretion was slightly increased during the metyrapone administration. The alteration of steroid excretion was more significant after the treatment with ACTH, but the increase did not reach the average of the controls. Plasma cortisol level was normal. In one group no significant change of cortisol level was observed after vasopressin administration, in another the concentration was increased following ADH treatment. The elevation of cortisol level after ACTH administration, was similar to that of the controls. According to our examination it is suggested that a reduced ACTH reserve may be present in patients suffering from primary hypothyroidism. But it is not excluded the possibility, that the decreased steroid excretion is due to damage of renal function in hypothyroidism.

54.

Effects of Synacthen-Depot on plasma cortisol level and urinary cortisol excretion in patients with hyperthyroidism and in healthy subjects

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Changes in plasma cortisol levels and urinary cortisol excretion were investigated in 11 healthy persons and in 10 patients with hyperthyroidism, after administration of Synacthen-Depot (CIBA). Blood was taken at 8 a.m., 4 p.m. and 12 p.m. in the course of the four day period. Urine was collected daily. 1 mg of Depot-Synacthen was given at 8 a.m. and 8 p.m. on the second day. Plasma and urine cortisol was determined according to Mattingly and Gantt, Hamwi resp. It was found that: 1. ACTH-induced increase in plasma cortisol was significantly less ($p < 0{,}001$) ni patients with hyperthyroidism than in the healthy controls; 2. The duration of

action was also significantly shorter ($p < 0.001$); 3. in response to ACTH urinary cortisol excretion increased to a lesser extent in hyperthyroidism than in the normal condition ($p < 0.01$). In the present study the diminished adrenocortical functional reserve capacity was confirmed by clinico-pharmacological methods. The clinical implication is: the response of patients with hyperthyroidism to synthetic ACTH is less intensive and of shorter duration than that of healthy persons.

55.

Pituitary-adrenal function after estrogen-treatment

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The changes in the function of the pituitary-adrenocortical system before and after a short period of estrogen treatment of pre- and postmenopausal women have been examined. The method used was the metopirone test. According to the results of the study, the endocrine changes following the onset of the menopause did not significantly affect the pituitary ACTH-reserve. Administration of estrogens in the periods of pre- and postmenopause lowered the pituitary ACTH-reserve to a similar extent. The data obtained may be of theoretical and practical importance in respect of the potential effects of postmenopausal estrogen treatment.

56.

Evaluation of urinary steroid excretion in obese subjects

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Previous observations relating to adrenal function in obesity are inconsistent in certain respects. In the present study, the changes in the excretory rate of androgen and corticosteroid metabolites mainly of adrenal origin have been examined in subjects with obesity. The results obtained are discussed under the aspects of age, anthropometric variables, features of obesity of the individuals and confronted with previously published findings.

57.

Intermediary cortisol metabolism following administration of dehydroepiandrosterone or dehydroepiandrosterone-sulphate to normal and obese subjects

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In earlier studies it was found that cortisol metabolism may be affected by exogenous androgens. The correlations in metabolism between the two groups of hormones have not been fully established. In the present study, the excretion of tetrahydrocortisol, allotetrahydrocortisol, tetrahydrocortisone and that of 11-deoxy-17-OH-corticosteroids in urine of normal human subjects and patients with simple obesity has been measured before and after the administration of dehydroepiandrosterone or dehydroepiandrosterone-sulphate. Alterations observed in the urinary output of individual metabolites following exogenous dehydroepiandrosterone and dehydroepiandrosterone-sulphate are interpreted in the light of the previous findings.

58.

Study of 20-DHF (11, 17, 20, 21-tetrahydroxy-pregn-4-en-3-one) in patients with active rheumatoid arthritis

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In recent years adrenal cortical function of rheumatoid patients was regularly checked by the authors and a number of data were collected on some parameters. The patients were found to excrete increased amounts of 20-DHF in the active period of rheumatoid arthritis. In the present study, the conditions under which this compound is formed were investigated in vivo and in vitro. The specific activity of 1-2 ^{3}H-20-DHF isolated from the urine of patients having been given previously 1-2 ^{3}H-cortisol iv. was lower than that of the individual cortisol metabolites; it is not suitable for the estimation of daily cortisol secretion. Labelled 20-DHF was prepared from 1-2 ^{3}H-cortisol and given i.v. in tracer quantities to controls and to patients suffering from active rheumatoid arthritis. The ability of the diseased organism to reduce and conjugate 20-DHF at a normal rate was investigated. The formation of 20-DHF from cortisol in peripheral tissue was studied on the ground of the survival of synovial membrane and its formation could be demonstrated in each case.

59.

Corticosteroid fractions of normal myocardium and in myocardial infarction

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The corticosteroid fractions in the myocardium were studied by paper chromatography in myocardial infarction against controls derived from 10 healthy males between 16 and 49 years of age having died within a few minutes as a result of some accident. The intact myocardium was found to contain 5 to 9 identified corticosteroid fractions in variable amounts, the total corticosteroid value being in the range of 4,2 to 10,8 μg per cent (mean: 5,8 μg per cent). The myocardial tissue for the actual tests had been derived from 12 males between 54 and 78 years of age having died of myocardial infarction. The infarct-free areas of the myocardium were found to contain 3 to 8 identified and 2 non-identified (X_1 and X_2) corticosteroid fractions at levels between 0,9 and 5,4 μg per cent, with a mean total corticosteroid value of 2,6 μg per cent, that is, by 55,1 per cent less than in the normal myocardium. The infarct-affected areas of the myocardium contained, in addition to 3 to 8 identified fractions, two different unidentified ones, each in one case. The mean levels of the fractions were between 0,9 and 3,7 μg per cent, the mean total corticosteroid value was 1,7 μg per cent, that is by 70,6 per cent lower than in normal myocardium serving as control. The results of the study seem to warrant the therapeutic use of corticosteroids im myocardial infarction.

60.

On the possibilities of clinical application of steroids in non-endocrine disturbances

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In a number of cases of alopecia totalis comprizing males and females of various age groups, prednisone administered in daily doses of 10 to 20 mg was found to produce an intense growth of hair in all its physiological regions. However, recurrences could be only avoided by maintenance doses which, as a rule had to be increased in winter and could be reduced again in summer. Practically no side-effects were encountered during the entire follow-up period extending to four years. The anabolic properties of the steroid seem to gain prevalence in these cases over its cushingoid effects consequent upon similar schedules of treatment in the majority of cases in other diseases. The action of glucocorticoids on the enzymatic systems involved in hair growth is discussed as a possible therapeutic mechanism. A final body height of 10 to 15 cm less than the calculated value could be obtained in girls with constitutional excessive tallness, by premature induction of puberty with mestranol and chlormadinone, if therapy was started at latest in the age of 10 to 11 years.

61.

Additional evidence concerning the mechanism of thymolytic action of steroid hormones

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The thymolytic potency (T_p) of 55 steroids was established using a previously published method. The T_p values of steroids were of the following order (in the case of biologically active hormones): hydrocortisone, cortisone, testosterone, 11-deoxycorticosterone, progesterone, androstenedione, estradiol-17B, androsterone, estrone, dehydroepiandrosterone. The 5B-steroids revealed a negative thymolytic potency. The most potent thymolytic steroids were found to produce a significant reduction in the RNA-m- and RNA-r-synthesis of the thymus nuclei as well as in the RNA-polymerase activity of isolated thymocyte nuclei and of isolated aggregates of enzyme complex after preincubation of nuclear suspensions with steroids. These steroid activities correlate well with the in-vivo effects. The capacity of the thymus to metabolize the steroid hormones is relatively poor, as confirmed by radiochromatographic studies of hydrocortisone, testosterone and androstenedione metabolites in which the steroids revealed a persistent activity even after their binding at the specific receptor sites in the cytosol or nuclei of the thymus gland.

HYPOTHALAMIC REGULATION

62.

On the connections between praeoptic region and hypophysiotrophic area

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Previous studies suggested that the neurogenic stimulus that triggers ovulation in the rat arises, at least in part, from the praeoptic-anterior hypothalamic area. It may be assumed that this region stimulates the hypophysiotrophic area (HTA) to cyclically release the luteinizing-hormone-releasing factor required for the release of the ovulating quota of luteinizing hormone. In order to study the neuronal connections between the two regions, (1) a frontal cut was made behind the optic chiasma; (2) the praeoptic area was deafferented from both sides, from anterior and from above, or (3) an electrolytic lesion was placed in the praeoptic region, and the HTA examined for secondary degeneration of axon terminals. Intervention (1) and (3) caused terminal degeneration in the HTA, while (2) had no such an effect. — The data indicate that the axone of the neurons in the praeoptic area have their terminals on the nerve cells of the HTA, i.e. there is a direct contact between the neurons of these two regions.

63.

On the site of action of reserpine on ACTH secretion

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The acute effect of reserpine (3.0 mg/kg body weight i.p.) on ACTH secretion was investigated in rats with partial or total deafferentation on the medial basal hypothalamus (the hypophysiotrophic area, HTA). Plasma corticosterone concentration was determined before and four hours after the administration of the drug. The reserpine induced marked rise in plasma corticosterone levels failed after complete isolation of the HTA and was also blocked in those rats in which only the posterior connections to the area were cut. Interruption of the anterior afferents to the HTA resulted in a partial blockade, while severance of the bilateral and superior connections did not interfere with the elevation of plasma corticosterone levels. The data suggest that several nervous structures outside the HTA might be involved in the action of reserpine studied and that the majority of the afferent pathways to the HTA causing the reserpine induced release of CRF from this region, reach the area from posterior direction.

64.

Effects of 5-hydroxytryptophane upon hypothalamo-pituitary--adrenal system after total deafferentation of medial basal hypothalamus

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In recent years a considerable amount of information concerning the role of biogenic amines in the central regulation of the pituitary-adrenal system has been obtained. The present study was undertaken to elucidate whether there are in the hypophysiotrophic area of hypothalamus tryptamine receptors connected with the pituitary-adrenocortical function. The method of Halász (1967) of total interruption of neural afferents to the medial basal hypothalamus was used. An hour after pretreatment of control rats with a serotonin precursor 5-hydroxytryptophane (5-HTP), 100 mg/kg, significant increase in serotonin content in the brainstem and elevation of plasma corticosterone level were found. Complete deafferentation of the medial basal hypothalamus did not block the hypothalamo-pituitary-adrenocortical response to 5-HTP and after 5-HTP administration to such rats the increase of plasma corticosterone level developed at a rate not different from the control group. The results indicate that there are tryptamine receptors in the hypophysiotrophic area of hypothalamus with facilitatory influences on pituitary ACTH secretion.

65.

Relation between hypothalamic estrogen receptors and the monoaminergic system of the hypothalamus

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The maximum cerebral uptake of ^{3}H-estradiol was found in the antero-basal hypothalamic areas of the castrated female rat. Less but still considerable amounts of labelled estradiol were retained by the midregion of the hypothalamus (region of the tuber cinereum) and no specific uptake was registered in the region of the mamillary bodies (posterior hypothalamus). (Flerkó, Mess and Illei-Donhoffer, 1969.) The question studied was whether the monoaminergic neurons situated in the above hypothalamic areas are identical with those accumulating estradiol. In spite of the destruction of the dopaminergic neurons by intraventricular injection of 6-OH-dopamine the estradiol-concentrating capacity of the anterior and mid-

-regions of the hypothalamus remained unaffected. Inhibition of intracerebral dopamine synthesis by α-methyl-dopamine administration, as well as blocking of serotonin synthesis by injection of parachlorophenylalanine (PCPA), likewise failed to affect hypothalamic estradiol uptake. Nor did enhancement of dopaminenergic effect by DOPA administration, or increase of serotonin synthesis by 5-hydroxy--tryptophan (5-HTP) have any influence on the intensity of hypothalamic estrogen retention. The results suggest that the monoaminergic neurons are not involved in the hypothalamic estrogen receptor system.

66.

Fiber degeneration in the hypothalamus and limbic system following the customary stereotaxic dorsal penetration into the hypothalmus

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Fiber degeneration in the hypothalamus and limbic system were investigated by the aid of the Fink—Heimer method and by electron microscopy in cases of usual dorsal penetration into the hypothalamus (hypothalamic lesions, electrode implantations and deafferentations). Numerous degenerated fibers can be seen in several regions of the hypothalamus (preoptic, anterior hypothalamic, supraoptic, arcuate, ventral premamillary, mamillary nuclei) and in various parts of the limbic system. Hypothalamic fibers destroyed by dorsal penetration originate from: *a)* the septal region, *b)* the hippocampus and *c)* the amigdaloid complex. A number of fibers in degeneration can be observed in the fimbria hippocampi and in the hippocampus itself indicating the presence of septal fibers which are afferent to the hippocampus. Some degenerated fibers of other than limbic or hypothalamic origin (cortical, thalamic and extrapyramidal) can be demonstrated in the thalamus and outside the diencephalon.

67.

On the mechanism of hormone release in the neurohypophysis

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The elementary granules of the neurosecretory nerve cells in the mammalian hypothalamus contain the octapeptides vasopressin and oxytocin associated with the carrier substance neurophysin (van Dyke protein). Two possibilities of the

hormone release in the posterior lobe are to be taken in consideration: 1) The granules lose their contents, the hormones reach the plasmalemma and pass through it. 2) The granules are released in toto via exocytosis. On this occasion their membranes are incorporated in the plasma membrane of the nerve terminals. The author observed the occurrence of exocytosis by means of the electron microscope and describes the ultrastructural details connected with this mechanism of release. The question is discussed whether this process takes place exclusively or whether different mechanisms of release in the blood stream are also in operation.

68.

Afferent neuronal pathways of the supraoptic nuclei

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The neuronal connections of the supraoptic nuclei were studied by the degeneration method of Fink—Heimer and by electron microscopy in experiments utilizing the technique of deafferentation of the hypothalamus. The following types of operations were made: *a)* total hypothalamic deafferentation, *b)* partial (anterior, posterior or dorsal) deafferentation of the hypothalamus, *c)* parasagittal cuts passing medially and laterally from the supraoptic nuclei, *d)* enucleations and *e)* removal of the cervical sympathetic ganglion. All types of deafferentation resulted in the terminal degenerations in the supraoptic nuclei. However, no degenerated fibers or terminals were found after enucleation or gangliectomy. Nerve fibers running in the fornix and in the medial forebrain bundle reach the supraoptic nuclei. The results of the present experiments suggest direct connections between the supraoptic nuclei and the hippocampus by way of the fornix and the septal nuclei (from the front), as well as the brain stem (from behind) through the medial forebrain bundle. Some fibers could be traced directly from the supraoptic decussation to the supraoptic nuclei.

69.

The effect of Lynestrenol and Lyndiol on the hypothalamic aminergic and peptidergic neurosecretory systems

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Lynestrenol or Lyndiol (2,5 mg Lynestrenol and 75 mg Mestranol) were given to female adult rats during 6 days in daily doses of 5 mg Lynestrenol in 1 ml of water daily by stomach tube. The neurosecretory Gomori-positive material was studied histologically in the supraoptic and paraventricular nuclei and in the median eminence. The adrenenergic structures were identified histochemically by means of fluorescent Falck's method in the supraoptic, paraventricular and periventricular nuclei, in the nucleus arcuatus and in the median eminence. The effect of the vaginal cycles on the nucleic sizes in the peptidergic neurosecretory cells and on the fluorescence in the outer zone of the median eminence was taken into account. Short-term application of Lynestrenol is followed by an increase of peptidergic neurosecretory material in the cell-bodies, particularly in the axons of the neurosecretory cells; the sizes of the nuclei and nucleoli in these neurosecretory cells were also increased, the increase being statistically significant and very marked in the paraventricular nuclei. The possible relationships between aminergic and peptidergic neurosecretory systems are discussed.

70.

Investigations of experimental pituitary tumours in tissue culture

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In our previous investigations we have got hormone dependent pituarity adenomas in the anterior lobe on the effect of a five-six months estrogenic hormone treatment. The adenomas consisted mostly of degranulated eosinophilic cells and secreted prolactin. In our present experiment we implanted stilboestrol hormone tablets into R Amsterdam inbred rats subcutaneously. The pituitary adenomas induced by the stilboestrol tablets were removed under sterile circumstances four-nine months later. One part of the tumour tissue was expanded on plasma clot, from the other part cell suspensions were prepared by tryptic dissociation. Organ cultures

were used, too. We have got also in an estrogen free milieu viable cell, tissue and organ cultures, on which histological and histochemical studies were performed. We have demonstrated somatotropin and prolactin in the pituitary tumour explanted in organ cultures. Prolactin was found in the medium of the tissue and organ cultures using the pigeon crop sac micromethod.

71.

Pituitary growth hormone (GH) and prolactin (P) content of rats treated with dehydroepiandrosterone (DEA) — and testosterone (T)

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DEA pellets were implanted subcutaneously into the back of mature female rats. Thirty days thereafter the anterior pituitary became enlarged showing hyperplasia in the majority of the animals. GH content of the glands diminished to degree unmeasurable by polyacrylamide-gel electrophoresis. Though P concentration was somewhat decreased, its absolute quantity increased considerably. Sixty days after the implantation the pituitary weights had increased but moderately; pituitary GH and P levels were the same as found in the control animals. The weight of the pituitary, its GH and P concentrations corresponded with the data of the control group when the implantations were repeated monthly for a 90 or 150 day period. The pituitary weight in female recipients of T-implants was found unaltered after 30 days. The concentrations of GH and P were increased by 50%. No hyperplasia of the anterior pituitary was found in mature males 90 or 150 days after DEA implantation. GH content was unchanged, the P content slightly increased. P concentration of the pituitary gland in males increased after T treatment, weight and GH content of the gland remained unchanged. The results of the study indicate that the responses of pituitary GH- and P-contents to the application of the substances referred to above are different in female and male rats. This may be due to differences in the peripheral metabolism of DEA and T in the two sexes, but then, DEA and T sensitivity of the neural structures regulating pituitary GH and P content and/or the sensitivity of the cells producing these polypeptide hormones may be different too.

72.

Histochemical basis of adaptive reactions of the neuroendocrine system in steroid imbalance

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The adaptive reactions of the neuroendocrine system of female rats, guinea pigs, and golden hamsters were studied in sex steroid imbalance (hyperestrogenisation). Morphological and histoenzymological studies of the hypothalamus, anterior pituitary, ovary, uterus, mammary gland were carried out along with biochemical determination of glucocorticoids in blood and pregnanediol in urine. Nucleic acid content and enzyme activity (NAD and NADP-diaphorases, esterases, phosphatases, 30-01 and 17-OH-steroidhydrogenases) were estimated histospectrophotometrically. Estrogen treatment resulted in the development of an adaptive reaction of the neuroendocrine system providing for the support of hormonal homeostasis for 60 days of the experiment. The reactions elicited showed two patterns of response: one with predominant glucocorticoid secretion, the other with sex steroid synthesis. While the former is mediated via the pituitary-adrenocortical system, the latter takes effect through the pituitary-ovary system with a possible sex steroid synthesis of the adrenal cortex. The development of each reaction is determined by a specific function of anterior pituitary. The ACTH- and gonadotrophic — patterns of pituitary response had different histochemical characteristics. It has been shown that the development of adaptive reactions comprizes the following stages: *a)* functional stress *b)* cytophysiological changes *c)* structural and functional disturbances. Distinctive histochemical parameters of the functional activity of pituitary-adrenal cortex and pituitary-ovary systems have been established. The involvement of each of the systems in the development of general adaptive reactions has been shown to depend upon the individual characters of the endocrine system of the species.

73.

Clinical value and mode of action of chlorpropamide in diabetes insipidus

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Chlorpropamide treatment was given to 11 patients with pituitary diabetes insipidus in the last two years, with definite success in all but one case where a combination of chlorpropamide and vasopressin (snuffing powder) has to be used in order to attain a more or less adaequate reduction in urinary volume. Only in 10 out of 11 could chlorpropamide be employed on a long-term basis. Chlorpropamide

was ineffective in a further (12th) patient with acquired nephrogenic diabetes insipidus. Initially daily 500 to 1000 mg of chlorpropamide was administered by mouth; the maintenance dose ranged usually from 250 to 500 mg a day. During prolonged treatment chlorpropamide antidiuresis progressively increased. The average maximal urine osmolality value was 571 ± 61 mOsm/kg H_2O against the control value of 109 ± 9 mOsm/kg H_2O. The difference is statistically significant ($p < 0.001$). Recurrent episodes of hypoglycaemia occurred in some patients, which could be prevented by the concurrent use of diazoxide. A progressive decrease in free water clearance without any consistent change in osmolar and creatinine clearance confirmed the vasopressin-like action of chlorpropamide.

HORMONAL EFFECTS ON GENERAL METABOLISM

74.

Preparation and biological properties of the reduced and alkylated derivatives of human pituitary growth hormone

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Human growth hormone (HGH) contains two disulfide bridges. According to the finding of C. H. Li the biological properties of the HGH derivative, produced by the complete reduction and carboxymethylation of disulfide bonds (tetra-S-carboxymethylated: RCM) change significantly. The activity of the reduced tetra-S-carbamidomethylated derivative (RCAM), however, appears to be similar to that of the native hormone. The difference in biological properties between the two derivatives can be interpreted by the assumption that the introduction of negatively charged carboxymethyl groups into the molecule results in conformational changes that may significantly modify its biological character. On the other hand, the rupture of the disulfide bonds itself is not accompanied by the loss of its activity. Our purpose was to study more thoroughly the biological properties of the RCM and RCAM HGH derivatives prepared in our laboratory and to determine the character of the conformational difference. The increased reactivity of the C terminal disulfide loop enabled the preparation of some selectively reduced and carboxymethylated derivatives as well. These derivatives represent intermediates between the reduced tetra--S-carboxymethylated and tetra-S-carbamidomethylated forms. The examination of their biological activity makes it possible to localize the conformational change wich is responsible for the alterations of their properties.

75.

Nutritive state and precursor dose on incorporation of orotic acid and uridine into kidney and liver of mice

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[6-^{14}C] orotic acid of low specific radioactivity injected into mice just after removal of food was incorporated at same rate in pyrimidines of RNA of kidney of normal and castrated mice but at a slightly higher rate in those of acid soluble fraction (ASF) of castrated mice after periods of 4—24 hrs. When food was removed 17 hrs. before orotic acid, incorporation of radioactivity was greater in castrated than normal mice at 2 and 4 hr. periods as previously reported (Biochem. 5:1696, 1966). Injection of orotic acid with high specific radioactivity into mice: (a) fed (b) deprived of food 17 hrs. prior to injection and (c) deprived of food just before injection resulted in a greater rate of incorporation of radioactivity into pyrimidines

of RNA and ASF of castrated than normal mice in all groups and was restored to normal by testosterone propionate (TP) treatment. Quantity of radioactivity incorporated, however, was greater in 17-hr. fasted than fed mice. Injection of orotic acid of decreasing specific activity but the same radioactivity resulted in a gradual disappearance in the difference between the castrated and normal mice. Incorporation of radioactivity into liver was not affected. [2-^{14}C]-uridine was not incorporated at a different rate in the pyrimidines of RNA and ASF of kidney or liver regardless of hormonal or nutritive status. Difference between normal and castrated mice appeared to be in pool of RNA precursors of de novo and not salvage pathway. Concentration of pyrimidines in ASF was not changed by hormonal conditions and was slightly decreased by starvation. Orotic acid was detectable only by its radioactivity. These experiments strongly suggest that size of pool or compartment of orotic acid and its metabolites and/or enzyme activities of de novo biosynthetic pathway were determining factor(s) in difference in labeling of ASF and RNA pyrimidines of kidney of normal, castrated and androgentreated mice. (These studies were supported by General Research Support Grs. FR-05300, FR-05349 and Gr. AM 11 060 from NIAMD, USPHS).

76.

Effects of the anabolic steroid, Madiol, on intravenous insulin hypoglycemia and on liver glucose-6-phosphatase activity in albino rats

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Insulin hypoglycemia was induced by injecting 10^{-2} I. U. insulin/100 g b.w. in the same group of male albino rats (150—180 g) before Madiol (17α-methyl-androst-4-on, 3β, 17β-diol) administration, 4 hours after i.m. administration of 0.5 mg/100 g Madiol and after a 14 day treatment with a daily dose of 0.5 mg Madiol/100 g b.w. Blood glucose was measured at 5—10 minute-intervals during 60 minutes after insulin administration. The rate of glucose removal was evaluated by using the angular coefficient *a* and the *i* coefficient according to Franckson's formula. The hypoglycemic effect of insulin was found to diminish in both cases of Madiol treatment (acute and chronic). The G6P-ase activity was studied in 3 groups of animals, i.e. in control rats, rats injected with Madiol 4 hours before sacrifice and rats treated 14 days with Madiol (sacrificed 24 hours after the last dose of Madiol). The results showed a significant increase of G6P-ase activity in the Madiol-treated groups compared to the controls.

77.

Genesis of Langerhans islets by acino-insular transformation in mature rats

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Acino-insular transformation was investigated in both mature intact rats and in rats with regenerating pancreatic tissue following partial pancreatectomy. Using the technique of semi-thin serial sectioning, it was established in intact animals that a cell mass equal to 1.5 per cent of the islet volume investigated showed signs of spontaneous transformation. Transformation of complete acini into islet tissue was observed in regenerating pancreatic tissue. Light and electron microscopic investigation suggests that acino-insular transformation is an important way of replacement of islet cells in postnatal life.

78.

Age dependent action of hydrocortisone hemisuccinate upon the intravenous glucose tolerance in white rats

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Intravenous glucose tolerance was studied in male albino Wistar rats of various ages (35, 60 and older than 360 days) before and after intraperitoneal administration of 0.5 mg Hydrocortisone hemisuccinate (Hc) per 100 g b.w. The rate of glucose disappearance from the blood was calculated using the glucose assimilation coefficient (K) according to Gonard's formula and Christophe's procedure. The glucose disappearance in basal conditions was expressed by K_1 and after Hc administration by K_2. It was established that Hc induced a significant decrease of glucose disappearance in all groups of animals. In the youngest rats the inhibitory effect of Hc was similar to that observed in old animals. In the 60 day old rats the inhibitory effect of Hc was significantly higher than in the above mentioned 2 groups. This difference is discussed on the basis of age-dependent insulin secretion and on the basis of Hc- and insulin-sensitivity of tissues.

79.

The role of pancreas hormones in the endotoxin induced blood sugar changes

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The mechanism of transitory hyperglycaemia following a single endotoxin injection and that of prolonged hyperglycaemia following a series of endotoxin injections has not been clarified yet. The majority of authors claim the early blood sugar increase to be a consequence either of the epinephrin mobilizing or of the hypophysis-adrenal cortex activating effect of endotoxin. We found the moderate early hyperglycaemia to develop even in adrenalectomized mice to endotoxin is taken into consideration and slight amounts of endotoxin are applied. We suggest the adrenals being only in part responsible for the early hyperglycaemia. The missing early hyperglycaemia after endotoxin administration in cobalt chloride pretreated rabbits draws the attention to the role of glucagon. In endotoxin-tolerant rabbits serially pretreated with endotoxin there is no blood sugar increase on a further provoking endotoxin injection, conversely a rapid but moderate hypoglycaemia develops. In contrast, in endotoxin tolerant, alloxan diabetic mice not only the blood sugar increase, but also the blood sugar decrease disappears indicating hereby the manifestation of the insulin-mobilizing effect of endotoxin even in endotoxin-tolerant animals. Either a tolerance develops against the glucagon mobilizing effect of the provoking endotoxin or glucose is not liberated from the liver of the tolerant animals. The finding that blood sugar increase on exogeneous glucagon is significantly lower in endotoxin tolerant animals than in the controls supports the latter assumption. According to our investigations the prolonged hyperglycaemia in endotoxin-tolerant rabbits can be traced back to an insulin deficient state. In the development of this disorder immunological factors might also be involved.

80.

The role of the hypothalamus—pituitary system in the endotoxine-induced mobilization of free fatty acids

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The free fatty acid levels in serum increase after administration of endotoxin to rabbits. Hypophysectomy abolishes this increase. The rabbit pituarity has a considerable lipolytic activity in vitro. In endotoxin-treated rabbits the lipolytic activity of the pituitary is much higher than that of the controls. On the evidence of the present experiments the hypothalamus of rabbits has a dual lipolytic activity,

i.e. a direct mobilizing effect on fatty acids from the adipose tissue in vitro and a stimulating effect on the lipolytic activity of the pituitary. The direct lipolityc activity of the hypothalamus of the endotoxin-treated rabbits is unaltered, but the mobilizing effect of the pituitary markedly increases compared with that of the controls. It is assumed by the authors that the endotoxin produces an increased secretion of a lipotropic hormone-releasing factor of the hypothalamus.

81.

The role of the hypophysis—adrenal cortex system in the mechanism of natural endotoxin resistance

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The pituitary-adrenocortical system plays an important role in the mechanism of natural endotoxin-resistance. This is proved by the enhanced sensitivity of adrenalectomized animals to endotoxin and by the fact that ACTH and cortisone belong to the most potent endotoxin antagonists. In the present experiments the enhanced sensitivity of adrenalectomized rats to endotoxin, could be ascertained by LD_{50} determinations as well by a method elaborated by the authors. The method is based principally on the linear regression between the endotoxin dose and the decrease of serum complement C′3 within a certain dose range. With this method the endotoxin-sensitivity of hypophysectomized rats proved to be higher than that of the controls, but still significantly lower than that found in adrenalectomized rats. Accordingly, the adrenal activity being outside the control of the hypophysis plays a significant role in natural endotoxin resistance. It is noteworthy that no full prevention of endotoxin-induced, dose-dependent reduction of adrenal ascorbic acid was attained by a 4 mg/100 g Prednisolone block, or by hypophyscetomy.

82.

The effect of oral contraceptive steroids on serum lipids

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Twenty-four women received Infecundin, 20 Bisecurin and 6 Mikrofollin + Colutoid for 3—4 months. The serum triglyceride-, cholesterol- and β-lipoprotein-level was determined before and after the drug administration. The serum triglyceride- and β-lipoprotein level increased in all cases taking Infecundin, the cholesterol level showed variable changes. The effect of Bisecurin and of Mikrofollin + Colutoid was compared with the effect of Infecundin.

83.

Effect of carbohydrate-intake on the fat mobilizing activity of urine extracts

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Urinary fat mobilizing substance (FMS) was extracted quantitatively by the method of Pawan. The urine was collected for 24 hrs, the precipitate was purified by chromatography and 5 per cent of the extract was injected to mice. The blood ketones were determined before and six hours after injection. The control animals received saline, which caused slight increase of the ketones (stress-effect). 30 obese persons were put on diets containing daily 300, 200 and 50 g carbohydrate and finally they fasted. The extracts of urines collected under low carbohydrate diet and fasting caused a very significant increase of ketones in mice. There was no difference in FMS activity between patients with normal and decreased glucose tolerance. Some data of the chemical analysis of the extracts will be pointed.

84.

On the role of some hormones in the treatment of stupors

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Stupor was found to regress completely (mostly in 3—7 days) under associated treatment with fluphenazine (4—6 mg/24 h), hydrocortisone (75—150 mg/24 h), testosterone (25—50 mg/24 h), estradiol (up to 5 mg/24 h) and zinc. protamin-insulin (4—8 I. U./24 h) in 44 schizophrenics with catatonic stupor, among these 5 patients where ES had seemed unwarranted because of circulatory disorders and failure of neuroleptics to give any benefit and 3 other patients having failed to respond to ES. Wistar-rats having been treated with the foregoing drugs for six weeks in doses corresponding to body-weight, revealed no significant abnormalities of brain, liver, kidney or spleen, in contrast to the following biochemical changes: significant accumulation of noradrenaline and adrenaline in the hypothalamus which might suggest a compensatory increase of catecholamine content in conditions of post-synaptic blockade and of decrease of nerve impulse flow. Using pertechnate ($^{99m}TcO_4$) a significant increase in both blood and brain radioactivity was found which might be an expression of facilitation of supply and penetration of some substances into the brain under the influence of the studied drugs. The output of glucose into the incubation fluid by the sciatic nerve in vitro in the absence of insulin increased proportionally to the glucose concentration in the medium. The basal glucose uptake and the above basal level uptake of rat epididymal adipose tissue under the influence of insulin remained unchanged.

THYROID GLAND

85.

Determination of the IG-type of the antithyroglobulin auto-antibodies in the early and late stages of autoimmune thyropathies

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The diagnostic significance of radioimmune studies (radioimmunoelectrophoretic and radioimmune diffusion procedures) was investigated in 100 cases of autoimmune thyroid disease (chronic thyroiditis, primary hypothyroidism, antibody-positive hyperthyroidism). As a result of the studies, the anti-thyroglobulin auto-antibodies could be identified as those of the IgG-, IgA- and IgM-types, 63 per cent of the antibodies studied belonging to the IgG-, 2 per cent to the IgA- and 6 per cent to the IgM class. The combination of the different IgG-type antibodies showed the following distribution: IgG + IgA 10 per cent, IgG + IgM 10 per cent, IgA + IgM 1 per cent, IgG + IgA + IgM 8 per cent. The study revealed definite correlations between the stage of disease and the immunoglobulin type of the antithyroid antibodies. While in the early stage of autoimmune thyropathy, antithyroglobulin-antibody mainly of IgM-type is formed, in its later stages antibodies prevalently of IgM-, less frequently of IgA-type are synthetised and are found in combination with IgM. As a further result of the investigations the radioimmune methods proved suitable for the determination of the specificity of passive haemagglutination. A short account is given of the various testing methods, including those of the authors, concerning the organospecific and non-organospecific immunopathies.

86.

Investigation of thyroxine-binding globulin, prealbumin and other plasma proteins in autoimmune thyroid diseases and hyperthyroidism

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The plasma concentrations of thyroxine-binding globulin (TBG), prealbumin (TBPA) and of other protein fractions were measured by zone-electrophoresis in autoimmune and non-autoimmune thyroid diseases. The autoimmune character

of the process was ascertained on the ground of the complement fixing tests (CF) and of passive haemagglutination test (TRC) these being suited for the demonstration of antibodies against the microsomal fraction of thyroid cells and against thyroglobulin, respectively. A significant reduction in the concentrations of albumin and an increase in those of gamma globulin were found in hyperthyroidism, regardless of the presence of autoimmunity. The increased levels of TBG and TBPA demonstrable in hyperthyroidism were likewise unrelated to autoimmune factors. The changes in the concentrations of the plasma proteins studied are connected by the authors with the hyperthyroidism rather than with autoimmunity to which however they also attribute a possible secondary role.

87.

Effects of the chlorphenoxyacetic acids on the T_3- binding capacity

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The chlorphenoxyacetic acids are well known herbicides the effects of which increase with the number of chlorine atoms. After i.p. administration to rats they elicit an increase in the ^{131}J-uptake by the thyroid, while reducing the protein-bound iodine levels in the serum. The effect of monochlorphenoxyacetic acid is the weakest, that of dichlorphenoxyacetic acid is stronger, trichlorphenoxyacetic acid is the most positive. According to the Hamolsky-test a competitive antagonism exists between the chlorphenoxyacetic acids and tri-iodothyronine for the tri-iodothyronine binding protein site. The expected differences in the effects of mono-di-trichlorphenoxyacetic-acid have been confirmed in this case too.

88.

Indication of surgical treatment in thyroid diseases on the basis of five years experiences

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In our last five years material 136 patients having thyroid diseases were surgically treated. Conservative therapy was tried first in every possible instances. The indications for surgical treatment were: solitary nodule (63 cases), hyperthyroidism

(22 cases), toxic nodular goiter (15 cases), diffuse or multinodular nontoxic goiter producing compression (31 cases) and carcinoma (5 cases). Although the number of cases reported here is low, it seems to be justified to deal with some aspects of the problem of surgical intervention.

89.

Immunosuppressive therapy in thyrotoxicosis

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In most of the thyroidities and in one part of thyrotoxic cases auto-immune aetiology may be supposed. The therapy of this illnesses is only partly solved at present. In problematic cases the immunosuppressive therapy can be used. Recently we got experiences treating the thyrotoxicosis with cytotoxic drugs and thymus X-irradiation. 17 cases were estimated. 10 were good result, 7 wrong. In connection with our cases we observed the immunological condition. (The behaviour of anti-thyroid antibodies, the blastoid transformation of lymphocytes, the delayed hypersensitivity reaction and the natural antibody titer before, under and after the therapy). The 17 patients treated for thyrotoxicosis, 11 of them with Proresid and 6 with Imuran. The dosage of Proresid was 800 mg per day and the dosage of Imuran was 2,5 mg/kg per day. Side effect: of the patients taking Imuran one developed a fall of white cell below 3000 per mm^3 after 10 months of treatment. The use of immunosuppressive drugs (and procedures) is still in a very early stage of development and all effects are not yet known, nor have they been evaluated statistically. But the clinical task with the presented laboratory investigations make clearly up the above mentioned good therapeutic effect of immunosuppressive treatment in thyrotoxicosis.

90.

Sex hormones and calcitonin sensitivity

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As a result of earlier investigations, a hypothesis has been advanced by the authors that the presence of sex hormones is essential to the in vivo effect of calcitonin. To test this claim, in male albino rats susceptible to calcitonin the testicles and adrenals were removed; another group of rats had adrenalectomy only. Both groups were given cortisone acetate as substitution. Ten days after surgery, calcitonin

sensitivity was compared in the two groups and in an age and sex-matched control group. While serum-calcium was depressed to 6.9 mg per 100 ml following the administration of 10 mU per 100 g bw. of porcine calcitonin in the untreated control group, the average serum-calcium concentration in the adrenalectomized rats was 7.5 mg per 100 ml, and in the castrated and adrenalectomized group its lowest level was 8.5 mg per 100 ml. The differences were statistically significant. The results are consistent with the authors' hypothesis that the full in-vivo effect of calcitonin requires the presence of sex hormones, both of gonadal and adrenal origin.

91.

Current status of laboratory and localizing tests for disturbed parathyroid function and adenoma diagnosis

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The clinical tests for the evaluation of parathyroid funtion or for the localization of parathyroid adenoma are still unsatisfactory in many respects. The diagnosis of hypo- and hyperparathyroidism still rest with the measurements of plasma total calcium concentration, but as a result of the discovery of calcitonin it has become clear that the state of hyperparathyroidism need not be accompanied in all cases by increased plasma calcium levels. Since the funtional alterations cannot be conclusively diagnosed clinically, selection and evaluation of laboratory tests is crucial; indirect assays appear to be the most useful (although non-specific) because they measure the main homeostatic function of the glands. It is generally assumed that variations in the level of, primarily ionic, calcium trigger changes in the rate of glandular secretion, and parathyroid-dysfunction on its part induces alterations of ionic serum calcium. There are also difficulties in interpreting the results of adenoma-localizing tests the results of which are often indistinctive or fail to demonstrate focal areas. The author's investigations are discussed in the context of the current status of parathyroid function- and localising tests and of the relevant issues.

92.

Hyperthyroidism syndrome without hyperthyroidism

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The clinical picture of hyperthyroidism — in typical cases — is very impressive and so much characteristic that it can be diagnosed with a considerable probability already at the first appearance without any objective examination. The authors

studied the course of different thyroid functional tests and their constellation in hyperthyroidism. It was determined that only one part of these clinical symptoms was accompanied by increased thyroid hormone production resp., increased hormonal level in the blood. In the other part of the cases, the following disturbances in the iodine metabolism resp., functional diseases of the thyroid were demonstrated: vegetative dystonia, chronic iodine deficiency, diminished hormonal space of the thyroid, latent hypothyroidism, condition after hyperthyroidism therapy showing a normal, or even a subnormal thyroid hormone production resp., thyroid hormone level in the blood. Accordingly, the clinical symptoms of hyperthyroidism — hyperthyroid syndrome — are not provoked by the hyperfunction of the thyroid resp., the greater quantity of thyroid hormones in the aeforementioned functional diseases of the thyroid, but they exist probably due to the functional disorder of the central nervous system, the disorder if the suprathyroidal control system.

The differential diagnosis of hyperthyroid syndrome — which is possible, among others, only by means of the thyroid functional tests — is indispensable considering the adequate therapy to be applied.

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