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IN
ENDOCRINOLOGY

By

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PREFACE TO THE SIXTH EDITION

In the rather short interval since the publication of the last edition no outstanding advance has been made, though there has been steady progress necessitating slight revision of a number of chapters, revision in the nature of extension, rather than of correction of previous work.

The production of artificial iodo-proteins with thyroid-like action and more active than desiccated thyroid, has reached the stage where commercial utilization is possible.

The employment of thiouracil in prolonged treatment of hyperthyroidism has, at least in mild or only moderately severe cases, become justifiably a means of replacing or postponing surgery, although thiouracil still remains for each patient a substance which, until proved otherwise, is potentially toxic. There is promise, however, that related compounds of inherently lesser toxicity may prove as efficacious or even more efficacious in combating thyrotoxicosis.

I am greatly indebted to Professor H. P. Himsworth, and to his patient whose case I have recorded, for furnishing me with the details of what is probably the most successful and prolonged treatment of a severe case of Addison's disease, and for allowing me to publish them. The earlier treatment of this disease with adrenal cortical extracts seemed disappointing, but this case again rouses our hopes that proper treatment may prove as efficacious for Addison's disease as insulin has proved to be for diabetes mellitus.

I am grateful to Dr. Harold Cookson and to the Editor of the "Lancet" for permission to reproduce the excellent illustration of a result of thiouracil treatment that is shown in Fig. 12.

A. T. CAMERON.

WINNIPEG, CANADA.

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RECENT ADVANCES IN ENDOCRINOLOGY

CHAPTER I

INTRODUCTION

THE pre-history of endocrinology is the story of gradual failure of detoxication theories to explain accumulating facts, demonstrable by experiment, concerning certain "ductless glands." All such theories are not even yet universally rejected.

The history of endocrinology as an exact branch of science scarcely antedates the present century; the name itself is still younger. Until chemical studies progressed sufficiently to result in isolation of several of the "internal secretions," and to emphasize the fact that these are specific compounds, with specific physiological functions, endocrinology was nebulous, and necessarily inexact. Now that we know the chemical nature of most of these compounds, and have learned much about their physiological activities, endocrinology has become an exact science, or branch of science, inseparably related to physiology, pharmacology and biochemistry.

It seems desirable to stress at the outset two fundamental concepts, whose truth, though still unadmitted by numerous investigators, is becoming more apparent with each advance. *The normal function of an endocrine gland is not a detoxication, but the production of one or more specific chemical compounds essential to the normal life of the whole organism. In the different pathological states of such a gland it may produce too much or too little of these specific compounds, but it does not produce abnormal compounds.*

The term *hormone* (from Gk. *hormōn*, rousing or setting in motion), originally proposed by Bayliss and Starling, has been universally adopted for endocrine compounds, though in its original sense it scarcely applies to all of them. Other suggested terms as *chalone* and *autacoid* are no longer used. *Endocrinology* (Gk. *endon*, within; *krinein*, to separate) is generally accepted as the name of that branch of science which concerns itself with the hormones, while the glands concerned are *endocrine glands*, and their "internal secretions" are *endocrine secretions*.

The terminology applied to the hormones themselves is gradually

becoming simplified and more definite, as these compounds are gradually being obtained in pure crystalline form. There is still too great a tendency to coin new names to avoid those employed by the larger pharmaceutical companies. Many of these firms are now employing the scientific names, as well as those they use for patent purposes. The physician is, therefore, more easily able to apply his own knowledge to the selection of his therapy.

Hormone production is associated with the thyroid, parathyroid, pituitary, and adrenal glands, the islet tissue of the pancreas, the mucous membrane of the upper part of the intestine, and the gonads and placenta. The thymus and pineal probably produce hormones. Apparently the kidney must also be included. Various claims have been made for others, to which short reference will be made.

By far the most perplexing problems in endocrinology are those concerned with the interrelationships of the actions of two or more endocrine compounds. Such interrelationships cannot be dealt with very systematically; they intrude into the majority of discussions of clinical cases exhibiting endocrine disturbances; they even intrude when normal functions are under consideration. They have suggested a multitude of syndromes, involving much unnecessary differentiation; the inaccurate conceptions underlying many of these suggested syndromes have led to much inaccurate therapy.

In so far as therapeutic treatment is dealt with in this volume, I endeavour throughout to indicate the logical treatment in light of present knowledge. If the assumption be true, as I believe, that almost all endocrine disorders are primarily associated with either hypo- or hyperfunction of only one endocrine gland, then this logical treatment seems obviously to consist in the application of replacement therapy for hypofunction and application of some means of depression for hyperfunction of that gland.

Rational replacement therapy must always take into account the fact that only two or three endocrine principles have been definitely demonstrated to be effective when administered by mouth. Our knowledge of the actual nature and of the actions of the others creates a demand for properly standardized concentrates suitable for injection, and such a demand is being met. Only such properly standardized preparations should be employed.

A useful addition to methods of treatment is the implantation of crystal pellets (suitably sterilized) of potent hormones. A single implant can produce a desired effect for weeks. The method has proved of service with the hormones of the gonads and the

adrenal cortex. The essence of the method consists in selecting material of very slight solubility, so that tablets of insulin, fairly soluble, are useless for the purpose (Parkes and Young), though the injection of insoluble protamine zinc insulin achieves the same purpose in much lesser degree.

Surgical treatment is an obviously correct procedure for the majority, if not all, conditions in which a hyperfunction exists. Claims for employment of X-ray therapy are frequent; the relative benefit to be obtained from it and the types of case which will obtain most benefit have not yet been fully established.

The *correct therapeutic dosage of endocrine preparations* is not a subject for generalization, but rather for individualization. It is not possible in this volume to do much more than indicate some of the many potential errors which may arise in connection with dosage.

Where pure endocrine principles or active derivatives are available, such as thyroxine, or crystalline insulin, then dosage can be based upon specific amounts of them. But if the treatment be in the nature of replacement therapy, each individual requirement must be different, for the amount of non-functioning endocrine tissue whose normal output has to be replaced differs in each patient. This is illustrated by Collip's *principle of inverse response*, which he defines: "The responsiveness of an individual to administered hormone varies inversely with the hormone content or production of the individual's own gland." This dictum aptly illustrates the impossibility of accurate dogmatism in endocrine therapy. Even when total replacement is necessary, as, for example, following total thyroidectomy, the requirements of individuals will be related to their body-volume or body-surface or both, while sex and age will also modify them.

When such pure preparations are not available, not only is accurate standardization necessary, but a correct basis of standardization. The same weight of desiccated thyroid may give very variable results if different preparations are at different times given to the same patient. Thyroid should be standardized according to its iodine content—it now frequently is.

Precision of dosage of preparations from the anterior pituitary is and will remain difficult, till complete separation of the hormones of that gland has been achieved; at present all commercial preparations are mixtures of several hormones in uncertain amounts.

Pratt, some years ago, published a thoughtful paper on this subject of dosage in endocrine disorders. He pointed out that the necessity of considering each individual separately is by no

means limited to endocrine therapy, and that the ordinary dosages prescribed for such established drugs as digitalis, arsphenamine, the belladonna group and sedatives frequently produce very varying, and sometimes dangerous, consequences, so that it is not surprising that precision of dosage is still not possible for the much newer endocrine compounds. He laid down the obvious but too often neglected dictum that *the reactions of the individual patient to any therapeutical agent should be the criteria for the final determination of the manner and amount to be administered.* It is equally obvious that error on the side of low dosage is the safest error.

Two of Zondek's fundamental hypotheses may well be quoted here ; the first also has a bearing on the variation of dosage for different individuals, and for the same individual at different times. " Hormonal effect is not an absolute but a variable quantity, depending not least upon the momentary condition of the organ on which it acts—more especially, the physico-chemical condition of its cells. Functional and anatomical changes in endocrine glands should not always be regarded as the cause of disease, but in many cases the reaction of the glands to morbid processes located in certain other organs."

Complete knowledge of the chemical constitution of certain hormones has led to attempts to improve upon nature. Oestradiol was produced in the laboratory and shown to be more potent than the natural oestrone, but, later, oestradiol was proved to be the true hormone of the ovary. Desoxycorticosterone was a laboratory product before it was isolated from the adrenal cortex. In those two cases nature was ahead of man's efforts. More recently Dodds and his collaborators have found synthetic oestrogens unrelated chemically to those produced in the ovaries (cf. Chapter VIII) and this type of research has already proved of very great value.

Since of all the endocrine glands the pituitary, by virtue of its control of many of the most important functions of the body, seems to be by far the most important, it seems at first sight logical to deal with that gland first. Yet a considerable part of the activities of the pituitary lies in the control of other endocrine glands, and these activities cannot be appreciated until those of the glands it controls have been dealt with. Thus in reality it is more logical to defer consideration of the pituitary until most of the other glands have been considered.

It is therefore useful to give at this place a very brief account of the general functions of the pituitary and its relationship to other

endocrine glands. The posterior pituitary produces, probably, only a single hormone, of such labile character that even solution in various organic solvents changes it to the two forms customarily considered as the hormones of this lobe. Through this hormone the posterior pituitary controls kidney tubule re-absorption of water, and the contraction of uterine muscle, and possibly also regulates capillary size.

The anterior pituitary by means of a still uncertain number of hormones controls (i) the thyroid gland, and thereby its control of certain oxidative and other chemical reactions in the tissues, (ii) the adrenal cortex, and thereby its control of electrolyte and carbohydrate metabolism, (iii) the gonads, and through their hormones the secondary sex organs and functions and the reproductive processes, and (iv) directly, by a specific hormone, the secretion of milk by the mammary glands. It also seems to possess direct control of certain growth processes, and thus to some extent of general growth, and of certain reactions which affect protein, carbohydrate and fat metabolism. It does not directly control the parathyroid glands, the islets of Langerhans, or the adrenal medulla.

The parathyroid glands control phosphorus and calcium metabolism, the islets of Langerhans, through their output of insulin, control carbohydrate metabolism, and the adrenal medulla, secreting adrenine, can increase blood pressure and mobilize glucose into the general circulation.

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CHAPTER II

THE THYROID GLAND

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INTRODUCTION

THE thyroid gland is built up of a large number of follicles of varying size and shape but tending to be spheroidal (cf. Fig. 1).

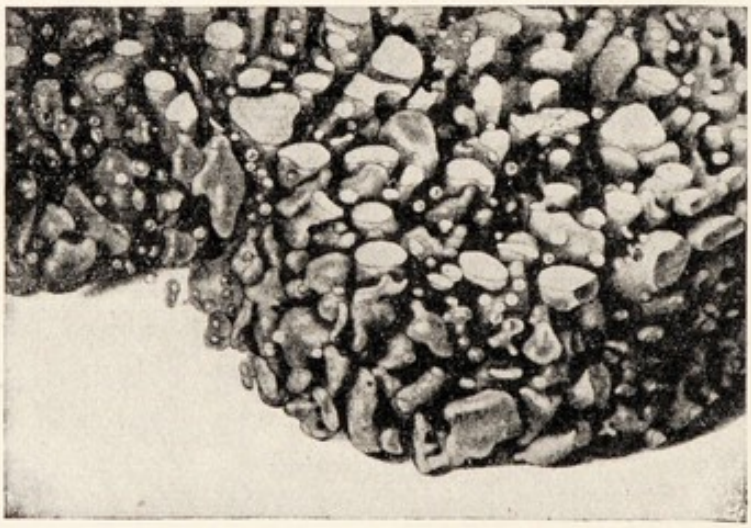


FIG. 1. Top and side view of wax model of normal human thyroid gland. (From Rienhoff, Medicine, 1931, x, 293.)

Follicles measuring 0·05 to 0·12 mm. in length predominate in the human gland. Each consists of a closed vesicle containing colloid material and lined with epithelium, the cells of which are columnar, cubical or flattened, according to the state of activity of the gland and degree of distension of the vesicles. The intervesicular substance is areolar tissue, which may contain lymphocytes and other cells, including epithelial cells (Sharpey-Schafer ; Jackson). The lymphatic system of the gland is a closed system, playing no rôle in the transmission of its hormone (Rienhoff).

In early foetal life vesicles develop from solid epithelial masses ; a little later colloid is produced and is stored in them. After birth secretory activity is marked throughout infancy and childhood ;

a small reserve of colloid is always present. Subsequent to puberty the colloid store increases, and, as judged by the histological picture, activity slowly decreases (cf. Cooper), and this is in agreement with a slow decrease in basal heat production. Cooper has stressed the striking histological resemblance of the gland of the human adolescent and that considered characteristic of (untreated) Graves' disease, and Abbott finds that this is true also for young domestic and wild animals; the thyroids of older animals, as of man, store more colloid and present a histological picture suggesting lessening activity. Hoar has reported a somewhat parallel picture in the thyroid of the Atlantic salmon.

The interfollicular epithelial cells can produce new follicles whenever adequate stimuli activate the gland. This has been shown for rats by Baillif, using cold as stimulus. Seasonal changes in temperature are accompanied by histological changes in the thyroids of farm animals (cf. Kendall). Somewhat similar changes occur in the thyroids of women during the menstrual cycle. Pregnancy appears to produce a hyperplasia, probably accompanied by an increase in function (Verdozzi; Abbott and Prendergast). Different diets also produce some degree of change in the histological picture.

Since under normal physiological conditions the histological picture of the thyroid can show such definite variations, it is evident that too great a differentiation of thyroid histology in pathological states may lead to error.

The blood volume of normal man moves through his thyroid once an hour (Lerman).

The blood supply of the thyroid is of importance in studying its pathological changes. Besides the four main arteries (paired superior and inferior thyroid arteries) and the occasional fifth (thyroidea ima) there are numerous unnamed irregular arteries, small in size under normal conditions, but capable of great enlargement in goitrous conditions; they arise chiefly from the pharyngeal, oesophageal and tracheal arteries. Beneath the true capsule of the gland there is a rich arterial anastomosis. The veins commence as a perifollicular plexus and follow the small arteries to the periphery of the gland, there developing into a plexus covering the whole gland. The finer lymphatic radicles are present in intimate association with the follicular epithelium and a plexus exists around each follicle. By their union a coarser network is formed, with ultimately a close-meshed anastomosis enveloping the whole gland (cf. Joll).

Control of Thyroid Secretion. It is frequently assumed that the

thyroid gland is under control of the sympathetic nervous system, and that this is affected in abnormal thyroid states ; in Graves' disease nervous excitation of the patient is a cardinal symptom.

According to Sunder-Plassmann each thyroid cell is under sympathetic nerve control through a terminal reticulum. Bachromejew and Ter-Ossipewa observed, following stimulation of the peripheral end of the superior laryngeal nerve, histological changes in the thyroid suggesting increased activity.

Nonidez has adduced anatomical evidence that the blood supply to the thyroid is under close control of the nervous system, which can thus indirectly influence the rate of secretion and discharge of the hormone. He found evidence for a specific thyroid nerve, and this has been confirmed and extended (in the dog) by Ross and Moorhouse. This nerve is made up of fibres from the superior cervical ganglion of the sympathetic, and parasympathetic fibres from the superior laryngeal branch of the vagus (or, frequently, from the ganglion nodosum or the vago-sympathetic trunk). The thyroid nerve terminates in branches which enter the gland with branches of the superior thyroid artery.

Stimulation of the thyroid nerve consistently slows the flow of blood through the gland, although histological changes in the gland from repeated stimulation in acute experiments have not been demonstrated (Ross and Moorhouse). Thus there seems to be an important *indirect control of the thyroid gland through nervous regulation of the blood supply and therefore of the output of hormone.*

Haney found that stimulation of the cervical sympathetic nerve in rabbits caused elevation of the basal metabolic rate, and this was partially confirmed by Friedgood and Bevin. Brock *et al.* found that bilateral cervical sympathectomy in rabbits caused a decrease in the basal metabolic rate. These changes also indicate sympathetic control of thyroid activity.

The thyroid gland is largely controlled by the thyrotrophic hormone of the anterior pituitary (cf. Chapter IX, p. 342).

Galli-Mainini concludes from *in vitro* studies of guinea-pig thyroids by the Warburg technique that the thyroid and thyrotrophic hormones are antagonistic, and that the amount of thyroid hormone in the blood itself acts as regulator of thyroid gland activity, which is inhibited by a rise in its level, and *vice versa.*

Iodine and the Thyroid Gland

It is now agreed that thyroid function is associated with the elaboration of a specific hormone rich in iodine, and that insufficient ingestion of iodine is one of the chief causative factors of simple goitre.

Iodine is widely distributed, though few materials are rich in it. The amount of it in plant food and in drinking water depends on the amount in the soil in which the plants grew or from which the water drained, and varies from practically nil to a few micrograms per cent. The same is true for land animal products such as meats, eggs, butter and milk. Such materials from different sources show great variations in their iodine content, due to corresponding variations in the content of the soils in different land areas. Marine animals are richer in the element, and many marine algae still richer. McClendon (1) has compiled valuable summaries of the available data (cf. also Lunde, and Salter).

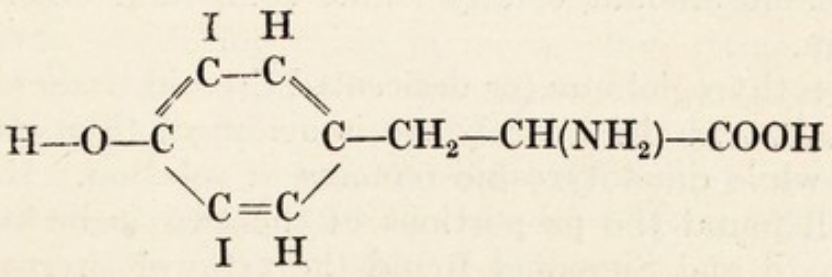
Iodine is present in measurable amounts in all mammalian tissue. Most endocrine glands contain relatively more than non-endocrine tissue, but the thyroid is relatively much richer still (adrenals and ovaries being next in order). The most accurate figures for *normal* human thyroids are still those of Zunz, who found that fresh glands of adult man from nineteen to forty-four years of age averaged 0·056 per cent. (extremes 0·023 and 0·068 per cent.); the corresponding figures for dried glands were: average 0·229, extremes 0·119 and 0·286 per cent. The human thyroid gland in Iceland is small and unusually rich in iodine, averaging 0·083 per cent. in fresh tissue; this is presumably related to a diet unusually rich in iodine (Sigurjonsson).

Unusually high figures (about 0·8 per cent.) have been reported for beef and hog thyroids from the south of India (Dey, Krishnan and Giriraj), and (up to 1 per cent.) for the desiccated glands of sheep pastured on kelp-strewn shores or fed iodide, and of elasmobranch fishes (cf. Cameron).

Iodine is present in both the cells and the colloid of the thyroid, the colloid being somewhat richer in it (Tatum; Van Dyke).

The Iodine Compounds of the Thyroid Gland. Three compounds have been isolated, diiodotyrosine, and thyroxine, both iodized amino-acids, and iodothyroglobulin, a pseudoglobulin.

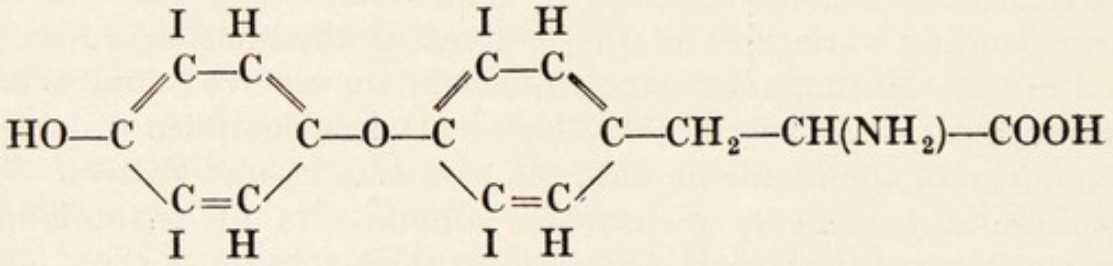
Diiodotyrosine contains 58·7 per cent. iodine. It has been



isolated from the horny axial skeleton (gorgonin) of certain corals (sea-fans) and the corresponding keratin-like spongin of sponges.

More recently Harington and Randall isolated it from the hydrolysed products of thyroid tissue and by enzymic hydrolysis of thyroglobulin, while Foster obtained it from chemically hydrolysed thyroglobulin. It is physiologically inactive.

Thyroxine contains 65·3 per cent. iodine. Kendall isolated it from thyroid tissue. Harington and Salter isolated *l*-thyroxine



from enzymatically digested thyroglobulin. The physiological activity of the racemic compound is due to its laevo-component ; the dextro-form has little or none (Reineke and Turner (2)).

Iodothyroglobulin appears to have a constant composition except for an iodine content varying from practically nil to 1·7 per cent. It hydrolyses to the usual amino-acids (White and Gordon), and, as indicated above, to small amounts of diiodotyrosine and thyroxine. The amount present in the thyroid varies considerably. Ultracentrifuge and similar methods suggest a molecular weight of the order of 675,000 (McClendon (2) ; cf. Salter) ; it shows a tendency to dissociate to smaller molecules (cf. Fraenkel-Conrat).

Harington and Salter, when digesting thyroglobulin enzymatically, obtained a fraction very resistant to peptidases ; this proved to be a mixture of thyroxine and a thyroxine-containing tri- or tetrapeptide.

Harington has prepared thyronine (thyroxine minus its iodine), diiodothyronine (with half the iodine content of thyroxine), and di- and tetrabromthyronine. Their physiological properties have some bearing on theories concerned with the etiology of Graves' disease.

Present evidence indicates that the normal gland contains no appreciable amount of any iodine compound other than thyroglobulin.

When thyroglobulin (or desiccated thyroid tissue) is hydrolysed by alkali, and the hydrolysate is acidified, thyroxine is precipitated, while diiodotyrosine remains in solution. Harington and Randall found the proportions of the two to be roughly equal. Blanchard and Simonnet found the ratio of thyroxine-iodine to total iodine in horse thyroid to vary from 28 to 60 per cent. However, this ratio, and the content of both diiodotyrosine and

thyroxine radicals in thyroglobulin seem very variable (cf. Palmer, Leland and Gutman ; McClendon, Foster and Cavett).

Cavett has studied the nitrogen distribution and the tyrosine and tryptophane radical contents in normal and goitrous human thyroglobulin. His results indicate that with the exception of tyrosine, diiodotyrosine and thyroxine radicals the amino-acid distribution in the thyroglobulin molecule is the same, whether it be obtained from a normal, colloid, or adenomatous gland, or from that of a patient with Graves' disease. His data seem to indicate that tyrosine radicals, present at certain points in the protein molecule, are capable of conversion to diiodotyrosine and thyroxine. This process is interfered with in goitrous glands, especially as regards formation of thyroxine radicals.

Thyroglobulin from colloid glands of untreated patients is very deficient in radicals of the iodine-containing amino-acids, while the content of tyrosine radicals is proportionately greater. After treatment of cases of toxic adenoma or of Graves' disease with Lugol's solution, the diiodotyrosine radical content is increased even to amounts above normal, but the content of thyroxine radicals is less affected, and that of tyrosine radicals is proportionately decreased.

Synthetic Iodo-proteins with Thyroid Activity. Iodine reacts with solutions of such proteins as egg-albumin and casein to give iodo-proteins and from these Oswald long ago obtained diiodotyrosine in amounts comparable with those obtainable from gorgonin and spongin. Subsequent to the discovery of thyroxine many attempts were made to obtain it from such iodized proteins. They were unsuccessful, though work by Abelin and later by Salter and Pearson, and Salter and Lerman suggested the presence of its radical.

More recently Ludwig and von Mutzenbecher showed that when proteins such as casein are allowed to take up iodine at low temperatures to the saturation point (100 gm. of casein will unite with some 50 gm. of iodine) the iodized protein exhibits little or no thyroid activity. But when such experiments are carried out under conditions simulating those in mammalian tissue (37° C. and a *p*H between 7 and 9 afforded by bicarbonate solution), and the iodization is not allowed to proceed to completion, compounds are produced exhibiting marked thyroid activity (as shown by effect on basal metabolism, and by loss of body-weight when administered to guinea-pigs). Moreover, from hydrolysates of these compounds both thyroxine and diiodotyrosine can be isolated with ease. Plasma proteins, silk fibroin and edestin give

similar results. They also isolated from the digests mono-iodotyrosine, shown by Harington and Rivers (1) to be the 3-iodo-dl compound.

Ludwig and von Mutzenbecher found further that when diiodotyrosine, dissolved in one equivalent of 0·1 *N* sodium hydroxide, is kept at 37° C. for one or two weeks, then diluted with 9 volumes of water, and sulphuric acid added to weak acidity, fine brown specks separate from which by appropriate treatment crystalline thyroxine can be obtained. Harington and Rivers (2) have determined the best conditions for such formation. The optimum *p*H is 10. Addition of hydrogen peroxide shortens the time of formation to fifteen hours at 38°, and one or two hours at 90°. Under these conditions, if the thyroxine is protected by extraction into butyl alcohol during the reaction, a yield of about 4 per cent. is obtained.

Reineke and Turner (4) have obtained similar results. They give as optimum conditions solution in 0·116 *N* sodium hydroxide at a *p*H 9·4–9·6, and a temperature of 60°, oxidation being facilitated by stirring or aeration or by presence of oxides of manganese with stirring. Their yield was 2·8 per cent.

The artificial iodization of proteins to yield products with thyroid activity has been greatly advanced by the work of Reineke, Williamson and Turner. They reported at first that the optimum *p*H range was 6·8 to 7·0, the optimum concentration of iodine (for casein) 7 per cent. (corresponding to iodine substitution of 2 atoms in the tyrosine ring) and the optimum temperature 70° C. From 100 gm. of a product so prepared they isolated 424 mg. of pure thyroxine, which is several times greater than the amount normally obtainable from desiccated thyroid tissue containing 0·2 per cent. iodine. Correspondingly, the iodo-protein showed proportionately greater activity than desiccated thyroid.

Reineke and Turner (3) have still further improved the process. By vigorous agitation during the reaction, and addition of oxides of manganese (especially Mn_3O_4) to catalyse oxidation, and by increasing the relative amount of sodium hydroxide, they find that iodine can be added in quantity to correspond to 6 atoms per radical of tyrosine. By such means thyroxine formation in the protein has been increased to a maximum of 3·37 per cent.

The July, 1945, number of the *Journal of Endocrinology* is a complete record of an excellent example of co-ordinated endocrine research directed to achieve practical ends. It had been shown much earlier by Graham and others that increased secretion of milk follows the feeding of desiccated thyroid to cows, or the injection of thyroxine

into these animals, but such procedures are unsuitable for commercial milk production. Reineke and Turner (1) suggested that iodinated proteins might possess this thyroid action. The British research started in 1941 and consisted in a search for a suitable iodinated protein. Iodinated ox-plasma proteins containing up to 1·5 per cent. acid-insoluble iodine (thyroxine fraction of the hydrolysed product) were prepared, also iodinated ardein (the mixed protein from ground-nuts) containing up to 1·4 per cent. and iodinated casein containing up to 2·8 per cent. The last proved the easiest to prepare on the large scale and showed the greatest biological activity. The conditions given by Ludwig and von Mutzenbecher, with the higher temperature incubation suggested by Reineke, Williamson and Turner were found satisfactory (Rivers and Randall).

Deanesly and Parkes, testing the biological activities, found that with the best preparations the acid-insoluble iodine content is more than ten times that of dried thyroid preparations of like biological activity, suggesting that most of this fraction is not thyroxine-iodine.

Blaxter showed that fractions of iodinated ardein and casein that possessed high biological activity stimulated milk production considerably, with concomitant increase in the cows' metabolism ; long treatment produced no permanent damage to the cows. The milk response is intimately related to the stage of lactation. In early lactation it is small, and at the end of lactation nil. In mid-lactation the percentage response increases as lactation declines, while the greater the initial yield, the greater is the response in pounds per day. The optimal stimulation (producing no unduly severe symptoms of hypermetabolism) gives a 20 per cent. increase in milk production. Iodinated casein can be incorporated in a cattle cube which is consumed satisfactorily.

The ingestion of one quart of such milk daily has no effect on the basal metabolism of normal healthy adults, but it is possible that the use of this milk with young infants calls for precaution (Robertson).

As bearing upon the thiourea and thiouracil treatment of hyperthyroidism (cf. p. 68) it is of interest to note that in a medium of 2 per cent. bicarbonate the combination of iodine with casein is stated to be inhibited by these compounds, as also by cysteine, reduced glutathione, and methionine, apparently due to competitive utilization of the iodine (Calvo and Goemine).

The Thyroid Hormone

When desiccated thyroid tissue is fed to normal or to thyroidectomized animals certain definite effects are produced. These include the restoration of thyroidectomized animals to normal condition and their maintenance in a normal state. It can therefore be concluded that the hormone withstands digestion and that the effects of oral administration can be attributed to the hormone. This affords a means of testing preparations of the hormone.

Various effects produced by administration of thyroid have been used for basis of comparison, and these were reviewed critically

by Kendall. They include (i) the effect on hypothyroid patients, (ii) the effect on oxygen consumption in the rat, (iii) increase of resistance of mice to acetonitrile poisoning, and (iv) decrease in growth rate and production of organ hypertrophy in young rats.

Comparisons using such tests indicate that thyroglobulin and the resistant thyroxine-polypeptide of Harington and Salter, when compared with thyroid on basis of iodine content, possess its full activity, while diiodotyrosine is inactive. Thyroxine, even *l*-thyroxine, while qualitatively equivalent to the thyroid, quantitatively does not seem quite as active (cf. Salter).

The problem of what is the thyroid hormone has recently been reviewed by Fraenkel-Conrat. He considers that it is neither thyroxine nor thyroglobulin. The latter can be tested for in the blood immunologically, and only appears in the blood following trauma to the thyroid. Evidence based on iodine-fractionation studies of the blood from hypothyroid, normal and hyperthyroid patients suggests that the hormone is an iodized albumin (cf. Riggs *et al.*), but recently Salter, Oncley and Wheeler have shown that while the major part of the circulating iodine is present in the blood plasma albumin fraction, its highest concentration is found with the alpha- and beta-globulins, in which resides most of the thyroid activity. They therefore consider that the thyroid hormone circulates as an integral part of the plasma proteins in much the same way as do antibodies.

It has been shown that the tissue cells of the thyroid secrete thyroglobulin into the follicles and that the colloid of the follicles possesses proteolytic activity. Presumably the thyroglobulin is broken down to the iodo-protein which is the true hormone and this passes into the circulating blood.

The formation of thyroglobulin is probably independent of iodine metabolism, its molecule constituting a scaffolding for subsequent iodination (Salter (2)). The formation of thyroxine or thyroxine-radicals within the globulin molecule is probably brought about by an oxidative process (Harington and Rivers (2)). According to Mainini a direct relationship exists between the oxidase content of the thyroid and its activity; Reineke and Turner (3) suggest that manganese acts catalytically in promoting thyroxine formation in the thyroid.

As judged by substitution therapy following thyroidectomy, the human thyroid produces daily an amount of hormone equivalent to about one-third of a milligram of thyroxine, and the daily intake of iodine needed to permit this production lies between 0·1 and 0·2 mg. (cf. Salter).

Histological Evidence Concerning the Path of Discharge of the Thyroid Hormone. This has been reviewed by Severinghaus (*cf.* also Baillif). The secretory cells of the thyroid pass through stages of activity and rest. They may secrete apically into the adjacent acinus or basally into the blood stream, and also normally transport stored secretion from the acini to the vascular channels at their basal borders. Formation of secretion is evidenced by cellular enlargement and formation of intra-cellular colloid vesicles. The Golgi apparatus enlarges to a prominent network and tends to move apically from its resting position applied to the nucleus. Fuchsinophil granules in the apical region may be antecedents of the colloidal secretion, which appears first as droplets in juxtaposition to the Golgi apparatus. In resting glands these may be passed apically to the lumen of the adjoining acinus, but in hyperactive glands whose colloid has been discharged they tend to move basewards, to be excreted directly into the blood. The Golgi apparatus retains its apical position during transport of colloid but does not enlarge, so that its size gives some clue to the action in progress. During transport from the acini the apical region of the cell expands to become dome-shaped.

There is some evidence that in the normal thyroid most of the parenchyma at any one time is functionally inactive and in reserve.

Recent work is in general agreement. Williams implanted living thyroid follicles in rabbits' ears and found that they all go through repeated cycles of activity, secretion towards the lumen, colloid release, partial collapse, and recuperation. In the second stage colloid seems to diffuse across the follicular wall, but is never extruded into the interfollicular space, being presumably hydrolysed first.

Algire transilluminated the thyroid gland of the living salamander, and observed that, following injection of a pituitary thyrotrophic concentrate, there occurred in sequence gradual enlargement of a granule into a colloid droplet, formation of new colloid droplets in proximity to the apical end of the nucleus, and movement of colloid droplets from the apical end of the cell to the basal position, presumably for direct secretion into the vessels.

Severinghaus has also studied the response of the thyroid to stimulation by the thyrotrophic hormone of the pituitary. Initially the thyroid cell is heightened, and transport of the stored follicular colloid to the blood stream is accelerated. During this stage the mitochondria increase in size and number, but the Golgi apparatus undergoes no appreciable change.

With continued stimulation the follicular cells commence to elaborate their secretion, the Golgi apparatus hypertrophying; transport of follicular colloid and elaboration of new secretion proceed simultaneously. With still further stimulation the cells hypertrophy and proliferate actively, pushing into the follicular cavity, and colloid inclusions of several cells can coalesce to form new follicles, about which

the cells polarize themselves. When the stimulation ceases, the structure of the gland returns to normal, but the gland remains enlarged.

Welch and Broders believe that the *position* of the Golgi apparatus is without significance, but its *size* is very significant as an indication of the condition of thyroid function. Their conclusion is based on a study of human thyroids removed at operation.

Thyroid, cultivated *in vitro* in the Carrell-Lindburgh apparatus, secretes iodine, stated to be chiefly in non-protein combination, into the perfusion fluid under stimulation of the thyrotrophic hormone.

Studies with Radioactive Iodine

Introduction. Metabolic studies now frequently use the so-called " tagged " atoms to trace the course and fate of specific compounds and radicals and the synthesis of others within the animal body. Examples of such " tracer " elements are deuterium (heavy hydrogen, H^2), heavy nitrogen (N^{15}) and radioactive phosphorus (P^{32}). They behave chemically like the ordinary elements. Very delicate methods are available for their detection and estimation so that the presence of the minutest amount of a " tagged " element amongst its fellows give a definite clue to what is happening to them.

Inherent in the property is the atom-by-atom alteration of the radioactive element to another, usually non-radioactive ; in a given interval of time a proportion changes which is in constant ratio to the amount present at the beginning of the interval. The rate of change is usually expressed in terms of the time-interval needed for half the material to lose its radioactivity, its " half-life." For metabolic studies artificial radio-elements are usually selected whose half-life is long enough to enable them to be accurately measured after at least twenty-four hours, if not several days.

Radioactive Iodine. Several radio-iodines have been prepared. Inactive iodine has an atomic weight of 127. When metallic tellurium is bombarded with deuterons in the cyclotron, the chief radioactive product is I^{131}, which has a half-life of 8 days. The treated material is dissolved in nitric acid, inert iodine is added, and the solution distilled. The iodine distilling over carries with it the radioactive iodine, and both are collected in carbon tetrachloride, from which they can be extracted by sodium thiosulphate solution, and subsequently converted into iodine compounds suitable for metabolic studies. Such a compound will contain a measurable proportion of the radioactive element. The rare gas xenon is believed to be the inert product when I^{131} loses its radioactivity.

For metabolic studies I^{131} has been of greatest service, though the short-lived I^{128} (half-life 25½ minutes) has proved useful in studying the initial stages of iodine metabolism. (Salter's book should be consulted for further details of the preparation and radioactive measurement of these iodines.)

Results of Studies with Radioactive Iodine. Salter reviewed the earlier work of Hertz and his collaborators and of Hamilton and Soley. Leblond has recently published a useful review of his own and other work, while among others Chaikoff and his co-workers and Lein have made important contributions. Many of the results deal with abnormal thyroid states and will be dealt with in the next chapter.

When a single dose of iodide (including radioactive iodide) is injected intravenously into a normal rabbit the thyroid takes up vastly more than it would were there uniform distribution throughout all tissues. Radioactive iodine is detectable in the thyroid within two minutes of injection, and according to Hertz there is practically a saturation within ten to fifteen minutes, though Lein's results are not in complete agreement. The percentage extracted by the gland from any single dose increases as the size of the dose decreases ; the gland operates more efficiently on a smaller dose. A subsequent dose leads to smaller uptake by the thyroid.

Most of the iodide from such injection is actually excreted through the kidneys, and the rate of excretion, as measured by radioactive methods, is the same as that determined by older methods (Hamilton and Soley ; cf. Salter).

According to Lein, following injection of radioactive iodide into rabbits, the inorganic iodine of the thyroid increases rapidly to a maximum in about ten minutes, and then slowly decreases, being transformed to organic iodine, such organic iodine being detectable within five minutes of the injection. After thirty minutes half the accumulation in the thyroid is in organic combination, while after some hours the total accumulation of organic iodine far exceeds the initial maximum of inorganic iodine, suggesting that after an initial saturation the thyroid has regained ability to distrain iodine from the circulation.

Hertz found that shortly after an injection there was but little iodine in thyroxine-combination ; later the ratio of diiodotyrosine- to thyroxine-iodine became fairly constant at about 2 : 1. When the thyroid is made hyperactive by injection of thyrotrophic hormone (cf. Chapter IX) relatively more iodide is taken up and relatively more iodine is present in thyroxine form. Hypophy-

sectomy (and thus removal of thyrotrophic stimulation) does not appear to lessen formation of diiodotyrosine, but does decrease formation of thyroxine.

Leblond stresses the fact that under normal physiological conditions, with minute amounts of available iodine, the thyroid can abstract about 50 per cent. of it, in contrast with abstraction of relatively minute amounts from large doses. Under physiological circumstances iodide is transformed to diiodotyrosine as it enters the thyroid, while later on thyroxine is slowly formed from this. When large doses of iodide are administered, initially the gland contains much iodide, which later changes to organic forms. *Only iodide is taken up by the gland.* Thus when diiodotyrosine is administered (and it has been recommended for therapeutic use) it is largely excreted, and the proportion taken up by the gland must be changed first to iodide.

Morton and Chaikoff, using radioactive I^{131} as tracer element, have shown that surviving tissue slices of thyroid from sheep, dog and rat will transform iodide into thyroxine and diiodotyrosine. When 300 to 350 mg. of rat thyroid were incubated in a bicarbonate-Ringer solution along with the iodine, subsequent tissue hydrolysis showed that 12 per cent. of the I^{131} was present in thyroxine radicals and 70 per cent. in diiodotyrosine radicals. Dog and sheep thyroids produced a smaller degree of transformation, but in similar ratio between the two. This *in vitro* incorporation of iodine failed to occur with homogenized glands (cf. Chaikoff *et al.* (2)).

Most of the above results confirm conclusions reached by older methods. Radioactive studies have suggested the unexpected conclusion that tissues other than the thyroid retain a primitive ability to synthetize thyroxine or some compound with like activity (Chapman ; Morton, Chaikoff *et al.* ; Chapman *et al.*).

The Function of the Thyroid

It is generally considered that thyroid function is linked with oxidative processes of the body cells, yet it is not possible to demonstrate that all the manifold changes associated on the one hand with thyroid deficiency and on the other hand with thyroid hyperactivity can be accounted for directly or indirectly by a change in the level of cell oxidation. To appreciate this some of these effects must be listed.

Experimental thyroidectomy produces in animals at all ages a

marked diminution of basal and general metabolism. In the young there follow retardation of general growth, of ossification and of development of the sex organs, delay in involution of the thymus, and slight enlargement of the anterior pituitary and the adrenal cortex. The skin thickens and its hairy covering develops imperfectly. Body temperature is subnormal. There is usually marked lack of intelligence, indicating involvement of the central nervous system and especially the brain.

Corresponding effects, as far as they are possible, are produced in the adult animal. Muscle loses tone and becomes weaker; muscular activity is diminished. Sexual function is depressed. The nervous system is affected; dullness and apathy are marked. The skin is dry; hair tends to fall out. Anæmia is usual. Tissue regeneration is retarded. Body temperature is subnormal; heat production is lessened and consumption of oxygen and production of carbon dioxide decrease. Carbohydrate tolerance is raised (cf. Sharpey-Schafer).

Artificial hyperthyroidism from administration of desiccated thyroid or of thyroxine produces most diverse results. The normal animal, so treated, loses weight and excretes more urea and creatine. It uses more oxygen and produces more carbon dioxide and more heat. It oxidizes more carbohydrate, and depletes its liver glycogen stores; there is frequently a hyperglycæmia (cf. Kendall).

In the young animal growth rate decreases, and heart, liver, kidneys, spleen, etc., hypertrophy (cf. Cameron and Carmichael; Robertson). Very high dosage produces toxic results and can result in death, preceded by a general acidosis suggestive of accelerated and incomplete tissue oxidation (Draize and Tatum).

When male fowls are fed small doses of thyroid, and a patch of feathers is plucked in either the neck, wingbow, or saddle (areas exhibiting secondary sex differences), the new feathers do not show the characteristic male plumage. Larger dosage produces rapid moulting and the new feathers show depigmentation (Hutt; Zavadovsky).

Changed level of oxidation seems a rational explanation for many of these phenomena, though it does not seem to explain all. Numerous *in vitro* experiments support the view that it is a fundamental effect. Mansfeld's summary of his own and earlier work, and that of Andrus and McEachern, permit the following conclusions.

Surviving hearts of thyroidectomized cats use less glucose than those of normal cats, while those of cats dosed with thyroxine use more.

Surviving tissues of thyroidectomized animals use less oxygen than those of normal controls ; those of thyroid-fed animals use more. Experiments in which oxygen uptake of minced tissue or of tissue slices is measured by Warburg's method indicate that the thyroid hormone produces acceleration of anaerobic oxidation in tissue cells. There is evidence of both peripheral and central action of the hormone.

Where the hormone increases oxidation there is a parallel increase in production of ammonia.

Mansfeld concluded that the thyroid hormone acts on the cells themselves, primarily in facilitating changes in protein metabolism, and that such changes involved others which included oxidation processes and therefore increased use of oxygen.

It is probably safe to state, with our present knowledge, that the various effects associated with thyroid action all involve oxidation processes, directly or indirectly, but that some of these effects may not necessarily be the result of the oxidative processes, but rather of pre-oxidation changes (such as amino-acid catabolism).

The Thyroid and Growth. While heavy doses of thyroid or thyroxine undoubtedly diminish growth rate, there is evidence that the thyroid hormone is actually needed for growth under physiological conditions. Thus it will be shown (p. 335) that the growth hormone of the pituitary is ineffective when injected into the thyroidectomized animal. The dwarfing of the cretin is removed by adequate early thyroid treatment (cf. p. 41). Recently Koger, Hurst and Turner have shown that minute daily doses of crystalline thyroxine, injected subcutaneously into young mice, slightly accelerated growth and body-weight increase over a period of several weeks, with corresponding increase in food intake. The treated animals had a higher percentage of water and nitrogen, and a lower percentage of fat than the controls.

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CHAPTER III

DISEASE STATES ASSOCIATED WITH ABNORMAL THYROID FUNCTION

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INTRODUCTION

It is possible to elaborate a complex differentiation of thyroid diseases, but from the endocrine point of view this possesses no advantage. Even in the following simple classification there is not complete exclusion between the few divisions : (i) inflammatory conditions, (ii) non-toxic goitre, (iii) hypothyroidism, (iv) hyperthyroidism, and (v) malignant tumours of the thyroid.

Before considering these it is desirable to discuss briefly various tests and metabolic studies which indicate differences due to variations in functional activity of the thyroid.

Basal Metabolism

While the determination of the basal metabolic rate is of great value in diagnosis of thyroid disease, in controlling the preoperative treatment of hyperthyroid patients and the result of operation, and in adjusting the thyroid dosage of hypothyroid patients, yet it is necessary to realize the degree of accuracy of its measurement, and to recognize that various other conditions, some not associated with disease, can cause deviations from normal.

While careful technique rules out most avoidable errors, yet with the clinical instruments usually employed a fasting respira-

tory quotient of 0·82 is assumed. The assumption is usually permissible, but does not hold for the unbalanced diabetic (though the error may be slight). The increased body-temperature associated with fever needs rather a large correction (the subtraction of 7 per cent. per degree Fahrenheit), which for the patient with a temperature of 101° F. or over can easily lead to wrong conclusions when the basal rate borders on the maximum high normal figure. (A sub-normal temperature requires no correction.) But the chief error can arise from the assumption that the normal heat production, proportional to body surface, can be calculated from the height and weight of the patient. This assumption leads to a variable error necessitating an allowance of ± 15 per cent. as normal limits, and in consequence it by no means follows, though it is frequently assumed, that a figure approaching the upper or lower limit of normal is truly normal for a particular patient.

While such standards as those of Aub and Du Bois (as modified by Boothby and Sandiford) are adequate for adults, it is generally agreed that the various standards available for children are less reliable, and that a somewhat greater margin of error (normal spread) should be allowed. DuBois (1) has dealt with the subject of basal metabolism exhaustively. The gradual change with age, and the variation with sex are fully allowed for in the calculations by the routine procedure. (For children, two to twelve years, see Lewis *et al.*)

Under-nutrition can markedly affect the basal rate, an abnormally low diet depressing it more than 20 per cent. Since so many patients are under-nourished this factor needs considering in the interpretation of low results. Protein of the diet also produces a definite effect. A protein-free diet, given to a normal individual, produces a rapid fall in his basal rate within a few days, while a high protein diet can raise the rate above normal.

There is a slight regular fluctuation during the menstrual cycle, insufficient to lead to false conclusions (Rubenstein). During pregnancy there is a slow rise, perceptible during the second half. According to Hanna, at the ninth lunar month figures may be as much as 16 per cent. above the pre-pregnancy level ; on the ninth day post-partum the rate is again normal.

Numerous studies have been made contrasting basal metabolic rates of normal persons in tropical and in temperate climates, and of non-Aryan and Aryan races. Earlier work suggested that both climate and race produced an effect, but more exact studies have not supported this view. A series of very accurate studies have been reported by DuBois, Castex and Schteingart, Campos,

Albagli and others in a special number of " Cultura Médica " (Rio de Janeiro), published in December, 1940. While most of the papers deal with Brazilian conditions, they have general application. DuBois (2) concludes from his own work and that of others that in general men have a uniform basal metabolism over a wide range of environmental temperature, but that women show a reduction of metabolism in the warm zone. Thus two men lying naked in the metabolism calorimeter showed no significant variation in their basal metabolism with environmental temperature varying from 23° to 35° C. during an experimental period of one to two hours. DuBois quotes Albagli's similar results with both naked and clothed men, which suggest an almost level heat production between 23° and 36°, and thinks the results show a zone of minimal metabolism for clothed men between 22° and 39° and for nude men between 24° and 34° C. DuBois' results with women showed a distinct minimal value at temperatures between 29° and 33° C., lower or higher temperatures giving higher rates.

The application of these results to actual measurements is important enough to quote : " In performing basal metabolism tests on men it does not seem necessary to take any special precautions as to room temperature as long as the men have suitable amounts of clothing or covering and are not uncomfortably cold or uncomfortably warm. . . . Due allowance should be made for high metabolism if the women are slightly cold and for low metabolism if the room is warm or the clothing heavy enough to bring the environmental temperature above 29° or 30° C."

Castex and Schteingart (Buenos Aires), dealing with the differing climatic conditions in different parts of Argentina, conclude from study of measurements of 2,000 normal persons that climate does not affect basal metabolism.

Campos (Sao Paulo) usefully summarizes earlier work and stresses the complexity of the problem.

Albagli summarizes his own valuable observations, concerning which DuBois remarks, " Albagli, in his large and carefully conducted series of determinations in Brazil, found that the basal metabolism of normal individuals, properly nourished, was independent of climate, of race, and of biotype."

Albagli himself says : " The factor which governs the modifications of basal metabolism is the habitual alimentary ration. An insufficient quantitative and qualitative alimentary ration causes decrease of basal metabolism on account of the progressive adaptation of the organism. . . . Super-alimentation of normal individuals causes an increase in the basic expenditure on account of the

consumption *de luxe*." Race is not a factor. Climate is not a factor. The basal metabolism of healthy persons in Rio de Janeiro corresponds with American and European standards.

In diseased states (excluding the effect of fever already referred to) probably over 90 per cent. of abnormal basal rates are directly attributable to abnormal thyroid function. Low rates are found in hypothyroid conditions, but also invariably in anorexia nervosa, sometimes in hypopituitary states (through pituitary control of the thyroid), occasionally in Addison's disease, rarely in cases of pernicious anaemia, and frequently if not invariably in nephrosis and nephrotic (wet) nephritis.

High rates are found in hyperthyroid states, but also in some proportion of cases of acromegaly (again, through pituitary control of the thyroid), and of the leukaemias, and occasionally in polycythaemia vera, pernicious anaemia, Hodgkin's disease, essential hypertension, and cardiac disease (cf. DuBois (1)).

It should perhaps be stressed that in thyroid disease altered rates are the rule, whereas in most of the other diseases mentioned they are the exception, or at most occasional findings. Nevertheless it is obvious that an altered basal rate is not diagnostic of thyroid disease, but is only a useful confirmatory check to clinical diagnosis.

Cytological Studies

The studies of Okkels and of Wahlberg indicate that there is no apparent qualitative difference in the mechanism of secretion in the normal thyroid and in the thyroid in its various pathological states. The Golgi apparatus of the follicular cells is not enlarged in non-toxic parenchymatous or nodular goitre. Thyroids from cases of hyperthyroidism show enlarged and often markedly enlarged Golgi apparatus, indicating marked hypersecretion (cf. p. 15). This persists during pre-operative treatment with iodine (cf. p. 61), although accumulation of colloid material indicates that follicular storage has for a time replaced discharge of the hormone into the circulation.

Welch and Broders found hypertrophy of the Golgi apparatus in thirty-four of thirty-five thyroids from patients with Graves' disease, nineteen of twenty-one from patients with toxic nodular goitre and five of sixteen from patients with apparently non-toxic nodular goitre. They consider that the size of the Golgi apparatus indicates the condition of cellular and glandular function of the thyroid more accurately than other criteria, though of course its measurement is unsuitable for diagnosis.

Metabolic Studies

It will be shown later that in hypothyroid states plasma cholesterol varies from high normal to much above normal values, and responds rapidly to thyroid treatment, so that its measurement has been suggested as a useful diagnostic procedure (cf. p. 42). In hyperthyroidism blood cholesterol tends to be low, but its value is not of special diagnostic significance (Man, Gildea and Peters).

The normal creatinuria of children tends to be decreased in hypothyroidism (cf. p. 42). The blood plasma albumin tends to be low or low normal in hyperthyroidism, high normal or slightly high in hypothyroidism (Cameron).

Bartlett reports that in hyperthyroid states an acidosis is present, and that on exertion there is a prompt decrease in the alkaline reserve.

Robertson has studied the calcium and phosphorus metabolism in hypo- and hyperthyroid patients. He considers that his findings suggest that the thyroid hormone directly affects the renal threshold for calcium, phosphate being affected secondarily. Thus hyperthyroid patients have diminished blood serum calcium and inorganic phosphorus, while there is increased urinary excretion of both. In hypothyroidism there is diminished excretion of calcium and phosphorus, though blood serum calcium and inorganic phosphorus are normal. Plasma phosphatase is low in hypothyroidism (cf. Talbot).

The non-ultrafilterable fraction of the blood magnesium is about 14 to 30 per cent. of the total. Total blood magnesium does not significantly vary from normal in either hyper- or hypothyroidism, but in the latter (myxoedema) the non-ultrafilterable fraction is entirely absent, while in hyperthyroidism it is consistently increased. Thyroid replacement therapy and thyroidectomy respectively restore this fraction to normal level. While the nature of the magnesium fraction so bound to protein as to be non-dialysable is still unknown, there is a rough correlation between its amount and the amount of organically bound iodine in blood plasma. (Cf. Soffer *et al.*, Dine and Lavietes.)

Blood Iodine shows Definite Changes from Normal in Thyroid Disease. Its estimation is not easy; recent figures for it are consistently lower than earlier ones. Thus Klassen, Bierbaum and Curtis found that the average figure for ten persons on a low iodine diet and without thyroid disease was, for whole blood, 4 micrograms per 100 c.c., and for plasma 7·1 micrograms. The corresponding figures for ten markedly hyperthyroid patients (average B.M.R. + 60 per cent.) were 10 and 18 micrograms. The

results indicate that about 95 per cent. of the blood iodine is present in plasma, both normally and in hyperthyroidism. The iodine content of the cerebrospinal fluid is not increased in hyperthyroidism.

Perkin and Lahey present slightly higher figures for a much larger number of persons. The average for normal persons per 100 c.c. of blood was found to be 6·8 micrograms (extremes 2 and 15). The average for a large group of hyperthyroid patients was 15·5 micrograms (range 2 to 100) ; 34 per cent. gave values within the normal range. Presence in any specific case of a normal or an elevated value roughly depended on the duration of the hyperthyroid state.

In hypothyroidism the blood iodine is low normal or below normal (Turner).

It has been pointed out that the thyroid hormone is present in the protein fraction of the blood plasma (cf. p. 14). The amount of it is proportional to the degree of thyroid activity. In marked hypothyroidism it almost disappears (Bassett, Coons and Salter). The protein-iodine fraction (presumed to be the hormone) is present in amounts of the order 2 micrograms iodine per 100 c.c. of blood in hypothyroid patients, 2·4 to 8 in normal blood, and 8 to 25 in that of hyperthyroid patients. (Cf. also Riggs, Lavietes and Man.)

Perkins and Cattell think that in mild hyperthyroidism the blood iodine value is a better criterion in differential diagnosis than is the basal metabolic rate. Salter, Bassett and Sappington find that in cases in which the basal metabolic rate and the clinical diagnosis are in agreement there is close correlation between the plasma protein-iodine and the basal rate. When there is no such agreement figures for plasma protein-iodine are more reliable for diagnostic purposes than the basal rate. However, the difficulties of present analytical procedures for the iodine estimations render it unlikely that such conclusions can be widely applied.

An iodine tolerance test has been suggested, and it has been shown that after injection of a specific dose of iodine the resulting curve of blood iodine for hyperthyroid patients is depressed below normal (cf. Watson). The same criticism applies to this test.

Studies with radioactive iodine (cf. p. 17) are producing valuable results. Experimentally produced goitrous (hyperplastic) thyroids take up a larger proportion of a dose of radioactive iodine than do normal glands. Similarly, the thyroids of patients with hyperplastic non-toxic nodular goitre are avid for iodine, which accumulates in the cellular portion of the gland and not in the colloid. Such glands form thyroxine more rapidly.

In childhood myxoedema (cf. p. 40) and in struma lymphomatosa (p. 30) the thyroid takes up relatively little iodine. In thyroid carcinoma (p. 86) the malignant tissue takes up very little iodine from a radioiodine dose, but the non-malignant tissue takes up a considerable amount. (Cf. Salter, LeBlond.)

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INFLAMMATORY CONDITIONS OF THE THYROID (AND HASHIMOTO'S DISEASE)

In rare instances the thyroid is affected by toxins of acute infections, tending to become hyperplastic, with sometimes an increased basal metabolic rate (cf. Cole). Rare chronic inflammatory conditions may be due to tuberculosis, syphilis, actinomycosis, etc., and include Riedel's disease and inflammatory conditions traceable to parasitic causes, such as Echinococcus disease, and Chagas' disease due to *Trypanosoma cruzi*.

Young's analysis of 2,900 thyroidectomies in Duluth hospitals during the preceding fifteen years gives some clue to the relative

incidence of inflammatory lesions in central North America. Only twenty-six thyroids were considered inflammatory, of which twelve were classed as chronic thyroiditis, and seven as acute thyroiditis (with average duration of symptoms preceding operation of thirty-five days). There were one case each of Riedel's and Hashimoto's diseases.

Thiouracil (cf. p. 68) has proved useful in the treatment of acute thyroiditis (King and Rosellini).

Within the last few years a number of papers have appeared dealing with Hashimoto's disease and stressing its non-identity with Riedel's disease. Joll differentiates between the two very thoroughly. Schilling has also published a comparative study, in which he adduced evidence that the " struma granulomatosa " of De Quervain is in reality a giant-cell variant of Riedel's struma. Hashimoto's disease is probably of non-inflammatory origin, but is included in this section for convenience.

Riedel's Disease (**woody thyroiditis**) is common before forty years of age, and the incidence is equal in the two sexes. The pathological change is usually unilateral, with the formation of a small and hard mass, along with, occasionally, a cyst or a calcified area. Lymphocytic infiltration is absent. Histological examination of the mass shows no trace of epithelium or of colloid, except at the periphery, where small groups of shrunken follicles may be found, surrounded by dense fibrous tissue (Joll).

De Courcy suggests that the (usually insidious) onset of the disease results from a vascular disturbance, commencing with a perithyroiditis which induces constriction of the vessels ; the thyroid responds by forming the characteristic ligneous tissue.

There is no evidence of thyrotoxicosis or of myxoedema (Joll). The basal metabolic rate is normal or slightly elevated (De Courcy). The dominant symptoms are the pressure effects with intense dyspnoea and asthma. Operative risks are relatively high and recurrence comparatively common. Post-operative myxoedema is rare (Joll).

Hashimoto's disease (**Struma lymphomatosa**) was first described by Hashimoto in 1912. Joll bases his findings on a study of 85 cases (51 from his own practice). The disease is rare before forty years of age, is much commoner in women than in men, and is commoner than Riedel's disease. The thyroid is diffusely enlarged, and of uniform smooth consistency throughout, the goitre being usually of moderate size. In the early stage of the disease the gland is friable, but later it develops a resilient toughness. Histological examination shows a diffuse lymphocytic infiltration, with widespread destruction of the thyroid parenchyma, followed

by fibrosis. Joll thinks that the pathological process is neither inflammatory nor neoplastic nor degenerative ; the cause of the disease is not known.

Its onset is insidious, the progressive destruction of the thyroid slowly leading to a myxoedematous state. The typical patient is a woman in her late forties, apathetic, inclined to obesity, with facies of early myxoedema and a low basal metabolic rate (sometimes very low). Pressure symptoms are slight, seldom more than dyspnoea on exertion.

The effect of radiotherapy should be determined before operation is decided on. The goitre is usually sensitive to X-ray. Surgery is seldom imperative, but when it is employed the operative risk is small. Post-operative myxoedema is to be anticipated. Recurrence is rare (Joll ; cf. also Ziskind and Schattenberg). Moore and Lloyd recommend that if appearance at operation (for hyperthyroidism) suggests a condition other than typical hyperplastic or adenomatous goitre a rapid frozen section should be made to exclude malignancy. If Hashimoto's disease is confirmed a generous subtotal thyroidectomy should be performed.

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NON-TOXIC GOITRE

Non-toxic goitre includes " simple " endemic goitre and non-toxic nodular goitre. Presumably the goitre of Hashimoto's disease is also included (cf. previous section), as well as amyloid goitre.

Endemic Goitre

Endemic goitre is associated with absolute or relative deficiency of iodine in the diet. In non-mountainous regions the goitre is of diffuse colloid type. Colloid accumulates ; the vesicles are distorted and enlarged. The goitre gradually increases in size till puberty, then tends to disappear. According to McCarrison (3), in mountainous regions the goitre presents a different picture,

suggesting hyperplasia and formation of many small new vesicles, and is poor in colloid. Solid masses of cells are present.

Deficiency of vitamin A has been suggested as a causative factor of a type of goitre in the experimental animal (and perhaps in man) which is not benefited by administration of iodine (cf. McCarrison (1)).

Dietary Iodine and the Incidence of Endemic Goitre. The wide variation in the amounts of iodine present in soils, drinking waters and foods has already been referred to (p. 9). In many regions over the whole globe there is a striking inverse relationship between the content of iodine in the diet and the proportion of goitrous individuals among the population. This has been demonstrated for such widely separated regions as Switzerland, Hungary, Argentina, China and New Zealand. Japan is practically non-goitrous ; the iodine consumption of the Japanese is more than double that of any other people.

Since iodine is excreted chiefly through the kidneys measurement of the urine content of iodine per twenty-four hours give a close clue to the daily iodine intake. Districts in Switzerland with a mean excretion of 19 and of 17 micrograms per day showed repectively an incidence of goitre in their children of 62 and 56 per cent. Similar goitrous districts in Norway, in which the incidence of goitre in children ranged from 30 to 60 per cent., showed a daily urinary excretion ranging from 87 to 29 micrograms. On the other hand, Effingen in Switzerland, with 1 per cent. goitre among its children, showed a mean excretion of 60 micrograms, and the Ligurian coast of Italy, the Vik i Sogn district in Norway, and Samoa, all goitre-free regions, gave respectively the mean figures of 112, 173, and 302 micrograms (v. Fellenberg ; Lunde ; Hercus and Aitkens).

The British Committee on iodine deficiency and thyroid disease, from studies of the relationship of the iodine contents of water, milk, and pasture to the occurrence of goitre in two English districts, confirm the relationship of environmental deficiency of iodine to incidence of goitre, but consider that there is no conclusive proof that this is the sole cause.

Robertson has recently reported on the incidence of endemic goitre in Yunnan province, China. There is a high incidence of thyroid enlargement, and frequent cretinism. He considered that well over half of the adult population working along the Burma Road exhibited goitre, though the incidence was not so marked in children. The vegetation in this district and Yunnan-mined common salt are both deficient in iodine. Normally 70 per cent. of the salt needs of China are supplied by sea-salt (relatively rich

in iodine). During the Japanese military occupation the hinterland of China was cut off from its coastal supply, and deprivation of the normal sources of salt was one of the greatest hardships. Large areas of free China are now being supplied from the Yunnan mines, and the increasing deficiency in iodine in widespread areas of China may be expected to lead to still further increase of goitre. Some recent incomers to Yunnan province developed a goitre within six months. Areas, especially certain towns, able to obtain salt from the Szechwan mines are freer from goitre, since this mined salt is not deficient in iodine.

Use of Iodine in Prevention and Treatment of Endemic Goitre. While burnt sponge (which contains iodine) was used as a remedy for goitre in the Middle Ages, and while Prout used iodine for this purpose in 1816, five years after the element was discovered, and Prévost advocated its use in 1849, subsequently the treatment fell into disuse.

Marine and Kimball carried out the first systematic large-scale attempt to combat and prevent goitre by iodine treatment in the schools of Akron, Ohio, in 1916. It was successful. Of those girls who were initially non-goitrous only 0·2 per cent. developed a goitre during four years of treatment, as compared with 27·6 per cent. among those whose parents refused to permit the treatment. Of those initially goitrous, 60 per cent. showed improvement during treatment, as compared with only 14 per cent. of the untreated group.

Immediately following the publication of these results similar treatment was instituted in other goitrous communities. Good results have been reported from Switzerland, Norway, Italy, Austria, Canada, New Zealand and elsewhere.

In these wholesale experiments sodium or potassium iodide or iodized fat at stated intervals, or iodized common salt continuously, have been used.

The Goitre Sub-Committee of the British Medical Research Council recently urged the addition of a trace of iodine to all common salt consumed in Great Britain (cf. Editorial, Lancet, 1944, i, 121).

Similar good results have been obtained with farm animals (Keith ; Evvard).

Further proof of the prophylactic benefit of iodine has been afforded by the action of certain European authorities in restricting its use, owing to fallacious views as to its potential danger to persons with non-toxic nodular goitre (*vide infra*). Thus Fischler reported that in one district in Bavaria in 1928, when iodized salt

was in full use, only 6 per cent. of the children were goitrous, while in 1933, after mischievous propaganda had lessened its use, 52 per cent. were goitrous.

Follow-up reports in Michigan continue to be satisfactory. In 1934, after ten years' general prophylactic use of iodine, only 1 per cent. of the children had goitre (McClure). Between 1924 and 1935 there resulted a 75 to 90 per cent. decrease in the incidence of goitre in those countries in which iodized salt was in use (Curtis and Fertman).

The incidence of goitre in new-born infants of goitrous mothers has markedly decreased following treatment of the expectant mother with iodized salt throughout pregnancy (cf. Kimball). Wespi reports that the prophylactic use of iodine in pregnant women in Switzerland has reduced the incidence of goitre in the new-born from 50 to 5·3 per cent., the amount of the decrease depending on the amount of iodine taken. A daily intake of 150 micrograms of potassium iodide during the last few weeks of pregnancy completely abolished goitre in the new-born. In over 1,000 women given such dosage there was no evidence of toxicity or development of a toxic goitre.

Parmelee records three cases of congenital goitre of undetermined origin, but which were certainly not due to iodine deficiency in the mother. Each mother had taken large doses of iodine throughout her pregnancy for asthma or for tachycardia. None of the mothers had goitre. All three babies had greatly enlarged goitres at birth, with cyanosis and dyspnoea. In all three the thyroids rapidly decreased in size and were normal in four months to a year, with subsequent normal development.

Experimental Production of Simple Goitre. Diets deficient in iodine have produced hyperplastic goitre in rats (Levine ; Remington ; J. Thompson) and in chicks (Palton). Mellanby produced goitre in pups by keeping the mothers on a diet low in iodine, and the young, after weaning, on a similar diet.

Excessive amounts of calcium salts in the diet accelerate and increase the hyperplasia in rats produced by an iodine-deficient diet, while increase in the iodine intake abolishes this effect (J. Thompson ; Krauss and Monroe). It may therefore be concluded that if the iodine intake be barely sufficient to prevent goitre, increased intake of calcium will produce a relative deficiency of iodine.

One of the most important recent experimental developments has been the production of goitre by excessive intake of cabbage. Rabbits kept for some weeks on a diet consisting largely of cabbage

develop diffuse hyperplastic goitres. Addition of a small amount of iodine to the diet completely prevents the development of the goitre (cf. Webster). The effect has also been produced in rats and guinea-pigs (Blum). The active material is possibly a glucosidic compound of an organic cyanide, and Marine *et al.* have shown that injection of organic cyanide into young rabbits will produce goitre and even exophthalmos. Of some importance is the observation that heavy iodine dosage to such goitrous rabbits converts a heat production from below normal into one two or three times the normal rate, with rapid loss of weight and death within two or three days. Smaller iodine dosage produces similar, but non-fatal effects, which must be considered as due to sudden increased production and output of the thyroid hormone from the enlarged and hyperplastic gland. These results are considered to throw light on the so-called " iodine-Basedow."

Hercus and Purves, and later Griesbach *et al.* have produced similar goitrigenic effects by feeding seeds of rape and other Brassicae to rats. All such effects, including those of thiouracil etc. (cf. p. 68), appear to be intermediated through the anterior pituitary (cf. p. 342).

Etiology of Endemic Goitre. Only a few of the many theories which have been suggested need consideration. Obviously the inverse relationship between dietary iodine intake and incidence of goitre, along with the experimental production of goitre by a diet deficient in iodine, stress such deficiency as an important factor.

McCarrison (2) has adduced evidence that certain drinking waters in India with a high degree of bacterial impurity are goitrigenic even in presence of an adequate amount of iodine, and that the substitution of a bacteriologically pure but iodine-poor drinking water for an impure but iodine-richer water has caused the rapid and complete disappearance of goitre from a place in which it had been endemic for seventy years.

Stott found Graves' disease absent from the United Provinces (India), but hypothyroidism and cretinism common, and confirmed the association between deaf-mutism, cretinism and goitre. Where this disease-group is prevalent it is associated with a water supply containing calcium salts in excessive amounts. This is especially true of the Cachins of North Burma, who, in addition to drinking water of this type, actually eat calcium carbonate in powder form. Wahlberg, from a study of goitre in Finland, considers that both relative deficiency of iodine and excess of calcium are factors, which, however, are probably more aggravating than

causal. He thinks that other important factors are low standard of living and familial disposition.

Other suggested factors are inability to absorb iodine from the gastrointestinal tract (Keith; Pighini), specific goitrigenic organisms (Crotti), and deficiency of vitamin A (cf. p. 32).

It seems justifiable to conclude that endemic goitre can arise from more than one cause, and that the most important causes are (i) absolute or relative deficiency of iodine, (ii) excess of calcium in the diet, (iii) goitrigenic agencies such as organic cyanides, and (iv) possibly a water-borne infective agency. The considered opinion of Marine (1), written in 1935, seems to sum up our present knowledge: "Goitre is a deficiency disease due to an insufficient supply of iodine. This iodine deficiency may be relative or absolute and may result from (i) factors that increase the needs of the body for (the thyroid hormone), such as puberty, pregnancy, the menopause, certain infections and intoxications, exposure to cold, excess of certain substances in the diet, including fats, proteins, and calcium (the ratios of the latter with phosphorus and magnesium are also important), and deficient oxidation (for instance, thyroid reaction in anaemias or in the presence of oxygen deficiency such as occurs at high altitudes), (ii) factors that interfere with the absorption or utilization of a normal intake of iodine, and (iii) factors that bring about an abnormally low intake of iodine."

Of more importance than the actual cause of endemic goitre is the undoubted fact that a sufficiency of iodine in the diet prevents it. *Iodine acts as a shield and iodine-prophylaxis is the most important preventive measure.*

Methods of Administration of Iodine. Since, as has been demonstrated by ordinary chemical methods and by the use of radioactive iodine, iodine ingested in any form of combination circulates in the blood as iodide, while the thyroid gland can only use it in the form of iodide (p. 18), obviously it is most economically administered in that form. The best method of its prophylactic use in any area depends upon whether the incidence of goitre is so great and widespread in that area as to make the problem of its treatment a community one or not. Wherever endemic goitre occurs or can occur the whole population can only be protected if the whole population be treated.

Of the various methods that have been used only the addition of iodide to common salt used for table and culinary purposes is suitable for treating whole communities. Chocolate coated tablets for children ignore the adult, who should not be ignored. Feeding

iodide to cattle and manuring of soils with iodide to get iodine rich milk or vegetables are extremely wasteful methods conferring no especial benefit. Iodization of drinking water means unnecessary duplication and does not reach a rural community. Increased consumption of marine products, desirable in itself, is an expensive method of acquiring iodine for those who dwell far from the sea.

Correct Dosage of Iodine. The amount of sodium or potassium iodide added to common salt has varied in different countries from 1 part to from 5,000 to 200,000 parts of salt. The optimal amount has been carefully considered recently by Curtis and Fertman, who point out that the needs of different individuals, and of individuals in different places, may vary. Iodine deficiency may be absolute, as in areas of subnormal iodine intake, or relative, through varying demands on the organism which may increase the need for it, or for the thyroid hormone (as puberty, pregnancy, lactation, infection, ingestion of toxic substances, a high intake of calcium salts, and any condition which interferes with the gastro-intestinal absorption of iodine). Obviously, therefore, an optimal iodine intake must be adequate to meet all such demands.

Curtis and Fertman consider that the optimal daily requirement is about 3 micrograms per kg. body-weight (and thus about 200 micrograms or 0·2 mg. for a 70 kg. person), and that the pregnant women may need more than this. They report that the National Study Committee on Endemic Goitre of the American Public Health Association at its 1941 meeting recommended that the addition of potassium iodide to sodium chloride for table salt and for consumption by domestic animals should be to the extent of 0·01 per cent. (along with an effective stabilizer). It is estimated that the daily average intake of sodium chloride by an adult in the United States is about 6·2 grams, which would yield 474 micrograms of iodine.

Sevringhaus and Barbour studied the urinary iodine excretion of ten children between 1·7 and twelve years of age from homes in which only iodized salt was used. Only one or two twenty-four hour estimations were made for each child, and, as was to be expected, considerable variations were found, the extremes being 53 micrograms (for the youngest child) and 594 micrograms (for a ten-year old). The average of all, 238 micrograms, was considered as indication that such salt furnished an adequate supply of iodine.

Alleged Potential Danger from Use of Iodized Salt. It has been generally recognized that *over-dosage* of iodine may induce a hyperthyroid state (so-called iodine-Basedow) in a patient with a previously non-toxic goitre (cf. Kocher). There is no evidence

that use of a properly iodized table salt can lead to such an effect, though for some time attempts were made to discredit and prevent its use on the fallacious assumption that this might occur. Marañon has adequately disposed of this assumption : " We have observed quite frequently the appearance of types of secondary hyperthyroidism in endemic goitre. Sometimes they appear spontaneously, especially during the critical period, *but almost always they are due to exaggerated " cures " with thyroidin, or iodine, or its derivatives*, which have been dispensed as a treatment of goitre itself, or for other reasons, principally against obesity. . . . *We have noticed symptoms* (of hyperthyroidism following administration) *only in the cases that had been treated with enormous quantities of iodine, and never in cases where judicious doses were dispensed, or some preparation of iodized kitchen salt.*"

Perhaps the best argument against risk to patients with non-toxic nodular goitre is McClure's report on ten years' use of iodized salt in Michigan. While for the first two years the number of cases of toxic nodular goitre operated on did increase, subsequently there was a rapid and steady decrease in operations both on toxic nodular goitre and toxic diffuse goitre. (Cf. also Curtis and Fertman.)

Treatment of Endemic Goitre. Iodine administration is not so certainly beneficial in treatment of an established goitre as it is as a prophylactic measure. Plummer and others have used small doses of desiccated thyroid or thyroxine with good effect, though Joll's results were disappointing.

In a recent paper Rienhoff reports that desiccated thyroid produces decrease in the size of the goitre and general improvement. The thyroid medication should be given in increasing dosage over a period of months, and a condition of mild hyperthyroidism must be induced before definite atrophic changes will take place in the goitre. Biopsy sections of goitres so treated showed atrophy. Vertán has made a similar report.

The use of large doses of intestinal disinfectants, following McCarrison's views, does not seem to have proved useful (cf. Joll).

Non-toxic Nodular Goitre

This condition, often termed *non-toxic adenoma*, usually arises from simple goitre. The adenomata vary in size from microscopic nodules to others several centimetres in diameter, and are usually multiple ; some substernal extension is common. Various types of degenerative changes may occur in goitres of long standing—formation of large gelatinous masses through coalescence of acini

distended with colloid, thick bands of scar tissue, formation of cartilage, etc. Adenomatous nodules may also arise from foetal "rests." According to W. O. Thompson, hyperthyroidism will develop in 25 per cent. of patients with non-toxic nodular goitre who are over forty-five years of age, and carcinoma in 0·5 per cent. Cole considers the potential danger greater. Of 192 cases (chiefly women) seen at the Illinois Research Hospital 17 per cent. had developed carcinoma, many from a foetal adenoma. It is frequently not diagnosed till operation. He believes that half the cases of nodular non-toxic goitres will probably develop thyrotoxicosis. Other complications are local pressure symptoms and systemic manifestations. Cole urges surgery therefore as a preventive measure, and Lahey is in complete agreement.

Amyloid Goitre

Walker recently reviewed the 58 cases of amyloid goitre in the literature. The commonest primary disease associated with amyloid infiltration of the thyroid is pulmonary tuberculosis. Purulent bronchitis with bronchiectasis or neoplastic processes are less common precursors. Amyloid infiltration of thyroid without amyloidosis of any other organ is extremely rare. The amyloid infiltration generally, but not invariably, causes thyroid enlargement. Patients show no evidence of thyroid insufficiency. The commonest diagnostic error in these cases is to conclude that malignancy is present.

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HYPOTHYROID STATES

Clinical hypothyroidism includes cretinism and childhood myxoedema, adult myxoedema and less extreme hypothyroidism in adults.

Cretinism and Childhood Myxoedema

Cretinism is a condition in which hypothyroidism exists from birth. The thyroid is atrophied and fibrosed, and even may be absent. Endemic cretinism is found among the offspring of several generations of goitrous mothers. Cases of so-called "sporadic cretinism" appear occasionally as offspring of apparently healthy parents.

Childhood or juvenile myxoedema is a condition in which the thyroid is presumably normal at birth, but subsequently becomes inadequate through damage by infection or some other cause. While the resulting syndrome is practically the same as that in cretinism, especially if the thyroid becomes deficient in the first two or three years of life, the differentiation is important, since treatment is definitely more effective in childhood myxoedema.

The typical hypothyroid child is dwarfed, and the ratio of the upper and lower skeletal segments remains that of a younger child. The naso-orbital development is infantile, so that the bridge of the nose is flat and broad, causing the eyes to appear wide-spaced, and the nose short and undeveloped. Osseous development is retarded, dental development is retarded and defective, and epiphyseal dysgenesis is frequently present. Brain development is retarded; there is physical and mental torpor. The peripheral circulation is poor, the skin pale, grey, and somewhat dry and rough. The hair is dry. Constipation is present. The stunted child looks younger than its years, is of stocky or chunky build, is over-weight but not markedly obese. The features are broad and coarse, the expression a little dull. (Cf. Wilkins and Fleischmann; Thompson; Rose.)

The typical case is easily diagnosed, but atypical cases are frequent, while wrong diagnoses are not infrequently made on the basis of but one or two of the above signs. "Almost any infant who is retarded in development, or who is peculiar or ugly, runs the chance of being branded as having hypothyroidism" (Wilkins and Fleischmann).

Early diagnosis of the true cretin is most important, since usually, before it is made, the brain has become irreparably damaged. When the typical cretinoid facies, dry scaly skin and pot belly have appeared diagnosis is easy, but is usually too late for complete restoration. Cretinism should be suspected at the first appearance of lethargy, constipation, and failure to grow in length or to nurse properly, and if proper treatment is then instituted almost complete normal development results (Thompson).

The atypical case may be nervous and hyperkinetic, instead of dull and sluggish, and underweight instead of overweight (Rose). Many cretins one to two years old are not grotesquely abnormal; some older cretins may be slender, wiry children, without cretinoid appearance (Wilkins and Fleischmann). Obviously the signs will vary with the age of commencement, and the duration and degree of the deficiency.

Measurement of the basal metabolism of young children or mentally subnormal children is not very satisfactory for diagnostic purposes, through difficulty in obtaining co-operation. Wilkins and Fleischmann report that only one-quarter of their hypothyroid cases have given satisfactory measurements. These, measured by the Boothby and Sandiford standards, give results ranging from — 25 to — 40 per cent., but many obese children who are not hypothyroid give figures just as low. Use of the Talbot height

standards is more satisfactory, since they give low values with hypothyroid children, and normal or high values with obese children. Yet Wilkins and Fleischmann conclude that even with these standards it is not justifiable to base a diagnosis of hypothyroidism on a low basal metabolic rate.

Rose thinks that the most consistent objective evidence is X-ray evidence of retarded bony development.

Wilkins *et al.* have attempted to find suitable biochemical means of diagnosis of the hypothyroid child. Serum cholesterol of normal children ranges from 100 to 300 mg. per 100 c.c. Untreated hypothyroid cases may show normal values and values much above normal (250 to 600 mg.), and frequently these show marked fluctuations. Creatinuria of normal children on a meat-free diet ranges from 0·6 to 7·8 mg. per kg. body-weight per twenty-four hours, and of hypothyroid children from nil to 3·8 mg. Thus high serum cholesterol and low creatinuria are suggestive of a hypothyroid state, but normal values do not exclude it. (Cf. also, as regards creatinuria, Poncher *et al.*)

Of more importance seems the observation of Wilkins *et al.* that dosage with 2 grains of thyroid daily will cause a much greater drop in the serum cholesterol value in hypothyroid than in normal children, while withdrawal of the treatment causes much greater increase. Likewise the effect of a single dose is much more prolonged (up to forty days or more, as compared with nine days for normal children).

(Radwin recommends estimation of total blood lipides—increased in hypothyroidism—rather than estimation of cholesterol).

The diagnostic use of thyroid medication may also be helpful in doubtful cases. If the patient responds favourably to properly controlled doses of a potent thyroid preparation given over an adequate period of time (at least four weeks for maximum effect) hypothyroidism has probably been present (Rose).

The mongoloid child is not hypothyroid, although Benda states that its thyroid is always hypoplastic, suggesting a resting colloid goitre, a condition which he believes is due to lack of pituitary stimulation.

Prevention and Treatment. Since childhood myxoedema probably results from some intercurrent infection, special preventive methods do not apply. Cretinism, usually associated with a goitrous mother, can best be prevented by adequately supplying the mother with iodide throughout her pregnancy, and such treatment should be extended to all women living in goitrous areas. In addition, Thompson recommends that conception should be pre-

vented in myxoedematous women for several months after their thyroid balance has been restored to normal, and even then their offspring should be carefully watched for development of hypothyroidism.

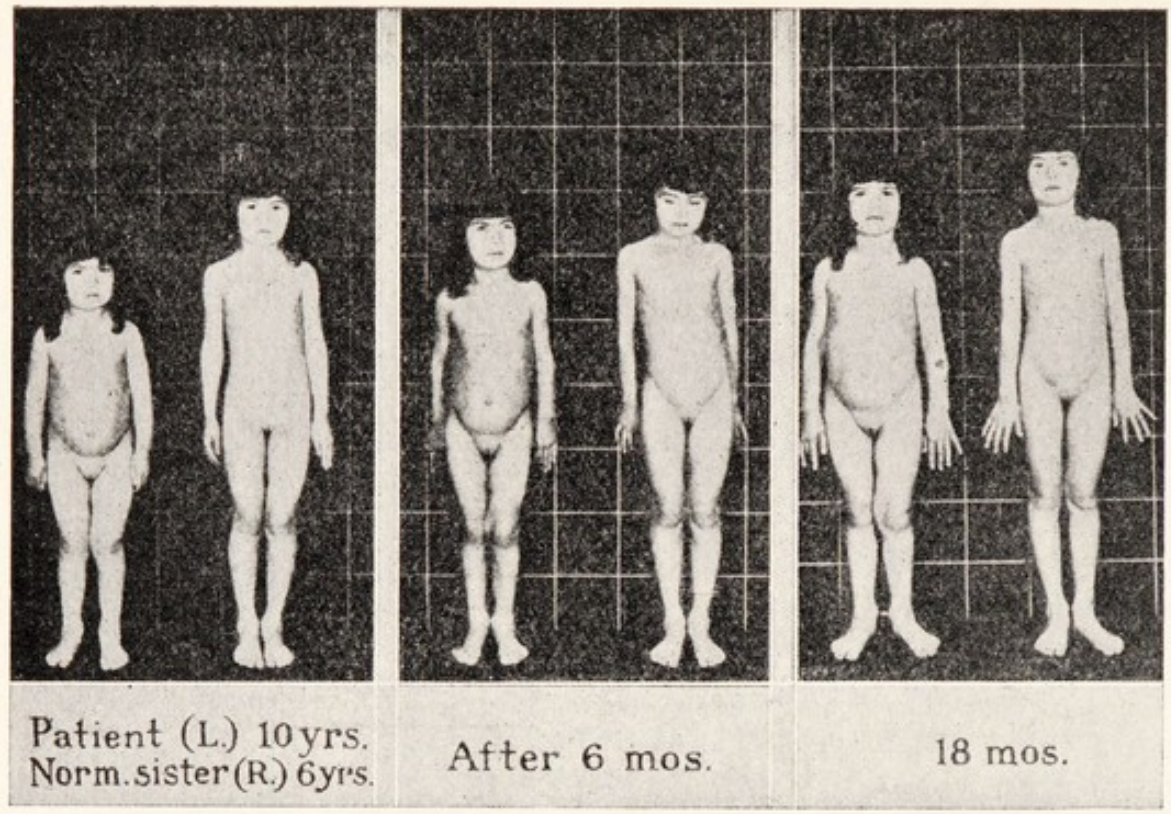
As soon as hypothyroidism is recognized, the child should be given thyroid. According to Thompson, the dose usually needed varies from 0·1 grain daily of desiccated thyroid containing 0·2 per cent. iodine at six months of age to 1 grain daily at puberty.

A. *B.* *C.* *D.*

FIG. 2. A case of cretinism successfully treated with thyroid. *A.* Eighteen months old. Large umbilical hernia. Just before treatment commenced. *B.* Twenty-three months old. The hernia has disappeared. *C.* Thirty-eight months old. *D.* Sixty-six months old. Weight, 46 lb. Height, 46 inches. Practically normal, both physically and mentally. (From Close, Guy's Hospital Reports, 1932, lxxxii, 155.)

If hypothyroidism has remained unrecognized for several years the development of the brain may be so primitive that cerebral inhibition is lacking; in such cases thyroid treatment may stimulate the patient to become unruly, and consequently some cretins in institutions for the insane are not treated (Thompson).

A good example of both physical and mental benefit following administration of thyroid to a cretin from an early age has been reported by Close, whose excellent results are shown by the photographs in Fig. 2.



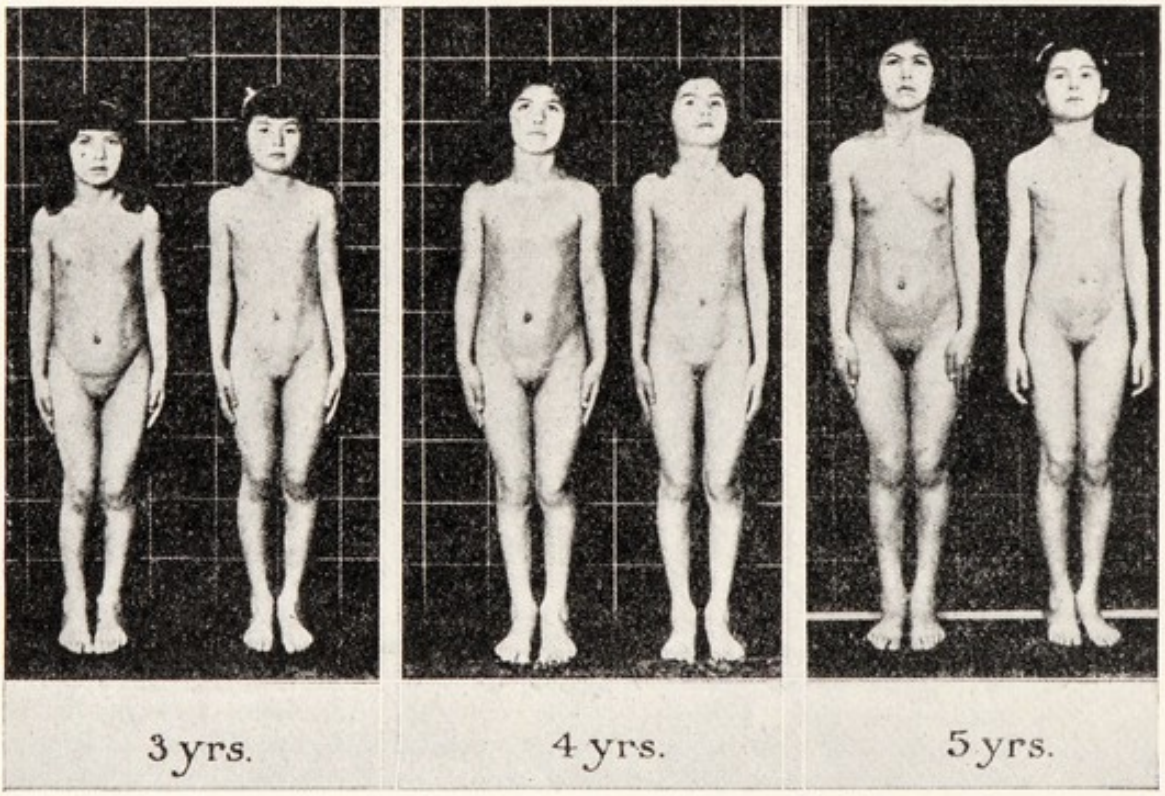


FIG. 3. C. R., initially aged ten years, at left in each photograph. Normal sister, initially aged six years, at right. Subsequent photographs were taken during the administration of 1 to 1½ grains of thyroid (0·2 per cent. iodine) daily. "The patient grew several hundred per cent. over the normal rate for the first year or two and then gradually settled down to a normal annual increment. Note that when she reached adolescence she shot ahead of her younger sister. The intelligence improved markedly, but a hypothyroid or myxoedematous child of ten years who has never received thyroid has in most instances suffered permanent damage to the central nervous system. This patient managed to keep abreast of her normal sister in school after two years on thyroid treatment. In other words, she was about four years' retarded when I last saw her." (From Shelton, Endocrinology, 1942, xxx, 1008–9.)

Kerley and Gesell have both reported excellent series. Shelton has published a beautiful photographic record of the development of a hypothyroid girl, who was untreated to the age of ten years. This is shown in Figs. 3 and 4. He stresses the marked growth which occurs in such cases during the first year or two of treatment ; subsequently the growth-rate drops to a normal increment.

Fournier and Cervino have reported a case of what was probably childhood myxoedema and not cretinism, in which the signs and symptoms were probably obvious at the age of three years, although

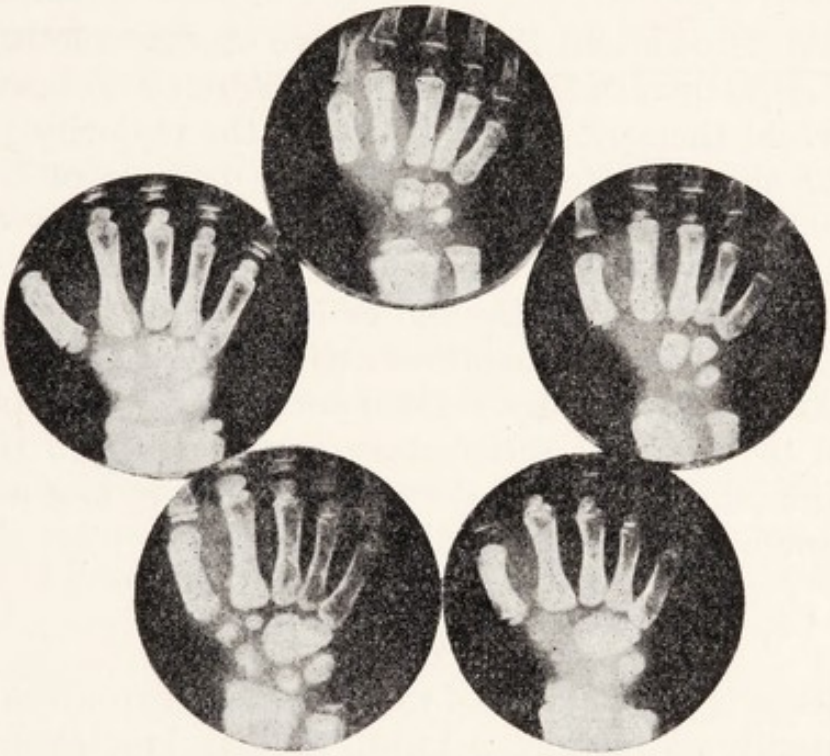


FIG. 4. (Read clockwise.) Carpal development of child C. R. (cf. Fig. 3). Uppermost photograph at ten years. This is approximately the two- or three-year development of a normal child. The other carpal roentgenograms were taken at six, nine, twelve and eighteen months after the beginning of treatment. (From Shelton, Endocrinology, 1942, xxx, 1010.)

thyroid treatment was only begun at ten years of age, when, although the usual physical disturbance and retardation had taken place, the mental age was normal.

Block reports the late outcome of three cases of profound childhood myxoedema, in which treatment was started in 1907 with a high dosage of 50 grains of thyroid daily, gradually reduced to 5 grains daily by 1921. The ultimate results were satisfactory, all three patients becoming completely normal. He thinks that often heavy dosage will give good results when timid therapy is ineffective (cf. also " H. R. W.", who advocates doses that are just sub-toxic) but Bruch and McCune consider that too vigorous

use of thyroid can have distinctly undesirable consequences, leading to serious disorders of behaviour, while sometimes the mental retardation is irreparable, being due to damage during prenatal life.

The thyroid treatment restores the normal metabolism. Serum cholesterol drops to normal values (Wilkins *et al.*) ; creatinuria is increased to normal (Fan).

Beard reports that treatment of cretinism with preparations of anterior pituitary growth hormone along with thyroid give no better results than are obtained with thyroid alone.

McDonald, Brown and Bronstein have studied the background and social adjustment of hypothyroid children who have received proper thyroid therapy. They find that the majority tend to be high grade mental defectives. The age periods of best social adjustment are one to seven and seventeen to twenty-one years. " The adjustment of the older group suggests that even with low intelligence, children with thyroid deficiency are able, with treatment, provided there are healthful attitudes towards them within the home, to be practically self-supporting, to be helpful in the home, and to work out satisfactory relationships in the family. However, glandular therapy does not overcome low intelligence or unwholesome parental attitudes."

Myxoedema

Myxoedema is a condition of marked hypothyroidism in adults which is usually not manifested until the basal metabolic rate has fallen to — 20 per cent. or lower, although there is the occasional striking exception to this. The majority of cases are of so-called "spontaneous myxoedema," of which the cause is not known. This is much commoner in women than in men (4 : 1), and is most frequent between thirty and sixty years of age.

Myxoedema also may follow a too complete thyroidectomy for hyperthyroidism, and usually follows thyroidectomy for struma lymphomatosa (cf. p. 30). In rare instances it replaces a hyperthyroid state which has disappeared spontaneously or may result from post-operative administration of iodine in Graves' disease. At autopsy of cases of spontaneous myxoedema the thyroid is usually found to be replaced by scar tissue, though sometimes a goitre is present (cf. Thompson).

From an anatomico-pathological study of ten cases of myxoedema, Bastenie (1) concludes that the condition is the result of a chronic, non-specific thyroiditis arising in degenerative alterations in the

parenchyma of the gland ; these may follow upon a variety of pathological states. In myxoedema there is an excessive output of the thyrotrophic hormone of the pituitary (cf. p. 342), which accentuates the degenerative process.

The outstanding manifestations of the disease are (i) puffiness of the face and eyelids, resulting in the characteristic myxoedematous facies, (ii) swelling of the tongue and larynx, resulting in typical hoarse, slow, slurred speech, (iii) dryness and roughness of the skin, (iv) general falling out of hair, with usually almost complete absence of axillary and pubic hair in consequence, while the eyebrows become sparse, (v) slowing of mental reactions and poor memory, (vi) constipation, and (vii) a low basal metabolic rate.

" The patient is slow and tortoise-like in his movements and mental reactions, with a dry, parchment-like skin which is frequently yellowish. There may be a butterfly patch of erythema across the cheeks and the bridge of the nose." The hands present a puffy appearance as well as the face (Rose).

There is a decrease in libido and often sterility. The effect on menstruation varies.

In addition, there may be present a secondary anaemia, decrease in the total volume of circulating plasma, and increase in plasma cholesterol (Thompson). The plasma albumin varies from high normal to somewhat above normal ; the plasma globulin remains normal (Cameron). The cerebrospinal fluid protein is usually increased. There is a marked decrease in the minute volume of the heart, with prolongation of the circulation time, accompanied by changes in heart muscle lessening its efficiency (Thompson).

The commonest complaints include fatigue, sensitivity to cold, mental and physical sluggishness, loss of memory, dryness and scaliness of the skin, loss of hair from scalp and eyebrows, vague aches and pains in back and extremities, constipation and flatulence, and sterility and loss of libido (Rose).

The myxoedematous patient is usually not overweight and is often ill-nourished. Any appearance of obesity is deceptive, due to a subcutaneous myxoid infiltration beneath the coarsened skin (Rose).

Bastenie, from a study of 29 cases of severe myxoedema, describes the intestinal disturbances which may develop as varying from simple constipation to the development of megacolon, and from abdominal distension to intestinal obstruction. He considers that intestinal paresis may appear as the first important sign of an unrecognized or latent hypothyroidism.

Little work has been done on the supposed oedema of myxoedema. Many years ago Boothby *et al.* described it as an albuminous deposit somewhat like eggwhite. Plummer states that the average amount of the "oedema" is about 13 lb., and that this does not increase with increasing severity of the disease. According to Trotter and Eden the deposit is a mucin, and its deposition is not essentially related to the hypothyroidism, since localized myxoedema can occur in hyperthyroid patients (see p. 78, and cf. Watson, p. 79).

The yellowish colour of the skin frequently present is due to a carotinaemia which Escamilla suggests is due to hindrance of conversion of carotene to vitamin A through deficiency of thyroid hormone. Under thyroid treatment it slowly disappears.

Stewart and Evans have shown that the peripheral blood flow is decreased in myxoedematous patients, the cardiac output is decreased, and the circulation time prolonged (conserving heat). Treatment with thyroid restores the normal condition. In hyperthyroidism peripheral blood flow is increased.

As judged by the urea clearance test renal function is depressed in myxoedema. The urea clearance value rises after thyroid therapy, but not to a normal figure. Less sensitive tests such as the urine concentration test, reveal no change (cf. Beaumont and Robertson).

Treatment of Myxoedema. Murray first administered thyroid to myxoedematous patients in 1891. His first treated case died in 1919 at the age of seventy-four from cardiac failure, after twenty-eight years of excellent health. A final report on a similar long-treated and spectacular case was published by Raven in 1924.

Mrs. S. developed myxoedema in 1870, at the age of forty-one; no treatment was instituted for over twenty years. At the end of this period she was bedridden, bald and demented. Treatment with thyroid extract was commenced in 1893; within fifteen months she was practically normal, even to well-marked growth of hair. She continued a normal existence until 1924, living "to a ripe old age—happy, healthy, and mentally active," and finally dying of bronchitis. Photographs of this patient are reproduced in Fig. 5.

When thyroid is administered to myxoedematous patients in non-toxic amounts it has no specific effect in reducing body-weight, except to the extent that it dissipates myxoedematous deposits and causes elimination of abnormal accumulation of fluid. By its effect on nutrition it may actually cause a gain in weight as basal metabolism becomes normal. Progressive and continued loss of weight following its administration indicates too great a dosage. It has no specific directional influence on vascular tension, but through its influence on nutrition it tends to bring either high or low blood pressure back to normal. In therapeutic doses thyroid has two effects on the heart—it increases its work promptly and rapidly, and improves its nutrition slowly. Therefore signs

of cardiac insufficiency do not contraindicate administration of thyroid, but do emphasize the need for care in its use and adequate

A. *B.*

C. *D.*

FIG. 5. Thirty years' successful treatment of a case of myxoedema with thyroid gland. *A.* Condition before treatment; aged 65. *B.* After five weeks' treatment. *C.* After fifteen months' treatment. *D.* At age 94, after about thirty years' treatment. (From Raven, Brit. Med. J., October 4th, 1924.)

curtailment of the patient's activities (Lawrence). Anginal pain sometimes occurs following administration of thyroid.

Thyroid Dosage in Myxoedema. This will vary with the grade of the myxoedema, to which the basal metabolic rate is the most

accessible clue. Individual requirements vary, but the analysis of results by Means and Lerman from study of a large number of cases with complete myxoedema provides a useful guide. The salient features of their data are reproduced in Fig. 6 (slightly

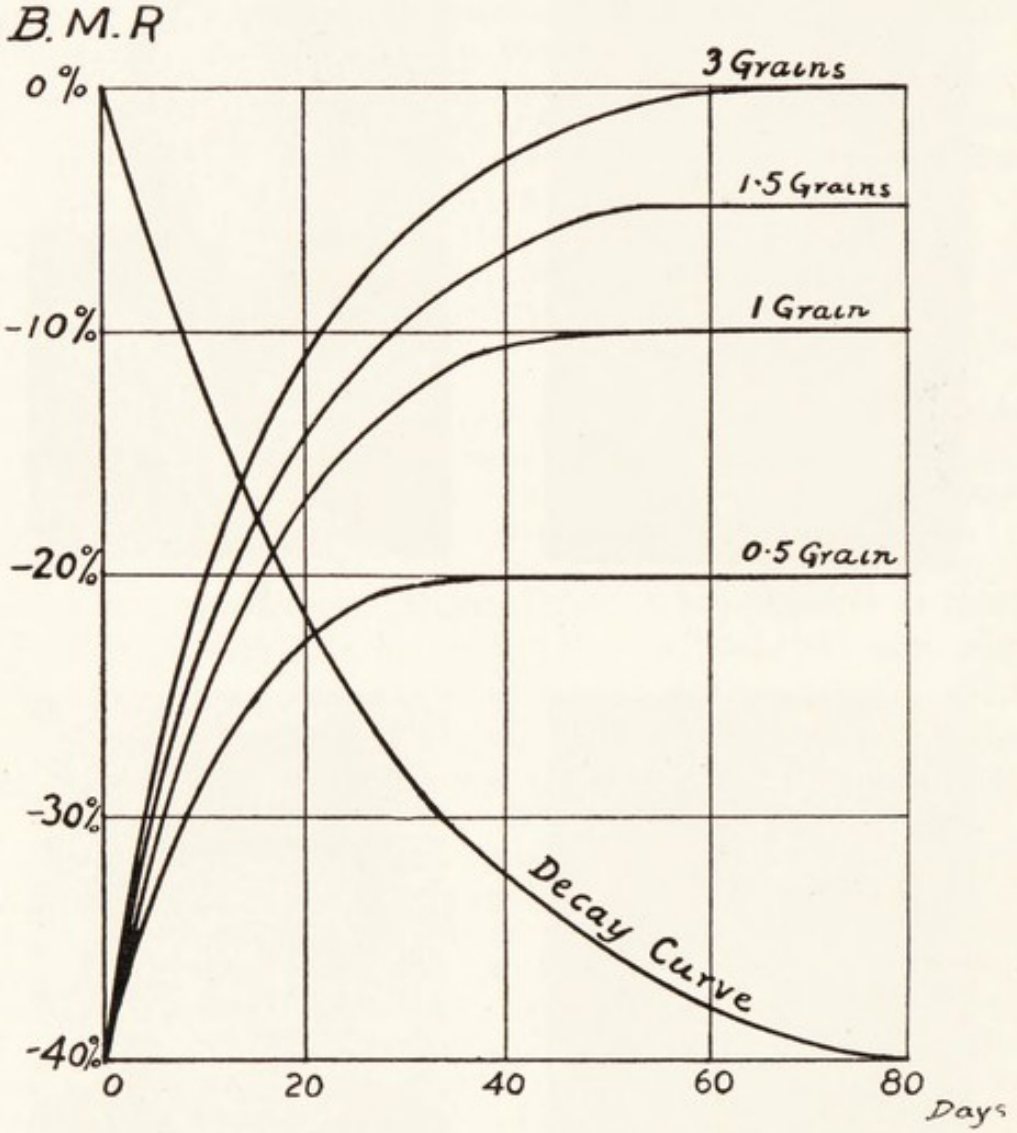


FIG. 6. Diagram showing the approximate relationships between basal metabolic rate, and daily thyroid dosage (in grains of thyroid, U.S.P., containing 0·2 per cent. iodine), in patients initially with complete myxoedema. The decay curve indicates the B.M.R. response to be expected following discontinuance of thyroid administration to a balanced myxoedematous patient, or complete extirpation of the thyroid of a person with a normal B.M.R. (Modified from Chart 1, Means and Lerman, Arch. Int. Med., 1935, lv, 1.)

altered from their diagram), and it is necessary to insist, with them, that it presents a generalization, portraying approximately what happens in most cases, and not precisely what happens, unless by chance, in any single case.

Thompson states that the average daily replacement dose for a

hyroidless adult is 1½ to 2 grains of a desiccated thyroid con-aining 0·2 per cent. iodine (the dosage *must* be based on the iodine ontent of the thyroid used). He recommends that treatment be ommenced with a dose known to be inadequate, which should e increased gradually after several weeks. The dose should only lowly be changed, because of the slow adjustment to it. (Fig. 6 hows that at least two months is needed for complete adjustment o any dose.) Large initial doses should be avoided, especially f the patient has arteriosclerosis or coronary disease, because of he danger of precipitating coronary thrombosis. If angina levelops during treatment, the metabolism should be adjusted at slightly lower level. Thyroxine given orally has no advantage ver desiccated thyroid. It should only be given intravenously n exceptional cases.

Although 3.5 diiodothyronine is much less active than thyroxine, its se has been suggested in myxoedema. A dosage of 50 to 75 mg. per lay, orally, has been found to restore to normal and control severe ases. This is over fifty times the requisite corresponding dose of hyroxine. The dosage quoted does not produce toxic symptoms Anderson, Harington and Lyon). Implantation of thyroxine pellets loes not control myxoedema, since absorption is insufficiently rapid Greene and January).

The Heart in Myxoedema. Zondek in 1918 was the first to report hat an enlargement of the heart sometimes accompanies myxoe-lema, an observation that has been repeatedly confirmed (cf. .g., Means). The enlargement can be greater than in any other ondition ; there is often a resemblance to a pericardial effusion, vhich in some cases is definitely present (Freeman). The heart-hange is characterized by generalized dilatation, usually con-idered to be at least in part due to oedema of heart muscle. The eart's action is sometimes very indolent, and there may be cardiac nsufficiency. The electrocardiogram shows complexes reduced in mplitude. The T-waves in leads 1, 2 and 3 may be inverted. Decompensation may develop, with characteristic pitting oedema f the dependent portion of the body (cf. Thompson).

Digitalis therapy has no effect, but following thyroid therapy here is often remarkable shrinkage towards normal size, with estoration of normal action. McGavack and Schwimmer have lealt thoroughly with the treatment of cardiac failure in nyxoedema.

Zondek, Michael and Kaatz have reported studies on the apillaries of the peripheral circulation in eight women with typical nyxoedematous heart. In seven the capillaries were markedly hanged, the most striking feature being pronounced narrowness

of the limbs. On administration of thyroid they were gradually restored to normal. Zondek associates the pre-cordial pain of the condition with this capillary constriction, retarding coronary flow.

Cardiac enlargement is rare in childhood myxoedema. Baratz and Bronstein have described four cases, of which one was marked. After thyroid therapy had caused a reduction in the size of the heart, with discontinuance of the therapy it again enlarged.

End Result in Myxoedema. Foster and Barr reported the case of a widow aged sixty, in whom the hypothyroidism had probably existed for at least twelve years. The clinical picture was characterized by atrophy of the skin, purpura, hypocholesterolaemia, hypoproteinaemia, ascites, and gross segmental dilatation of the sigmoid colon. The unusually low basal metabolic rate, — 46 per cent., was attributed to the combined effects of undernutrition and hypothyroidism. The emaciation, atrophy, and low plasma proteins indicated the profound undernutrition which may have been responsible for the low blood cholesterol (120, 126, and 137 mg. per 100 c.c. in three determinations).

At post-mortem the thyroid acini were almost completely replaced by dense fibrous tissue ; the pituitary and adrenals were practically normal. Characteristic lesions were demonstrable in the cells of cardiac, skeletal and smooth muscle ; they consisted in degeneration of the central portion of the sarcoplasm, with production of vacuoles containing basophilic granular or homogeneous material which staining reactions suggested may be related to fibroblastic mucoid. These lesions were morphologically similar to those seen by Kountz and Hempelmann in three cases of spontaneous rupture of the aorta in hypothyroidism induced by complete thyroidectomy.

Unusual Cases of Myxoedema. Some proportion of cases of Simmonds' disease present the characteristic picture of myxoedema, although they do not respond properly to thyroid treatment (cf. p. 357).

Trotter and Wallace treated a woman with myxoedema and a basal metabolic rate of — 49 per cent., in whom thyroid given orally produced vomiting, by thyroxine, given intravenously. They found that the maximum dose which could be tolerated was 7·5 mg., and that its effect persisted for four weeks. The general result was good, although the type of treatment resulted in fluctuations of the basal rate between — 1 and — 30 per cent.

Zondek has reported the case of a woman aged thirty-three, with marked myxoedema. On thyroid treatment she became pregnant and thyroid was discontinued. She remained free from myxoedematous symptoms until birth of the child, when the myxoedema rapidly recurred, the basal metabolic rate falling to — 29 per cent. Evidently the thyroid hormone can pass from the foetal to the maternal circulation.

Zondek and Wolfsohn have described a case of myxoedema in a young woman who developed the mental changes characteristic of schizophrenia. Thyroid treatment produced recovery from the psychosis within a fortnight; this was considered due to dehydration of the cerebral tissues.

Foggie describes an unusual case of myxoedema following thyroidectomy. In a young woman a tense and discrete tumour, situated in the mid-line at the root of the tongue, was removed on account of obstruction. It was partly cystic, and was composed of thyroid tissue. Within six months myxoedema developed, which reacted promptly to thyroid medication.

Another peculiar case has been reported by Kobacker. A forty-eight-year-old woman with moderate, diffuse, thyroid fullness was treated for hypertension with potassium thiocyanate for seventeen months. A myxoedematous condition resulted, with basal metabolic rate of − 30 per cent. Cessation of the thiocyanate treatment plus thyroid therapy brought return to normal in two months. A year later renewal of thiocyanate therapy induced mild myxoedema.

Mild Hypothyroidism

Numerous cases of hypothyroidism have been described in which frank myxoedema was not present. It does not greatly matter whether they be described as atypical myxoedema, or masked myxoedema, or hypothyroidism in absence of myxoedema. Such cases may be difficult to diagnose and the chief proof of presence of hypothyroidism may rest on disappearance of the symptoms which brought the patient to the physician, following thyroid medication. A low basal rate is not definite evidence, since, as Thompson points out, in some persons with normal thyroids basal rates of — 20 to — 25 per cent. may be found (though such are very rare).

Rose has listed a variety of different clinical pictures which may be due, in particular cases, to hypothyroidism. His list includes the following presenting complaints: (i) Vague pains, aches, and stiffness in back and extremities, which may have been treated ineffectively under mistaken diagnoses of arthritis, myositis, neuritis, and spondylitis; (ii) indigestion, flatulence, constipation, anorexia, or insomnia; (iii) various gynaecological complaints, which may include menorrhagia, metrorrhagia, amenorrhoea, dysmenorrhoea, sterility and frigidity, without other evidence of thyroid deficiency; (iv) anginal and congestive circulatory symptoms; (v) (occasionally) nervous and psychic phenomena such as schizoid or anxiety states; (vi) physical and mental fatigue (many such patients give histories of prolonged and ineffective treatment under such diagnoses as hypotension, neurasthenia, anaemia, and vitamin deficiencies); (vii) (very

occasionally) " paradoxical " hypothyroidism, the patient being underweight, nervous, fatiguing easily, and complaining of insomnia, palpitation, etc. The following are illustrative cases:

Lisser reported a case of sexual infantilism in a woman of twenty-seven, associated with a basal metabolic rate of — 27 per cent., and but slight evidence of myxoedema. She was restored to normal by a year's treatment with thyroid.

Hamilton *et al.* found that in four patients with some clinical evidence of hypothyroidism along with abdominal discomfort the latter was associated with gastric hypermotility. Three were treated with thyroid. With restored basal rate, the gastric motility became normal and the pain ceased.

Moehlig reported a series of cases with gastrointestinal disturbances simulating peptic ulcer, chronic cholecystitis, chronic appendicitis, or mucous colitis. Blood cholesterol was elevated, and the basal metabolic rate was low. Three-fourths of these patients complained of headaches. Sixty-nine per cent. were relieved by thyroid therapy, but the remainder were not improved.

Obesity is seldom associated with hypothyroidism (Handelsman and Gordon). When hypothyroidism is present there is better response to thyroid than when it is absent.

Cavanaugh, Shelton and Sutherland have suggested that osteochondritis juvenilis (Legg-Perthes' disease) is due, at least in some cases, to a thyroid deficiency (cf. also Schaefer and Purcell). Gill has carefully studied 20 cases of the disease, and can find no evidence supporting the view that it is due to hypothyroidism.

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HYPERTHYROID STATES

It is customary to differentiate between two different hyperthyroid states, of which one is termed *Graves' disease*, Basedow's disease, exophthalmic goitre, toxic diffuse goitre, diffuse goitre with hyperthyroidism, primary toxic goitre, and by still other names, while the other is termed toxic adenoma, or hyperfunctioning adenomatous goitre, or *nodular goitre with hyperthyroidism*, or secondary toxic goitre. As certain of these names suggest, the former is characterized by a diffuse, the latter by a nodular goitre. Intermediate forms exist, and Marine (1) does not believe in such differentiation. Nevertheless, as Joll points out, the distinction is convenient. Since there is some recent suggestive (though not conclusive) evidence that toxic goitres can exist in absence of hyperthyroidism (cf. p. 85), it may prove misleading to use the term " toxic " as indicating a hyperthyroid state. Nevertheless at present the term " toxic adenoma " will be used when necessary in place of the cumbrous but more accurate " nodular goitre with hyperthyroidism."

Graves' disease occurs most commonly between the ages of fifteen and fifty years, and much more frequently in females than in males (about 4 : 1). The goitre and the symptoms of hyperthyroidism usually appear rather abruptly and at about the same time. There are numerous signs and symptoms.

A goitre is almost always present. Even in its absence the gland is firmer than normal. According to Rose, tachycardia is an even more constant symptom. Others usually present are loss of weight, objective and subjective nervousness, emotional instability, tremor, palpitation, dyspnoea, fatigue and muscular weakness. Exophthalmos is present in 60 to 70 per cent. of cases. Patients may exhibit puffiness of the eyelids, lid-lag (von Grafe's sign), and poor convergence (Möbius). A systolic thrill and bruit, generally most marked over the superior poles, are usually present. Increased perspiration is common, diarrhoea, pressure symptoms and increased appetite sometimes present, but nausea and vomiting are rare, and are unfavourable symptoms when present. (Cf. Thompson ; Rose.)

The basal metabolic rate is always raised ; any value from high normal to + 100 per cent. may be found. The occasional case gives a value within normal limits, and the inability to record an elevated rate in such a case is due to the lack of delicacy of the method for calculating the normal value for any particular individual.

Hypertension is not present. Exophthalmos is not peculiarly associated with hyperthyroidism and will be dealt with in the following section.

Various atypical cases arise through exaggeration of one or more of the signs and symptoms just detailed. In some patients a nutritional deficiency is predominant ; they may have been diagnosed as suffering from vitamin deficiencies, malignancy, etc. Such patients need especially careful pre-operative treatment. In some patients psychic, emotional or personality changes are dominant. They may have been treated for psychoses or neuroses. In still others symptoms of heart disease are outstanding. One type suffers from recurring attacks of tachycardia or arrhythmias (usually auricular fibrillation), which eventually become continuous ; another type may first be seen by a physician after onset of congestive heart failure. Rose, referring to such atypical cases, writes : " In any patient with tachycardia, continuous or recurrent arrhythmia, or congestive heart failure, in whom the cause is not obvious, hyperthyroidism should be suspected."

Muscular and neuro-muscular dystrophies can also occur,

resembling myasthenia gravis or progressive muscular dystrophy, and exhibiting marked creatinuria (cf. Breidenbach and Apfelbaum).

Certain of these less usual types of Graves' disease will be dealt with later.

Nodular goitre with hyperthyroidism (toxic adenoma) is rare in young persons. The presence of a nodular goitre usually long precedes manifestations of hyperthyroidism. The condition is commoner in women, the incidence between the two sexes being about the same as in Graves' disease.

An enlarged nodular goitre and tachycardia are outstanding features. While most of those listed for Graves' disease may also be present in this hyperthyroid state, exophthalmos is rarely if ever present in the unmixed form. Thrills and bruits are absent and nervous phenomena slight. There is a tendency to hypertension, though Bisgard states that the hyperthyroidism merely precipitates or exaggerates a latent hypertension.

The basal metabolism is always above the true normal value for the person undergoing test; it rarely exceeds + 50 per cent.

Experimental hyperthyroidism in animals, produced by feeding desiccated thyroid or administering thyroxine, produces tachycardia, some nervous excitability, loss of weight, tremor, perspiration, and of course an increased basal metabolism. Exophthalmos is not usually produced. Obviously many of the symptoms of clinical hyperthyroidism are due to the hyperthyroidism itself; others, such as exophthalmos, are not.

Etiology of Clinical Hyperthyroidism. It is not yet possible to make a definite statement as to the primary fault which leads to a hyperthyroid state. Various theories have been put forward, incriminating the adrenal cortex, the anterior pituitary, the sympathetic nervous system, and so on. None can be regarded as proved, and indeed it is probable that there is no single etiological factor. This is especially true for those cases of nodular goitre exhibiting hyperthyroidism for which Boothby's statement in 1921 still holds: "About middle age the adenomatous tissue after a considerable quiescent period begins to furnish an excessive amount of the normal thyroid hormone. . . . The underlying cause or stimulus that activates the thyroid to adenomatous growth and over-secretion is not known."

The rôle of heredity in Graves' disease is becoming increasingly emphasized. Thus Bartels claims that 60 per cent. of 204 patients presented a family predisposition, which seems to be to thyroid

imbalance rather than to Graves' disease specifically, since Bartels considers that such predisposition may also lead to non-toxic goitre and to myxoedema.

(Maheux (2) has suggested that fever can accentuate thyroid damage in Graves' disease by stimulating a sharp increase in the output of the thyroid hormone, which the normal gland easily produces, but the gland of Graves' disease does not.)

Metabolic Changes and Diagnostic Procedures. In presence of the full-blown syndrome of hyperthyroidism a raised basal metabolic rate is merely confirmatory evidence. When the syndrome is not so pronounced, the other disease states in which basal metabolism may be increased (cf. p. 26) must be carefully borne in mind. When, in addition, the basal rate itself is but doubtfully increased, other diagnostic data may prove of value. In any case, the degree of increase of the rate above normal is not a reliable index to the severity of the hyperthyroidism. The basal rate is useful in differentiating various unrelated disorders which may be mistaken for hyperthyroidism, such as functional nervous disorders, and certain organic diseases as Sydenham's chorea and the early stages of Parkinson's disease. Hypertension, especially when accompanied by tremor, tachycardia, nervousness and loss of weight, needs greater care in differentiation, since in it the basal rate is also sometimes raised.

Within the last few years a number of papers have been published stressing the value of the galactose tolerance test for hyperthyroidism. Since it has not proved completely satisfactory as a test for liver function such claims must at present be viewed somewhat critically, although it would appear that in hyperthyroidism the test may not be a measure of liver function only.

Althausen, experimenting with rats, found that administration of thyroid facilitated the absorption of galactose and other sugars from the intestine, supposedly by stimulating their phosphorylation. Since therefore these sugars reach the liver faster, more is likely to pass this portal to the general circulation, thus producing a raised tolerance curve which is not evidence of reduced tolerance. Althausen found that all of 130 patients with hyperthyroidism showed a blood galactose tolerance curve following oral administration of galactose which was much higher than that given by normal persons with the same dose of galactose. He considered this test particularly useful for diagnostic purposes with patients whose basal metabolic rates were below + 20 per cent.

Hyperthyroid patients frequently exhibit hyperglycaemia and glycosuria, and often give a raised glucose tolerance curve exactly

corresponding to that in mild or even moderately severe diabetes. Since in the experimental animal fed thyroid the liver glycogen stores are depleted it is usual to consider the apparently lessened glucose tolerance as due to such depletion. However, Althausen thinks that all peculiarities of carbohydrate metabolism in hyperthyroidism can be satisfactorily explained by abnormally rapid absorption of the sugars, combined with increased utilization of glucose by body tissues, the latter in itself leading to depletion of glycogen. If this view is correct only a raised fasting blood sugar is of significance in hyperthyroidism, and the results of a sugar tolerance test are without significance in this condition.

John considers on the other hand that the hyperthyroidism is not directly responsible for the disturbance in carbohydrate metabolism. Hyperthyroid patients show some tendency to become diabetic. Thyroidectomy removes the hyperthyroidism, but does not invariably restore the carbohydrate metabolism to normal. John considers that the liver is affected, and that subsequently the islet tissue of the pancreas tends to become affected by stimulation from a constant hyperglycaemia. Yet Blanck has shown that in experimentally produced hyperthyroidism in rabbits the liver is still able to form and store glycogen. He attributes absence of liver glycogen, when this is found, to loss of appetite in prolonged experiments.

There is no doubt that liver damage frequently does occur in hyperthyroidism (*vide infra*). The relationship of hyperthyroidism to diabetes will be discussed in Chapter V.

Maclagan and Rundle consider that an abnormal galactose tolerance test with hyperthyroid patients is due to liver damage. They found in experiments with rabbits that following seventeen days' administration of thyroxine there was impairment of galactose tolerance and focal liver necrosis.

Rosenkrantz, Bruger and Lockhart find that patients with hyperthyroidism, Bright's disease, upper respiratory infections, malignant disease, and those who have recently received sulphanilamide therapy, frequently show a raised galactose tolerance curve, which is most marked in hyperthyroidism, both because of increased absorption and of hepatic damage.

King and Barnes think that a galactose tolerance test may be preferable to a basal metabolism determination with extremely nervous patients, and with those who are already receiving iodine medication, while it provides a useful accessory test in early hyperthyroidism. They find that it yields positive results in absence of liver damage. Similar views are expressed by Smith, Jondahl and Ochsner.

The test is usually carried out by giving a specified amount of galactose by mouth, and estimating the galactose in blood at the usual time intervals of a tolerance test, blood glucose being decomposed by yeast.

Achlorhydria frequently accompanies hyperthyroidism and often disappears after thyroidectomy (Berryhill and Williams).

Liver Function in Hyperthyroidism. It has become realized during the past few years that the condition of the liver is of considerable importance in determining the pre-surgical treatment of the hyperthyroid patient.

Maclagan and Rundle consider that deaths from hyperthyroidism may in large part be liver deaths. Crile finds that liver damage is a definite factor. The clinical features pointing to such damage are (i) confusion or delirium on the second or third post-operative day, (ii) a sallow colour or jaundice on the third or fourth post-operative day, (iii) an icterus index above normal, (iv) a tendency to develop terminal pneumonia, and (v) the patient is almost always elderly. (Wyndham is not in agreement.)

Lichtman reports that the liver changes may vary from simple acute fatty degeneration and necrotic changes to chronic atrophy and cirrhosis. As judged by the various tests for liver function, 45 to 90 per cent. of all cases of hyperthyroidism show some degree of functional impairment, usually slight to moderate. Severe functional impairment is uncommon. Jaundice is relatively uncommon and only present in a severe hyperthyroid state. Cases of true acute yellow atrophy directly attributable to the hyperthyroidism are extremely rare. Lichtman believes that the basic cause of the liver disturbance is the glycogen depletion; there are actual anatomic changes in the liver cells.

McIver points out that autopsies of patients dying from hyperthyroidism or from operation for hyperthyroidism in the days before pre-treatment with iodine showed presence of liver damage in the vast majority of cases, while in a small percentage the degree of damage was comparable with that in severe acute yellow atrophy. Chronic changes consisted of hepatitis, cirrhosis and atrophy. He quotes Means' view that the lesions of the liver should be considered a secondary complication in hyperthyroidism, the liver being then particularly vulnerable to injury, perhaps through its depletion of glycogen. Sealy stresses the importance of infection.

It has been found by several investigators that the hippuric acid test (one of the best liver functional tests at present available) is positive in the majority of cases of hyperthyroidism (cf. McIver). Schmidt, Walsh and Chesky carried out a hippuric acid test on 203 consecutive patients with hyperthyroidism; 113 showed some evidence of hepatic insufficiency, while 34 of these gave an excretion below 70 per cent. of normal, suggesting appreciable

liver damage. The degree of insufficiency was found to show no consistent correlation with the basal metabolic rate, and seemed more related to the duration and intensity of the hyperthyroid state than to the type of goitre.

Treatment of Hyperthyroidism. This consists of surgery or application of X-radiation, or medical treatment, or some combination of these. According to Thompson (2) the treatment of choice is still subtotal thyroidectomy. Lerman has recently published a number of brief case reports excellently illustrative of the various types of treatment and their adaptation to different patients.

Thyroidectomy needs adequate pre-operative preparation and post-operative medical care. The pre-treatment with iodine has rendered the operation relatively safe, while recent realization of the danger from liver damage, which has led to the necessary pre-treatment to combat this, will probably still further lessen the risk of operation.

The actual form of iodine medication used is immaterial, provided the amount given is adequate. Whatever the vehicle of the iodine, there results a drop in the basal metabolic rate, which is accompanied by a fall in pulse rate, decrease of nervousness, and increase of body-weight. Even inhalation of ethyl iodide is effective (cf. Lerman and Means). Iodine is usually given in the form of Lugol's solution, a solution of iodine in potassium iodide, but iodide is equally effective (cf. Figs. 7 and 8). This is to be expected, since the action is almost certainly directly on the thyroid, and since it has been shown that the thyroid only takes up iodine in the form of iodide (cf. p. 18). The mechanism by which benefit is produced has still to be definitely determined.

Mechanical blockage of hormone output by rapid formation of colloid has been suggested (Marine (2)) as also a mass-action effect in the direction of synthesis and storage rather than of discharge (Salter and Lerman). De Robertis and Nowinski have shown that iodine inhibits the proteolytic activity of the thyroid colloid and that iodization *in vitro* inhibits the proteolytic activity of toxic goitrous tissue. They state, however, that this is due to free iodine and not to iodide, and there is no evidence that free iodine is present in the thyroid, while, as just stated, iodide is as effective in preoperative treatment of thyrotoxicosis as is Lugol's solution.

The histological changes seen in the gland following treatment with iodine are varied, but are chiefly in the nature of a marked degree of involution, the general change in appearance being

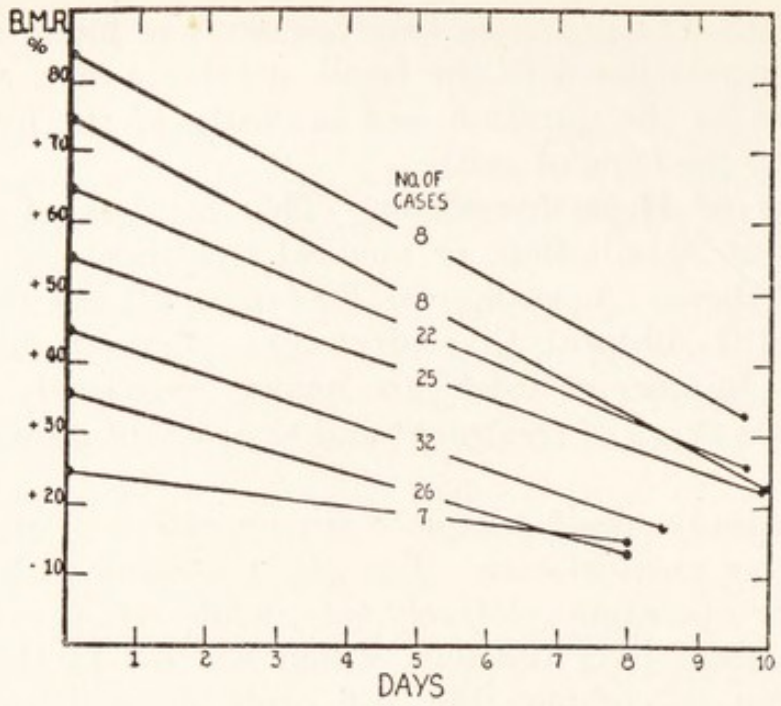


FIG. 7. Response to iodine in Graves' disease. The average basal metabolism before is compared with that after the usual course of iodine in the form of Lugol's solution. The abscissae represent the average time required for the characteristic response. A total of 128 cases was divided into groups according to the pre-iodine metabolic rates, each ten-point rise defining a group. (From Means, Thompson, and Thompson, Trans. Assoc. Am. Physicians, 1928, xliii, 146.)

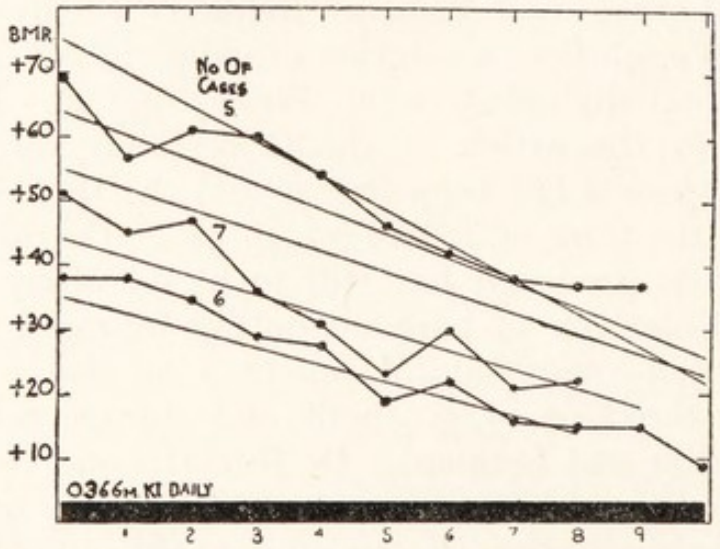


FIG. 8. Comparison of the metabolic rate changes produced by Lugol's solution (cf. Fig. 7) and potassium iodide in Graves' disease. The cases treated by the latter are arranged in three groups, with initial rate less than + 45, between 45 and 59, and + 60 per cent. or over. (From Lerman and Means, Am. J. Med. Sci., 1931, clxxxi, 745.)

towards that seen in an ordinary colloid goitre. The change is so marked, and the use of iodine in pre-treatment is now so universal, that the appearances which used to be regarded as typifying

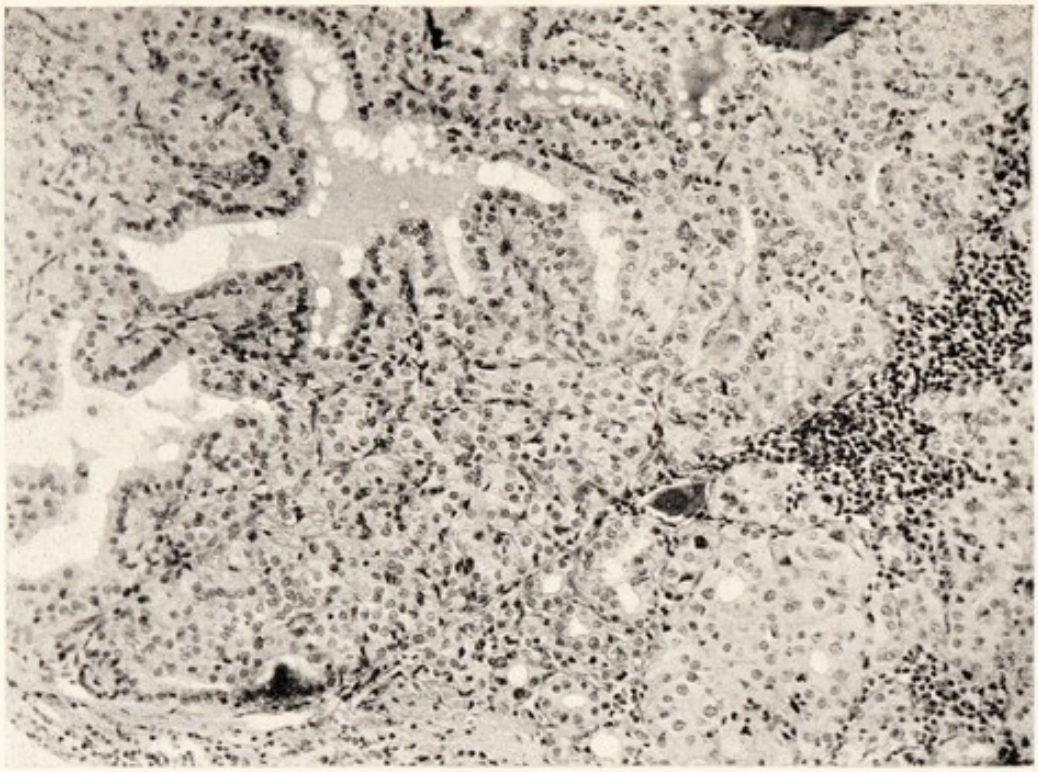


FIG. 9. Graves' disease untreated with Lugol's solution. The acini are for the greater part filled with hyperplastic epithelium. Absorption of colloid, especially along the line of contact with the epithelium. To the right there is a small collection of lymphoid tissue. × 130. (Photo-micrograph and description by Professor William Boyd.)

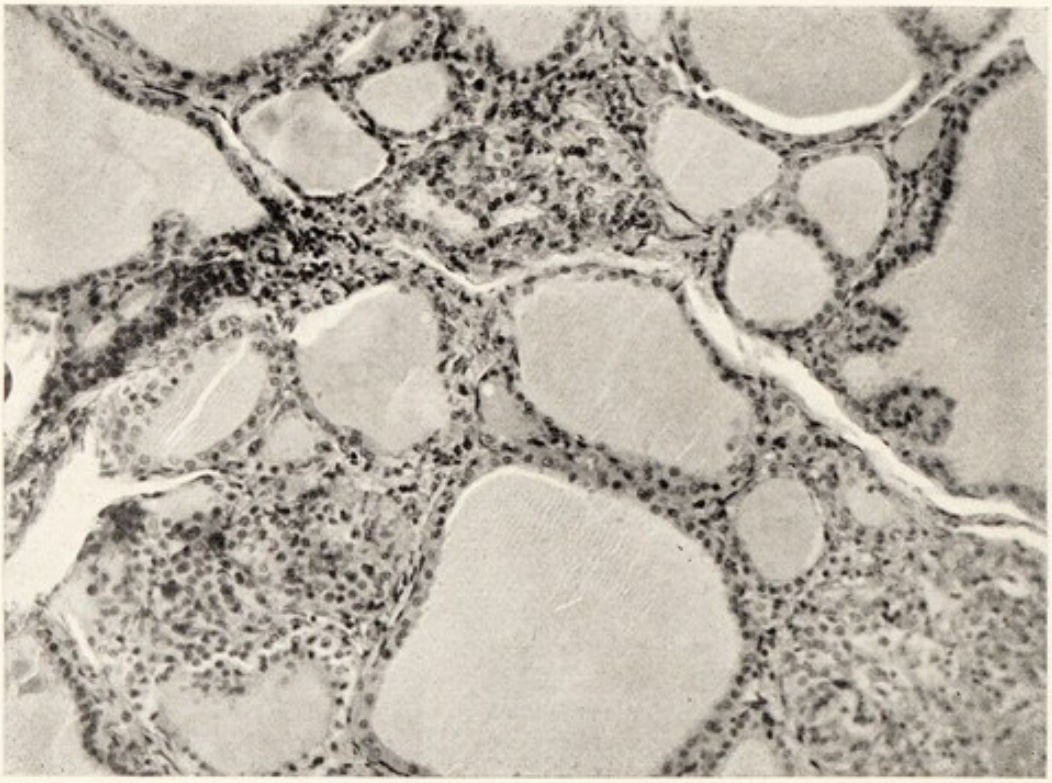


FIG. 10. Graves' disease treated for a short time with Lugol's solution. A few epithelial buds are seen at the right, but most of the hyperplasia has disappeared, and the acini are filled again with colloid. × 130. (Photo-micrograph and description by Professor William Boyd.)

[*To face p.* 63.

Graves' disease are now seldom seen. Through the kindness of Professor William Boyd, a typical picture of a thyroid section from an untreated case of Graves' disease (old material) is contrasted, in Figs. 9 and 10, with an average picture obtained after correct treatment with Lugol's solution.

It is generally agreed that the untreated goitre of Graves' disease is iodine-poor, colloid-poor, and stains poorly with eosin. After treatment with iodine the goitre tends to become iodine-rich and rich in colloid, and stains well with eosin. Hyperthyroid nodular goitres show somewhat similar changes (Holst and Lunde). The iodine treatment naturally increases the inorganic-iodine fraction in the blood, but causes a decrease in the (hormone) protein-iodine fraction to normal or nearly normal limits. (Cf. Lunde, Closs and Pederson ; Dodds *et al.*)

Diiodotyrosine has been frequently recommended in place of Lugol's solution as a vehicle for iodine (cf. Wass). For the reasons already given, its greater value is extremely doubtful. Laroche claims that it is better tolerated.

Thompson (2) says that the size of dose and the form of iodine administration are not of much importance. A daily administration of 5 minims of Lugol's solution (containing 40 mg. of iodine) will always produce a maximum effect (but he uses 5 minims two or three times daily).

Iodine treatment produces objective and subjective improvement in 97 per cent. of cases. The remainder are unimproved or grow worse. Nine-tenths of those who respond to the treatment respond slowly, and the effect lasts only a few weeks, when they become refractory to iodine. The remaining tenth respond promptly (Rose).

Kearns and Starr state that those who do not respond to iodine are usually in the older age group. If such patients have the iodine medication slowly withdrawn, and are subjected to bed-rest and sedatives with possibly the addition of X-radiation, along with a diet low in iodine, and high in proteins, vitamins and carbohydrate, after two to four months they will respond to iodine in the usual way.

Some patients are sensitive to iodine, but unfavourable reactions from its use are very rare. Barker and Wood report seven cases of severe febrile iodism in 400 cases of hyperthyroidism treated at Johns Hopkins Hospital during ten years. The temperatures varied from 101° to 105° F. A cutaneous eruption occurred in four cases, conjunctivitis in four, coryza and pharyngitis in six, enlargement of the lymph nodes in four, jaundice in one ; one case

only showed fever. One death occurred. Three of these cases were given a course of iodine treatment later, with satisfactory results.

As has been mentioned, the majority of patients develop refractoriness to iodine in about three weeks, when the basal metabolic rate starts to increase again, and unfavourable symptoms may return. Bed-rest without iodine for several weeks is necessary before the patient will again respond to iodine.

It has been usual to consider that in severe cases of Graves' disease operation should be performed as soon as the maximal reduction in the basal rate has been attained, which is usually after about ten days of iodine treatment. Nevertheless, in a recent paper entitled "Changing concepts in the treatment of toxic goitre," Thompson (2) states: "At present we worry very little about the development of refractoriness even though it may occur in rare instances. We almost never perform a thyroidectomy as soon as the maximum reduction in metabolism takes place, but nearly always wait for seven to ten days longer in order to allow the patient time to derive the benefit from the lowered rate of metabolism. In some instances operation is delayed for several months. If the metabolism rises slightly it is no cause for concern. If the metabolism fails to show any reduction during the administration of iodine it may usually be disregarded, provided the patient is gaining weight steadily. The reaction to iodine which troubles us is a rapid increase in metabolism during its administration. This phenomenon does not occur very often, and when it does Roentgen ray therapy should be instituted at once."

The usual medical treatment, prior to operation, includes, besides the administration of iodine, bed rest, and a diet sufficiently high in calories to produce a gain in weight, along with digitalis in cases with cardiac decompensation. Thompson (2) says that the most important favourable sign during this period in gauging the outcome of operation is gain in weight. Concerning bed rest, Thompson may be quoted further: "Our ideas about bed rest have been modified. While confinement to the hospital is very important in the pre-operative preparation, complete bed rest appears to be harmful except in the presence of a crisis or cardiac decompensation. It causes loss of muscle tone, reduces the appetite, and makes patients unnecessarily nervous."

Where the hippuric acid or some other reliable liver functional test indicates liver damage, additional pre-operative preparation is needed, since the added stress to the liver of anaesthetic and operation must be faced. As McIver points out, early recognition

of the hyperthyroidism will usually avoid this complication, since it is only present in severe or long-standing cases. When it is present, pre-treatment includes a diet high in protein, carbohydrate, and the B-complex vitamins, careful protection from infections, and choice of an anaesthetic with minimum toxic effect on the liver. (Intravenous glucose with insulin, bile salts, liver concentrate, and even glycine, have been advocated by some surgeons.)

Concerning the desirability of operating in one or more stages,

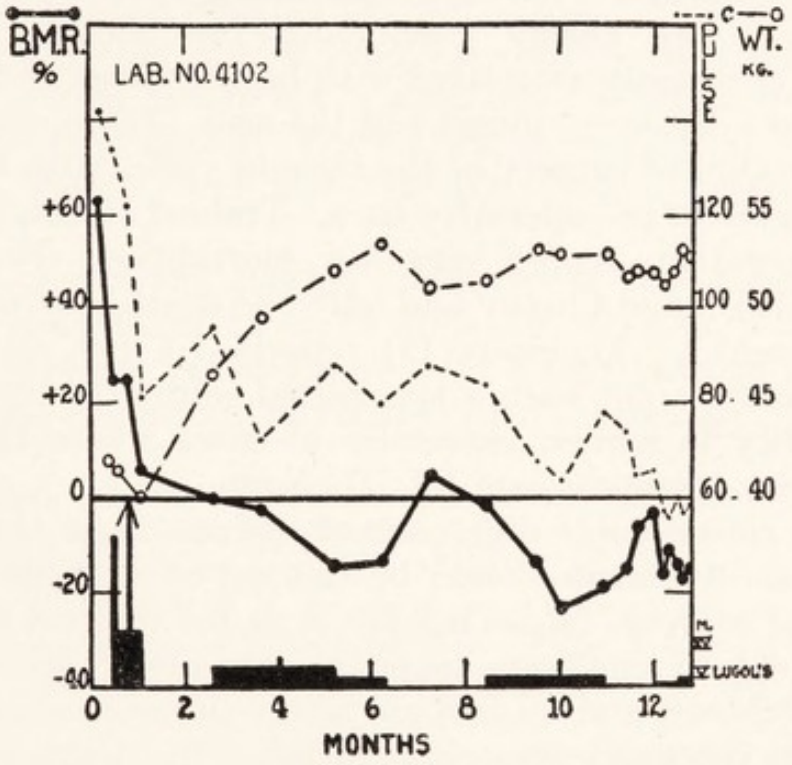


FIG. 11. Iodine responses in a case of residual thyrotoxicosis following subtotal thyroidectomy (arrow) for exophthalmic goitre. The case was characterized by residual nervousness, which disappeared under the iodine treatment. (From Means, Thompson, and Thompson, Trans. Assoc. Am. Physicians, 1928, xliii, 146.)

Thompson remarks that the necessity for multiple stage operation may be avoided in most cases by producing maximum improvement before operation.

Iodine administration is continued in the immediate post-operative period, while it is usually employed when there is some degree of residual hyperthyroidism or of recurrence (cf. Fig. 11).

Following operation the basal metabolic rate drops to normal in ten to fourteen days. In 20 to 25 per cent. of cases it may later drop to sub-normal figures, though the development of myxoedema after subtotal thyroidectomy is rare. In 5 to 10 per cent. of cases the rate is unaffected, or a high rate recurs with

recurrence of hyperthyroidism (Thompson ; cf. Preston and Thompson). Such recurrence is commoner with Graves' disease than with toxic nodular goitre.

The improvement in basal metabolism is paralleled by general improvement. Nervousness is invariably improved but not always banished. Most patients gain weight. Graham and Wallace, surveying the late results in 125 cases, reported that 90 per cent. were rendered fit to work.

Adequate pre-operative care can virtually eliminate post-operative crisis (see p. 75). Excluding this, post-operative complications are chiefly pneumonia and sudden respiratory difficulties commonly associated with haemorrhage and formation of clots under the strap muscles of the neck (Thompson (2)).

The mortality of surgery of the thyroid varies with the surgeon and the degree of pre-operative care. Trained teams, specializing on this operation, report very low mortalities. For example, Schmidt, Walsh and Chesky had only one death in 370 operations (0·27 per cent.). Thompson (2) reports 1·5 per cent. Where thyroidectomy is not such a specialized routine event, naturally the mortality is higher, especially in cases where there is less adequate pre-operative care (cf. Thompson (2)).

There is considerable difference of opinion as to the extent to which hyperthyroidism should be treated by X-radiation to the exclusion of surgery. Rose regards it as the method of choice in cases of mild to moderate severity, in Graves' disease in pre-pubertal children, and in patients who refuse operation or whose condition is too grave for surgical risk. (The treatment may so improve this last class of cases as to justify subsequent surgery.) It is also useful in post-operative cases which do not respond properly to iodine.

In a recent discussion on the place of radiotherapy in treatment of hyperthyroidism published in the Proceedings of the Royal Society of Medicine, Martin advocated its use in cases not requiring early operation, in children and adolescents, in post-operative relapse, and in cases in which operation was refused. He considered that it should not be employed in cases of nodular goitre with hyperthyroidism, in those with cardiac failure or auricular fibrillation, or with tracheal compression, or when either the diagnosis of hyperthyroidism itself, or differentiation between its primary and secondary form, was doubtful.

Soley and Stone claim that X-ray treatment, if in adequate dosage, brings about subtotal destruction of the thyroid, producing in the majority of patients relief of clinical symptoms, fall of the

basal metabolic rate to normal, and decrease of the thyroid to normal size. A small proportion of cases show an increase of the exophthalmos, but that can also occur after surgery.

Various forms of medical treatment of hyperthyroidism have been advocated. The most conservative, rest and intermittent iodine administration, occasionally gives good results, but needs considerable care in the selection of the cases to which it should be applied. The rest needs to be both physical and mental, the diet should provide a high calorie and high vitamin intake, sedatives should be given, and possibly psychotherapy. Rose considers that it has little to recommend it except in certain cases of ophthalmopathy (see p. 83), and in a few mild cases in which an optimum environment is available. Graves' disease seldom responds completely to iodine, and hyperthyroid nodular goitre requires surgery.

Bram is one of the leading advocates of medical procedures. In his large series of cases he considers that only 2 per cent. needed surgery (or radiotherapy, which he thinks as effective as surgery). He is a strong advocate of psychotherapy.

Clinical and experimental studies indicate that requirements for vitamins A, B_1 and C are increased in hyperthyroidism, and if they are not met a relative deficiency of the vitamins will ensue (cf. Drill).

According to Puppel *et al.* inadequate intake of calcium and phosphorus in hyperthyroidism often produces some degree of osteoporosis which can lead to osteomalacia and spontaneous fracture. Such developments are preventable by increasing the intake of these minerals and vitamin D. Hyperthyroid patients ordinarily need 2 gm. of calcium daily to maintain calcium equilibrium.

Reports have been made on a number of new and unusual methods of treatment in the past few years. Some of them appear to have yielded results which suggest that further trial of them may be merited.

Rienhoff gives desiccated thyroid in pre-operative treatment of severe hyperthyroidism, for usually about three weeks (4 grains of a thyroid preparation containing 0·2 per cent. iodine daily in 1 grain doses). He claims good results.

Postlethwaite injects the thyroid with a sclerosing agent, " sylnasol," a 5 per cent. solution of the sodium salt of a vegetable oil from psyllium seed. This fibroses the gland. He claims good results in a number of cases.

Treatment of hyperthyroidism by oestrogens. There is various experimental evidence suggesting an antagonism between oestrogens and the thyroid hormone. For example, oestradiol benzoate, injected into rabbits, depresses basal metabolism and lessens the calorigenic effect of thyroxine given simultaneously. Maheux (1) suggests that the oestrogen acts on the " pituitary-diencephalic complex."

Oestrogens have been administered in clinical hyperthyroidism by a number of investigators. Neither Spence nor Cookson could detect

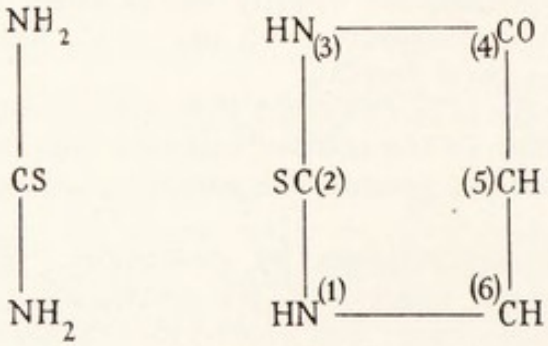
any improvement, but good results have been claimed by Donald, Goldman *et al.*, Storck *et al.*, and Shute and Shute. Storck considers that collateral oestrogenic therapy is especially appropriate when the hyperthyroidism is severe or when there is unsatisfactory response to the usual methods of pre-operative treatment. However, Farbman finds that while large doses of oestrogen seem to have inhibitory effect on the thyroid it is not enough to be apparent in cases of even moderately severe toxicity; it may be effective in mild hyperthyroidism. Dodds and Robertson (personal communication) have tested stilboestrol in six cases of thyrotoxicosis and find it absolutely without effect.

Treatment of hyperthyroidism by thiouracil and similar agents. The chief recent advance in the treatment of hyperthyroidism is the application of such drugs as thiouracil, either in pre-operative treatment, or for continuous medical therapy. Such drugs are sometimes referred to as goitrigenic, and as anti-thyroid. Neither term is particularly suitable. Methyl cyanide, a powerful poison, is goitrigenic. "Anti-thyroid" suggests an anti-hormone action, and anti-hormones are now usually considered to be antibodies (cf. p. 429).

Only a proportion of the many papers in the recent literature can be referred to.

The development of this type of treatment arose from observations that administration of the sulpha-drugs and similar compounds produced in the experimental animal thyroid hyperplasia associated with hypothyroidism, effects which could be counteracted by thyroxine (cf. Cutting and Kuzell, Mackenzie *et al.*, T. H. Kennedy, Astwood (1)). The production of myxoedema by prolonged dosage with thiocyanate has been referred to (p. 53).

Among the early papers claiming good results by administration of thiouracil or thiourea to cases of hyperthyroidism are those of Astwood (1), Williams and Bissell, and Himsworth (1).



Thiourea 2-Thiouracil

Very many compounds have now been tested for such actions, as judged by the effects on the thyroids of rats and other laboratory animals. Astwood, Bissell and Hughes, using a method combining

effect on thyroid weight, and on iodine concentration in the thyroid, found 115 compounds out of 220 tested to have some degree of activity. They took 2-thiouracil as standard, and its activity as 1·0 ; 25 compounds were found to be more active or as active as it. The most potent were thiouracil derivatives (their relative activities are given in brackets) : 6-n-propylthiouracil (11), 6-benzylthiouracil (10), 6-tertiary-butylthiouracil (9), 6-isopropylthiouracil (9), and 6-ethylthiouracil (8). Thiourea, by their test, had only a value of 0·12, while no substituted thioureas had values above 0·4. Certain non-sulphur compounds such as 4-4′-diamino-diphenyl-methane also possessed slight activity of the order of 0·4.

Williams and Frame, using the goitrigenic effect on rats as rough test, found that the descending order of activity was : 6-methylthiouracil, thiouracil, o-phenylenethiourea, 5-methylthiouracil, benzylthiouracil, 6-phenylthiouracil, tetramethylthiourea, diethylthiourea, thiourea. These results do not quite agree with those of Astwood.

The thyroid action and the toxicity of such compounds are not parallel. It seems to be agreed that clinically thiourea is less beneficial than thiouracil, and more toxic. McGavack and Vogel, testing certain thiouracil derivatives, found them slightly less goitrigenic than thiouracil, but much more toxic.

All such compounds are administered orally, both in experimental and clinical work.

Mode of action. Thiouracil seems to antagonize all the various effects of the thyroid hormone, apparently through inhibiting its formation. Given to young rats thiouracil causes nearly complete disappearance of iodine from the thyroid in five days, and a threefold increase in the size of the thyroid in two weeks. These effects are prevented by hypophysectomy, or by injection of thyroxine. If the thiouracil is withdrawn after eight days, there is a prompt decrease in the size of the thyroid, which rapidly reaccumulates iodine (Astwood and Bissell). If the administration commences at birth it produces marked retardation of growth, arrested development, mild anaemia, and the general picture of cretinism (Hughes). The retardation of growth affects the whole body except the thyroid, but there are no appreciable histological effects on other organs (Williams *et al.*) except perhaps the adrenal. Baumann and Marine have recently stated when thiouracil is fed to rats it produces shrinkage of the adrenal cortex to half-size in three or four weeks, all three zones being affected ; there is extreme congestion in the reticular zone and often haemorrhage. On the other hand, Glock has reported that in the terminal stages of fatal poisoning by thiourea or thiouracil rat adrenals are frequently enlarged and dark reddish brown in colour.

Thiourea causes thyroid hyperplasia in rabbits even when large amounts of iodine are given simultaneously (Baumann, Metzger and Marine).

The thyrotrophic hormone of the pituitary, by stimulating production of thyroid hormone, accelerates metamorphosis of tadpoles ; thiouracil inhibits this action (Hughes and Astwood). Thyroid fed to mice confers resistance against the toxic action of acetonitrile ; thiouracil counteracts this thyroid effect (Malkiel). It seems to inhibit the peroxidase activity of the follicular cells of the rat's thyroid (Dempsey).

Thiourea causes a rise in plasma globulin and non-protein-nitrogen, which is not due to reduced food intake also produced by the thiourea (Leathem).

Thiouracil administration lessens the capacity of the rat's thyroid to take up injected radio-iodine and to convert it to diiodotyrosine and thyroxine (Franklin, Lerner and Chaikoff). Two weeks after withdrawing the thiouracil the thyroid gland is again normal. Similar results have been obtained with the chick (Larson *et el.*).

The hyperplasias of the thyroid produced by thiocyanate and by thiouracil are not comparable. Administration of tracer doses of radioactive iodine indicated that the iodine uptake by the thiocyanate-goitrous gland was much greater than normal, and by the thiouracil-goitrous gland much less (Rawson *et al.*).

General effect when administered to patients. Thiouracil causes a reduction in the basal metabolic rate and in the protein-bound iodine of the blood plasma which are roughly parallel (Lowenstein *et al.*).

It is rapidly absorbed from the gastrointestinal tract and readily excreted in the urine. A daily dosage of 0·2 to 1·2 gm. gives a blood concentration of 0·8 to 6·4 mg. per cent., daily excretion of 16 to 600 mg. in the urine, and none in faeces. It is rapidly destroyed by stomach and intestinal contents and in many of the body tissues. In the blood it is present chiefly in the red cells, but in greater concentration in the white cells. Pleural and ascitic fluids contain it in amounts of the same order as blood, cerebrospinal fluid, oedema, and pericardial fluid in distinctly less amount, and milk in three times greater concentration. At post-mortem examination of patients given the drug during several days before death it was found present in practically all the body tissues, and sometimes in relatively large amounts in bone marrow, thyroid, ovaries and pituitary; the liver, testes and striated muscle contained relatively little. In the tissue of thyroid adenomata it is found to be more concentrated than in relatively normal thyroid tissue (Williams, Kay and Jansdorf).

Post-mortem studies in a patient aged seventy-four, whose thyrotoxicosis had been satisfactorily controlled over some period by thiouracil (178 gm. in 381 days), showed significant changes in the thyroid, pituitary, adrenals, spleen and bone marrow, and little alteration in other tissues. The pituitary was slightly enlarged and showed early atrophic changes, the adrenals showed marked lipoidosis, while the glomerular zone was but a thin sheet, and the bone marrow was hyperplastic (Reveno).

Thyroid tissue removed at thyroidectomy shows many acini small and contracted, the lumena almost disappearing, although the occasional lumen is enlarged. The acinar cells are tall and columnar. There is an increase in interstitial tissues, and sometimes increased lymphoid hyperplasia. The appearance is quite different from that of a gland after treatment with iodine, and the effect is as marked after one as after eight months. When both iodine and thiouracil have been given the histological picture of the thyroid varies, but the iodine effect tends to predominate (Williams and Clute), though the incidence of involution is not as frequent as when iodine is used alone (Lahey *et al.*). (Cf. also Halpert, Cavanaugh and Keltz.).

Effect of thiouracil on thyrotoxicosis. Present opinion seems well

expressed by the statement of Rose and McConnell, written in 1944 : "While much further work remains to be done before the clinical usefulness of thiouracil can be finally evaluated, it may tentatively be concluded that this drug effectively controls most of the phenomena of thyrotoxicosis in the large majority of patients, and that its use at present is justified in the protracted treatment of mild or moderately severe cases and in the preoperative preparation of selected patients for thyroidectomy. It may also prove of considerable value in patients regarded as unacceptable surgical risks."

Use in preoperative preparation. Moore *et al.* consider that thiouracil is superior to iodine, since it will always ultimately produce a normal basal metabolic rate. Histologically, it intensifies the hyperplasia of the thyrotoxic gland, but the result is a non-functioning goitre. The increased vascularity and friability of the gland is occasionally a disadvantage rendering surgery more difficult and haemostasis arduous. Prior or simultaneous iodine administration delays the response to thiouracil.

Lahey *et al.* recommend a dosage of 0·6 gm. per day, and state that approximately one day's treatment is needed for each per cent. elevation of the basal metabolic rate at the start of treatment. They believe that Lugol's solution should also be given for the three weeks preceding operation, with discontinuance of thiouracil during the final week. (Cf. also Williams and Clute ; Williams (2).)

Boyd and Connell think that in toxic nodular goitre thiouracil treatment should be limited to pre-operative preparation ; Grollman and Gryte do not seem to be in agreement.

Protracted treatment with thiouracil. Astwood (2), writing in 1944, stated that administration of 0·2 to 0·6 gm. daily in two doses quickly controls all the manifestations of hyperthyroidism in previously untreated cases of Graves' disease. The response is slower if the patient has previously received iodine. Toxic nodular goitre also responds more slowly. He noticed in some cases a transient enlargement of the thyroid with increased vascularity. Exophthalmos usually improves slowly. Iodine remains effective, both during and after thiouracil therapy. In 9 cases (of 62) which received adequate treatment with thiouracil for more than six months, it was possible to discontinue the therapy.

Williams and Clute also record the occasional transient increase in the size of the thyroid but state that ultimately it decreases in size. The plasma protein-iodine tends to become normal before the basal metabolic rate, which requires from three to five weeks according to its original height. Discontinuance of treatment may cause a relapse within three weeks, but renewal of the drug again produces remission.

Donald and Dunlop, reporting encouraging results in 30 of 31 cases, recommend a dosage of 0·6 gm. daily for three or four weeks, and then 0·2 gm. daily as maintenance dose. With proper dosage a significant enlargement of the thyroid does not occur, but overdosage can produce marked enlargement with low basal metabolic rate and mild myxoedema (cf. Himsworth (2)) such enlargement being considered due to overstimulation of the pituitary by the thiouracil, with resulting production of excess thyrotrophic hormone.

Grainger, Gregson and Pemberton claim that toxic nodular goitre does not respond to thiouracil as well as does Graves' disease.

McGavack *et al.* summarize their results on 78 patients (10 men, 68 women ; 53 cases of Graves' disease and 25 of toxic nodular goitre) as follows : Nervousness, apprehension, palpitation and loss of weight, amongst the commonest symptoms, were among the first to disappear. Exophthalmos, present in 38 cases, decreased in 17. Thyroid enlargement, present in 65 cases, showed a transient decrease in 20, and a slower increase in 21. Auricular fibrillation, present in 18, disappeared in 12 without other therapy. In 18 of the patients the treatment was used preoperatively. In the other 60 cases a maintenance dose of 0·1 to 0·4 gm. was given daily with different patients. It was successfully discontinued later in 14 of them (5 after two and a half months, 1 after four months, 1 after five months, two after six months, 2 after seven and 3 after eight months). (Eleven of their cases had pre-existing diabetes ; 3 showed no change in glucose tolerance.)

The treatment seems to be contraindicated in " malignant exophthalmos " (Astwood (2) ; Boyd and Connell), and to be particularly indicated for thyrotoxic patients with severe cardiac involvement, or who refuse surgery (Boyd and Connell).

Cookson (3) has written an excellent account of the course of the disease during thiouracil treatment, based on his results with 33 cases, of which 30 were of toxic nodular goitre. Initially, he gave 0·2 gm. three times a day, and after three or four weeks this was reduced to 0·2 or even 0·1 gm. daily. " Within a few days or a week the patient may say she feels better, but it is unusual to get much objective improvement in less than three weeks. From the end of this time a change in appearance becomes obvious, the face fills out, and its strained, lined appearance goes, while the complexion, which is characteristically sallow or pigmented, becomes lighter. The pulse-rate falls, weight is gained, appetite improves in the older patient though it may diminish in the young, the skin becomes cooler and drier, and tremor and nervousness are lost. The patient becomes calm and can sit still ; she looks and, as she often expresses it, ' feels quite a different person.' Her movements are not so quick and jerky, yet she has much more energy to do her work. The effect on eye signs is not so striking ; stare and lid retraction and eyelid swelling diminish, but exophthalmos is not reduced. On the other hand, no instance of increased exophthalmos or of diplopia or ophthalmoplegia has been noted after thiouracil. In the first weeks no change can be detected in the size or consistence of the thyroid gland." (Cf. Fig. 12.)

" The general effect in this group of patients was similar to that of a subtotal thyroidectomy, and, though the immediate results are less rapid, a patient is doing her work at an earlier date than if she had undergone a thyroidectomy. About three months is required for normal health and activity to be regained. It was fairly easy to produce myxoedematous symptoms in this group of patients by giving thiouracil 0·6 or 0·8 gm. daily after the B.M.R. had reached normal. This was noted in six patients."

After some months the thyroid was larger and firmer in some cases, and only in a small number was it smaller and softer. In only 2 cases was it possible to omit the drug for longer than three months without recurrence of symptoms, though these responded well to renewal of the treatment.

Five patients in the series failed to respond to the therapy, of whom 2 were pregnant women and 3 had fibrillation.

In other patients with goitre but without definite thyrotoxicosis results were not striking. Such cases did not develop myxoedema in spite of prolonged and relatively heavy thiouracil dosage.

Williams (2) has recorded results with 126 patients, not submitted to thyroidectomy, but receiving prolonged treatment with thiouracil.

(*a*) (*b*) (*c*)

FIG. 12.—Woman aged seventy-seven. History of nervousness and loss of weight from 152 to 70 lb. in two years; general pruritus, dysphagia, husky voice, failing vision, and prominence of eyes for a few months. A very small thyroid nodule palpable deep in the suprasternal notch; pulse-rate 104, normal rhythm; BP 185/90 mm. Hg; BMR + 40 per cent.; blood-cholesterol 95 mg. per 100 c.c.

(*a*) September 6th, 1944, before treatment; weight 70 lb.

(*b*) October 4th, 1944, after thirty days' treatment with thiouracil (23 gm.); weight 89 lb.; pulse-rate 80; eyes less staring; BMR −9 per cent.; blood-cholesterol 158 mg. per 100 c.c.

(*c*) February 13th, 1945, after five months' treatment; weight 109 lb.; pulse rate 76; BP 190/110; at work all day. Has been followed up for a further five months and keeps in excellent health on 0·1 gm. thiouracil twice daily; thyroid no longer palpable. (From Cookson, Lancet, 1945, ii, 485.)

All experienced a remission of the disease, maintained as long as the treatment was continued. It was stopped in 100 cases (usually after many months). In 49, receiving no treatment over periods varying from three to twenty-one months, there were no relapses. In the other 51 relapses occurred within 0·5 to five months (and usually early). In the milder cases which had received relatively longer treatment there was less liability to relapse. In nearly two-thirds of those cases receiving thiouracil for at least eight months the thyroid decreased in size; in a few cases the size increased.

Comparative clinical results with different compounds. Thiourea is more toxic than thiouracil (Paschkis *et al.* ; Johnston), but Danowski, Man and Winkler state that smaller doses are effective.

In experiments with the rat, thiobarbitol seemed more effective than thiouracil in inhibiting thyroid function (Astwood *et al.*). However, Astwood (3) has tested it clinically with 30 cases, giving a daily dose of 0·1 to 0·4 gm., and reports that while it is twice as effective as thiouracil in controlling hyperthyroidism, it is more toxic when the minimum effective dose is exceeded, there being in this series one death from agranulocytosis, one from acute liver disorder, and 6 cases gave febrile reactions.

Williams (1) tested tetramethylthiourea with 30 patients with thyrotoxicosis. The results were similar to those obtained with 152 patients given thiouracil. There was no significant effect on the white cell count, but, as with thiouracil, there were occasional febrile and skin reactions. On the other hand, sym.-diethylthiourea was less effective than thiouracil and was toxic to most patients.

Leys has reported satisfactory results with 6-methylthiouracil given in 16 cases of (apparently mild) hyperthyroidism. Initial dosage was 200 mg. daily, stepped up by 200 mg. every day or every other day till the effective dose was attained, but limited to a maximum of 0·8 gm. When gain of body weight was considered satisfactory a maintenance dose of 100 or even 50 mg. was substituted. Phenobarbitone was also given in the early stage of treatment. There was usually improvement within two or three weeks, but no reduction in the size of the goitre.

Astwood and VanderLaan find that 6-ethylthiouracil, tested on 14 patients, and 6-n-propylthiouracil, tested on 37 patients, are five times as effective as thiouracil itself. The former gave one urticarial reaction. There were no other bad effects. Dosage for propylthiouracil was 25 mg. at eight or twelve hour intervals until equilibrium was produced, then 25 to 50 mg. daily. Initial dosage for ethylthiouracil was 75 mg. daily.

Toxicity. Different reports show a different incidence of toxic reactions to thiouracil. While the majority of patients do not develop unpleasant side reactions, and while thiouracil is definitely effective in the treatment of hyperthyroidism, its toxicity is unpredictable, and it may produce serious damage, especially on the bone marrow and liver (cf. Gargill and Lesses).

It is generally considered that leucopenia (granulocytopenia) is the greatest potential danger (cf. Lahey *et al.*). Grainger, Gregson and Pemberton state that nearly every one of their 29 cases showed some degree of granulocytopenia, but, as pointed out by Williams, Clute *et al.*, leucopenia and neutropenia may occur in untreated cases of thyrotoxicosis, so that they do not consider white cell counts between 3,500 and 5,000 as conclusively due to thiouracil treatment. These writers have dealt exhaustively with the types of reactions that may be associated with the treatment. They say in this connection : " Of 793 reported cases with data satisfactory for analysis there were 38 patients (4·8 per cent.) with leucopenia and 5 (0·6 per cent.) with agranulocytosis. Three of these patients died. Of the 247 patients whom we treated there were 13 (5·2 per cent.) with white cell counts that decreased to

3,800 or below during treatment and 3 (1·2 per cent.) that developed agranulocytosis. In 1 of the 3 cases the agranulocytosis may have been due to sulfathiazole. All of these patients recovered." In their own series toxic reactions developed in 14·5 per cent. These included febrile reactions, maculopapular eruptions, oedema of the legs, urticaria, neuritis, arthritis, enlargement of the submaxillary salivary glands, and, rarely, complaints of headache, nausea, vomiting and diarrhoea. They note that others have reported haematuria and jaundice. The occasional development of psychoses they consider is probably not attributable to the thiouracil (cf., in this connection, Simpson; Pearson; Atkin).

Cookson has summarized the literature dealing with toxicity, and states that no series so far reported is entirely free from such reactions, the incidence varying between 10 and 20 per cent. The marked enlargement which may result from overdosage has already been referred to.

There seems to be some potential danger in treating pregnant women with thiouracil; in such a case where death occurred from other causes during the sixth month of pregnancy, the thyroid of the foetus was found to be enlarged and hyperplastic (Davis and Forbes).

Treatment of agranulocytosis from thiouracil. Good results have been reported by administration of pyridoxine hydrochloride (Cantor and Scott; Fishberg and Vorzimer). Goldsmith *et al.*, from experiments with rats, suggested that a liver extract, or folic acid, would have value in treatment. Williams, Clute *et al.* have tested such therapy and do not find it effective.

Comment. While this new means of medical treatment of thyrotoxicosis seems the best so far available, it is not ideal. The underlying cause of the thyrotoxicosis is not eradicated but at best persuaded into such quiescence that all treatment can be discontinued at least for a time. The occasional and unpredictable occurrence of toxic reactions, sometimes severe, also detracts from the value of the treatment.

The varying reports from different clinics on the effect on thyroid size may be in part due to use of different dosages.

The most promising feature is probably the fact that degree of effectiveness of such drugs is not paralleled by the degree of their toxicity, and this is illustrated by the definitely better results obtained by Astwood, using certain derivatives of thiouracil.

Treatment of hyperthyroidism with radioactive iodine. Early reports on the use of the product obtained by deuteron bombardment of tellurium claim that it is highly effective, though myxoedema is not infrequently produced, and occasionally also reactions resembling Roentgen-ray sickness (cf. Hertz and Roberts; Chapman and Evans).

Thyroid crisis is apparently due to sudden marked increase in the degree of the hyperthyroidism. It can develop in either the treated or untreated patient. It is characterized by restlessness, loss of appetite, nausea, vomiting, gradually increasing heart rate, marked weakness, and loss of weight. Sometimes delirium, diarrhoea, and fever (to extreme hyperpyrexia) are present. If iodine has not previously been given the patient can sometimes

be controlled by it, but he usually fails to respond to any remedial measure, passes into coma, and dies (Thompson (1) ; Rose).

Crisis developing subsequent to operation is usually due to inadequate pre-operative care (Thompson ; Schmidt *et al.*).

At autopsy of such patients liver damage is frequently found, but McIver considers that this is not the cause of the crisis. Maclagan and Rundle believe, however, that liver failure is the commonest single cause of post-operative confusion and delirium.

Graves' Disease in Children and Adolescents. Thyrotoxicosis in children is almost invariably that of Graves' disease. It is rare before the age of ten ; 80 per cent. of the cases occur between the ages of ten and fourteen. The ratio between girls and boys is 6 to 1. It tends to be more acute, clinically, than in adults. The commonest manifestations are nervousness, goitre, exophthalmos, and tachycardia ; exophthalmos occurs more frequently than in adults. Tremor is usually present, and occasionally is so general as to simulate chorea. Loss of weight is not marked, and in the early stage there may be gain of weight (" R. H. W.").

Schereschewsky considered that the disease develops most frequently following infection, especially of the naso-pharynx. It can evolve rapidly, and can disappear as rapdly.

Skeletal growth is hastened and may actually precede symptoms of hyperthyroidism, suggesting undue pituitary stimulation. Closure of the epiphyses is not affected. Sexual maturity is delayed (Reilly ; Hertz and Galli-Mainini).

In cases where there is difficulty of diagnosis a therapeutic test with iodine or thiouracil is of value (" R. H. W.").

It is becoming agreed that subtotal thyroidectomy is less satisfactory in children than in adults. This is borne out by the Mayo Clinic figures for the period 1921—45. In 109 operations the mortality was 3. Follow-up data for 102 cases showed 7 recurrences, 1 death and hypothyroidism in 23 cases. In the same period 14 cases were treated medically. Results were good in 10 cases, fair in 3 and poor in 1 (" R. H. W."). Reilly reported on 62 cases ; of these surgery was only employed in 34, who showed severe and persistent toxicity. In half the cases the thyroid hyperplasia was relatively benign, self-limited, and not a serious menace to health. The disease showed multiple cycles, each succeeding cycle tending to be less severe and shorter, and usually there was arrest by the eighteenth year. In those cases treated medically, rest in bed or iodine medication, or both, arrested or improved the condition.

Nixon has reported on a series of only 8 cases. Two mild

cases treated conservatively recovered. Of the 6 cases operated on, 4 died within the subsequent year. His comment seems logical: "Because the thyroid probably is not the primary pathogenic factor and because it plays a tremendously important part in the growth and development of the normal child, it would seem advisable to treat Graves' disease in children on a conservative basis. Thyroidectomy should be performed only on those children who do not show definite improvement after a comparatively long period of treatment on a carefully planned and executed medical *régime*."

Adults, recovered from adolescent hyperthyroidism, are often tall and with a heavy skeleton. In women menstruation is normal (Reilly).

The Heart in Hyperthyroidism. The usual opinion is that hyperthyroidism *per se* has no toxic or direct pathological action on the heart, although, indirectly, it may accelerate the development and progress of pathological lesions arising from other causes and from the load thrown upon it by the increased metabolism of the whole body. Relief of the hyperthyroidism relieves the heart. (Cf. Cookson, and the Symposium Report in the American Heart Journal.)

Greene and Hurzthal point out that the fundamental difference between congestive heart failure due to hyperthyroidism and that due to intrinsic heart disease is that in the former the heart cannot maintain the circulatory needs of the increased body metabolism, while in the latter it cannot maintain the needs of a normal metabolism. The superimposition of auricular fibrillation in either group greatly increases the heart's inefficiency.

They publish a follow-up of 469 thyrocardiac cases subjected to operation between 1922 and 1937. Of 303 operated on during the period 1922–32, 164 are living, and of these 122 have normal heart rhythm; the other 42 continue to have auricular fibrillation. Of the subsequent cases 128 are living, 98 with normal heart rhythm. Although most of the patients have been restored to normal activity, their expectancy of life is less than normal.

Rasmussen deduces from experiments on dogs that the essential action of the thyroid hormone on the heart is not to produce increase, but variability of the heart rate. The power of evoking paroxysms of sinus tachycardia is a peculiar and characteristic property of the thyroid hormone and can lead to circulatory failure and death of the animal.

(A later section entitled "cardiotoxic goitre" should be read in connection with the above.)

Unusual cases of hyperthyroidism. McEachern and Ross have described 3 cases, and associated them with 10 in the literature, of a condition they term "chronic thyrotoxic myopathy," a muscular atrophy associated with hidden hyperthyroidism. The condition is usually seen in males past middle age, and is characterized by progressive loss of weight, marked weakness, fatiguability, wasting and coarse fasciculation of the skeletal muscles, most marked in the shoulder and pelvic girdles (which helps to differentiate it from progressive muscular atrophy). There are no signs of pyramidal tract involvement. Muscular symptoms dominate the picture, masking the usual evidences of hyperthyroidism, although apprehensiveness, emotional lability and sweating are usually present, and tremor is prominent. Creatinuria is present. The basal metabolic rate is moderately increased. The thyroid, if enlarged, is only moderately so. The distribution of muscular weakness and fatiguability is not that of myasthenia gravis, but the condition, nevertheless, may respond temporarily to prostigmine. Thyroidectomy is followed by complete recovery.

Zondek describes the case of a woman who at the age of thirty-four presented typical signs of hyperthyroidism (including slight goitre, tremor, exophthalmos, and a basal rate varying from + 23 to + 30 per cent.). After treatment with iodine and irradiation of the thyroid in the course of a year she developed typical myxoedema (with amenorrhoea, a blood cholesteral of 290 mg. per 100 c.c., and a basal rate of − 20 per cent.). The myxoedema lasted nearly four years, during which time, on thyroid medication, she became pregnant. During her pregnancy thyroid treatment was stopped; she remained in good health. At the end of this interval emotional disturbances led to a return of signs of Graves' disease (exophthalmos, a basal rate of + 23 per cent., but no thyroid enlargement). She was given rest, sedatives, and injections of glucose, and gradually recovered.

Osteoporosis is present in some proportion of cases of hyperthyroidism, due to an increased excretion of calcium (cf. p. 27), due to increase in the output of the thyroid hormone (Brunner).

Rose and Wolferth report 3 cases of hyperthyroidism which, during or shortly after irradiation of the thyroid, developed severe precordial or retrosternal pain, aggravated by thoracic movement, and suggesting an acute, non-infectious, mediastinocardiac reaction.

Eden and Trotter report a case labelled "lymphadenoid goitre," associated with the clinical picture of Graves' disease, with a basal metabolic rate varying from + 39 to + 48 per cent., which completely recovered following thyroidectomy. Sevringhaus (1942) comments that this case either represents the fortuitous concurrence of hyperthyroidism with Hashimoto's disease, in the same thyroid, or else that the pathological picture seen is an exaggeration of the lymphatic infiltration commonly found in Graves' disease.

Localized Pretibial Myxoedema Associated with Hyperthyroidism. Trotter and Eden have published an excellently illustrated article on this subject, dealing with 4 cases of their own and 73 in the previous literature. The condition is always associated with a past or present hyperthyroid state (usually Graves' disease). Its incidence in their series of cases of hyperthyroidism was 3 per

cent. The patients seldom complain of symptoms in the legs. " In the gross cases there may be some aching of an indefinite sort, and occasionally pricking or tingling sensations. The appearance of the lesions is quite characteristic, and when once seen can readily be recognized, even in early cases. As a rule the lesions first appear on the antero-lateral aspect of the lower half of the legs. Later, they may extend upwards as far as the knees and also to the back of the legs ; occasionally also to the dorsum of the feet. The lesions are usually bilateral from the first and always become so eventually. In the affected areas the skin is raised in irregular firm swellings, the uneven contours of which are the most characteristic feature of the condition. This unevenness is often best appreciated by touch. The swellings are in the skin rather than beneath it, for the skin cannot be moved independently. The attachment of hair follicles to deeper structures often produces a characteristic dimpled or ' pigskin ' appearance. The skin is commonly a faint pink or sometimes brown colour." According to some authors, the skin temperature is subnormal ; their own cases had normal skin temperature. " There are no objective sensory changes and sweating . . . is normal. The growth of coarse hairs from the affected skin is a marked feature in some cases."

The lesions seem to disappear over a period of years, although this is not certain. Thyroid therapy is without effect. " Our conclusion is that (the condition) is probably unaffected by any treatment which has yet been employed, and that it follows a fluctuating course, which may lead to eventual disappearance."

A different type of *localizéd* myxoedema may occur anywhere in the body, and only infrequently in the legs. It can be of various types, not constantly plaque-like, not constantly associated with hyperthyroidism, but only very rarely associated with hypothyroidism (and these rare cases do respond to thyroid treatment).

Trotter and Eden point out that the cause of deposition of the " mucin " (cf. p. 48) must be some factor present in both hypo- and hyperthyroidism, and suggest the possibility that an overactive pituitary may be the common factor.

Watson, reporting two cases of pretibial myxoedema associated with Graves' disease, points out that actually " myxoedema " is a pathological condition involving the skin and other tissues, only one cause of which is hypothyroidism. Biopsy skin material from his cases showed a higher content of the mucopolysaccharides hyaluronic acid and chondroitin sulphuric acid than did skin material from patients without this condition.

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EXOPHTHALMOS

Exophthalmos is no longer considered as a condition peculiarly associated with hyperthyroidism. It is true that it can be produced in some, though not in all, laboratory animals by inducing artificial hyperthyroidism (Kunde), and apparently markedly so in the young of some species of fish (Grobstein), and that it occasionally results in human beings from continued thyroid overdosage (Brain). Yet poisoning with methyl cyanide produces exophthalmos in thyroidectomized rabbits, and injection of the thyrotrophic hormone of the pituitary will produce it in both normal and thyroidectomized guinea-pigs (cf. p. 342). Marked bilateral and equal exophthalmos is produced in the Atlantic minnow Fundulus within a few hours of injection of small amounts of sheep pituitary extract (Albert). There are a number of authenticated cases of Graves' disease in which, after removal of the thyroid, exophthalmos subsequently developed, at periods varying from three to twelve months, with no later improvement. In several of these the basal metabolic rate was below normal ; in some even myxoedema was present (cf. Zimmerman).

Smelser found that exophthalmos is readily produced in thyroidectomized (but not in normal) guinea-pigs in twelve to twenty days by daily injection of an extract of beef pituitary. It is just as marked in the eye from which the sympathetic innervation has been removed as in the normal eye, so that it does not depend on functional sympathetic innervation or the contraction of a smooth muscle. It is produced by oedematous infiltration of the retrobulbar tissues, there being marked oedema of orbital fat

and connective tissue (other fat deposits in the body being similarly affected). The picture is similar to that in clinical exophthalmos. The production of this experimental exophthalmos is unaffected by coincident administration of sodium iodide, or of diiodotyrosine, but simultaneous injections of thyroxine produce a marked enophthalmos and ptosis, and reduce the incidence of the pituitary exophthalmos from 86 to 52 per cent. It can be produced in hyperthyroid guinea-pigs, but in less degree than in the hypothyroid animal. The pathological changes are independent of Muller's orbital muscle, and are unaffected by unilateral or bilateral extirpation of the cervical sympathetic ganglia.

It is now generally agreed that human exophthalmos is of two types, the classical syndrome associated with thyrotoxicosis, tending to develop after the hyperthyroidism is established, and to regress after the hyperthyroidism has been controlled, and a rarer, more severe type, sometimes preceding thyrotoxicosis, and not relieved but often accentuated by thyroidectomy.

Oedema of orbital tissues is probably the cause of the classical and commoner type, the process being reversible (Friedgood). Dalrymple's sign, retraction of the upper lid, which widens the palpebral fissure and produces the familiar " stare " of patients with Graves' disease, occurs earlier than true exophthalmos (Adler).

The severer type has been variously termed " progressive exophthalmos," " malignant exophthalmos," " ophthalmic ophthalmoplegia " (Brain (2)), or the " special ophthalmopathic type of Graves' disease " (Hertz, Means and Williams). The last-named writers state that it occurs in 4 per cent. of cases during the post-operative hypothyroid phase. Brain (3) states that the sexes are equally affected, that the condition follows thyroidectomy in less than 20 per cent. of the total number of cases, and that in this post-operative group males are affected four times as often as females. It is relentlessly progressive, corneal ulceration may develop from exposure of the globe, and finally loss of the eyes (Adler).

Friedgood considers that one should hesitate to operate on patients, especially males, in whom exophthalmos is a more striking part of the hyperthyroid syndrome than the hyperthyroidism or the goitre, and should regard with suspicion, as indicating this severe and dangerous type of exophthalmos, any chemosis, lachrymation, or puffiness and venous congestion of the eyelids. Adler states that the earliest sign is oedema of the lids, often with oedema of the bulbar conjunctiva.

Postoperatively, treatment is difficult. The exophthalmos does not respond well to thyroid administration. Oestrogen is said to give good results occasionally (Brain (3)). In some cases radiation to the orbit (Friedgood) or to the pituitary (Hertz, Means and Williams) is stated to be beneficial. Surgical treatment has been described by Naffziger, and by Thomas and Woods. (Mann, and also Salter and Soley, have recently dealt with the general treatment).

Reverting again to the classical type of exophthalmos, Soley, using an ophthalmometer, found that patients with toxic nodular goitre tend to have eyes more prominent than normal, but less prominent than those with Graves' disease. He made the somewhat surprising statement that the eyes of 50 per cent. of patients with Graves' disease become measurably more prominent after subtotal thyroidectomy ; in only a small percentage do they become less prominent, the apparent benefit being due to loss of the " stare." (In connection with all such measurements it is desirable to remember that normal values for protusion of the eyes vary considerably. Using a Hertel ophthalmometer Adler found that they range from 11 to 19 mm. in males, and from 9 to 16 mm. in females, so that it is difficult to diagnose slight bilateral exophthalmos without a knowledge of previous measurements on the same individual.)

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ACUTE THYROTOXIC BULBAR PALSY

This name, suggested by Laurent, describes a condition of acute muscular weakness which occasionally, but rarely, develops in the

course of severe thyrotoxicosis. The muscles innervated by the cranial nerves are particularly involved. "Ptosis, diplopia, difficulty in chewing and swallowing, facial weakness and inability to keep the head upright, appear suddenly and the weakness rapidly spreads to the limb muscles. Recovery is extremely rare and survival for more than a few weeks unusual."

The condition has been given various names, as "cerebral nerve disturbances in exophthalmic goitre" (Heuer), "myasthenia gravis associated with exophthalmic goitre" (Cohen and King), "Coma Basedowicum" (Zondek), and "acute thyrotoxic myopathy" (Brain).

Zondek, using complex drug treatment, had 4 recoveries in 15 cases. Laurent states that prostigmine relieves the muscular weakness, so that thyroidectomy might be possible. Sheldon and Walker recently reported the case of a woman of fifty, who developed the hyperthyroidism and profound muscular weakness simultaneously. Iodine produced no improvement. Prostigmine greatly improved muscular power, but made her general condition worse. Following partial thyroidectomy, along with iodine and prostigmine, the patient made a rapid recovery, and after five months was able to dispense with the prostigmine completely.

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CARDIOTOXIC GOITRE

Meyer *et al.* found that thyroids from normal animals, when fed to thyroidectomized rats, behave essentially like thyroglobulin, but that when commercial desiccated thyroid preparations are fed, a greater heart-accelerating action is produced. Hyperplastic thyroids from cases of Graves' disease (which had been treated with iodine) produced a similarly greater effect on the rats' hearts. A heart-accelerator substance could be demonstrated in the blood from patients with Graves' disease but not in blood from normal individuals or persons with non-toxic goitre. It disappeared from the blood of patients with Graves' disease following treatment with iodine, concomitantly with the drop in their basal metabolism.

Meyer and Marine, using the same test method, found that the effect of thyroid glands from rabbits rendered goitrous by a cabbage diet, and of goitrous sheep thyroids depended on the presence or absence of iodine and colloid in the glands. When colloid was present there was little effect on the heart-rate. In actively hyperplastic glands without colloid the heart-stimulating factor may be present, although there may be almost complete absence of the usual metabolic effect. A single dose of iodine to a rabbit with such a gland will lead within two days

to an accumulation of iodine in the gland, and a proportional appearance of the metabolic effect when the gland is fed thyroidectomized rats, though the iodine treatment does not demonstrably change the amount of heart-accelerator factor present.

Meyer and Marine do not appear to postulate a perverted secretion. They write : " Whether or not the heart-accelerator substance is a normal constituent, or a product of the thyroid ordinarily present in quantities too small to be proved by these tests is still a moot question."

Schmidt and Hertzler write : " In all types of goitres of many years' duration cardiac disturbances eventually become the most dominant feature of the thyrotoxic state, while significantly elevated metabolic rates become the exception rather than the rule. . . . Obviously, in the absence of elevated metabolism, the thyrotoxic symptoms cannot be due to excessive (thyroxine-hormone) liberation. Inasmuch as thyroidectomy alleviates the thyrotoxic symptoms, the question of an abnormal thyroid secretion becomes a subject for investigation." The colloid of such glands is abnormal. Sometimes the staining is poor, sometimes the reaction becomes basophilic (orange with Mallory's stain, instead of the usual blue). When the thyroglobulin from these glands is hydrolysed, the thyroxine-iodine fraction is decreased, the diiodotyrosine fraction increased. If the glands are extracted, the extract contains a principle which stimulates the heart-rate of thyroidectomized rats without an associated increase in oxygen consumption. Schmidt and Hertzler think that the results are best explained by a perverted secretion.

Such a suggestion has danger. There is at present no evidence that any altered hormone is formed in disease, and more evidence should be required before this ancient idea is reintroduced.

Though they probably have no bearing on the above results, Hogg's observations may be quoted here. He finds that when fluid from thyroid cysts (presumed to contain degenerative material) is injected into mice, it is very toxic. When repeated injections are made in sub-lethal doses, they appear to produce premature ageing and thymic involution.

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MALIGNANT TUMOURS OF THE THYROID

Cancer of the thyroid generally arises from pre-existing adenoma. One of the best reviews of it, according to Thompson, is by Pemberton.

Friedman considers that so-called " benign metastasizing goitre " is in reality malignant. Intercranial lesions in patients with goitre should be considered metastatic unless proved otherwise, even though the thyroid lesion appears to be insignificant, and call for radical

surgical removal of primary and secondary lesions, followed by radiation.

It is important to remember that carcinoma of the thyroid can give rise to *functioning* metastases. Thus Parkes Weber has reported a case of primary carcinoma of the thyroid with metastasis to bone. After thyroidectomy hyperthyroidism developed. Removal of the metastasis led to myxoedema (cf. also Engelstadt and Simpson).

Joll states that in areas where endemic goitre is prevalent, malignant disease of the thyroid is relatively common.

Reimann has reviewed the literature on " Hürthle cell tumours " of the thyroid gland and added the eighteenth case. Sixteen were women, most of them in the fifth or sixth decade, though a case in an infant has been reported. Hyperthyroidism is inconstantly associated with these tumours. They are slow-growing, of uncertain benignity, and, if malignant, are slow to metastasize. Metastases have been reported to regional lymph nodes, lungs and vertebrae.

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ADMINISTRATION OF THYROID IN VARIOUS CONDITIONS

Good results have been reported in hebephrenic dementia praecox (Hoskins and Sleeper). Many gynaecological cases which exhibit as symptoms amenorrhoea, amenorrhagia, and sterility or abortion are apparently relieved by administration of thyroid and by no other treatment (Cooke). Thyroid administration is said to be of some service in the treatment of cataract (Kerr), in some proportion of cases of arthritis of hypertrophic type (Hall and Monro), and, in slight dosage, in treatment of certain types of alopecia (Gordon). Local application of thyroxine is stated to be of some value in treatment of otosclerosis and similar types of deafness (Gray).

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THYROIDECTOMY IN HEART DISEASE

Complete thyroidectomy has been performed on patients with congestive heart failure or angina pectoris in whom there was no evidence of an abnormal thyroid condition. At first good results were claimed. Developing myxoedema was controlled by administration of thyroid. Recently the treatment has been reviewed more critically. The after results of Clark, Means and Sprague indicated that the operation was only successful in one-fourth of their cases. Cutler and Hoerr reported similarly. The best results were obtained in angina ; those with congestive heart failure were disappointing.

Use of thiouracil in angina pectoris. With the same underlying idea Raab has used the less dangerous thiouracil treatment with 10 patients, and obtained good results with 7.

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CHAPTER IV

THE PARATHYROID GLANDS

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THE GLANDS AND THEIR HORMONE

Introduction. The parathyroid glands in man are usually adjacent to the dorsal surface of the thyroid. They are frequently described as a superior and an inferior pair, but they show variations in both number and location. In somewhat more than half the cases examined by Heinbach there were four glands, and somewhat more than half of the glands found were opposite the middle third of the thyroid. They vary in size from 3 to 15 mm. long and 2 to 3 mm. broad and thick, and are yellowish-red to brown-red in colour. Small accessory glands are not uncommon, especially near or embedded in the thymus (Cowdry).

The glands are relatively very vascular. They are each supplied by a special arteriole from a thyroid artery ; from it sinus-like capillaries come into close relationship with the cells themselves (Sharpey-Schafer).

Hermann, from an extensive study both of human cadavers and of fresh autopsy material, finds that in man on each side of the neck a branch of the inferior thyroid artery joins with a branch from the recurrent laryngeal nerve (given off at the point at which this nerve crosses the main branch of the artery), to form a " stalk " to an inferior parathyroid gland, and similarly a branch of the superior thyroid artery is joined by a fine filament from the external branch of the superior laryngeal nerve to form a " stalk " to a superior parathyroid gland. He states that these four stalks are constant in number, though each may lead to more than one gland. Some of the nerve fibres terminate in the vessel walls ; many penetrate between epithelial cells, forming nodular endings (Rhinehardt). Transplantation experiments suggest that the glands can function adequately in absence of all nervous connections (Rhinehardt ; Lewis and Gerschman).

According to Sharpey-Schafer the glands are composed of epithelial cells, which either form a compact mass, or are divided into lobules by strands of vascular connective tissue. The latter conveys the capillaries. Two forms of cells are described—

ordinary or principal cells, small, and either clear and somewhat granular, and larger cells, containing oxyphil granules and staining with eosin. Both types contain fatty granules or minute spherical globules, which increase in number with age. Small colloid vesicles are sometimes found; the number of these also increases with age.

Studies on different species of animals are not in complete agreement, presumably due to use of different fixation and staining techniques. In a recent paper Baker describes the parathyroid glands of the monkey as containing four cell types, the predominant pale principal cells (whose cytoplasm, with Bouin fixation, stains weakly with eosin or aniline blue), dark principal cells (distinguishable by Champy fixation followed by the Sevringhaus stain), slightly larger dark oxyphil cells (which stain a deep red with acid fuchsin subsequent to Zenker-base fixation), and still larger pale oxyphil cells. The majority of the dark oxyphils were essentially mitochondria-filled cells; the cytoplasm of the pale oxyphils was filled with granules.

Cytological studies, stressing changes in the size of the Golgi apparatus and in the mitochondria under varying conditions, have been carried out by Rosof and by de Robertis on the rat parathyroid, and by Foster on the mouse parathyroid. The latter's work is especially illuminating. In the mouse the gland undergoes a transition from the uniform cell arrangement present in the infantile mouse to the globular arrangement of the adult between the age of one and five weeks. Up to the age of ten days the gland consists of " chief " cells only, characterized by fairly compact Golgi bodies applied peruke-like to the nucleus, and by cytoplasm with but little affinity for stains. Then these gradually disappear and a succession of new cells are seen : (*a*) dark cells with a basophilic cytoplasm, (*b*) clear cells with more abundant but practically non-stainable cytoplasm, and (*c*) transitional forms. Foster considers that the dark cells originally arise from the chief cells, and represent a non-secreting storage phase, while they change through the transitional forms to the clear cells, from which the secretion has been released. There is evidence that these cells pass through more than one transition before becoming senescent. A small proportion of the clear cells possesses ill-defined membranes and shows other signs of cellular degeneration; such cells are regarded as senescent and incapable of functioning in further secretory cycles.

Extirpation of the parathyroids in an animal (usually accomplished by removal of the whole thyroid-parathyroid apparatus), and removal of too much parathyroid tissue in human thyroidectomies, lead quickly to depression of the blood plasma calcium, elevation of the plasma inorganic phosphate, and diminution of the urinary excretion of phosphate, while a condition of tetany supervenes, which, if unrelieved, can end in death.

Calcium is probably absent from the red blood cells; it is normally present in blood plasma to the extent of 10 to 11 mg. per 100 c.c. (extreme normal limits are slightly wider). About

half of this is loosely combined with plasma protein (chiefly albumin) and is in consequence non-diffusible through tissue membranes. The remainder is chiefly present as calcium ions. The nature of combination of the small amount of un-ionized diffusible calcium has not been definitely determined.

When plasma calcium is decreased, as following removal of the parathyroids, or is increased (as occurs in the condition of hyperparathyroidism), all three fractions (protein-linked, ionic, and the diffusible non-ionized fraction) are proportionately affected (Smith and Sternberger; Herbert). Since parathyroidectomy can cause a fall from 10 mg. to 4 mg. per 100 c.c. plasma, obviously the ionized calcium can drop to a low level.

Tetany can result from many causes. It is characterized by a hyperexcitability of the nervous system. If it be "manifest" there are spontaneous attacks of tonic spasm, which may be limited to groups of muscles, or which may involve the whole body. Usually in milder attacks groups of muscles associated with certain nerves are affected, producing in man such characteristic phenomena as the "obstetrical hand," extension of the knee with supination of the foot, laryngospasm, facial spasm and trismus. Associated with these are pains in the muscles during spasms and paraesthesias, especially in the distal parts of the extremities. The phenomena vary somewhat in different species, but tremors, chorea-like jerky movements, and, in extreme tetany, convulsive fits of varying degrees of violence alternating with quiescent periods, are common to most animals after complete parathyroidectomy.

If the tetany be merely "latent," significant phenomena can be elicited by use of such tests as Trousseau's and Chvostek's (cf. p. 105).

Tetany is almost invariably produced following *complete* parathyroidectomy in all mammals, and in birds (Thomson and Collip). Variations in susceptibility to parathyroidectomy in different species are probably traceable to dietary differences (Shelling). When tetany is so produced, if blood is taken during an active seizure the serum calcium is found usually to be at some value between 7 and 4 mg. per 100 c.c., instead of the normal 10 or 11 mg. In latent tetany somewhat higher values may be found. If the calcium level is raised by any treatment the tetany is relieved. Small doses of curare temporarily abolish parathyroid tetany in dogs, indicating the association of the nerves with the hyperexcitability (Hartridge and West).

Spontaneous human hypoparathyroidism is rare, and spontaneous human tetany is usually due to some other cause.

Tetany occurs in those cases of rickets in young children which are accompanied by a low plasma calcium. Some cases of infantile tetany show normal plasma calcium and are traceable to an alkalosis resulting from gastrointestinal disturbances, vomiting (causing loss of hydrochloric acid) and diarrhoea. Similarly, severe vomiting or continued gastric lavage in adults may lead to tetany.

Cases of idiopathic steatorrhoea may exhibit tetany, associated with low plasma calcium ; this seems to be due to formation of calcium soaps in the intestine, such formation diminishing absorption of calcium.

Lung hyperventilation produces a deficit of carbon dioxide ; in the resulting " hyperventilation tetany " blood plasma calcium is normal or slightly raised, and calcium therapy is ineffective.

" Milk-fever " in cattle, associated with a hypocalcaemia, is probably a tetany and due to unusually rapid drainage of calcium from the blood at the height of a vigorous lactation. The " lock-jaw " in Welsh mountain ponies, occurring in suckling mares soon after their being housed, and in ponies of either sex at the end of a railway journey, is accompanied by a marked hypocalcaemia, with high blood phosphate and high alkaline reserve ; its cause has not been explained.

Magnesium deprivation can lead to tetany ; so-called " grass tetany " of cattle is due to this cause. Such magnesium tetany has been reported in a young child by Miller. Oral magnesium sulphate gave prompt relief.

Tetany is occasionally seen in hyperthyroidism recurring after thyroidectomy. Such tetany is probably due to slightly deficient parathyroid function, accentuated by increased calcium excretion due to the hyperthyroid state.

The underlying disturbance in the production of tetany is an upset in the ratio of certain ions in blood and tissues. The work of Loeb and others has demonstrated that the degree of irritability of tissues depends upon the ratios between the ionic concentration of potassium, sodium and calcium in the fluids in contact with these tissues ; increase of either of the first two, or decrease of the third, increases irritability. The different methods of experimental production of tetany, and of causing relief from this tetany, suggest that the ionic ratio is somewhat more complicated, in so far as it is related to tetany. There seems to be a balance between sodium, potassium, and hydroxyl ionic concentrations, on the one hand, and calcium and hydrogen ionic concentrations on the other. Any increase in any one of the first three, or any decrease of either of the last two, conduces to tetany. Opposite changes tend to banish an established tetany.

There are possibly other factors. Thus in an interesting study of a fifteen-year-old boy, McQuarrie, Hansen and Ziegler showed recently that the convulsive reactivity is not dependent alone on the factor of hypocalcaemia. Increase in mineral intake, insufficient to affect the levels of plasma calcium and phosphorus,

definitely gave increased protection against production of tetanic convulsions. It was thought that the degree of hydration of brain tissue was the variable factor, low mineral intake leading to an increase of tissue water, including that of brain. Calcium salts appear to have a dehydrating effect. Administration of parathyroid extract induces diuresis, and this may be expected to remove excess of water from tissue. (Induction of sweating seems to render a sufferer from tetany less liable to convulsions.) The authors finally conclude : " It is highly probable . . . that the essential factor in the increase in convulsive reactivity in active tetany is not the excess water in the tissues, but an associated disturbance in the surface functions of the brain cell membranes, which permits the building up of abnormal electrical potentials."

Chronic Effects of Parathyroidectomy. These cannot easily be studied in most species of mammals, since in them, on the one hand, complete parathyroidectomy rapidly causes death, while, on the other hand, partial parathyroidectomy is followed rapidly by sufficient regeneration to restore normal conditions. In the rat, however, although accessory parathyroids are usually absent, extirpation of the glands is seldom fatal, and chronic effects are thus ascertainable. Bones become somewhat decalcified ; analyses show them to be low in ash, calcium, and phosphorus, though relatively high in magnesium (Thomson and Collip) ; such results are not easily explained, since in hyperparathyroidism the bones are also denuded of calcium. Erdheim first showed that the teeth are affected, becoming opaque, brittle, and distorted (Thomson and Collip). Stour, Chandler, and Tweedy find that there is, in parathyroidectomized young rats, an initial increased calcification of the dentine, and subsequently defective calcification and formation of both dentine and enamel, in the nature of a fluctuation in the degree of calcification, causing the brittleness.

Parathyroidectomized rats show an increased appetite for calcium salts (Richter and Eckert).

Evans, Szurek, and Kern report that when thyroparathyroidectomized dogs are kept free from tetany by administration of calcium lactate or gluconate, after a varying period this treatment can be discontinued without tetany developing, although blood plasma calcium and phosphorus remain at tetany levels. Such dogs have been kept for nine months in good condition. There is no significant change in blood sodium, potassium, magnesium, or chloride during this period. The authors believe that some neuro-muscular adjustment permits this survival.

Preparation of the Parathyroid Hormone. In 1924 Hanson obtained a slightly active preparation by boiling ox parathyroids with weak hydrochloric acid. At the same time, and independently, Collip established beyond doubt the existence of the parathyroid hormone and obtained a highly active preparation of it.

His method consisted essentially in boiling fresh minced glands with dilute hydrochloric acid for thirty to sixty minutes, cooling and removing fat, then adjusting the *p*H to 8·0 or 9·0 until suspended material had dissolved, and again to 5·5 when a precipitate formed. This was filtered off, and the active principle salted out of the filtrate, redissolved in dilute alkali, and purified by similar procedures.

Various modifications of Collip's method have been suggested, but until recently none has produced a marked improvement, and even yet the hormone has not been obtained in pure crystalline form.

Ross and Wood (1942) state that Collip's best preparations were twice as physiologically active as any produced by modifications of his method, but that their own preparations are three times more active than his.

In their method acetone-dried and defatted glands are restored to their original weight by addition of water, and are then extracted with dilute hydrochloric acid at 100° C. After cooling, alcohol is added to give 80 per cent. by volume, at *p*H 4·0. Inert protein is precipitated and removed. Addition of ether to the alcoholic solution precipitates the hormone and impurities, and the precipitate is dried with acetone. (From 15 lb. of fresh glands they obtained in all 850 grams of a grey powder.) The powder is dissolved in excess of water and ammonium hydroxide added to give a *p*H of 8·0. Then an equal volume of 2·5 *M* ammonium sulphate is slowly added and the *p*H is adjusted to 6·0 by addition of 1 *M* sulphuric acid. Protein including the hormone is precipitated and centrifuged off, then suspended in water, ammonia added as before, and the process repeated several times. The final precipitate is suspended in water and dialysed till almost free from sulphate. It is then dissolved in dilute hydrochloric acid at *p*H 3·5 to a clear brown solution. This contains half the hormone present in the original glands.

In the final stage 5 per cent. sodium benzoate is added to this acid solution. Benzoic acid slowly separates, and, after several hours at 2° C., it is filtered off, with the hormone adsorbed to it. The treatment is repeated with the mother liquor to give more adsorbate. The combined adsorbate, with a little water, is treated with peroxide-free ether to remove benzoic acid. A little protein material goes into solution and is recovered by shaking the ether with dilute acid. The protein solution is freed from last traces of benzoic acid by shaking with ether in a separation funnel, and then dialysing. During the latter process the

solution becomes neutral and the hormone is precipitated. It is dissolved in dilute hydrochloric acid to a clear brownish yellow solution and is concentrated *in vacuo* or in a frozen state. The dry, non-hygroscopic material may be kept indefinitely in the cold. The yield corresponds to 40 per cent. of the activity of the original material.

Properties of the Parathyroid Hormone. The purest preparations behave as a protein. Two of Ross and Wood's preparations gave nitrogen values of 12·6 and 13·1 per cent., somewhat lower than those for earlier preparations. Their amino-nitrogen values lay between 6·5 and 7·0 per cent. Molisch's test is invariably negative, indicating absence of carbohydrate radicals. The preparations are soluble in water and in 80 per cent. alcohol, but insoluble in ether, acetone and pyridine. Dilute acid solutions are stable.

The ultraviolet absorption spectrum of solutions is nearly identical with those of numerous other simple proteins, and shows only a single absorption band, characteristic of that due to tyrosine, tryptophane and phenylalanine radicals.

The preparations are decomposed by hydrolysis with moderately strong boiling acid or alkali, and are extremely sensitive to pepsin and trypsin, yielding inactive products. This explains why *the parathyroid hormone is ineffective when administered by mouth.* There is no evidence of any active group with low molecular weight.

Ketene acetylation also inactivates the hormone, and since subsequent liberation of the phenolic hydroxyls by alkaline hydrolysis does not restore activity, Wood and Ross consider that this activity depends on the presence of free amino-groups.

Even the purest material still appears to contain inert protein. Examination in the ultracentrifuge supports that view, and indicates further that the molecular weight of the hormone is between 15,000 and 25,000 (Ross and Wood).

The best method of *assay* is based on the increase in dog's serum calcium produced by subcutaneous injection of preparations of the hormone. The U.S.P. " unit " of activity is defined as one one-hundredth of the amount of hormone required to raise the serum calcium of a 10 to 12 kg. dog 1 mg. within sixteen hours, as based on the average of results for ten to twelve dogs. It is one-fifth of the " Collip " unit. Ross and Wood define the " nitrogen potency " of a preparation as the number of U.S.P. units per mg. of nitrogen in a preparation. By this definition Collip and Clark's preparation had an activity of about 110, Ross and Wood's about 300.

Effects following Administration of an Active Extract. When a potent extract is injected, subcutaneously or intramuscularly, into a normal dog, the most striking and conspicuous effect is an increase in the concentration of the plasma calcium. This continues for from twelve to eighteen hours ; the maximum attained, following a single dose, seldom exceeds 18 mg. per 100 c.c. serum. The calcium then slowly falls to normal value. Intravenous injections produce their maximum effect earlier—in four to eight hours—and this is relatively slight (Thomson and Collip).

When continued injections are given, with only three- or four-hour intervals between injections, they produce within a relatively short period of time a very characteristic and striking train of events, which has been exhaustively studied and reported by

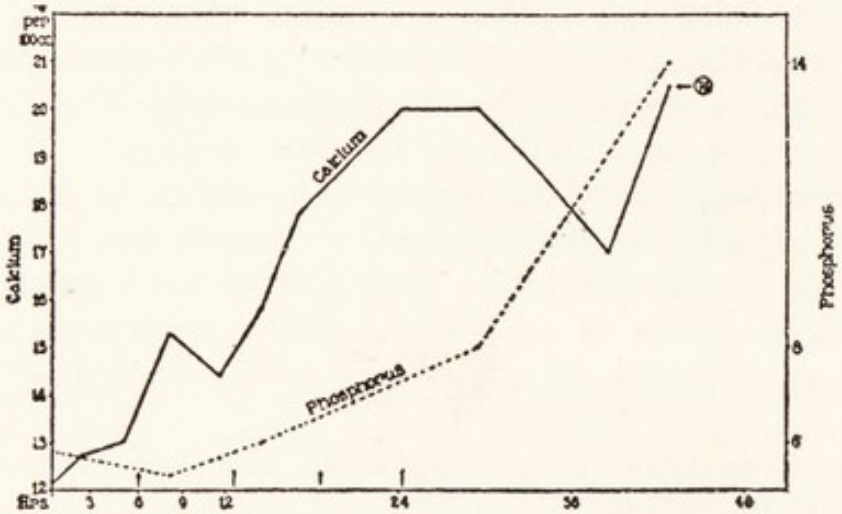

FIG. 13. The blood serum calcium and whole blood inorganic phosphorus curves in continued parathyroid overdosage in the normal dog. (From Collip, Medicine, 1926, v, 22.)

Collip. During the first twenty-four hours, while the blood calcium is rising steadily to a peak of about 20 mg. per 100 c.c. serum, the animal has occasional attacks—commencing some hours from the start of the injections—of vomiting and diarrhoea, and may manifest uneasiness of manner, but otherwise appears normal. The peak height of calcium may be maintained for several hours ; it then starts to fall. Occasional attacks of vomiting and diarrhoea continue. The animal becomes more and more depressed ; respiratory distress may be noted.

As the blood calcium falls inorganic phosphorus rises and more serious symptoms appear. Vomiting continues. The animal commences to pass blood by the bowel. Blood urea and non-protein nitrogen increase greatly. Blood volume diminishes and the blood thickens. Its coagulation time diminishes. (Blood

samples are obtained from peripheral veins only with difficulty.) The kidney practically ceases to function. Death follows.

A number of these changes are illustrated in Figs. 13 and 14.

Studies of carbon dioxide content, combining power and *p*H of the blood plasma indicate that there is a condition of compensated alkalosis on the first day, which passes into a condition of compensated acidosis, and this changes to uncompensated acidosis just prior to death.

Post-mortem examination discloses marked congestion of the alimentary canal, and presence of blood in the stomach and

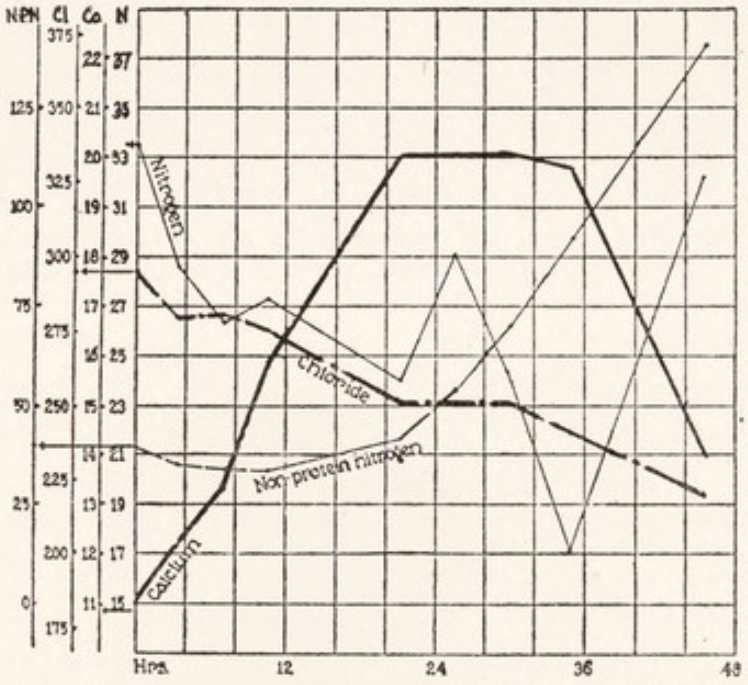

FIG. 14. The blood serum calcium, whole blood chloride, nitrogen and non-protein nitrogen in the normal dog as affected by repeated injections of potent parathyroid extracts and frequent bleedings. (From Collip, Medicine, 1926, v, 23.)

intestine. Calcification has been observed—especially in the space of Bowman's capsule and lumina of the tubules of the kidneys, and also in the walls of the lesser arteries and the Küppfer cells of the liver (Thomson and Collip).

This pathological picture of acute effects following overdosage can be almost exactly paralleled by combined injection of calcium chloride and acid sodium phosphate (NaH_2PO_4), whence the actual symptoms may be ascribed to coincident hypercalcaemia and hyperphosphataemia (Thomson and Collip).

Different species of animals vary greatly in their response to injections of active extracts. Cats are much more refractory. Rats are almost immune, and rabbits seem immune to repeated injections The response of man is similar to that of the dog, although

he seems more resistant to overdosage. Some of the contradictory results with animals that have been reported in the literature seem

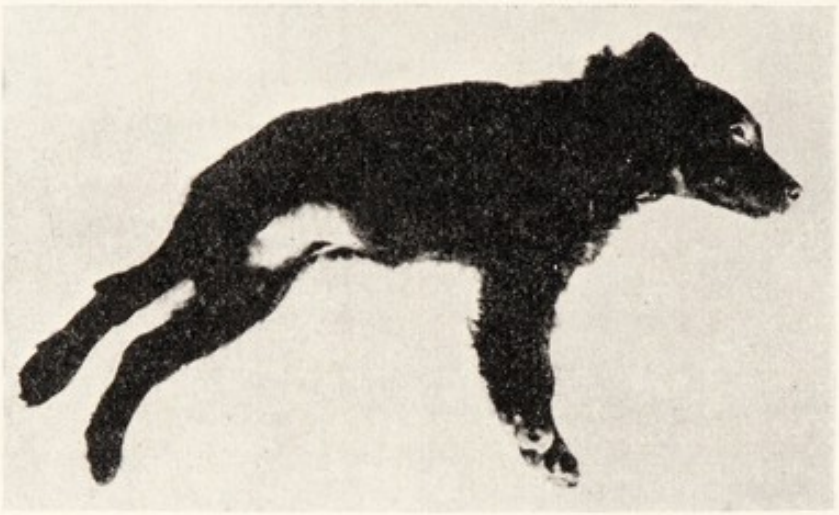

FIG. 15. Dog in tetany, fifty-nine days after thyroparathyroidectomy. (From Collip, J. Biol. Chem., 1925, lxiii, 400.)

FIG. 16. The same dog as in FIG. 15. Complete recovery three hours after subcutaneous injection of a potent parathyroid extract. (From Collip, J. Biol. Chem., *loc. cit.*)

due to difference in the diets of these animals, others to differences in rate of excretion of calcium (Thomson and Collip).

Shelling considers that many of the effects of acute hyper-

parathyroidism are due to continued diuresis and the resulting anhydraemia leading ultimately to anuria, azotaemia, and death, so that rational treatment of such condition is to replace water and electrolytes.

Apparently some degree of immunity is conferred by repeated injections. When these are given at intervals of several days (so that the blood calcium returns to normal before further injection is given) the second may produce a greater effect than the first, but later injections show a decrease in response—apparently tolerance to the principle is increased (Thomson and Collip). Rats also appear to develop an immunity (Pugsley).

Taylor has succeeded, by giving gradually increasing doses of parathyroid extract to dogs, starting with 2 units per day, and increasing the dose at weekly intervals, in producing in two or three months a state of tolerance to the hormone, in which the dogs remained apparently normal and with normal serum calcium. At this stage of tolerance to doses which usually prove fatal the dogs were also immune to massive doses of irradiated ergosterol. Serum from these dogs, injected into others along with parathyroid hormone, failed altogether to alter the normal response to the hormone (thus giving no evidence of anti-hormone production ; cf. p. 429).

With suitable dosage experimental chronic hyperparathyroidism has been produced in dogs, guinea-pigs, and rats, and presents a picture markedly resembling that seen in clinical osteitis fibrosa (Thomson and Collip ; Johnson ; Olsen).

The parathyroidectomized dog responds to injections of parathyroid hormone in a manner precisely comparable to the normal animal. Tetany is relieved coincident with increase of blood calcium above the calcium level, and the slight increase in blood phosphate disappears. Collip kept parathyroidectomized dogs alive for over a year by daily injections of potent extracts. Withdrawal of extract at any time led to early onset of tetany. The effects are shown clearly in Figs. 15 and 16. His results have been repeatedly confirmed.

(If injections are repeated at short intervals, the same pyramided effect is produced as with normal dogs, and the same lethal result with sufficiently prolonged treatment.)

Parathyroidectomized cats are similarly restored to normal. Rabbits, following removal of the glands, rapidly develop tetany, with a marked preterminal rise in blood phosphorus. The tetany can only be controlled by immediate injection of the hormone (Collip).

The rise in serum calcium and the following fall, resulting from a single injection of the parathyroid hormone, are paralleled by a rise and fall in the serum citric acid content (Alwall), which is probably associated with the fact that bone mineral is a reservoir for citric acid (cf. Dickens).

The Control and Function of the Parathyroid Hormone. Various attempts have been made to show that the anterior pituitary secretes a parathyrotrophic hormone, but this view is at present discredited. Houssay and Sammartino have described lesions occurring in the parathyroids of dogs after hypophysectomy, but they considered that these were due to nutritional disturbances resulting from removal of the pituitary, and not directly to removal of any specific pituitary factor. Recently Baker found that hypophysectomy of monkeys resulted in a *possible* slight atrophy of the parathyroids, but could find no cytological evidence of an effect.

de Robertis has produced cytological evidence that injection of parathyroid hormone leads to degeneration of the normal parathyroid cells of rats, and Sevringhaus infers that the activity of the glands depends in part on the amount of hormone circulating in the blood.

Hypocalcaemia produced by injection of oxalate or by transfusion of decalcified blood is followed by a rise in blood calcium in normal dogs, but not in thyro-parathyroidectomized animals (Patt ; cf. Gersham). This perhaps suggests that the level of plasma calcium is a regulatory mechanism of the secretion of the hormone.

It is obvious that the parathyroid glands are concerned with calcium and phosphorus metabolism. For a long time it was considered that the primary effect was on calcium metabolism, that of phosphorus being secondarily involved through their close chemical association. Slowly accumulating evidence has largely reversed these views.

Calcium and phosphorus metabolisms are also controlled by vitamin D, while dihydrotachysterol, one of the products of the ultraviolet irradiation of ergosterol, produces effects closely resembling those of the hormone, and has therefore become an important agent in replacement therapy.

Certain of the evidence which has led to the change of views concerning the hormone's action may be briefly mentioned.

Albright and Ellsworth suggested on clinical grounds, as long ago as 1929, that the hormone was primarily concerned with phosphate excretion. Goadby and Stacey produced further clinical evidence

to support this view, while Morgan and Stacey, from a study of tissue changes in rats treated with the hormone, drew a somewhat similar conclusion.

Tweedy *et al.* could find no evidence that the hormone produces any action on the blood and tissue calcium of nephrectomized or ureter-ligated dogs. Their results have been confirmed by Collip and Neufeld, who have shown that injection of the hormone into rats, cats or dogs immediately after nephrectomy, or ligation of the renal vessels, or of the ureters, produces no effect on the blood plasma calcium, but that if the ligated ureters are cut the usual parathyroid hypercalcaemia develops. Similarly, during anuria produced by injection of posterior pituitary extracts, no parathyroid hypercalcaemia is produced by the hormone. If, following injection of parathyroid hormone, the plasma phosphate level is maintained at normal height by repeated intravenous injections of sodium acid phosphate, no rise of plasma calcium occurs.

Nevertheless Selye claims that in the rat complete nephrectomy does not prevent the action of the parathyroid hormone on bone, in producing osteoclastic absorption and thus mobilization of bone mineral. (Cf. also McLean and Bloom.)

Cohn, Cohn and Aub have recently analysed all the pertinent experimental data, and their conclusions permit the following statements.

The primary function of the parathyroid hormone is to control phosphorus metabolism through control of phosphate excretion through the kidneys. Increase in the amount of hormone which is acting causes decrease in the re-absorption of phosphate from the glomerular filtrate passing through the kidney tubules, while decrease in the amount of hormone permits increased reabsorption of phosphate. Increasing hormone action therefore lowers blood plasma inorganic phosphate so that bone mineral is distrained upon to restore it, and this automatically leads to the increased plasma calcium present in experimental and clinical hyperparathyroidism. The hormone has no effect on calcium retention, any hypercalcaemia being the result of a slower rate of calcium than of phosphate excretion through the kidneys. Such views are supported by the results of Tweedy and Campbell, who, using radiophosphorus to label phosphate, found in experiments on rats that administration of parathyroid hormone appears to produce an immediate increase in the urinary excretion and a somewhat delayed increase in the faecal excretion of phosphate, while it does not seem to accelerate the uptake by, or promote the retention of phosphate in bone. (Since the parathyroids are

so essentially concerned with phosphate excretion, it is possible, as Helfet suggests, that their activity is governed by the level of plasma inorganic phosphate.)

There is some evidence, not so final, that a second function of the parathyroid hormone is to act directly on bone osteoclasts and mobilize bone mineral from them. (Cf. Ingle.)

Vitamin D decreases the excretion of phosphate by increasing the rate of its reabsorption through the kidney tubules. In small dosage it causes deposition of bone mineral at the provisional (epiphyseal) zone of calcification (its antirachitic effect). Thus, at least in small dosage, its effects are opposite to those produced by the hormone. In larger dosage it removes bone mineral from bone shaft (its hypercalcaemic effect).

Dihydrotachysterol is said to increase phosphate excretion, behaving like the hormone, but in addition it is considered to increase the retention and absorption of calcium slightly.

These varying effects must be borne in mind in considering the clinical treatment of hypoparathyroidism.

Babkin, and his pupil Schiffrin, have shown that the level of blood plasma calcium (as affected by injection of parathyroid hormone or by thyro-parathyroidectomy in the dog) affects the volume and composition of the gastric juice. A hypercalcaemia inhibits the nervous phase of gastric secretion and so decreases volume and acidity of the juice and increases the concentration of pepsin in the Pavlov-pouch dog, while a hypocalcaemia increases the volume and decreases the concentration of pepsin. Hypercalcaemia produced by adequate administration of irradiated ergosterol causes similar results to those which follow injection of the hormone.

In view of the present conception of parathyroid function such an effect must be considered, as far as these glands are concerned, as only linking their function with gastric secretion very indirectly, since the level of plasma calcium is maintained as a secondary effect through their control of phosphate excretion.

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HYPOPARATHYROIDISM

Hypoparathyroidism may be traumatic or idiopathic. Even with the best thyroid surgery the variability in position of the glands renders removal or damage to them a not too remote possibility. This variability in position has been mentioned (p. 89), and in connection with thyroidectomy must be stressed. Rose points out that parathyroids are sometimes found lateral to the thyroid, and even on its anterior surface. Glands may be embedded within the thyroid or the thymus. They may be low in the neck, or dependent on pedicles within the mediastinum, or between the trachea and oesophagus. They may be embedded in fat or in loose areolar tissue and may closely resemble lymph nodes.

Where there is an unusual distribution the difficulty of avoidance in thyroidectomy is only exceeded by the difficulty occasionally encountered in finding an aberrant adenomatous gland in hyperparathyroidism. Nevertheless the frequency of parathyroid tetany following thyroidectomy is small. Swinton in 1937 reported an incidence of 0·2 per cent. among 13,000 patients operated on at the Lahey Clinic.

It should be noted that parathyroid tetany following removal of a parathyroid adenoma in hyperparathyroidism is common and often marked. Here the cause is usually not absence of adequate parathyroid tissue, but the fact that the over-functioning adenoma has caused the remaining glands to pass into a resting state. They are " asleep " and do not immediately respond to stimulus to renewed activity.

Idiopathic parathyroid tetany is rare. There are some 70 cases recorded in the literature. Its etiology is obscure. When once it has become established it persists. Symptoms may first appear following an acute infection (Rose).

The signs and symptoms of parathyroid tetany may be active or latent, and are the same whether the condition be surgical or idiopathic. Acute symptoms may be seen shortly after a thyroidectomy, or during an acute infection, or menstruation, or pregnancy, or after cessation of the treatment controlling a chronic case. There may be a sudden onset, with generalized convulsions simulating those of idiopathic epilepsy, or acute psychotic symptoms, or generalized muscular rigidity or opisthotonus, or stridor and dyspnoea. Such extreme phenomena are uncommon ; the more usual attack is less sudden, with early symptoms of numbness, tingling, a sensation of stiffness round the mouth and face, twitching of facial and peripheral muscles, and flexion of fingers and hand to produce the " accoucheur hand." Contraction of muscles of the abdominal wall or of gastrointestinal muscles may cause abdominal pain. Less often there occur constipation, nausea and vomiting, diplopia, headache, dyspnoea and stridor from spasm of laryngeal muscles. The patient tends to be irritable (cf. Rose).

(Rose warns that the possibility of parathyroid tetany must always be considered in the differential diagnosis of any case in which convulsions, attacks of unconsciousness, or syncope occur.)

When acute tetany develops from a traumatic cause it may be transitory, and disappear spontaneously as the remaining parathyroid tissue hypertrophies to meet its increased load. If,

however, adequate readjustment is not possible, the condition becomes chronic.

When the tetany is latent its classical signs are easily elicited. Trousseau's sign, flexion of hand and fingers, follows constriction of the upper arm for one to three minutes. Chvostek's sign, spasmodic twitching of the homolateral muscles of face and mouth, follows tapping of the facial nerve where it emerges from the facial canal. Erb's sign is an increased electrical excitability of the motor nerves. Positive results, of course, indicate latent tetany, but do not indicate the cause of that tetany.

(O'Donovan considers that Chvostek's sign is unreliable in latent tetany. When Trousseau's sign is negative or uncertain, he recommends combining the test with hyperventilation. After releasing the tourniquet used for the test, hyperventilation should be immediately employed for not more than 80 seconds, and if within this time unilateral carpal spasm develops, latent tetany is indicated.)

In chronic tetany of long duration trophic and metabolic changes tend to occur, such as lenticular cataract, perivascular cerebral calcification, dry and brittle hair and nails, dry skin, muscular weakness, constipation, insomnia, etc. (cf. Rose).

Hypoparathyroidism is characteristically associated with lengthening of systole ; the electrocardiogram shows an increase of the Q–T interval of from 0·3 second to even 0·6 second (Rose).

The chemical changes are precisely those shown by the experimental parathyroid-less animal. There is decreased urinary excretion of phosphate, which leads to increased plasma inorganic phosphate. This results in decreased plasma calcium, and there follows decreased urinary excretion of calcium.

Most of the signs and symptoms can be attributed to a lowering of the level of plasma (and tissue) calcium, with increased muscle-nerve irritability (cf. p. 92), but this does not appear to explain the trophic and metabolic changes of chronic hypoparathyroidism.

Concerning the psychotic symptoms sometimes seen in hypoparathyroid tetany, in a recent editorial in the *Journal of Clinical Endocrinology*, Hoskins has drawn attention to a paper by Greene and Swanson. They reported that of 18 patients with hypoparathyroidism 5 had an associated psychosis. The usual type of psychosis was a toxic delirium, although other types, including dementia, have been seen, and no type can be regarded as characteristic of the parathyroid deficiency. Among the nervous symptoms seen have been anxiety, depression, a sense of impending disaster, and, in severer cases, delusions and hallucinations. Suicide may be attempted. Such a psychosis,

if it develops, occurs within the first three or four months of the onset of the tetany, and the parathyroid deficiency may itself be missed unless search be made for its characteristic signs. The condition may persist for several months, but the prognosis is usually good, and recovery follows maintenance of a normal blood calcium level. There would appear to be no residual damage to the central nervous system. Hoskins agrees with Greene and Swanson that the association of psychosis with hypoparathyroidism is probably more frequent than the literature suggests.

A case which illustrates in extreme degree many of the trophic changes which can occur in chronic hypoparathyroidism has recently been reported by Learner and Brown. Thyroidectomy in a thirty-year-old woman led to tetany. For some years calcium lactate gave relief. When seen by Learner and Brown at the age of fifty she had been receiving injections of parathyroid hormone for the preceding six years, gradually increasing dosage being needed, in spite of which the tetany was increasingly less effectively controlled.

Some years after her operation she had noticed an increasing dryness and coarseness of the skin. At about the time when parathyroid therapy was started she developed a vesicular skin eruption involving the chest, the lateral aspects of the trunk, the post-auricular areas, and the dorsal surfaces of the forearms. This soon became dry and crusted, and disappeared in two months. During the period of the eruption the tetany episodes were more frequent and more severe. Two years later the skin lesions recurred, and were associated with moderate loss of hair and complete shedding of the finger and toe nails ; there was concomitant exacerbation of the tetany. Five months later the skin was again normal and new nails had appeared. Since then these manifestations had appeared each January and disappeared each June ; tetany attacks were rare in the latter half of each year. Fissures in the angle of the mouth (cheilitis) developed in winter and disappeared in summer. At the time of the second appearance of the skin lesions vision began to fail, and a year later a left cataract extraction was done.

The skin lesions were solid, purplish-red patches, sharply marginated from the uninvolved skin. The mouth showed an angular cheilitis, and a smooth, reddened tongue. When she was first seen by Learner and Brown the blood serum calcium was 6·8 mg. and inorganic phosphorus 5·8 mg. per 100 c.c.

On dihydrotachysterol therapy the tetany, ectodermal disorders, cheilitis and glossitis all disappeared, while the gradual loss of vision was arrested, and no further loss of hair occurred.

The pronounced seasonal effect in this case has also been recorded for other patients. Learner and Brown comment that the cheilitis and glossitis are not easily explained, since the patient's usual diet was rich in the B-complex vitamins.

It is a common observation that there is no close inverse relationship between the level of blood plasma calcium and the severity of tetany. Lachman states that this discrepancy is more pronounced in idiopathic than in post-operative hypoparathyroidism, while, possibly because the condition often remains

undiagnosed and untreated for much longer periods, the trophic changes seem to be more common and more severe.

Idiopathic tetany and epilepsy can occur simultaneously, and hypocalcaemia is one of the factors precipitating epileptic seizures (Grinker). Taubenhaus and Engle report such a case, a young woman with very low serum calcium and high phosphorus. Treated with calcium chloride and dihydrotachysterol, she had had complete remission from seizure for four years at the time of the report.

Treatment of Hypoparathyroidism. Various methods are available, which include the administration of calcium salts, injection of parathyroid hormone, oral administration of calciferol or dihydrotachysterol, and parathyroid implants.

Acute parathyroid tetany calls for combined treatment with calcium salts and parathyroid hormone; the latter must be injected (cf. p. 95).

Calcium gluconate or chloride (10 c.c. of a 10 per cent. solution) should be injected, if possible intravenously, but otherwise intramuscularly, while at the same time hypodermic or intramuscular injections of parathyroid hormone should be started. Depending upon the severity of the symptoms 10 to 50 (U.S.P.) units should be injected daily. The size and frequency of the dose must be determined by the patient's response to initial treatment and the changes in his blood plasma calcium. Estimations of serum calcium should be made at least once daily, until the patient has been brought under control. If the patient displays undue apprehension or irritability, administration of sedatives may be a desirable accessory treatment (Rose).

In the rare instances where there is persistent laryngeal obstruction tracheotomy or laryngeal intubation may be necessary (Rose).

Chronic parathyroid tetany cannot conveniently be treated by continued injections of calcium salts, while long continued injections of parathyroid hormone usually lead to a refractory state. Some years ago Lisser and Shepardson published the end results of a case which displayed in a striking manner the gradual production of tolerance to larger and larger doses of the hormone, and a final completely refractory condition terminating fatally.

Mild cases of chronic parathyroid tetany are now usually controlled by diet and calcium salts; severer cases need, in addition, either vitamin D in relatively large dosage or dihydrotachysterol.

Dietary Treatment. Food constituents rich in calcium seem the obvious need. But it has been shown that absorption of calcium is facilitated by a diet in which the ratio of calcium to phosphorus

is at least 2 : 1 (Shelling ; Anderson and Lyall). Most foods which are rich in calcium are also rich in phosphorus, even cheese and milk having a ratio of only about 1·3 : 1. Hence diet alone will not give a suitable ratio, and calcium salts should be given orally in addition. The gluconate, lactate and chloride may be given though large amounts of calcium chloride often prove irritable to the gastrointestinal tract. Rose points out that since excess is not likely to prove dangerous it is better to err on the safe side. Doses can be used varying from 2 to even 60 grams daily (according to the severity of the condition) and should be taken two hours after each meal.

Dihydrotachysterol (anti-tetanic substance No. 10, frequently referred to as A.T.10) is a derivative of tachysterol, one of the products of irradiation of ergosterol (cf. p. 178). Holtz introduced this compound into therapy in 1933 ; a review of his results was published in 1941. Its pharmacological action is similar to that of tachysterol, but the dihydro-compound is more stable. Numerous reports concerning results from its use are now available.

It has been pointed out (p. 100) that its action more closely resembles that of parathyroid hormone than that of pure vitamin D. It is effective by oral administration but not when given subcutaneously or intramuscularly. It is slow-acting. The effect of a single dose is apparent after forty-eight hours, maximum after four to seven days, and ended in from one to three weeks. Intravenous has no advantage over oral administration. There is no habituation to the drug.

Dosage varies with the severity of the tetany. In mild cases 0·2 to 1 c.c. of a 0·5 per cent. solution in oil can be given daily, or 1 to 6 c.c. once a week (the larger dose for cases with a serum calcium below 6 mg. per 100 c.c.). Accurate serum calcium analyses should be made every two or three weeks. If there are symptoms of manifest tetany with marked hypocalcaemia, 8 to 15 c.c. may be given as first dose, followed by a daily dose of 1 c.c. and the blood calcium is checked at about the seventh day of treatment. (Though Holtz modifies this statement by mentioning that up to 15 c.c. in single or divided dosage may be given without a serum calcium determination, which, however, must be done before more is administered.)

Since, like parathyroid hormone, it produces a cumulative hypercalcaemia, there is some danger of overdosage, and patients should therefore be warned of the danger of careless therapy and should report to a physician at least every two or three months.

In rare instances, following the first dose there result cardiac palpitation, weakness, mild nausea, and headache ; these symptoms all disappear within a short time.

The occasional patient does not respond to dihydrotachysterol ; this would appear to be due to its non-absorption from the intestine.

Holtz considers that the danger from overdosage is unduly stressed.

A rapidly transient hypercalcaemia (up to or even above 15 mg. per 100 c.c. serum) is tolerated without bad after effects, but should be recognized in time, so that it does not persist for weeks. In most cases reduction of the dose, or interruption of the therapy suffices to abolish the hypercalcaemia. The lowering of the calcium level can be hastened by intramuscular injections of oestrogen, though this should be used cautiously (since large doses given to dogs have produced a fatal thrombopenic purpura.)

The first symptoms of overdosage are loss of appetite and nausea ; then follow thirst and exhaustion, and frequently constipation. But the hypercalcaemic patient often remains symptomless.

Once the dosage of dihydrotachysterol is adjusted, Holtz considers that control blood analyses are only needed every two to four months. Increased dosage is needed in febrile diseases, in pregnancy, and with unusual physical exertion.

Holtz says, finally : " Our experiences with dihydrotachysterol now extend over more than six years. So far no case has been observed wherein a patient has been injured through dihydrotachysterol therapy, although some tetany patients have taken the preparation for six years, and although dihydrotachysterol has been given to ambulant patients by a large number of physicians far from clinics, for a number of years. However, everyone who prescribes dihydrotachysterol must realize that unwise prescription of the medication and lack of control of the patient may result in as much serious harm with dihydrotachysterol as with other medications."

In cases of marked kidney damage dihydrotachysterol tends to be unable to increase urinary excretion of phosphate (Weber and Richardson ; Rose).

A number of hypoparathyroid women have been carried through pregnancy successfully by judicious use of dihydrotachysterol (Holtz ; Anderson and Musselman).

Dihydrotachysterol versus *Calciferol.* Excellent results in prolonged treatment of hypoparathyroidism have been achieved with pure vitamin D_2, " calciferol." McLean states that in comparable dosage the two compounds have similar qualitative and quantitative action (cf., however, p. 102) and that neither has proved superiority over the other.

When calciferol is used a daily dosage of 1·25 to 12·5 mg. (equal to 50,000 to 500,000 I.U. of vitamin D) is required (Rose). The effect is slowly produced, and needs frequent control by serum calcium determinations or the Sulkowitch urine test (cf. p. 119). McLean believes such control adequate to prevent any toxic overdosage.

Rose thinks that the use of calciferol is not quite so expensive ; Sevringhaus, that it is more expensive , but Cutting, Wells and Carnes find, as judged by the respective amounts needed as the controlling dose, measured on the same patient, that the effective cost of the two drugs is identical.

Whether or not pure calciferol is non-toxic in high dosage, Tumulty and Howard have recently reported 2 cases of poisoning from use of large doses (750,000 I.U. daily for twelve and seventeen days respectively) of an irradiated ergosterol estimated to be one-half calciferol and one-half a mixture of lumisterol, tachysterol and toxisterol. They admit that frequently much larger doses have been given without toxic results, and think that in their cases the effect was intensified by administering the drug in milk, and so facilitating its absorption. Both cases recovered with suitable treatment, though the hypercalcaemia was of long duration.

Himsworth and Maizils report the case of a boy of thirteen years, who suffered from both congenital thyroid and parathyroid deficiency. Basal metabolism was kept normal on 1½ grains of thyroid daily. The two deficiencies were apparently independent of each other. Calciferol, 1,500,000 I.U., given daily for two weeks, increased serum calcium to 12·2 mg., while inorganic phosphate fell to 3·6 mg. per 100 c.c. The treatment was then stopped, yet the blood serum calcium remained at 9 mg. for three months (suggesting some storage of calciferol in the organism). Himsworth and Maizils found that this patient responded better to calciferol than to dihydrotachysterol, while pure vitamin D_3 (the natural vitamin) was as effective as calciferol.

Sevringhaus and St. John maintained 6 women with severe and persisting hypoparathyroid tetany free from symptoms for two years and more by oral medication with vitamin D (daily dose between 150,000 and 400,000 units) and calcium salts. One patient during that time had an uneventful pregnancy and delivery. None showed signs of hypervitaminosis. The diet was unrestricted as far as meat, eggs and milk were concerned.

Time will determine whether calciferol or dihydrotachysterol is the better, but it is definitely satisfactory to know that adequate means are now available for prolonged treatment of hypoparathyroidism without fear of development of refractoriness. It would seem that some degree of control of the patient is desirable, whichever drug be used.

Parathyroid Implantation. Manfredi and Castillo have reported three reasonably successful implantations of human parathyroid

glands into patients with parathyroid tetany (two post-operative, one idiopathic). In the first of these cases chronic severe hypoparathyroidism developed in a youth of twenty years, following thyroidectomy for Graves' disease. It was not controlled satisfactorily by the usual treatments, so that eight months after his operation three parathyroid glands removed from a normal infant who had died of birth injury were transplanted into the subcapsular region of the right kidney. The treatment abolished the tetanic phenomena, and nineteen months' later there was no sign of tetany, while blood plasma calcium and inorganic phosphorus levels were normal, as was the neuromuscular galvanic excitability.

A second similar case developed tetany shortly after operation, and exhibited bilateral cataract a year later. After a further year implantation of infant's parathyroids was performed. Equally good results followed, which persisted at least twelve months (to the time of the report), while the cataracts, stationary for a while, had commenced to show slow regression.

The case of idiopathic tetany, a man of forty-three with a nine years' history of insufficiency, gave good results for four months following the implantation ; subsequently the symptoms of tetany recurred.

Glands of newborn infants were used preferably, because of the marked regenerative power of foetal tissue, and because the possibility of agglutination reactions with foetal blood is slight.

Stone, Owings and Gey grew parathyroid tissue in the serum of donor and of host as preliminary to grafting and in 1934 reported 2 cases of successful parathyroid cross-grafts in human beings. Houghton, Klassen and Curtis reported another similar successful case. Reid and Ransohoff have described a method of achieving intravascular pulmonary grafts of parathyroid tissue in dogs, following such culture, and consider it efficacious.

Pseudo-hypoparathyroidism. Albright *et al.* recently described three cases of a condition they term "pseudo-hypoparathyroidism —an example of Seabright-Bantam syndrome," because apparently in this condition the organism does not respond to the hormone, just as in the male Seabright bantam hen-feathering indicates a similar failure of response or abnormal response to the testicular hormone.

These patients, a woman aged twenty-eight years, a girl of twelve, and a boy of three years, all with clinical findings of idiopathic hypoparathyroidism, were all resistant to administration of parathyroid hormone, in that their low serum calcium and high serum inorganic phosphorus were not affected by it when

given in large dosage, while the first two, when injected intravenously with the hormone, did not respond by a phosphate diuresis. The first case was surgically explored, and normal parathyroid tissue was found present. In none of the three cases was resistance to the hormone due to refractoriness (since it had never been previously given). All three reacted to dihydrotachysterol, but seemed somewhat resistant to its action. All three had a peculiar physiognomy characterized by a round face and a rather thick-set figure.

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HYPERPARATHYROIDISM

The important dates associated with this clinical state are 1891, when von Recklinghausen differentiated generalized osteitis fibrosa from osteomalacia (so that the former is alternately termed von Recklinghausen's disease of bone), 1904, when the condition was associated with a parathyroid tumour by Askenazy, 1926, when the first operation for the condition was performed by Mandl, who found and removed a tumour, and 1934, when Albright drew

attention to the occurrence of hyperparathyroidism without marked bone involvement, but with kidney lesions and renal stones of calcium phosphate type.

Hyperparathyroidism is a rare condition, yet Cope, writing in 1943, was able to report that 70 proved cases have been seen at the Massachusetts General Hospital, while Chapman, summarizing the literature on the condition in 1941, dealt with 205 cases. The majority of patients are between the ages of thirty and sixty, the extreme ages so far recorded being thirteen and sixty-nine (cf. Bowers). The condition is more frequent in women.

In hyperparathyroidism the normal action of the parathyroid hormone is exaggerated. In consequence elimination of phosphate through the kidneys is faster than normal, with resulting lowered level of plasma inorganic phosphate. Either indirectly resulting from this, or through direct action of the hormone on bone, bone mineral is mobilized. The resulting phosphate is excreted, the calcium (usually) less rapidly so, hence calcium level rises in blood plasma and the soft tissues it feeds. There follows a tendency to metastatic calcification, especially in kidney tissue.

Hence the two chief pathological phenomena in hyperparathyroidism are denudation of bone mineral, which, when marked, leads to softening of bone, and formation of calcium phosphate deposits in the kidneys, usually as kidney stones. When the effect on bone predominates there results the typical picture of osteitis fibrosa. Patients exhibiting this may have renal stones as well. A large proportion of patients form kidney stones before there is such a marked denudation of bone mineral that bone pain and softening result, or even any change in bone density as revealed by X-ray examination. The degree of reaction of the kidneys to the additional hormone stimulus possibly determines the type of result.

The onset of the disease is insidious. It may last many years, and a history of thirty-nine years has been recorded (cf. Albright (1)).

The primary bone change is an osteoporosis, resulting from demineralization. As the latter progresses, fractures may occur, and bending of bone resulting in deformity. There may be a kyphosis of the dorsal and lumbar spines, with partial collapse of numerous vertebrae, such changes leading to reduction in height. The thighs and forearms become bowed (cf. Figs. 17 and 18) and the tibiae sabre-like. X-ray examination reveals a generalized osteoporosis, cysts and giant-cell tumours, and fractures. A finely granular mottling is seen (but is not specific, since it is also

seen in osteoporosis of the aged, and sometimes in Paget's disease). The X-ray abnormalities are seen, especially, in the skull, femur, radius, ulna, and pelvis. (Cf. Bowers ; Soffer and Cohn.)

Histological examination of the bone from autopsy material shows a generalized osteoporosis, lacunar resorption, apposition,

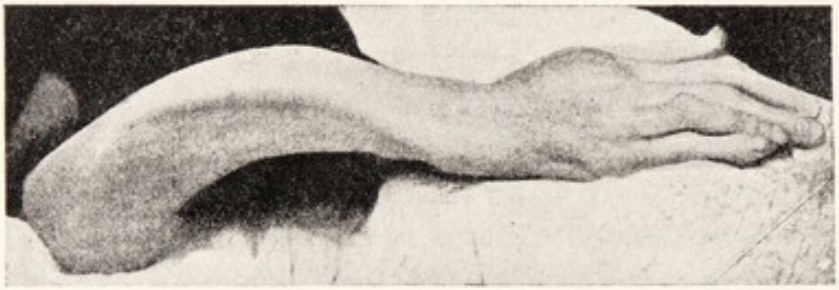

FIG. 17. Antero-external curvature of forearm and large bony swelling on dorsum of right hand from a case of generalized osteitis fibrosa. (From Hunter, Proc. Roy. Soc. Med., 1931, xxiv, 489 ; Clin. Sect.)

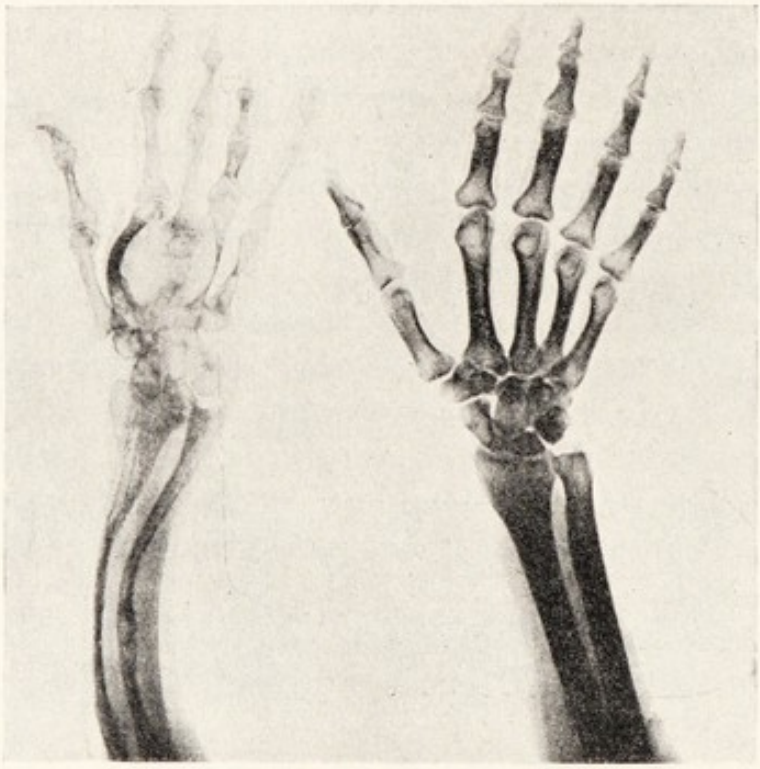

FIG. 18. Controlled radiograph of right hand and forearm (cf. Fig. 16). (From Hunter, Proc. Roy. Soc. Med., *loc. cit.*).

fibrosis of marrow, and formation of osteoclastomata and cysts. (Cf. Hodges ; Compere.)

More stress is continually being laid on the renal type of hyperparathyroidism. This is well brought out by two recent papers by Cope (2) (reviewing 78 cases occurring in the preceding twelve years at the Massachusetts General Hospital), and by Keating

and Cook (reviewing 24 cases diagnosed at the Mayo Clinic in the preceding two and a half years). The apparent increased incidence of the disease is in reality due to a higher index of suspicion, and to revision of the criteria necessary to make a diagnosis, and its actual lesser rarity is in agreement with Albright's (1) views expressed as early as 1934.

In the Boston cases the classical bone picture was present in 16 of 27 cases referred from various parts of the country, and in only 7 of 51 cases diagnosed at the hospital itself. Of the latter 36 showed only renal symptoms. Cope considers that 10 to 15 per cent. of cases of renal lithiasis are due to hyperparathyroidism.

Of the 24 cases at the Mayo Clinic 7 were the classical osteitis fibrosa cystica generalisata (and 5 of them had had pathological fractures), 9 showed mild or atypical bone disease, and 8 showed no evidence of bone disease at all. Calcification of the kidneys or renal calculi were present in 22 cases, while in 18 (three-fourths) the symptoms produced by renal calculi were the chief clue to the diagnosis.

Keating and Cook agree with Albright that every patient with renal calculi should be suspected of hyperparathyroidism until the contrary is proved or some other etiological factor is demonstrated. The average age of their patients was forty-four and a half years (extremes twenty-five and sixty-eight years); there were 14 males and 10 females. The average duration before diagnosis was twice as long (thirteen years) in the second group as in the others.

The symptoms of hyperparathyroidism are variable, according to the type, and also within each type. Those referable to the skeleton vary from vague aches and pains to disability and pain accompanying pathological fractures, cysts, etc. Renal colic, haematuria, and passage of stones may be expected where renal calculi are the outstanding abnormality.

The general symptoms, which may be severe or mild, may include pronounced muscular atony, weakness, fatigue, constipation, anorexia, loss of weight, nausea and vomiting. They can be roughly correlated with the degree of hypercalcaemia. Sometimes there is persistent polyuria and polydipsia. In 16 of the Mayo Clinic cases the specific gravity never exceeded 1·015, suggesting possibly a hypercalcinuria or impaired kidney function.

Chemical examination of the hyperparathyroid patient shows blood plasma calcium usually high (recorded figures vary from normal to 29·4 mg. per 100 c.c. (Shelling)), plasma inorganic phosphorus usually low (from 2·5 to 1·0 mg.), phosphatase often

but not always above normal, and marked increased urinary excretion of calcium and phosphorus. In cases of renal involvement of long duration leading to kidney failure, however, the blood plasma phosphorus may be above normal.

Keating and Cook point out that the actual height of the blood plasma calcium is affected by that of the plasma proteins, which hold the non-diffusable calcium in combination. In multiple myeloma and sarcoidosis hyperproteinaemia may be present, and with it a secondary hypercalcaemia. Hypoproteinaemia, on the other hand, is seldom marked enough to hide a hyperparathyroid hypercalcaemia. Increase of plasma (alkaline) phosphatase reflects bone disease, but not hyperparathyroidism *per se*.

The majority of the renal calculi in hyperparathyroidism are composed of calcium oxalate ; some consist of calcium phosphate, or of a mixture of phosphate and oxalate, or of phosphate and carbonate (Albright (1) ; Keating and Cook).

At operation in the majority of cases only one parathyroid adenoma is found ; very occasionally two are present. A small proportion of cases show no tumour, but hyperplasia of all glands (*vide infra*). The tumours are seldom palpable and are often difficult to find. They vary greatly in size, varying in weight from about 2 to nearly 30 gm.

When hyperparathyroidism is diagnosed, operation is the treatment of choice. The surgical technique needs to be meticulous (cf., *e.g.*, Churchill and Cope ; Cope). Difficulty in finding the adenomatous gland is frequent. The considerable variation in normal positions of the glands has been mentioned (pp. 89 and 103). Cope has dealt exhaustively with the occurrence of parathyroids in the anterior mediastinum. Of fifty-eight adenomata in fifty-four of his patients eleven were in the anterior mediastinum, five in the posterior mediastinum, and the rest in the neck. There are two causes for the mediastinal position, embryological descent, and displacement.

Since adenomata, when present, result in atrophy of disuse of the uninvolved glands, when an atrophied gland is found at operation it is a clue to the undeniable presence of disease in one of the other glands (Cope).

The parathyroid tumour is almost always a benign adenoma. Malignant tumours with hyperparathyroidism have been reported by Meyer, and by Wilder (cf. Wellbrock). The few malignant tumours reported in the literature usually were in patients displaying no evidence of hyperparathyroidism.

Cope points out that the size and shape of the normal glands show considerable variation. Autopsy of a patient without parathyroid disease showed normal glands which weighed respectively 20, 21, 40 and 60 mg. The gland is soft, and its shape is determined by surrounding firmer organs. If moulded to the surface of the thyroid it may be flat, but if free in fatty or areolar tissue or embedded within the thymus it is globular.

Operation abolishes pain in almost all cases. Restoration of calcium and phosphorus metabolism to normal occurs with varying rapidity. A hypocalcaemia frequently develops shortly

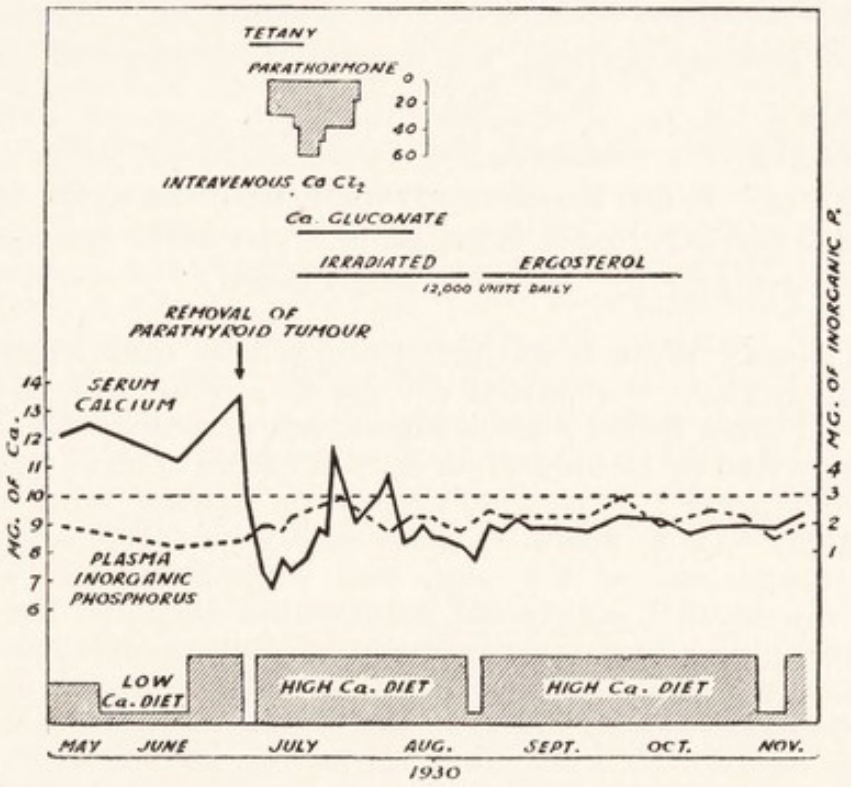

FIG. 19. Chemistry of the blood of Hunter's case of generalized osteitis fibrosa. The blood was examined for two months before and for five months after operation. The low calcium diet was that given during the investigation of the calcium balance. The high calcium diet was not weighed. (From Hunter, Proc. Roy. Soc. Med., *loc. cit.*)

after operation, and latent or open tetany may occur, and needs treatment. General symptomatic improvement takes place, and crippled patients may recover sufficiently to be able to walk without artificial aid. Fig. 19 shows the pre- and post-operative blood chemical changes in one of Hunter's patients.

When the post-operative tetany is marked, the same routine treatment for tetany is needed as in that following thyroidectomy (cf. p. 107).

Occasionally a recurrence occurs, due apparently to the presence of a second adenoma, missed at operation.

Excellent illustrations of the extreme degree of deformity which

can occur, and the degree of recovery possible following removal of a tumour, are to be found in a paper by Quick. Recalcification is sometimes marked (Brook).

When formation of kidney stones is the outstanding phenomenon, pyelonephritis often ensues. More rarely deposits of calcium phosphate in the parenchyma (without stone formation) lead to inflammatory changes, sclerosis and contracted kidney, sometimes suggestive of glomerulonephritis (cf. Albright (1)). Albright (2) considers that the renal stone type of case does not usually develop post-operative hypocalcaemia. Where kidney damage has become marked, the degree of recovery of that organ is uncertain.

Albright (1) has stressed the possible occurrence of serious kidney damage from the nephrocalcinosis, etc. It may lead, directly or indirectly, to a fatal issue, even after removal of the parathyroid tumour (cf. Keating and Cook).

Unusual Cases. While it seems not improbable that when a normal blood serum calcium is reported several determinations on the same patient would often reveal fluctuating values, sometimes above normal, yet a case reported by Baumgartner does not seem open to this explanation. A woman aged fifty-eight, with fairly marked bone changes of long duration, had a serum calcium of 9·0 per 100 c.c., with low inorganic phosphorus of 2·4 mg., and phosphatase 2·8 Bodansky units. At operation a substernal parathyroid adenoma the size of a lemon and weighing 29 gm. was removed. (Post-operative tetany was treated by parathyroid extract.) Sevringhaus, commenting on this case, considers the calcium value due to the long duration of the disease, most of the easily mobilizable calcium having already been dissolved away and excreted. Another possibility is unusual ability of the kidneys to excrete calcium, sufficiently great to prevent development of a hypercalcaemia.

Snapper reports the unusual case of a woman of forty-four years who had had fainting spells for eleven years, exhibited albuminuria, a blood pressure of 210/130 mm., and a blood urea of 50 mg. per 100 c.c. Snapper states that the diagnosis would have been chronic glomerulonephritis with hypertension and uraemia, had not a biopsy specimen of a bony tumour of the forehead showed an osteoclastoma. Further examination then showed serum calcium 17·2 mg., phosphorus 2·75 mg., and high phosphatase. X-ray examination revealed small cysts in tibia, fibula and mandible, in addition to the giant-cell tumour of the forehead. At operation a parathyroid adenoma weighing 2 gm. was removed. Subsequently renal function improved considerably, the osteoclastoma ossified completely, but there was only a transient improvement in the blood pressure.

Couch and Robertson have reported a case which postoperatively exhibited a marked acidosis, successfully treated by intravenous sodium bicarbonate, and point out that acidosis and tetany can occur together. In a second case the skeletal changes closely resembled those

in Paget's disease, perhaps due to successive decalcifications and recalcifications during exacerbations and remissions of the disease.

Laboratory Aids in Diagnosis of Hyperparathyroidism. Blood serum calcium and phosphorus determinations, along with phosphatase, often give adequate information to confirm the clinical and X-ray picture. Determination of the calcium balance (which should be negative) involves a metabolic study which the ordinary clinical laboratory cannot easily undertake.

Sulkowitch's test has value (cf. Barney and Sulkowitch). It gives a rapid, if rough estimate of the amount of calcium in urine. An oxalate-buffer mixture is prepared by dissolving 2·5 gm. of oxalic acid, 2·5 gm. of ammonium oxalate, and 5 c.c. of glacial acetic acid in distilled water to a volume of 150 c.c. Five c.c. of the mixture is added to an equal volume of urine in a test-tube. The urine must be acid to litmus, or made acid previous to addition by adding 50 per cent. acetic acid solution drop by drop. The test-tube is inverted and shaken, and the degree of turbidity observed after two minutes. Urines of normal individuals show a slight turbidity, while those of hyperparathyroid patients give a marked turbidity. A negative result rules out hyperparathyroidism, but a positive result is suggestive and not final evidence. (The patient should be tested on a diet free from milk or acidifying agents, since these increase urinary calcium excretion.)

Hamilton has devised a test for presence of increased amounts of parathyroid hormone in blood, based upon increase in the blood serum calcium of a rabbit under controlled conditions, following the injection of 30 c.c. of blood of the patient under test into the thigh muscles of the animal (cf. Hamilton and Highman ; Winer). Gilligan could not confirm Hamilton's results.

Hyperparathyroidism Due to Hyperplasia. Hyperplasia of the parathyroids may be primary or secondary. Secondary hyperplasia is a compensatory mechanism resulting from an increased physiological demand for the hormone, which can occur in a variety of conditions (as in multiple myeloma, carcinomatous metastases to bone, rickets, osteomalacia, and Cushing's syndrome) but is found more especially in chronic renal disease. When such hyperplasia follows kidney failure it seems most likely due to additional stimulus to the parathyroids from the resulting hyperphosphataemia.

The characteristic case with secondary hyperplasia is that of a patient with renal disease of long duration and chronic acidosis, in whom extensive bony changes have developed. X-ray examination shows as a rule extensive decalcification of bony structures and often metastatic calcification elsewhere (Cope ; Soffer and Cohn). The parathyroid glands may be markedly hyperplastic, but the cells are always of the solid chief type (Castleman and Mallory). (Soffer and Cohn point out that it is possible to get, as sequences of a parathyroid adenoma, renal calculi, chronic renal

failure, and then resulting hyperplasia of the remaining parathyroids.)

In secondary hyperplasia the blood calcium is *usually* normal.

Primary hyperplasia of all the parathyroid glands results in marked hyperparathyroidism. The condition is rare; Cope has had seven cases. It is important to recognize the condition and to differentiate it from presence of adenomata, since removal of a single hyperplastic gland (mistaken for an adenoma) does not benefit the patient. The hyperplastic glands have a broken, irregular surface, with frequent peninsulas or pseudopods, while by contrast adenomata have a smooth surface and few peninsulas. The colour of a hyperplastic gland is a darker brown than that of an adenoma (Cope). The cells are all of water-clear type (Castleman and Mallory).

Cope points out that primary hyperplasia of the parathyroids corresponds to Graves' disease of the thyroid, parathyroid adenomata corresponding to toxic nodular goitre, the relative frequency being reversed.

The following is an abbreviated report of Cope's seventh case, which he considers illustrates the type. A large obese man of sixty-three years was awakened from sleep by a sharp severe pain in the chest. There was apparently but little pertinent history. Four years previously he had passed a small stone through the urethra.

X-ray examination showed a fractured rib, mild diffuse decalcification of the spine, and bilateral kidney stones. The skull showed no evidence of decalcification. The blood serum calcium was 14·5 mg. and phosphorus 2·6 mg. per 100 c.c.; four days later the figures were 13·3 and 2·3 mg. The urine by Sulkowitch test showed excess of calcium.

At operation an enlarged parathyroid was uncovered behind the lower pole of the thyroid. It was at first thought to be an adenoma, but on lifting it the indentations and irregularities characteristic of a primary hyperplastic gland were noted, while the colour was darker than the usual adenomata. The three other glands were therefore searched for and found to be of similar type. A biopsy of one showed in frozen section water-clear cells, characteristic of primary hyperplasia.

The three larger glands were removed entirely, and a part of the fourth gland also, leaving an amount judged adequate for normal parathyroid function. The total excised material weighed 3·39 gm., and it was estimated that 0·08 gm. was left *in situ*.

Post-operative convalescence was uneventful. Blood serum calcium and phosphorus returned to normal levels in a few days. There was no tetany. The Sulkowitch test became negative in four days. The kidney stones have given no symptoms, and the patient has continued well for over a year.

Non-surgical Treatment of Hyperparathyroidism. Merritt and Caulk claim to have obtained good results by X-ray irradiation of the parathyroids in a number of cases of hyperparathyroidism of the

" spinal osteoporotic " type. Sevringhaus considers that X-ray therapy may have a place when surgery is not available.

Helfet treats cases of apparently secondary hyperplasia by administration of soluble aluminium salts (the acetate, or preferably the gluconate) in small dosage. He claims that there is slow, steady improvement, evident in six to eight weeks by X-ray examination.

Acute Hyperparathyroidism. This condition is extremely rare. Mellgren, in 1943, listed seven fatal cases in the literature, including two of his own. In one other (non-fatal) case the acute condition was due to accidental overdosage of parathyroid hormone. The experimental production of acute hyperparathyroid poisoning with resulting death has been described already (cf. p. 96).

The most outstanding case is that of Hanes. A woman aged forty-nine was admitted to hospital complaining of pain in the right chest and a feeling of tiredness. At previous examinations elsewhere pyelitis had been found, with some calcification of the kidney and slight elevation of blood serum calcium ; impairment of kidney function had existed for at least five years. There had been marked loss of weight. She now exhibited by X-ray examination decalcification of bones and typical metastatic calcification of kidneys. Her serum calcium was 20 mg. per 100 c.c., with 4·7 mg. inorganic phosphorus ; these values changed in three days to 22 and 4·8 mg. There was a definite nodule (subsequently shown to be parathyroid) of about 2 cm. diameter at the lower left pole of the thyroid. This was undoubtedly subjected to repeated palpation, which may have been the cause of the final parathyroid intoxication from which the patient succumbed four days after admission. Death was preceded by marked asthenia, nervousness (in contrast to previous cheerfulness), and slight fever, with generalized aching pain. The cause of death was apparently circulatory failure from the parathyroid intoxication. (The high and increasing phosphorus values correspond to the pre-mortal rise in blood plasma inorganic phosphorus in acute experimental poisoning by the parathyroid hormone.)

Post-mortem examination showed a necrotic and partially calcified parathyroid tumour, composed of chief cells, and diffuse visceral and vascular calcification, the kidneys being involved ; the picture was analogous to that seen in experimental parathyroid poisoning.

Oliver has described two cases in which women, aged fifty-seven and fifty-six years, showed prior to death none of the customary stigmata of hyperparathyroidism, but, as prominent symptoms, only repeated nausea and vomiting, anorexia, much loss of weight, obstinate constipation, and, terminally, rapidly increasing drowsiness. Blood urea was high in both cases. The patients rapidly became comatose and died without definite diagnosis. Post-mortem findings included parathyroid adenomata, blood serum calcium of 17·4 and 19·6 mg. per 100 c.c., and severe kidney necrosis with deposits of calcium salts, and calcification of other tissues.

Smith and Cooke have described the case of a woman aged forty-four, who during the previous two years had developed a limp and some bowing of the legs. Severe pain in the legs was not relieved by treatment, and she took to her bed on account of " rheumatism."

Admitted to hospital, after sixteen days she was conscious but critically ill, with nausea, dry skin, furred tongue, and distended tender abdomen. Three and a half hours before death her blood glucose was normal, urea 155 mg., and serum calcium 23 mg. per 100 c.c. At post-mortem a 7 gm. parathyroid adenoma (of chief cells) was found. The kidneys were deeply congested, with focal cloudy swelling and necrosis of tubular epithelium and widespread calcinosis. The iliac bone and femur showed osteitis fibrosa cystica.

In 1934 Albright pointed out that, judging from experiments with animals, clinical cases of acute parathyroid poisoning might show anuria, with calcium deposits in the kidney parenchyma and elsewhere, but no chronic renal changes. Smith and Cooke consider that their case comes within this category, and it is possible that Oliver's cases belong here also. It is to be noted that a markedly diminished urinary output does not appear to have been an outstanding feature in these cases.

Rogers has recently described 2 cases, not diagnosed until autopsy, but considered to be acute hyperparathyroidism associated with duodenal ulcer.

A comparable kidney picture is produced in acute parathyroid poisoning in rats (Chown) or by excessive administration of acid phosphate to rats (Duguid).

Mellgren stresses the multiple thromboses present in his own cases, in that of Arnold, and of Smith and Cooke, as of importance in leading to the fatal termination. He considers that the outstanding general symptoms of acute hyperparathyroidism are asthenia, and as a rule vomiting and abdominal pains, the somewhat uncharacteristic syndrome resembling most nearly an " acute abdomen."

Lowenburg and Ginsburg described a case of acute parathyroid poisoning in a boy aged five years, due to accidental administration of overdoses of the hormone (in experimental treatment of purpura haemorrhagica). Prior to treatment his blood calcium was normal. On the sixth day of treatment, when the error in dosage was discovered, the serum calcium was 19·6 mg. per 100 c.c., the inorganic phosphorus 4·4 mg. (He recovered following continuous venoclysis of physiological saline.)

At the height of the induced hyperparathyroidism the outstanding phenomena were vomiting, increasing in severity, general physical depression, lethargy, listlessness, slow reaction time to questioning, etc., and fever.

While it is evident that patients may develop a state of marked hyperparathyroidism, with none of the symptoms commonly associated with that state, it is doubtful whether all of the cases just described can truly be described as acute, nor are the symptoms common to these cases sufficiently characteristic to suggest their underlying cause.

Localized Osteitis Fibrosa. In 1932 Frances Braid published a report on the association in a young boy of osseous dystrophy with icterus gravis neonatorum, and noted that there was an extensive brown birthmark on the face and neck. She made a further report on this case,

and a second similar case, in 1939. McCune and Bruch reported a similar case associated with icterus gravis in 1937. In 1937 also, Albright, Butler, Hampton and Smith, on the basis of study of five cases of their own and thirteen cited from the literature (not including Braid's case) described a syndrome characterized by osteitis fibrosa disseminata, non-elevated areas of brown pigmentation, and endocrine dysfunction, with precocious puberty in females. Bone changes are localized. Calcium and phosphorus metabolism is normal, and hyperparathyroidism is absent.

Several other cases have been reported, and Falconer, Cope and Robb-Smith have recently made a thorough study of two cases, have reviewed the literature, and have suggested that the syndrome be named after Albright.

These two new cases differ somewhat from those previously reported, in that sexual precocity was observed in a male patient but was not present in a female patient. Both cases showed features suggestive of acromegaly, and also leontiasis ossea with visual disturbance.

Falconer and Cope advocate a broader concept of the disease. Its essential features are a characteristic multifocal fibrous dysplasia of bone, occurring in association with endocrine disorders of variable type. Skeletal precocity is common ; patches of cutaneous pigmentation are usual. Less constant features are sexual precocity, thyroid disease, and acromegalic changes ; when present they may dominate the clinical picture.

The bony dystrophy is identical with a variety of " localized osteitis fibrosa " termed by Lichtenstein " polyostotic fibrous dysplasia." It can be distinguished from the bony dystrophy of hyperparathyroidism by absence of generalized osteoporosis, absence of a demonstrable disturbance of calcium metabolism, and by a characteristic histological picture indicating a disturbed development of the undifferentiated mesenchyme with resultant fibre formation. It is not associated with hyperparathyroidism. It can occur without cutaneous pigmentation or endocrine features, but, when associated with these, constitutes the syndrome of Albright's disease.

The syndrome appears in childhood and becomes stationary in adult life. It is not fatal. There is no evidence that it is hereditary. Albright considered that it is probably due to some embryological or trophic neurological disturbance. Falconer and Cope suggest that it is the result of a congenital disorder of development involving both the bony skeleton and the hypothalamus.

The importance of recognizing the disease is to differentiate it from generalized osteitis fibrosa and so prevent fruitless exploration of the parathyroids.

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CHAPTER V

THE ISLETS OF LANGERHANS AND INSULIN

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THE ISLETS OF LANGERHANS AND INSULIN

Introduction. From the early studies of von Mering and Minkowski on the depancreatized dog, and the subsequent work of Allen, it became evident that diabetes mellitus was associated with a deficiency of some endocrine principle of the pancreas. The discovery of insulin by Banting and Best in 1921, working in Macleod's laboratory, its association with the islets of Langerhans of the pancreas, and its preparation for clinical use, in which Collip largely participated, led not only to successful treatment of diabetes mellitus, but also to rapid acquiral of more exact knowledge of carbohydrate metabolism. The effects of overdosage of insulin, due to the resulting hypoglycaemia, were at once understood, since by good fortune the same effects were about the same time accurately described by Mann and Magath for the hepatectomized dog, in which they were also due to the resulting hypoglycaemia.

The pancreas consists of acinar tissue and the islets of Langerhans. Since the work of Macleod on the encapsulated islets in fishes, it has been generally accepted that the islets are tissue *sui generis*, whose function is not related to the acinar tissue, but is concerned solely with the elaboration of insulin, and, further, that insulin is only produced by islet tissue.

The islets, distributed throughout the pancreas, are small but numerous, so that their total volume may be about 1 per cent. or more of that of the pancreas itself (Waters and Best).

Susman has estimated the islet content of the pancreas in 202 unselected cases, of which 51 were diabetic. He finds that an islet tissue content of 0·9 to 2·7 per cent. may be considered normal for adults, and 0·9 to 3·6 per cent. normal for infants. When the content is less than 0·9 per cent. this is presumably significant as indicating a deficiency of insulin secretion, since it occurs in the great majority of cases of diabetes mellitus. Over 3·6 per cent. is regarded as high and probably an indication of potential or actual hypoglycaemia.

Ogilvie, taking no account of disease in a similar study, found 78 per cent. of his cases within 0·9 and 3·5 per cent. He considered that

during the first year of life the amount of islet tissue is augmented by an increase in the number of islets. During childhood and adolescence any increase is through hypertrophy, while by twenty-one years of age the amount of islet tissue has become established. Susman agrees.

The number of cells in an islet varies greatly, but in the dog averages about thirty (cf. Waters and Best). Bensley showed that there were two types of cells, A or alpha cells, relatively large, with large elliptical or spherical nuclei, and B or beta cells, smaller, more numerous, with smaller nuclei, and with cytoplasm packed with granules (cf. Opie). He also described a third type, C cells, rare, and non-granular. Bloom has described another granular type of cell in the human pancreas, which he terms D cells, and which may be identical with a type previously described by Bowie in the teleost *Neomaenis griseus*. Epithelial cells of the small ducts are considered to be the parent cells of both islet and acinar tissue, and can give rise to new islet cells. When islet tissue is subjected to a severe strain (such as can be produced, for example, by removing nine-tenths of the pancreas of a dog, and feeding the animal a high carbohydrate diet), the beta cells develop characteristic lesions (so-called hydropic degeneration). While in different islets the numbers of the three cell-types present vary widely, typical figures (for the dog) are, in percentage, alpha cells 20, beta cells 75, D cells 5 (cf. Waters and Best).

Van Campenhout's "sympathetico-insular complexes" in the embryonal pancreas are termed by Simard "neuro-insular complexes," and he has shown that they are permanent structures, present in adult animals, including adult man. They are situated in the inter- and intralobular septa and consist of an intimate association of nervous and epithelial elements. Simard states that the epithelial cells of the complexes are insular cells, and that the endocrine pancreatic gland is diffuse and intimately mixed with the exocrine gland, not being limited solely to the islets of Langerhans. He regards the alpha and beta cells as representing probably the different histo-physiological stages of the endocrine secretion. He suggests that the complexes may contribute to chemical transmission of nerve impulses, and that their absence, or reduction in their number, might play a *rôle* in the pathogenesis of diabetes.

There is some evidence that the islets are under the control of the vagus (cf. Macleod), yet Etcheverry found that, when deprived of intrinsic innervation, they still can regulate carbohydrate metabolism normally, while Houssay grafted a dog's pancreas into the neck of a second, depancreatized dog, and obtained perfect function for many hours with this denervated preparation.

Insulin has been obtained from the pancreas of several domestic animals by various procedures, and of the amorphous preparations obtained many are almost pure. It was first crystallized by

Abel in 1926, and pure crystalline insulins have been frequently prepared and thoroughly studied (cf. Jensen and Evans ; Jensen ; du Vigneaud). The present large scale preparation of crystalline insulin at the Connaught laboratories has been described by Romans, Scott and Fisher.

The crystals are well defined ; they seldom exceed 0·01 mm. in diameter. They give the biuret, Pauly, Millon, and ninhydrin reactions, Sakaguchi's test for arginine, and positive tests for cystine. Tryptophane, hydroxyproline and methionine radicals, the sulphydryl group, and carbohydrate radicals appear to be absent (cf. also Fraenkel-Conrat). Nor has any evidence been obtained for the presence of a prosthetic group, nor of any new, specific, amino-acid radical.

Hydrolysis yields the following percentages of amino-acids : tyrosine 12, cystine 12, arginine 3, histidine 4, lysine 2, proline 10, glutamic acid 17·5, leucine 13·5, threonine 2·6, serine 3·6, phenylalanine 7. There is evidence that radicals of isoleucine and valine are present. All the sulphur, approximately 3·3 per cent., is present in cystine radicals.

The most recent evidence from data obtained from ultra-centrifugal sedimentation and diffusion constants of carefully re-crystallized insulin indicates a molecular weight of 46,000.

The molecular size of insulin suggests that, like Bence Jones protein, it is potentially excretable through the kidney glomerulus. After injection into rabbits it rapidly disappears from the circulation, and the rate of disappearance is decreased after excluding the kidneys from the circulation (Goadby and Richardson). Several investigators claim to have demonstrated its presence in urine. However, Cutting has recently carefully re-examined this possibility, and has devised a method which will detect the presence of 0·25 unit of insulin per 100 c.c. of urine. She could find no insulin in normal urine, and concludes that, if it be present, the amount must be below this limiting detectable quantity.

Crystalline insulin usually contains a trace of zinc or some similar element (according to the salts present in the crystallizing medium). Cohn *et al.* find that the zinc content varies from 0·3 to 0·6 per cent., depending on the *p*H of crystallization and independent of the amount of excess of zinc in the solution. Repeated extraction with water decreases the zinc content of all preparations to about 0·3 per cent. Pancreas contains 20 to 40 mg. of zinc per kg. fresh tissue, and Sahyun has prepared zinc insulin crystals directly from pancreatic extract (without addition of zinc) ; these only contained 0·15 per cent.

Crystalline insulins have been prepared by Scott and Fisher without metallic elements, but, instead, with isoamylamine, *n*-amylamine, or

piperidine. These retain the activity of the original insulin. Since these products are free of metallic ions it would appear that such ions are not a necessary constituent of a crystalline insulin.

Numerous attempts have been made to associate the physiological activity of insulin with some particular portion of its molecule ; all the experimental results have led to the conclusion that the activity is associated with the molecular architecture of the whole molecule (cf. du Vigneaud). In so far as further conclusion is possible, there is some evidence that the activity is essentially linked with the disulphide linkage of the cystine radicals.

The potency of insulin preparations is expressed in terms of an international unit, which is defined as that of 0·125 mg. of a specific preparation. Crystalline insulin has a potency of 24 I.U. per mg.

Insulins from ox, beef, pig, fish, human and bison pancreases do not differ in potency or crystalline appearance (Scott and Fisher), and are immunologically identical (Wassermann and Mirsky).

Reduction of the disulphide linkages results in loss of physiological activity. Treatment with alkali, or iodine, or hydrolysis with acid or with proteolytic enzymes leads to irreversible inactivation. Acetylation diminishes the activity.

Action of Insulin. Following its subcutaneous injection into man or other animals the most striking phenomenon is the lowering of the concentration of blood glucose. If the dosage is great enough to produce a marked degree of hypoglycaemia various hypoglycaemic phenomena such as convulsions ensue.

Biological assays of insulin depend on these effects. The fall in blood sugar produced in rabbits by injecting a measured amount of an insulin preparation is measured under standard conditions. A second method of assay is based on the production of convulsions in fasting mice (cf. Waters and Best).

The lowering of concentration of glucose in blood under the action of insulin suggests that insulin promotes some chemical change in glucose, either in the blood or in the tissues. The first possibility can be ruled out, since *in vitro* experiments indicate that there is no direct action on blood glucose. There is abundant evidence that the second possibility is correct, and Macleod termed the action the creation of a " vacuum for glucose " in the tissues ; with lowered concentration in them the glucose diffuses from blood to them.

For example, when a surviving heart preparation is perfused with a fluid containing glucose and insulin, the heart muscle tissue

removes glucose at a faster rate than when the perfusion fluid contains glucose but no insulin.

Again, glucose tolerance curves in normal persons show a marked difference between venous and arterial values, suggesting that glucose is removed by the tissues at a fairly rapid rate during its passage through the capillaries, once the concentration has

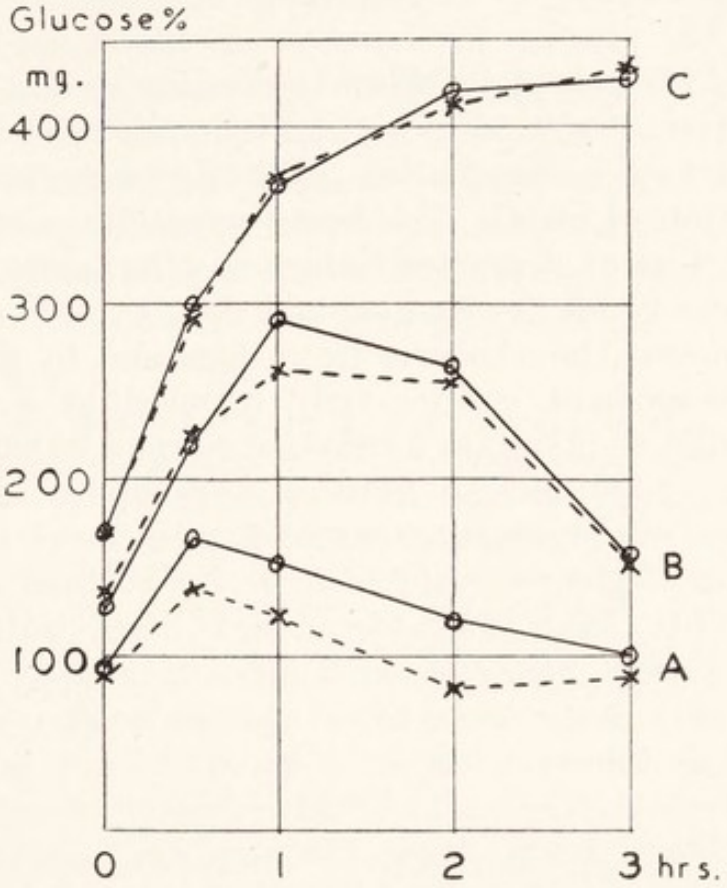

FIG. 20. Curves illustrating the lessened difference between arterial and venous blood glucose in diabetes mellitus, following ingestion of 1·75 gm. glucose per kg. body-weight. Continuous lines, arterial blood; broken lines, venous blood. A, normal; B, a case of mild diabetes; C, a case of severe diabetes. Data from Glassberg, Arch. Int. Med., 1930, xlvi, 608.

risen distinctly above the fasting level. This normal difference tends to disappear in the diabetic, and the severer the diabetes the more closely the curves approximate, indicating loss of tissue power to withdraw glucose from the blood (presumably because of loss of power to utilize it). This is well shown in the curves in Fig. 20, constructed from Glassberg's data. The insulin-balanced diabetic exhibits normal tolerance curves again (Macleod). Mann

and Magath showed that the presence or absence of the liver in an animal had but little effect on the rate at which glucose is removed from blood under the influence of insulin ; muscle tissue is of greater importance. Macleod considered that the chief sites of insulin action are the cardiac and skeletal muscles.

The normal curves in Fig. 20 show that the initial rapid increase in blood sugar level, following a glucose meal, is succeeded by a slower fall to fasting level, and that, between the second and third hours, the glucose level in venous blood not infrequently (though not invariably) falls below the fasting level. These effects have often been attributed to a stimulation of the islets resulting from the increased concentration of blood glucose and leading to increased output of insulin, this being sometimes large enough to lead to the transient depressed values so often seen. Soskin has shown that this is not the true explanation.

Soskin removed the pancreas from dogs and by an automatic pumping arrangement continuously injected at a steady rate sufficient insulin to maintain a constant normal blood sugar level. Under such a condition an induced hyperglycaemia could not stimulate a non-existent pancreas to furnish more insulin. Yet administration of glucose resulted in a normal tolerance curve.

On the other hand, hepatectomized dogs, with a normal pancreas, and with glucose injected intravenously in amount just adequate to maintain normal blood glucose level, responded to a glucose meal by tolerance curves of the diabetic type.

It would thus appear that the liver mechanism itself controls the height of blood sugar. When the supply of insulin is adequate, as in the normal animal, its liver responds to administered glucose by decreasing its own supply of glucose to the blood (glycogenolysis decreasing or ceasing). When the blood glucose falls to (or below) fasting level the liver mechanism of supply again comes into action.

This liver mechanism is under a balanced control of insulin on the one hand, and on the other of one or more pituitary hormones, and in lesser degree those of the thyroid and adrenal cortex. (There is, in addition, an emergency mechanism for increasing the liver output of glucose, through the nervous system and the adrenal medulla.)

Thus in Soskin's view, apparently based on sound experimental evidence, the regulating mechanism of blood sugar level is the liver (acting under endocrine control) plus the height of blood sugar itself. When the endocrine control of the liver is disturbed, the sugar level to which it reacts becomes altered.

While the precise chemical actions of insulin have still to be determined, data are accumulating as to what exactly it does and does not do. It does not appear to affect the conversion of fructose into glycogen (Macleod). It facilitates and perhaps controls the formation of muscle glycogen from blood sugar. Its control of liver glycogen may be indirect. In low concentration it seems to promote glycogen storage, perhaps by inhibiting glycogenolysis; in higher concentration it tends to decrease glycogen storage in the liver (Frank).

It is still uncertain whether insulin facilitates disposal of glucose in any other way than by formation of glycogen. Lawrence, for example, thinks not, but Macleod (2) believed its action to be less limited. The problem will only be solved when more is known about the precise chemical reactions in the tissues in which the insulin molecule takes part; present knowledge of these is very slight.

Krebs and Eggleton have shown that insulin, *in vitro*, facilitates the citric acid catalysis of glucose oxidation in pigeon muscle, but the degree in which the citric acid plays a *rôle*, or more than a minor *rôle* in oxidation-reduction processes in mammalian tissues has still to be determined.

According to Rice and Evans, insulin causes pyruvate utilization and is involved in the maintenance of the enzyme systems governing reactions between pyruvic acid and both fumaric and oxalacetic acids.

Gill and Lehmann have shown that insulin inhibits the formation from glycogen and phosphate in muscle extracts of that mixture of hexosemonophosphates termed the Robison ester, and that for this action the $-S-S-$ groups of insulin (in its cystine radicals) are necessary, but they infer from other evidence that the Robison ester may not be an intermediate step in the oxidation breakdown of glycogen.

Sacks, using radioactive phosphorus, injected as disodium hydrogen phosphate into cats, found that insulin caused a marked increase in the turnover rate of phosphocreatine and adenosine triphosphate in resting muscle during glucose absorption, but did not cause any increase in turnover of glucose-6-phosphate beyond that produced by the glucose itself.

The fate of insulin in the organism is still undetermined. As has already been mentioned, any excretion through the kidneys can only be in negligible trace. Goadby and Richardson, experimenting with rabbits, found that apparently the liver does not destroy insulin.

Commercial preparations of amorphous insulin, when injected intravenously into animals, may produce an initial transient hyperglycaemia. Crystalline insulin does not do this, and it must be attributed to impurities, such as traces of proteoses and peptones (cf. Geiling and De Lawder; White, Joslin and Pincus).

Control of Insulin Secretion. Any control through the vagus (cf. p. 126) is not an essential but an additional mechanism. There is adequate evidence, as Soskin admits, that a hyperglycaemia stimulates the islets to secret insulin (cf. also Foglia and Fernandez) even though this is not the mechanism controlling the normal level of blood glucose. Soskin considers that the purpose of the islet response is not yet clear, but that it is perhaps an additional safety factor for regulation. (The increase in islet output of insulin leads to increased formation of muscle glycogen and tends to decrease carbohydrate storage in the liver.)

There is no adequate evidence that the islets are under direct control of any pituitary hormone ; indirect control exists, through pituitary hormone effects producing hyperglycaemia, which stimulates the islets. (Cf. Long ; also Chapter IX, p. 349.)

Animals can be rendered diabetic by continued injections of pituitary extracts (p. 346). The early changes in their islets are degranulation of islet cells, some of which show hydropic degeneration, others mitotic activity. Later the principal changes are beta-cell degranulation, reduction of islets to small groups of alpha cells, and gross hyalinization ; in some instances there appears to be selective replacement of beta cells by hyaline material (cf. the histological picture in human diabetes mellitus, p. 151) (cf. Richardson ; Ham and Haist ; Lukens and Dohan). Houssay *et al.* consider that these changes are due to a direct effect of a pituitary hormone on the islet tissue. This view is not generally accepted.

Alloxan Diabetes Mellitus. Jacobs reported in 1937 that when alloxan (produced by action of strong nitric acid on uric acid) is injected into rabbits, there is a transient hyperglycaemia, followed by a profound hypoglycaemia, which can lead to convulsions and death, and which is relieved by intravenous injection of glucose. The related dialuric acid does not produce the effect.

Recent studies have shown that alloxan, repeatedly injected into rats, rabbits or dogs, produces changes in the islet cells of the pancreas, and chiefly in the beta cells. If the animals survive long enough they exhibit hyperglycaemia, glycosuria, and sometimes the cardinal symptoms of diabetes mellitus. It has been suggested that the initial hyperglycaemia is due to release of adrenine, the succeeding hypoglycaemia to release of insulin from dead and dying islet cells, and the subsequent diabetes to lack of insulin. (Cf. Dunn *et al.* ; Goldner and Gomori ; Hughes, Ware and Young.) Adrenalectomy reduces the diabetes or causes its complete disappearance. (Janes and Friedgood). Tipson and Ruben have obtained some slight evidence that alloxan is normally present in various tissues including the liver, and have suggested that its over-production, or lessened ability to destroy it, may be an etiological factor in the causation of some cases of clinical diabetes. This does not seem too likely, since it has been shown that alloxan is rapidly destroyed in blood, damage to the islet cells occurring only in the first few minutes after injection (cf. Cori and Cori).

Lazarow has found that intravenous injection of large doses of

glutathione or of cysteine one or two minutes prior to injection of a diabetogenic dose of alloxan completely protects rats from diabetes mellitus. If the protecting dose is given one minute after the alloxan partial protection is conferred, but if given three or more minutes after there is no protection. Alloxan combines with sulphydryl groups, and Lazarow considers that the protective compounds use it up, so that it can no longer attack compounds possessing free —SH groups and essential to cell activity. A dose of 40 mg. alloxan per kg. consistently produces diabetes mellitus in the rat.

Other Presumptive Hormones of the Pancreas. Depancreatized dogs tend to develop fatty livers, and this tendency is largely counteracted by the inclusion of raw pancreas in their diets. Best and his associates have shown that this effect of pancreas is due to its choline content. Dragstedt has prepared an alcoholic extract of pancreas which seems to have an effect similar to that of choline. He considers that this extract contains a specific hormone, which he has termed *lipocaic*, and which, it has been suggested, is elaborated by the alpha cells of the islets. While the action of lipocaic resembles that of choline, they are not identical.

However, McHenry and Gavin have obtained definite evidence that various materials such as the extract termed lipocaic, rice polishings, and yeast, contain a *dietary factor* which is not identical with choline, but which is equally, or more potent in preventing fatty changes in the liver. Lipocaic should probably therefore not be considered a hormone. Gavin and McHenry state that its action is similar to that of inositol.

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HYPOINSULINISM AND DIABETES MELLITUS

Introduction. " Diabetes mellitus " is an illustration of that combination of Greek and Latin words repulsive to the stylist. Literally, it means a sweet polyuria, a copious flow of sweet urine. Stedman's Dictionary defines it as " a disease of metabolism in which sugar is excreted continuously in larger or smaller quantities in the urine and is also present " in undue amount " in the blood ; the amount of urine is greatly increased, and the patient suffers from excessive thirst, sometimes bulimia, and progressive emaciation." By definition, therefore, diabetes mellitus is associated with certain definite symptoms, and not with disease of any particular tissue.

Diabetes mellitus used to be considered as due to lesions of the islets of Langerhans resulting in deficient output of insulin ; within recent years the conception of its etiology has been widened to include any disturbance in the normal balance of regulatory endocrine factors that will result in the symptom-complex (cf.

Houssay ; Long). These endocrine regulators are, on the one hand, insulin, and on the other, hormones of the pituitary, thyroid, and adrenal cortex, whose effects counteract those of insulin. If, especially, there is increase of pituitary hormone effect without corresponding increase in insulin output, the balance is upset, and a *relative* insulin deficiency is present, which can lead to the characteristic definitive picture of diabetes. However, in the great majority of cases of diabetes mellitus an actual deficiency of insulin is present.

This wider conception of the disease differentiates it from *hypoinsulinism*, in that while all cases of the latter are diabetics, all diabetics do not exhibit hypoinsulinism.

Some authorities still prefer to regard diabetes mellitus as essentially a pancreatic disorder. Wilder stresses the hyperglycaemia as the outstanding feature, and considers that in presence of a permanent hyperglycaemia diagnosis of (pancreatic) diabetes is justified. Joslin (2) stresses the fact that in the experimental pituitary diabetes of Young (cf. p. 346) the islets of Langerhans are ultimately damaged by exhaustion, and defines diabetes as a " hereditary disease, characterized by an increase of sugar in the blood, and the excretion of sugar in the urine ; it is dependent upon the loss or decrease of the insulin secreted by the islands of Langerhans of the pancreas, and is functionally interrelated with other endocrine glands, particularly the pituitary, but also the adrenal and thyroid, and the liver."

Even though 99 per cent. of cases of diabetes come within the more limited definition, the wider conception is of value, in stressing the similarity of the diabetic syndrome, whether it be due to a pancreatic or pituitary anomaly.

Differentiation between Diabetes Mellitus and Renal Glycosuria. Within recent years attention has been drawn more and more to the occurrence of sugar in urine in conditions other than diabetes mellitus. With more precise methods and more accurate and extended observations the number of such cases detected is increasing steadily.

Of those cases in which a sugar other than glucose is present, only the lactosurias of nursing mothers are relatively common. Differentiation is easily possible by the yeast-fermentation and osazone tests. True fructosuria is rare. Excellent studies have been published by Barrenscheen, Heeres and Vos, and Anschal. Differentiation is not too easy. In cases of pentosuria the sugar seems to be either arabinose or xyloketose. Somewhat less than 100 such cases have been reported. Greenwald has summarized the literature critically. Bial's test serves to discriminate the sugar of the urine from glucose. All the cases of lactosuria, fructosuria, and pentosuria are relatively harmless anomalies, requiring no special treatment, and in no way associated with hypoinsulinism.

The commonest non-diabetic condition which exhibits a persistent (though not necessarily continuous) glycosuria is that due to a lowered kidney permeability for glucose ; it is termed variously *renal diabetes*, *renal glycosuria*, *renal glycuresis*, *diabetes innocens*, and *benign* or *innocent glycosuria*. Of all such terms, *negligible glycosuria* suggested

by Leyton, is most apt, since it describes the importance of the condition with precision. The condition is relatively common. It exhibits various grades of severity, with no sharp line of demarcation between them ; these are combinations of varying kidney thresholds with either normal sugar tolerance, or a somewhat diminished tolerance (Graham (1)).

A sufficient number of cases of these renal glycosurias have been observed over long periods of time to warrant the conclusion that the duration of life of those so affected is not shortened by the condition. Cases have been reported with histories of twenty-five, twenty-nine, thirty-two, and even forty-four years (Weber). The importance of correct diagnosis in these cases is illustrated by the fact that many of them have quite unnecessarily been dieted for years as diabetics, and many others have been refused life insurance on the ground that they were diabetics.

Most cases of renal glycosuria can be diagnosed correctly, and diabetes mellitus ruled out, by a glucose tolerance test. The former usually exhibits a normal or slightly depressed curve, with glycosuria present through all or most of the test. The fasting value of the blood sugar is normal or low. (Diabetics exhibit a heightened curve, with slow return to normal, and usually a definitely increased fasting value.) In certain of the severer cases of renal glycosuria the tolerance curve simulates that of a mild diabetes, and sometimes only a long history of absence of diabetic symptoms with unchanged degree of glucose excretion justifies exclusion of diabetes mellitus. An extreme example of such a case has been reported by Powelson and Wilder. The tolerance curve reached the value of 0·28 per cent. at the end of the second hour of the test, and maintained it to the end of the third hour, although a history of thirteen years definitely excluded diabetes. Faber has devoted attention to this severer type ; only a few per cent. ultimately develop diabetes.

In an interesting analysis of 1,700 cases of diabetes mellitus and 224 cases of non-diabetic glycosuria, it was shown that while one-third of the latter were symptomless, only 2 per cent. of the true diabetics showed no symptoms (Murray-Lyon).

Cases of hyperthyroidism frequently exhibit a glycosuria, but the simultaneous occurrence of hyperthyroidism and diabetes mellitus is rare (Joslin and Lahey).

Diabetes mellitus of hepatic origin (hepatic diabetes) has been postulated by certain French authors as a condition occurring chiefly between the ages of forty and fifty, in persons eating and consuming alcohol somewhat too heartily. The liver is generally considerably enlarged, and often tender ; it tends to become smaller during treatment. Glycosuria is mild, polydipsia and polyuria absent. Dietary treatment leads to good results ; insulin is of slight, but only slight, value. Motzfeldt has reviewed the literature.

The Signs, Symptoms, Course and Differential Diagnosis of Diabetes Mellitus. Joslin says, in the latest edition of his Text, " If a patient has sugar in the urine, it is a safe rule to consider the diagnosis to be diabetes until the contrary is proved." This rule, however, is distinctly unsafe, unless the patient manifests

definite clinical symptoms of diabetes. In the past many a patient with renal glycosuria has been condemned to a rigorous dietary regimen, and some to insulin treatment, because further investigation has not been made. Wilder (2) comments : " I also would urge that proof be obtained in every case, before the patient is condemned indefinitely to the disciplined regimen required for satisfactory maintenance in true diabetes," and " Physicians who make a speciality of diabetes frequently are consulted concerning children, as well as by adult patients, whose lives have been made miserable by treatment which they did not need."

Onset of the disease is usually insidious. The commonest early symptoms are, in order of frequency, polyuria, polydipsia, and loss of strength. Polyphagia is common, as is loss of weight (cf. Joslin (2)).

In the untreated diabetic the course of the abnormal metabolic changes is (i) hyperglycaemia, increasing until it is accompanied by (ii) glycosuria, (which at first may occur only after meals, and later may be continuous). As the glycosuria increases, since excretion of glucose must be accompanied by excretion of extra water, this causes (iii) polyuria, which induces (iv) polydipsia. Distorted carbohydrate metabolism is followed by distorted protein metabolism, so that an undue amount of protein is catabolized to glucose and excretory nitrogenous compounds and so causes (v) an increased azoturia. The carbohydrate and protein wastage may be sufficient to lead to (vi) loss of weight and (vii) polyphagia. Ultimately fat metabolism becomes distorted, acetoacetic acid is formed in too large an amount for its correct catabolism, and so (viii) the " acetone bodies," acetoacetic acid, beta-hydroxybutyric acid, and acetone, appear in the urine, and acetone may appear on the breath. Finally, through the large efflux of these two acids into the blood, its mineral balance is disturbed, and (ix) the plasma base becomes inadequate to carry the normal amount of carbon dioxide from tissues to lungs, so that accumulation of carbon dioxide in the tissues stimulates the respiratory centre to " air-hunger," coma ensues, and the patient dies.

Treatment with insulin prior to the onset of coma (or even in its early stages) rapidly restores normal carbohydrate metabolism, and the other disturbances become corrected.

The etiology of the disease will be dealt with later. But from some cause or other there results an upset in the balance of endocrine control of carbohydrate metabolism, so that there is always a relative, and usually an actual deficiency of insulin.

If Soskin's views are accepted, then this relative or absolute deficiency of insulin alters the liver mechanism for adjustment of blood glucose, whose threshold level—to which the liver responds by stopping glycogenolysis—rises, so that, with increased output of glucose, there results a hyperglycaemia, and when this surpasses the level of the " kidney dam " glycosuria follows. The hyperglycaemia stimulates the islets of Langerhans to further activity, which can lead to exhaustion.

The relation of hyperglycaemia to lesions of the islets is illustrated by the experiments of Lukens, Dohan and Wolcott on cats ; these showed that neither partial pancreatectomy nor injections of anterior pituitary extracts would cause hydropic degeneration of the cells of the islets in absence of hyperglycaemia, but both caused such degeneration after hyperglycaemia had been present for a week or two. Even a hyperglycaemia caused by continuous perfusion of glucose can result in minor lesions to the islets.

Hydropic degeneration of the islets, however, seems to be rare in human diabetes (cf. p. 151).

One or more of the pituitary hormones seem to control conversion in the liver of amino-acids to glucose. With upset in the insulin-pituitary balance and the brake to glucose production improperly adjusted, undue glucose formation results not only from undue glycogenolysis, but also from undue protein catabolism. The liver " tap " for glucose is no longer shut off at the proper level, and the liver turns everything possible into glucose.

The tissues are flooded with glucose, in spite of which it seems probable that its utilization in the tissues is decreased in the diabetic (cf. Waters and Best), increasing the degree of its wastage.

The metabolism by which fat metabolism becomes involved is still disputed. Various investigators still believe that glucose can be formed in the organism from fatty acids ; the majority reject this view. The balance of evidence favours the view that Macallum long ago expressed, that normal fat catabolism can only proceed at a certain maximum rate, and that when, because of deficient carbohydrate oxidation, fat catabolism is speeded up to meet increased body need for energy, the process becomes faulty.

Introduction of exogenous insulin at an adequate rate restores the normal endocrine balance, and this quickly leads to normal control of carbohydrate metabolism, which involves restoration of normal protein and fat metabolism.

The "Houssay dog," minus pancreas and pituitary, exhibits an endocrine balance of less perfect type, easily disturbed (cf. p. 345).

The Incidence and Etiology of Diabetes Mellitus. Some idea of the incidence of diabetes is given by an estimated figure of two-thirds of a million people in the United States in 1935. In 1938, 31,037 were listed as having died from it in that country (Joslin (2)). Lawrence (quoted by Joslin) estimates the number of diabetics in the United Kingdom as of the order of 150,000 to 200,000. The majority of countries show similar figures. The incidence appears to be increasing.

The onset of the disease can occur at any age, but is commonest in the United States between the ages of forty and sixty, nearly half of Joslin's cases having a history of onset during this age-interval. The disease is somewhat commoner in females than in males. Race is apparently of some significance. The incidence among Jews is high; it is also said to be high among the Irish, while it is relatively infrequent and mild among the Chinese (cf. Joslin (2)). This apparent racial factor may in reality be attributed to differences in dietary habits.

Diabetes has no single cause. Heredity, obesity, and in slight degree hyperthyroidism, are all potential causes. Its association with acromegaly illustrates the rare type in which there is a relative insulin deficiency and in which pituitary hyperfunction is the outstanding cause.

Naunyn maintained that the primary cause of diabetes is an inborn biological inferiority of the insulin reserve (cf. Wilder (2)). Murray-Lyon found a hereditary incidence in about 16 per cent. of diabetics, Cammidge in 40 per cent., and Joslin *et al.* in 25 per cent. The existence of a hereditary predisposition is indicated by the more frequent occurrences of diabetes (of the same grade of severity) in similar than in dissimilar twins, and it has been suggested that the potentiality for developing the disease is transmitted as a simple Mendelian recessive (Umber; Pincus and White; White and Pincus).

Joslin's view concerning obesity is illustrated by his statement: "Diabetes appears to be largely a penalty of obesity, and the greater the obesity, the more likely is Nature to enforce it." Obesity is certainly a predisposing factor, but the cause of the diabetes is probably to be traced rather to some one or more of the factors which have led to the obesity. Himsworth (2) speaks of a dietary disposition, and has adduced evidence that in diabetes following obesity the patients prior to their obesity had diets relatively high in fat and low in carbohydrate, diets which he has

shown (p. 142) impair sugar tolerance and the degree of response to insulin.

That hyperthyroidism can lead to diabetes is shown by the greater incidence of diabetes in hyperthyroid patients (about 3 per cent.) than in the general population (not more than 1 per cent.) (cf. Wilder (2), and also Houssay's "metathyroid diabetes").

Mosenthal (1) has attempted to associate chronic pancreatitis in elderly persons (resulting from arteriosclerotic and senescent processes) with the slow progressive diabetes of middle and old age. There is some evidence that a considerable proportion of patients recovered from acute pancreatitis develop diabetes (cf. Wilder (2)).

Trauma is very rarely the cause or precipitating factor in diabetes (Joslin (2)). Persistent emotional stress leading to persistent hyperglycaemia (and glycosuria) has been postulated as an etiological factor in some cases (Bollmeier and Meyer).

Obesity is the exception in diabetic children, and infections do not appear to be a definite predisposing factor. White stresses the hereditary disposition as the essential factor. Precocious growth is common, suggesting an earlier transient pituitary hyperfunction.

The immediate factor leading to the diabetes is almost certainly a persisting hyperglycaemia, although such a hyperglycaemia in itself may not lead to the damage of the islets causing the diabetes (cf. Lukens).

Priscilla White (2) recently reviewed a series of 1,250 patients with juvenile diabetes from the angle of Houssay's theory of the nature of the disease. She stresses the lack of evidence of a pathological pancreas in these children. She considers that 176 of her cases showed evidence of prolonged pituitary involvement, in almost all cases a hypoactivity. These included ninety-four dwarfs, twenty-two with signs of Fröhlich's syndrome, and fifty-one with signs of infantilism. The dwarfism followed and did not precede the diabetes, and was not usually recognized until the fifth year of the disease. It was of pituitary type. (It is not easy to explain hypopituitarism as a causative factor of the diabetes.)

The Treatment of Diabetes. Numerous excellent texts are available, dealing thoroughly with the treatment of the diabetic patient. Only some notes on trends in treatment are given here.

Diet. In pre-insulin days the diabetic was kept alive by gradually decreasing the proportion of carbohydrate in his diet and replacing it by fat. Ultimately very high fat diets were advocated, especially by Pétrén, and by Newburgh and Marsh. The limit was fixed almost solely by the necessity of avoiding

ketonuria ; the ketogenic-antiketogenic ratio provided by the diet was made maximal.

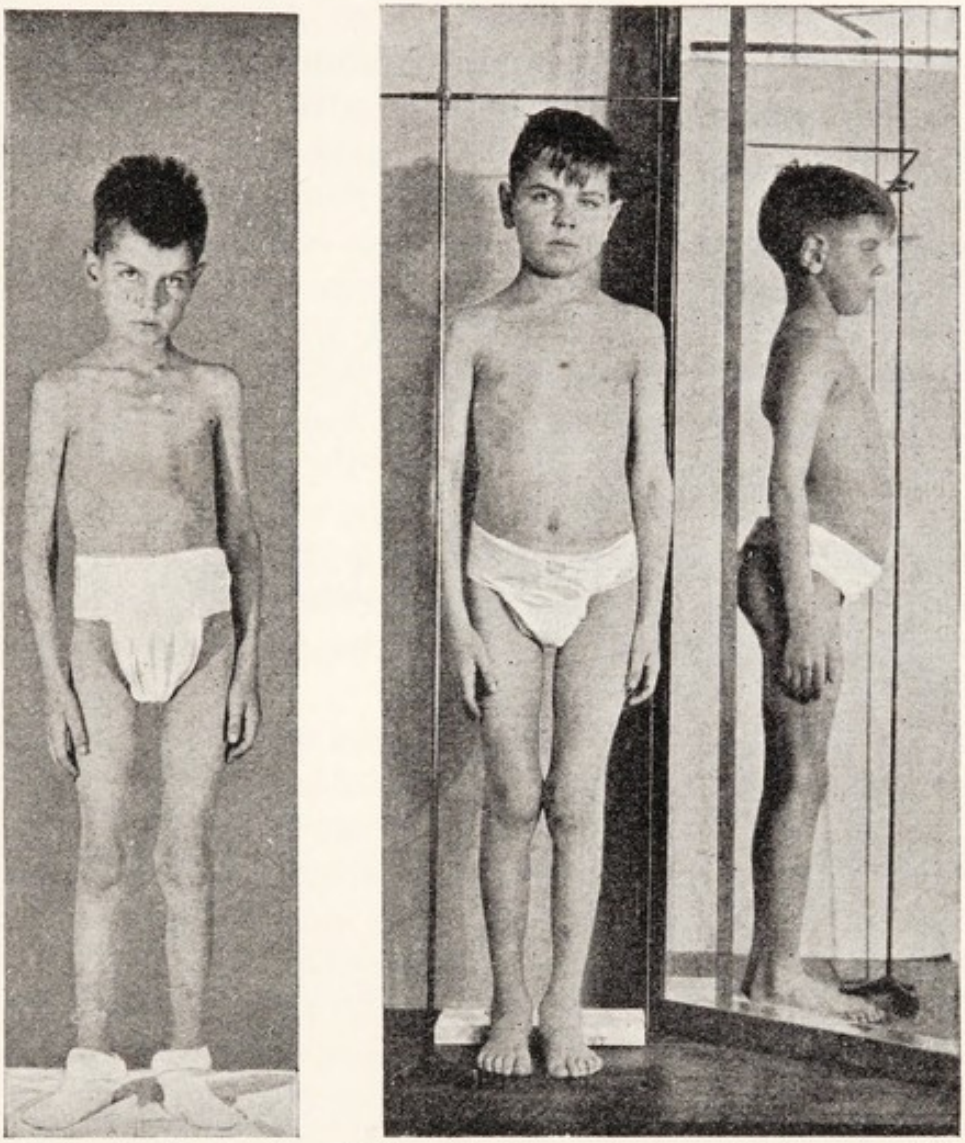

FIG. 21. A. September, 1931. Photograph of an eight-year-old boy after six months' treatment for severe diabetes, on a diet of 50 grams protein, 100 grams fat, and 50 grams carbohydrate, with initially 20 units of insulin daily, gradually increasing to 35 units. During this period he gained 4 lb. in weight, his urine was never completely sugar-free, and he frequently excreted acetone bodies. He could not be kept on the prescribed diet. At the period of the photograph he was tired, drowsy, and presented a pathetic figure. He was transferred to a diet of 65 grams protein, 50 grams fat, and 130 grams carbohydrate, with 30 units of insulin.

B. November, 1931. Appearance nine weeks later. During this interval he had gained 16 lb. His insulin requirement was now only 14 units daily. He appeared and was a happy, contented schoolboy. (Reproduced by the kindness of Dr. H. Medovy.)

When insulin became available, the high-fat low-carbohydrate diet, life-prolonging in absence of insulin, was persisted in ; the

habit had become difficult to alter. Slowly evidence became available that such a diet actually depressed sugar tolerance and the insulin mechanism (cf. Hamman and Hirschman ; Sweeney ; Porges and Adlersberg). Porges and Adlersberg in Vienna, Sansum in San Francisco, and Rabinowitch in Montreal commenced to advocate diets normal as regards carbohydrate content and protein, and normal to low in fat and calories, with adequate insulin. The great advantage of a more normal diet is now generally recognized, and such a diet is usually employed. Only in mild diabetes in mature adults, where glycosuria can be prevented by slight dietary adjustment without insulin, is such adjustment proper to avoid insulin injection.

It is noteworthy that when patients balanced on high-fat diets were transferred to a normal diet, their insulin requirement decreased. An excellent example of the rapid improvement such change of diet produced is shown in Fig. 21.

The experiments of Ellis, and of Himsworth (1), give an adequate explanation of the better effect of the increased carbohydrate diet.

Ellis treated a number of severe cases of diabetes with glucose and insulin, given hourly, and with no other food for a number of days. He found that 600 grams of glucose daily could be tolerated with no greater insulin than on a restricted diet, while in some cases there was a marked reduction in the amount of insulin necessary. In one—an extreme case—before this special treatment was instituted, 192 units of insulin per day were necessary, while on the twenty-first day of the treatment only 9 units were required. In no case was there any exacerbation of the diabetes.

Himsworth has carried out careful experiments on normal healthy subjects which completely confirm the results of Hammon and Hirschmann, Sweeney, and Porges and Aldersberg. Glucose tolerance curves were determined on normal individuals habituated to a high fat, low carbohydrate diet, and contrasted with curves on the same individuals subsequently habituated to a low fat, high carbohydrate diet of equal caloric value. Typical results are contrasted in Fig. 22, A. They show definitely that the high carbohydrate diet increases the tolerance and the high fat diet decreases it. (The values are for capillary blood.) Himsworth also contrasted, again on the same subjects, the relative effects of injecting 5 units of crystalline insulin during each of the two states (habituation to high fat and to high carbohydrate respectively). Typical results are shown in Fig. 22, B. It is clear that *the effect of the same dose of insulin is greater on high carbohydrate*

than on high fat régime. The increased tolerance is due not to change in caloric value nor to change in ketogenic-antiketogenic ratio, but solely to the increased amount of carbohydrate in the diet (Himsworth (2)).

In discussing these results, Himsworth refers to the important finding of Allan in 1923 with depancreatized dogs. There is no direct linear relation between the carbohydrate ingested and the

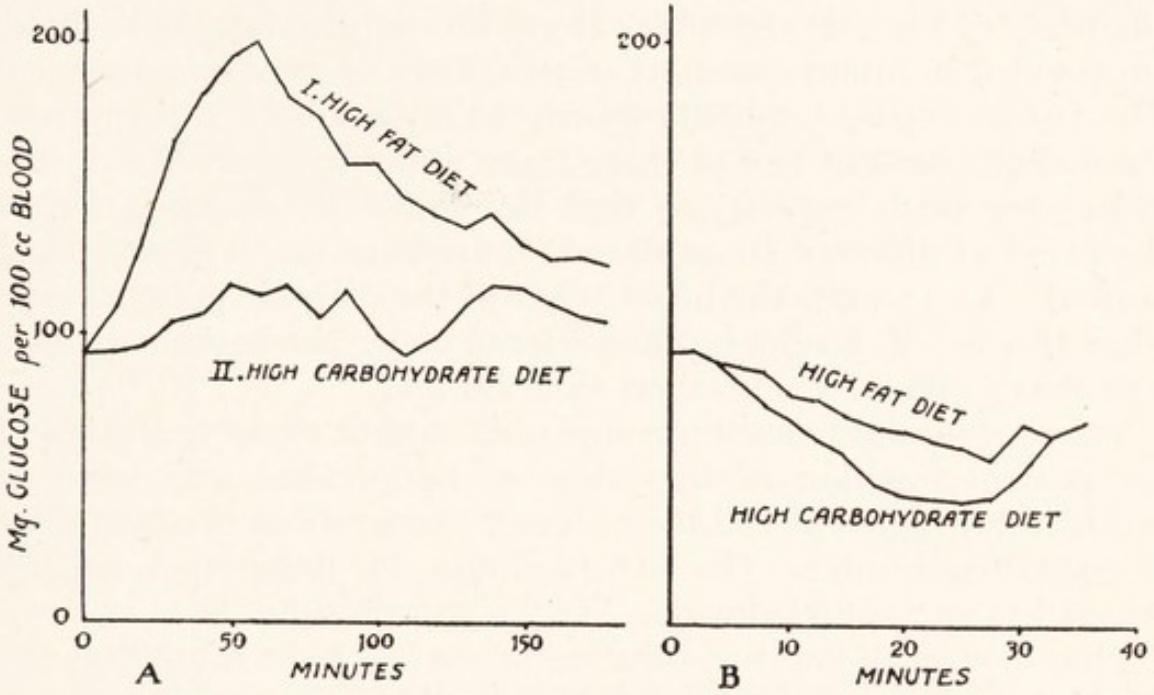

FIG. 22. A. Two sugar tolerance curves after 50 grams of glucose, determined on the same healthy subject : (i) when accustomed to a high fat diet ; and (ii) when accustomed to an equicaloric high carbohydrate diet. B. Two blood sugar curves following intravenous injection of 5 units of crystalline insulin. Both were obtained on the same healthy subject, the one during a period of high fat diet and the other when on an equicaloric high carbohydrate diet. (After Himsworth, Brit. Med. J., 1934, ii, 57.)

amount of insulin needed to care for it and prevent glycosuria. The relationship is approximately logarithmic.

The greater the relative amount of carbohydrate, the greater is the amount metabolized by each unit of insulin.

Insulin. Like other proteins, insulin is decomposed when given orally. It must be injected hypodermically two or three times daily. Numerous attempts to find other methods of administration have failed. It has, for example, been given sublingually, or coated to resist peptic digestion, or endonasally as a snuff, or injected in pellet form mixed with some insoluble compound as cholesterol. By all such devices the amount of insulin absorbed is either negligible or uncontrollable.

Attempts have been made to find substitutes for insulin which could be taken orally. Those hitherto tested, as for example the synthalins, do not have the same physiological action as insulin, and are toxic.

The most significant advance in insulin therapy in recent years has been the production of insoluble compounds of insulin, which, when injected, produce because of their insolubility slow but prolonged action. The insulin secreted into the circulation from the islets of Langerhans under the action of physiological stimuli is provided in minute amount continuously or semi-continuously. The insulin injected subcutaneously as replacement therapy into the diabetic patient two or three times a day is absorbed into the circulation fairly rapidly, so that the available concentration in the blood at different times shows fluctuations much greater than normal. As a result, the blood sugar of the diabetic patient, even when this *soluble* insulin is administered under the best conditions, also shows greater fluctuations than normal.

The new insoluble insulin compounds permit closer imitation of the normal function of the islets of Langerhans and have in considerable part replaced the ordinary preparations of amorphous or crystalline insulin. The latter are now, for distinction, usually referred to as " soluble insulin " or " regular insulin."

The iso-electric point of insulin, its zone of least solubility, lies at *p*H 5·3. Tissue fluid is less acid ; its *p*H varies from 6·5 to 7·5, from slightly acid to slightly alkaline. In consequence, tissue fluids hold insulin in solution fairly easily.

The insoluble insulin now chiefly used for diabetes, *protamine zinc insulin*, is the result of studies of Hagedorn and his collaborators in Copenhagen, and of observations of investigators of the Toronto school.

Insulin is a protein, and therefore amphoteric, capable of combining with acid or with base. Its compound with nucleic acid has an iso-electric point still more acid than that of insulin itself. Hence Hagedorn prepared compounds with the alkaline proteins, the histones and protamines. Compounds with the proteins clupein (from herring sperm), scombrine (from mackerel sperm), and salmine (from salmon sperm) still proved too soluble in tissue fluids, but the compound formed by insulin with the protamine prepared from the sperm of the rainbow trout, *Salmo irideus*, proved to be only very slightly soluble at *p*H 7·3, and its extensive trials on diabetic patients gave most favourable results, the insulin effect being prolonged, and there being no rapid sudden drop in blood sugar level.

Scott and Fisher (1) found that a concentration of 0·1 per cent. zinc greatly delayed and prolonged the effect of insulin in rabbits, and exaggerated the delaying effect of protamine. As a result, " protamine zinc insulin " has become generally available for the treatment of diabetics.

Both the original protamine insulinate, and its modification with zinc, have been received with a practically unanimous chorus of praise, and the papers recording success with them are far too numerous to list. Root, White, Marble and Stotz first confirmed

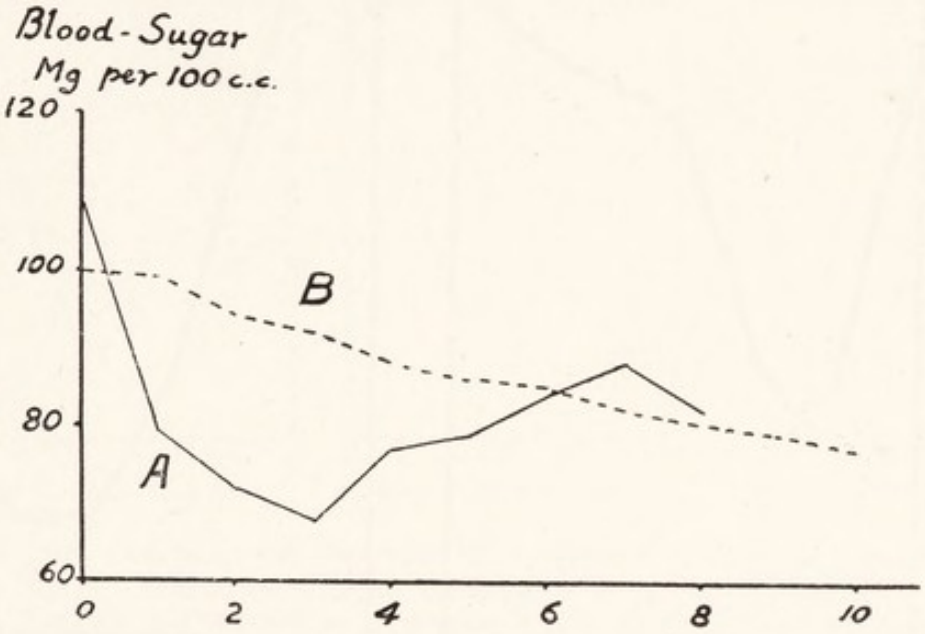

FIG. 23. Contrast of the effects of insulin and protamine insulinate on the blood sugar. Miss M. G., normal, aet. 25, nurse-dietitian. Both tests after an over-night fast. No food taken during the tests. A. October 23rd. Effects of 8 units of insulin (Lilly) given subcutaneously. B. October 25th. Effect of 10 units of protamine insulinate (equivalent to 7·3 units of insulin (Lilly)). (After Root, White, Marble and Stotz, J. Am. Med. Assoc., 1936, cvi, 180, Fig. 1.)

the statements of the Danish investigators, concerning protamine insulinate, and these statements were further quickly endorsed by Kerr, Best, Campbell and Fletcher, Lawrence and Archer, Sprague, and many others.

The effect of the insulinate in lengthening and dampening down the insulin effect is shown in Fig. 23.

The clinical aspects of the use of protamine zinc insulin have been dealt with by Wilder (1), Rabinowitch (3), McCullagh, Dunlop, Lawrence, Joslin (2), and others.

Protamine insulinate was originally prepared by adding together solutions of protamine, phosphate (as buffer), and insulin under

sterile conditions. The precipitated insulinate was injected in suspension. The mixture was not very stable, and thus needed frequent fresh preparation.

Scott and Fisher (2) have succeeded in preparing satisfactory protamine zinc insulins with various protamines. The advantage of addition of a trace of zinc salt is twofold. The " insulinate " is

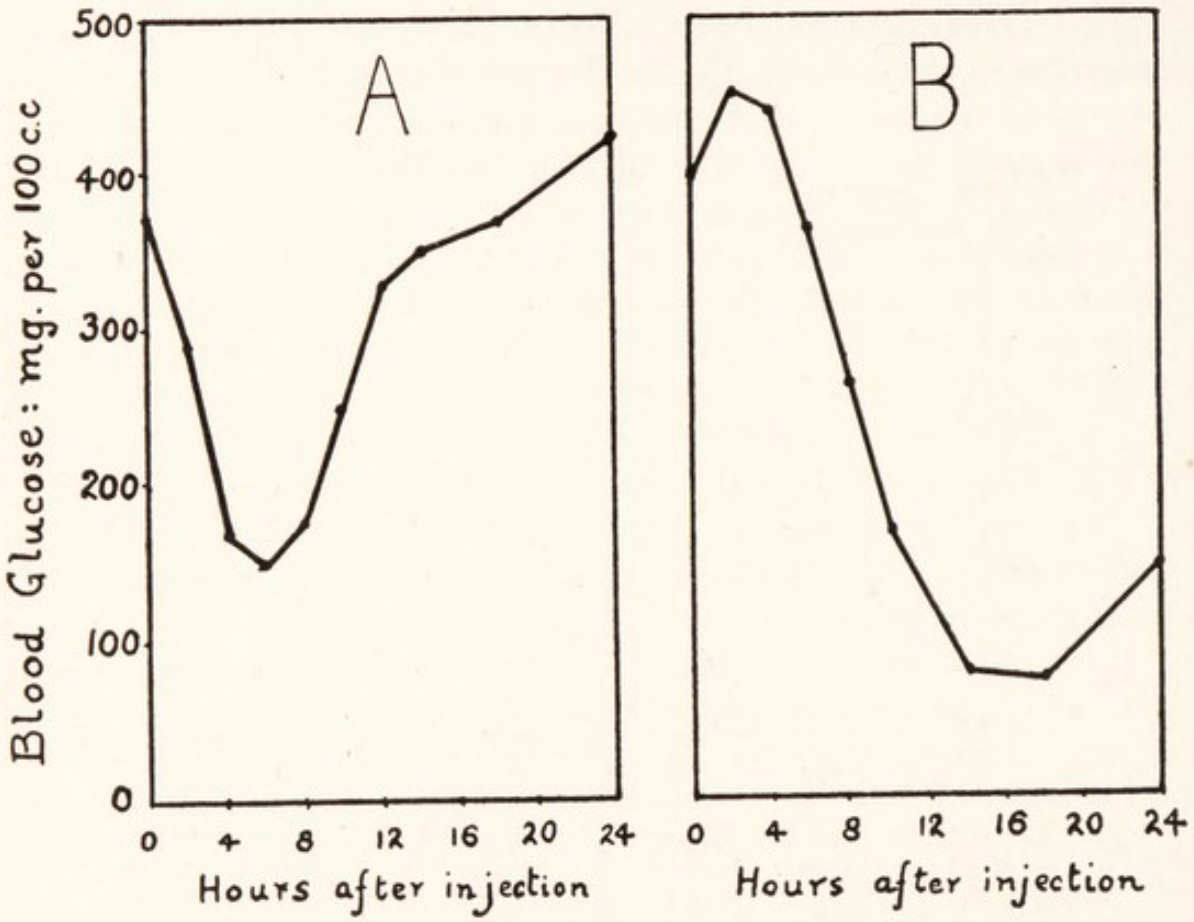

FIG. 24. Comparative duration of action of (A) ordinary insulin, and (B) protamine insulin, as contrasted on the same severely diabetic patient under like conditions. Injection (35 units) at 8 a.m. Breakfast twenty minutes later (30 grams carbohydrate, 18 grams protein, 44 grams fat) ; no noon or evening meal. At the end of twenty-four hours in test (A) there was marked acidosis ; in test (B) there was no evidence of acidosis, and no glycosuria. (After Wilder, Ann. Int. Med., 1937–38, xi, 14.)

stabilized, so that a single solution can now be furnished commercially. In addition, as has been stated, the zinc exaggerates the protamine effect, possibly by still further decreasing the solubility (cf. Fazekas and Himwich).

Addition of a trace of calcium salt also increases stability but lessens the delaying effect of protamine (Wilder (1)). Such effects are illustrated in Figs. 24 and 25.

Protamine zinc insulin possesses the greater advantage over

ordinary soluble insulin that, with many cases of mild diabetes, a single morning injection suffices for the twenty-four hours. In more severe cases it is possible to combine one morning injection of protamine zinc insulin with one of soluble insulin.

It has been a matter of dispute whether the two insulins can be safely mixed prior to injection. Wilder (1) stated that excess protamine may precipitate the soluble insulin. Wauchope found the mixture less efficient and recommended separate injections. On the other hand, Colwell, Izzo and Stryker claim that suitable mixtures of the two insulins may be prepared which produce any desirable intermediate

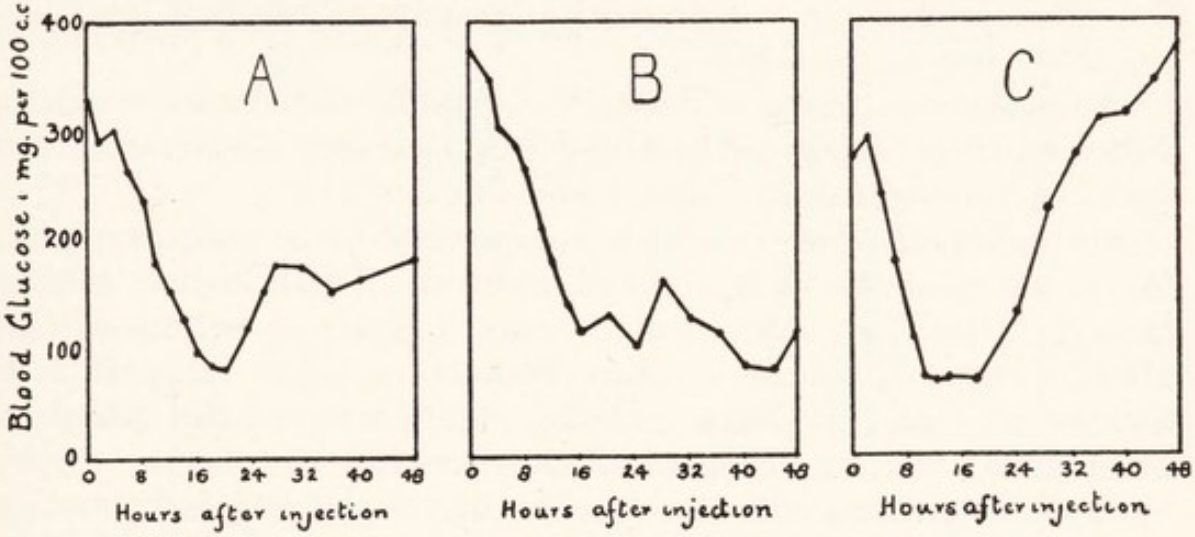

FIG. 25. Comparative duration of action of (A) ordinary insulin, (B) protamine insulin in presence of a trace of zinc salt, and (C) protamine insulin in presence of a trace of calcium salt, as tested on the same diabetic patient under comparable conditions. In each case 50 units were injected ; food was withheld during each forty-eight hour period. (After Wilder, Ann. Int. Med., 1937–38, xi, 16.)

action as regards promptness, intensity and duration of effect, and enable severe diabetics to be controlled by a single daily injection.

While the delayed action renders protamine zinc insulin inadequate for treatment of diabetic coma, yet claims have been made that, both in acidotic conditions and in actual coma, the additional use of the protamine compound with adequate soluble insulin improves treatment (Rabinowich (3) ; Wilder (1)).

According to McCullagh, a single dose of protamine zinc insulin produces an effect during a period of fifty to sixty-five hours, and maintains its maximum effect twelve to eighteen hours. Obviously a single daily dose can produce a cumulative effect, which may ultimately lead to hypoglycaemia, but a hypoglycaemia far more delayed than that produced by ordinary insulin. As Wilder (1) has pointed out, this hypoglycaemia sets in so insidiously that the

secondary symptoms attributable to adrenine (cf. p. 162), and acting as danger signals, the tremor, sweating, tachycardia, and increased pulse rate, may not occur. The chief effects noticeable in this delayed hypoglycaemia may thus be only those of cerebral origin—lassitude, fatigue, and headache or nausea—and loss of consciousness is not likely to occur. Yet Bollman's animal experiments (quoted by Wilder) indicate that prolonged hypoglycaemia may give rise to dangerous brain lesions.

Hence it seems desirable that patients using the new insulin should be trained to take greater precautions than before to avoid the effects of fasting, and should take sugar at frequent intervals whenever meals are missed.

Protamine zinc insulin has given equally satisfactory results with diabetic children (White (3)). Comparable effects are given with depancreatized dogs (Kerr and Best).

A number of other insoluble compounds have been prepared, for which good results have been claimed. These include insulin tannate (Gray *et al.*), insulin zinc tannate (Jenkinson and Milne), thymus-histone insulin (Biasotti *et al.*; Gray *et al.*), histone zinc insulin (Barnes *et al.*), globin zinc insulin (Reiner; Baumann), spermine zinc insulin (Scott and Fisher (2)), hexamethylene tetramine insulin (cf. Feinblatt) and haematin insulin (Barnard). Joslin (4) has recently contrasted the effects of certain of these insulins. Regular insulin exerts an action for six hours, crystalline insulin for seven hours (presumably because of its zinc content), protamine zinc insulin up to forty-eight hours. Joslin considers that histone zinc insulin and globin zinc insulin have certain advantages over protamine zinc insulin. The histone compound combines to some extent the prompt action of crystalline insulin with the prolonged action of the protamine compound. The globin compound is slightly more delayed in action than the histone compound.

(He also points out that children practically always need a quick-acting insulin along with protamine zinc insulin.)

MacBryde and Roberts have also made a careful study of different insulins. They find that "clear" ("acid" or "soluble") protamine zinc insulin, which has a *p*H of 3·3 to 3·5, and contains more protamine and more zinc than the usual turbid preparation, gives less satisfactory control of diabetic patients than the latter, having less sustained effect. They consider that histone zinc insulin also gives poorer diabetic control.

They recommend a new insulin modification, containing about three parts of ordinary protamine zinc insulin to one part of soluble insulin, and prepared by mixing equal parts of protamine zinc insulin (which

contains a 40 per cent. excess of protamine) and soluble insulin, with buffer added to adjust the *p*H to 7·2. They found that single daily injections of this mixture would regulate mild diabetics and even control more severe ones. (del Fierro and Sevringhaus agree.)

They consider that multiple forms of insulin are not necessary and should be discouraged, and that two forms should suffice : (i) a modified protamine zinc insulin of the type described, and (ii) regular (crystalline) insulin, for use when emergency therapy is necessary.

Lawrence (3) is adverse to the use of globin-zinc-insulin, and believes that there is danger in using two *clear* solutions, one acting rapidly, and one acting only slowly, since the patient may well mistake one for the other. Cf. also Marble.

Williams thinks that before flooding the market with new preparations of uncertain value better standards of evaluation are needed.

Allergic and Other Toxic Reactions to Insulin. A summary of the earlier literature dealing with allergic manifestations following injections of insulin was published in 1932 by Allan and Scherer. They pointed out that while the first impure preparations of insulin caused local irritation of the skin and subcutaneous tissues at the site of injection, in a few cases there appeared general symptoms of an anaphylactic reaction. Such phenomena were observed less frequently as methods of extraction and purification improved. Possibilities of anaphylactic shock were recognized early, but it was found that in most cases sensitization effects were absent. Occasional sporadic cases of hypersensitiveness have been recorded. Summarizing observations made at the Mayo Clinic, Allan and Scherer stated that hypersensitiveness to insulin occurred in approximately one out of eight or ten cases. Of 100 consecutive cases manifesting such hypersensitiveness, four showed generalized symptoms of anaphylaxis, in eighty-four there was only a mild reaction at the site of injection, usually relieved by a change in the type of insulin or by spontaneous desensitization, and in twelve cases there was a severe local reaction with less relief from change in insulin.

Such results appear to suggest, especially in those cases where benefit is obtained by change of the insulin material employed, that the allergic phenomena may be due to protein impurities and not to insulin itself. However, the purest material can produce the effect. Campbell, Gardiner, and Scott report that " one patient shows marked sensitivity to beef, hog, sheep, fish, and human insulin obtained from different sources. He is also sensitive to crystalline insulin though the reaction is less intense."

The problem has more recently been reviewed by McDaniel. He states that small localized reactions at the site of insulin injections are common at the beginning of therapy with either

regular or crystalline insulin, and are probably more frequent with protamine zinc insulin, occurring in 15 to 30 per cent. of cases. These reactions are usually mild and of short duration. Generalized reactions are exceedingly rare ; of a group of 16,000 diabetics only twelve were known to have exhibited insulin hypersensitiveness with generalized reaction. Such cases may occur after insulin has been omitted for a period of months, when the therapy is resumed.

Goldner and Ricketts have recently described a series of eight cases with generalized symptoms attributable to the insulin itself.

Since there is evidence that insulin from the different species of animals usually employed for preparing the therapeutic material is chemically and immunologically one and the same compound with human insulin (cf. p. 128), it is difficult to explain these occurrences, except that even crystalline insulin contains slight amounts of protein impurity or else that a trace of it is chemically altered during preparation to become a foreign protein (cf. Waters and Best).

Corcoran has described a method of desensitization, starting with very frequent but very minute doses.

Other still more unusual toxic manifestations have been recorded, as, for example, a transient haematuria (Lawrence and Hollins), headache, dizziness, and lack of muscular control (Payne and Poulton), and transient hemiplegia. These early recorded evidences of toxicity were undoubtedly due to impurities.

Resistance to Insulin. Diabetic patients exhibit very varying response to insulin, and some proportion of them require such large dosage as to lead to the idea of an undue resistance to its action. For example, Wiener reported the case of an elderly diabetic whose diabetes rapidly became severe, so that he was admitted to hospital in a pre-coma state and needed 3,250 units of insulin in twenty-four hours to prevent coma, subsequently requiring 440 units a day to establish his balance.

Resistance to insulin (in the sense of a lessened response to a definite dose) can be produced by a number of factors, which include infections, allergic reactions, coma with acidosis, hyperthyroidism, and hyperpituitarism (cf. Waters and Best).

Various explanations of the unusual insulin resistance encountered in some patients have been offered. To those who hold the wider view of the etiology of diabetes mellitus the presence in undue amount of an opposing hormone seems a plausible explanation. There is some degree of evidence to support it. Thus Glen

and Eaton, Boller *et al.* and de Wesselow and Griffiths have each reported that the blood of such patients contains a substance capable of inhibiting the action of insulin, though Dohan, and Himsworth and Kerr could not confirm this. Wayburn and Beckh have recently studied a case of this kind thoroughly, and report that a substance capable of elevating the blood sugar of rabbits was repeatedly demonstrated to be present in the patient's blood.

Himsworth (3) suggests that the ordinary patient who responds easily to insulin is suffering from a deficiency of insulin, while in the resistant type there is not a shortage of insulin, but an impairment of insulin action. Graham (2) does not accept Himsworth's view and inclines to the alternative explanation.

Pathology of the Islets in Diabetes Mellitus. Warren, from study of his own large amount of human material, and reports in the literature, draws a number of important conclusions. He finds that the most typical lesion is hyalinization, which involves the islets unequally ; some may be completely spared, and some but partly affected. Very rarely, the hyaline becomes calcified. This hyalinization may be considered as due to production of intercellular substance, by fibroblasts, and possibly by endothelial cells. As a result the islets are slowly destroyed or are separated from the blood capillaries by an impenetrable membrane, and a diabetes results, usually mild on account of the slow progression of the lesion.

The most frequent change is (slight) fibrosis. Lymphocytic infiltration around the islets is occasionally seen, and then usually in young persons. Warren associated it with severe diabetes.

While hydropic degeneration of the islets is an important lesion in experimental diabetes (in which it appears to be, not the result of injury, but of excessive functional strain), it is rare in human diabetes (present in only about 4 per cent. of Warren's series). Warren remarks that port-mortem change can produce a somewhat similar picture.

About a quarter of Warren's cases showed no demonstrable pathology of the islets. " Cases of diabetes absolutely identical with one another from the clinical standpoint show no evidence of structural disease in the islands of Langerhans in one instance, and show marked injury of various types in others."

Congenital hypoplasia of the islets is very rare. Warren found six cases in the literature, of which three were associated with diabetes. Of his 484 pancreases from diabetic patients, 95 showed an apparent appreciable decrease in the number of islets.

Prognosis in Diabetes. Except in rare cases resulting from infection, such as Schmitz's case referred to by Naunyn, and in certain cases of hyperpituitarism in which diabetes was present, complete recovery has so far not been recorded. There is no doubt that early treatment leads to marked improvement in degree of tolerance to carbohydrate.

Watson as hmade an interesting study of glycosuria in students, the results of which lead him to infer that diabetes in this age group progresses slowly through the stages diminished tolerance, diminished tolerance and assimilation, chemical diabetes, and finally clinical diabetes. He believes that if the progressive changes can be arrested by dietary treatment (restriction) sufficiently early, then carbohydrate tolerance can be restored to normal, and onset of clinical diabetes arrested, but that to maintain normal carbohydrate metabolism subsequently there must be continued restriction of diet to keep weight normal or subnormal.

It must be remembered, however, that a proportion of renal glycosurics show such decreased tolerance and only a few of these progress to diabetes (cf. p. 136).

The prognosis for length of life of the diabetic is steadily improving. This is strikingly exemplified by the records for Joslin's patients. Of deaths from diabetes between 1898 and 1914 only 1·8 per cent. were of patients who had suffered from the disease at least twenty years. In the period 1937–40 the figure had risen to 16·4 per cent. The average duration of life of all the deceased patients subsequent to the onset of their diabetes has steadily increased between 1898 and 1940 from 4·9 to 12·5 years, that of children less than ten years old at time of onset from 1·3 to 11·4 years, and of children between ten and nineteen years from 2·7 to 8 years. Introduction of protamine zinc insulin has improved the figures for the past few years, and since the proportion of survivors, especially of children, is now much greater, the above figures, good as they are, still partly mask the great increase in duration of life.

Wilder (2) considers the prognosis is governed by the following factors (*a*) early diagnosis in acute cases, (*b*) degree of severity of the diabetes, (*c*) age of the patient, (*d*) availability of effectiveness of insulin, (*e*) adequacy of diet, and (*f*) intercurrent complications. The outlook, in any but the milder cases, depends primarily on the effectiveness of treatment. If it be adequate (excluding, in older patients, accidents related to associated arteriosclerosis), Wilder thinks that life-expectancy ought to be as great as that of the normal population. The general healthiness of the individual should be normal. In most cases vigorous minds and sturdy

bodies are obtainable. Adults can pursue their usual occupations with customary energy, and children develop normally, attend school, and enjoy play.

However, the death rate of the diabetic is still much in excess of that of the general population.

Wallace has recently reviewed 70 cases of diabetes in childhood. Eighteen had died (the average duration of their diabetes was 2·3 years). The causes of death were coma (11), coma associated with some infection (4), uncomplicated infection (2), and prematurity and atresia of the pancreas (1). Of the 52 survivors carbohydrate tolerance had improved in 17, diminished in 26, and was unaltered in 9. The tolerance had diminished more frequently in the younger child (less than six years of age) than in older children.

Zisserman analysed the primary cause of death in 155 diabetics in one hospital. The results illustrate the difference between age and youth. Thirty-eight died between the ages of forty and forty-nine, 107 between fifty and sixty-nine. The listed causes of death were : gangrene of the leg, 33 ; myocardial degeneration, 18 ; cerebral vascular disease, 15 ; bronchopneumonia, 15 ; acute coronary occlusion, 8 ; lobar pneumonia, 7 ; diabetic coma, 6 ; nephritis with uraemia, 6. Cholelithiasis was present at autopsy in 27·6 per cent. of the cases, in contrast with 11 per cent. of general medical deaths.

Richardson and his colleagues have reviewed the progress of the disease as seen during ten or more years in 100 patients (69 over fifty years of age) controlled by insulin and measured diet. The diabetes does not always become more severe. It did not advance in 45 during a five-year period, while the insulin requirement actually lessened in 10. Neither the duration nor the severity of the diabetes influences the incidence of hypertension, infection, or ocular sclerosis, but prolonged diabetes appears to increase the incidence of deep retinal haemorrhage and exudate and superficial haemorrhage in the eyes. The hypertension in their cases was attributed to the earlier high-fat low-carbohydrate *régime*. The incidence of cardiac enlargement in the 38 hypertensive cases (all over fifty years) was about half that in non-diabetic hypertension. In patients under fifty years the incidence of cardiovascular disease was lower than that previously reported in diabetics. Arteriosclerotic occlusive disease of the lower extremities was present in 46 per cent. of the women and only 22 per cent. of the men.

Spuehler concludes from clinical and autopsy studies that about a third of all diabetics develops a gradually increasing benign high blood pressure, with corresponding progressive pathological arteriosclerosis of the kidneys. This conclusion does not accord with Richardson's.

Complications of Diabetes Mellitus. Joslin, writing in 1928, said, " The outstanding features of the diabetes of to-day are the prolongation of the lives of diabetic children and the replacement of coma by arteriosclerosis as the cause of death." Increased blood cholesterol has been suggested as one of the causes of arteriosclerosis (Aschoff) and as predisposing to diabetic gangrene (Wendt and Peck), and such hypercholesterolaemia has been

viewed as due to persistent use of a high fat diet (cf. Rabinowitch (2)), a view which has not met with complete acceptance.

Hypertension is a frequent accompaniment of diabetic arteriosclerosis, but all the characteristic vascular lesions of diabetes (retinal haemorrhages, coronary occlusion, gangrene) are found in diabetics with normal blood pressure as well as those with hypertension, though presence of hypertension increases the incidence of these lesions. Root and Sharkey, in reviewing a number of cases, conclude that premature and excessive development of vascular disease in the diabetic occurs predominantly in muscular arteries under the greatest physical strain, especially in obese patients, and is due to the metabolic changes of the diabetes itself, and probably to a disordered lipide metabolism. Hypertension is an important contributory factor since it imposes additional strain. They conclude further that insulin with modern dietary treatment is lessening the frequency of arteriosclerosis in the legs of children.

Arteriosclerosis is apparently responsible for neuritic symptoms (pain) in diabetes. Sandstead and Beams state that oral administration of sodium chloride relieves such pain.

Perhaps the neuritic symptoms are associated with the lowered phospholipide, cholesterol and cerebroside content of the nerves from diabetic patients, which Jordan and Randall believe is associated with arteriosclerosis in the diabetic. Jordan describes fully these neuritic manifestations.

Hepburn and Graham from heart studies on 123 cases of diabetes mellitus, fifty-six of which showed serious electrocardiographic abnormalities at the beginning of diabetic treatment, found that in a fairly large percentage the electrocardiograms returned to normal after the diabetic condition was controlled by treatment.

An atrophy of the subcutaneous fat at the sites of insulin injection has been reported in a number of cases. Avery, reviewing twenty-one of these cases, found no relation to insulin dosage, duration of treatment, or the original fat condition of the patient. He suggested that the effect was the result of undue local stimulation of carbohydrate metabolism, leading to local fat catabolism. No evidence affording an explanation has been found at autopsy (Price).

Lipohypertrophy resulting from use of insulin is much rarer. When it does occur, the patient is usually juvenile. There are only twenty cases in the literature (cf. Goldner).

Little need be said here concerning complications associated

with the diabetic surgical patient ; the general principles involved in such cases are now well understood.

Greene, Swanson and Jacobs claim that there is no relationship between the degree of hyperglycaemia and of glycosuria and the incidence of delayed healing of wounds, or of infection in originally clean wounds in diabetes mellitus. They find that delayed healing is about 4 per cent. more frequent in diabetic than in non-diabetic patients of the same age and sex, and think that possible causes are a lowered degree of utilization of glucose, and a greater degree of arteriosclerosis. Joslin and McClure, in appendices to this paper, commented sceptically.

Diabetic coma. Root has reviewed the cases occurring in Joslin's clinic between 1923 and 1944. Diabetic coma is an emergency due to acute insulin deficiency. It requires adequate and often large doses of insulin during the first three hours of treatment. During the years 1923–27 the dosage was only 83 units ; it was then gradually increased. Over the whole period 1923–40, there was a 12 per cent. mortality in 478 cases. During the period 1940–44, with the much increased administration of 216 units in the first three hours, in the 123 cases the mortality was only 1·6 per cent. Intravenous or subcutaneous injection of a large volume of isotonic sodium chloride is a useful aid to overcome shock and impending anuria, and to compensate for dehydration and loss of blood base. It can be given up to 10 or even 15 per cent. of the body weight.

Glucose is harmful, though its effect may be masked by that of insulin simultaneously given. Glucose will convert moderate coma into severe coma, while in advanced coma, whether given orally or by injection, it may cause anuria and death.

Elkes recently reported the case of a woman aged thirty-one, with no previous history of diabetes, who developed within forty-eight hours of air-raid shock an extreme hyperglycaemia, reaching 1·96 per cent. of glucose, and abrupt coma. Drastic insulin treatment led to recovery from the coma within three days, and the diabetes was subsequently easily balanced.

Retinopathy. A number of recent studies have been made of diabetic retinitis. Lee considered that there is scarcely ever any change in the ocular fundus of diabetic patients under forty years of age. " In the majority of cases of diabetic retinitis there was associated arteriosclerosis, hypertension, nephritis, or a combination of these, frequently combined with myocardial degeneration. (Cf. also White and Hassard.)

Anderson, on the other hand, stresses duration of the diabetes, rather than age of the patient, and finds that diabetic retinitis is

essentially a vascular disease and part of the generalized arteriosclerotic process common in diabetic patients who have had the disease for eight or more years. He considers that the best preventive treatment is correct diet and adequate insulin.

Bloch records two cases in young diabetics, both women, one aged twenty-six with a diabetes of seventeen years, and one aged thirty-seven with diabetes for fifteen years. Neither showed renal changes or abnormal blood pressure. O'Brien records 23 cases of retinopathy in 555 diabetics under thirty-one years of age.

O'Brien also remarks that diabetic cataract is fairly common in young patients (recording 36 cases in 260 patients under twenty-one years of age).

Lawrence (2) states that retinitis is extremely common in diabetics; probably about 15 per cent. show it, mostly elderly, and in many it is already established when diabetes is diagnosed. It occurs chiefly in long-standing uncontrolled mild cases. He is convinced that there is a true diabetic retinitis without arteriosclerosis or renal complicating factors. The first manifestations are punctate haemorrhages of venous origin (more typical than the arterial haemorrhages which may occur) deep in the retina; later light exudates occur almost anywhere, which, still later, become hard, white and thick, often edged with black pigment, and very different from renal manifestations. Once the process is established, it is checked but not cured by good diabetic control, though a few cases develop retinitis proliferans and go completely blind.

Lawrence has seen ten cases of retrobulbar neuritis, clinically indistinguishable from tobacco amblyopia, but four occurring in non-smokers were directly due to severe diabetes. Early and adequate diabetic treatment restores normal vision.

Diplopia is not uncommon, usually from VIth nerve neuritis, and mostly in elderly patients, who recover with adequate treatment.

He has noticed that curious focussing changes in accommodation are found present at some stage in most diabetics, if careful enquiry be made. They are transient.

Severe dehydration in precomatose conditions produces great water changes in the eyes, the *eye tension* becoming extremely low, and quite diagnostic of diabetic coma. Curious changes can be seen in the lens; the capsule looks wrinkled, and quite dark opacities can be seen with a + 15D lens of the ophthalmoscope. With correct treatment (insulin and fluids) these changes disappear and leave no permanent effects.

Acute cataracts occur in children and adolescents who have been badly controlled, and do not improve.

Rudy and Epstein, from a review of 100 cases existing over periods of from one to ten years, conclude that diabetic retinopathy is part of a generalized neurological disturbance, developing most frequently in

patients over fifty years of age, and associated with a deficiency of the B-complex vitamins. Prolonged therapy with these vitamins, with properly controlled hyperglycaemia, produces slow recovery.

Anderson points out that with the advent of a normal diet in the treatment of diabetes lipaemia retinalis is now very rare.

Pregnancy. The general consensus of opinion is that diabetes is more menacing to a pregnancy than is the pregnancy to the diabetes. Walker wrote as long ago as 1928 that, although diabetes must be considered as a serious complication of pregnancy, if the patient is treated with insulin and properly dieted there seems to be no special incidence of puerperal complications, and the pregnancy does not appear to have any ill-effects on the diabetic condition (cf. also McIlroy). Foetal mortality is not lessened by such insulin treatment (Skipper), and exact control of the pregnant diabetic is necessary to prevent undue demands on the islet tissue of the foetus (Duncan and Fetter). Potter and Adair quoted statistics in 1938 which indicated that while the use of insulin has markedly reduced maternal mortality, foetal mortality is still 30 to 40 per cent.

Priscilla White, writing in 1935, considered that prevention of the death and decay of the overripe foetus can be achieved by premature delivery by Caesarian section (cf. also Wilder). Writing in 1940, White and Hunt claim that abnormal rise of chorionic gonadotrophin in blood after the twentieth week of pregnancy leads in the diabetic to premature delivery, stillbirths, and neonatal deaths, which are preventable by continuous substitutional therapy with oestrogen (oestradiol or stilboestrol) and progesterone (or pregneninolone) in replacement doses. Caesarian section is favoured in this group of patients, normal delivery in those in whom the abnormal rise of the chorionic gonadotrophin does not occur.

Hurwitz criticized this view, and both White (4) and Joslin (3) replied to the criticism. (Cf. also Bigby and Jones.)

Barns recently reviewed twenty-five pregnancies in twenty-one diabetic patients of average age thirty-one years. He found that the incidence of late toxaemia of pregnancy was not much above normal, the prognosis of life was good, the pregnancy did not increase the severity of well-treated diabetes, but the prognosis for the foetus was poor (the foetal mortality was 44 per cent.). Insulin requirement was increased in 74 per cent. of the cases. He recommends administration of extra sugar to the newborn infant.

Mosenthal (2) has reviewed the whole subject, and concludes : (i) pregnancy accentuates an existing diabetes ; (ii) pregnancy

favours the development of diabetes in later years; (iii) the average age of diabetic mothers is older, and this is a predisposing factor in stillbirth; (iv) large amounts of thiamin (aneurin) are needed during pregnancy, and especially in the presence of diabetes; (v) the impression is growing that asphyxia of the infants of diabetic mothers is a frequent cause of neonatal death; (vi) it seems probable that Caesarian section should only be performed when there is an obstetrical implication sufficient in itself to call for Caesarian section; (vii) it seems probable that complete regulation of the diabetic from the very beginning of pregnancy will abolish all the complications of pregnancy to which mother and foetus are liable.

He points out that sudden and marked variations in the severity of the diabetes may occur, especially during the second and third trimesters, which may call for either more or less insulin; hence the diabetic should be regulated during this time every seven to ten days, and he remarks further that during labour most meticulous care should be taken to check acidosis and prevent hypoglycaemia in the mother. Occurrence of dangerous hypoglycaemia in the newborn can apparently be prevented by controlling the insulin administration to the mother.

Unusual Types of Diabetes. *Menopausal Diabetes.* Levy Simpson has stated that carbohydrate tolerance is usually somewhat decreased at the climacteric and can be restored to normal by administration of oestrone. Mazer and Israel treated three patients who developed diabetes at the menopause solely by use of at least 0·4 mg. of oestradiol benzoate every fourth day, no insulin being necessary.

Cantilo reports that in forty women at menopause or postmenopause who exhibited diabetes mellitus the carbohydrate disturbance remained unchanged with insulin and diet treatment, but was restored to normal with oestrone and progesterone in large dosage. Subsequently these patients apparently remained free from diabetes. Cantilo regards such diabetes as of pituitary type, and thinks that the beneficial effect of the therapy is produced by depression of pituitary function.

Young, however, finds that oestrogen treatment does not benefit experimental pituitary diabetes in the dog.

Diabetes Due to Tumour of the Adrenal Cortex. Sprague, Priestley and Dockety recently reported a case of diabetes mellitus of three years' duration. The female patient exhibited a fasting blood sugar varying at different times from 252 to 375

mg. per 100 c.c. No other endocrine manifestations were present. At operation a malignant (grade 2) adrenal cortical tumour was removed, of the size of a football, and weighing 1,550 gm. The blood sugar then fell steadily. On the third postoperative day the fasting value was 107 mg., on the fifth day 88 mg. All glycosuria ceased the day following operation. On the twenty-fifth postoperative day a sugar tolerance test was normal. The patient subsequently remained normal.

Diabetes Mellitus and Addison's Disease. While the literature shows several cases in which diabetes preceded Addison's disease or the two appeared simultaneously, Rhind and Wilson, and Thorn and Clinton have each reported a case in which the diabetes developed in a patient with pre-existing Addison's disease; in the second case the Addison's disease preceded the diabetes by four years.

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HYPERINSULINISM AND HYPOGLYCAEMIA

Harris observed in 1923 certain symptoms in non-diabetics which were identical with those resulting from overdosage of

insulin, and so coined the term *hyperinsulinism*. One such patient, a physician aged sixty, had a blood sugar of 0·065 per cent. His symptoms were relieved by administration of sugar. He died after four years of such treatment. A second patient, a labourer aged fifty-two, with similar low blood sugar and symptoms controllable by food, could still be controlled in this way after eight years of treatment.

Since Harris's early observations numerous cases of hyperinsulinism have been described in the literature. In addition, hypoglycaemia, and symptoms associated with it, may arise as a transient or a permanent condition from causes in no way associated with excess of insulin in the organism.

Very varied symptoms are associated with clinical hypoglycaemia, although marked cases exhibit a fairly definite syndrome comparable with the sequelae of removal of the liver in dogs, reported in Mann and Magath's classic experiments and with the symptoms observed in diabetic patients following overdosage with insulin. Most of the symptoms are probably traceable to disturbances originating in the central nervous system, due to the fact that it is peculiarly susceptible to glucose starvation from low blood sugar, since it has only a negligible store of glycogen.

Experimental evidence is becoming available that such brain starvation does actually occur (Dameshek *et al.*; Baudouin). It has been shown that chronic insulin intoxication in rabbits and dogs produces marked, though not specific, histological changes in brain tissue (Stief and Tokay; Grayzel) (compare Kerwin's case (p. 152). Malamud and Grosh trace such results to direct toxic action of insulin on brain tissue. In light of what we do know about the nature of insulin action, such a conclusion seems unwarranted.

Wauchope has published an excellent review of the subject. He lists the symptoms according to relative time of onset: (i) fatigue and lassitude, restlessness, malaise; (ii) (due to compensatory secretion of adrenine) pallor or occasional flushing, cold clammy perspiration, palpitation, tremor, often hunger or thirst, fear; (iii) senses clouded, with frequently behaviouristic resemblance to alcoholic intoxication, bravado, negativism, hallucination; (iv) convulsions and paralysis, with loss of memory; (v) coma; and in the extreme cases (vi) death.

Transitions from one stage to the next may be gradual or rapid. The attack can be completely aborted at any stage by administration of carbohydrate. It may be arrested at any stage even without treatment, and there seem to be no permanent ill-effects. But the hypoglycaemia tends to exhaust the glycogen stores and

so predisposes to another attack, and recurring attacks tend to be more severe.

In the severe attacks " The convulsion is usually over in from a few minutes to half an hour, and even without food the patient, dripping with sweat and saliva, becomes conscious. Recovery is complete, without memory of the accident." (Gammon and Tenery.)

Insulin shock therapy (cf. p. 175) has greatly helped in the study of *hypoglycaemic symptoms*. They are divisible into several groups of which the first (sweating, salivation, muscular relaxation, clouding of consciousness, etc.) appears while the blood sugar is falling, and the others (onset of coma and various primitive movements ; tonic spasm, torsion spasm ; extensor spasm ; shallow respiration, pale skin, pin point pupils, lowered temperature) appear successively at the low level of blood sugar. The order is invariable, and is due to the regions of the brain successively affected, the first being the cerebral hemispheres and parts of the cerebellum, these being the newest portion of the brain, in which metabolism is at the highest level and is therefore early affected by deficiency of glucose. The other regions affected are at successively lower metabolic levels. The fifth stage is dangerous, and calls for immediate administration of glucose ; if there be any further cerebral depression, recovery is not complete. (Cf. Frostig ; Himwich.)

Symptoms develop at variable levels of blood sugar. Extremes of 26 and 70 mg. per 100 c.c. have been reported. The precise values are of course complicated by the fact that many ordinary methods of estimation give too high values for glucose by from 10 to 20 mg. It has even been reported that the " true " sugar value in rabbit's blood at the incidence of insulin convulsions is zero (Dotti). Wauchope, using what I have elsewhere termed " enhanced-glucose " values, considers as approximately correct generalizations : normal fasting value 100 mg. per 100 c.c. blood ; initial symptoms 80 mg. ; severe symptoms 50 to 45 mg. ; death at about 25 mg. Some of these values are almost certainly too high, even for " enhanced-glucose."

There is evidence, not yet quite convincing, that symptoms can occur in some cases associated with a marked sudden fall of blood sugar level, rather than a fall to a specifically low level (Wauchope ; Sunderman *et al.*). Such cases, if they do occur, are rare.

The fasting blood sugar level of the hypoglycaemic patient is often below normal. However, a glucose tolerance curve may be normal for the first three hours (or may even show an undue rise at the end of one hour) ; at the fifth and sixth hours such curves often drop to low levels.

A low fasting blood sugar in itself does not signify hypoglycaemia. This is well exemplified by the study of Hart and Lisa of 21,000 routine fasting blood sugars determined in one hospital. They were all estimated by the Folin-Wu method, which gives slightly "enhanced" values. In 2,371 instances the value was below 80 mg. per 100 c.c. blood. These were distributed as follows: 1,620 (7·7 per cent.) were between 70 and 79 mg.; 493 (2·3 per cent.) between 60 and 69 mg.; 166 (0·8 per cent.) between 50 and 59 mg.; 74 (0·34 per cent.) between 40 and 49 mg.; 12 (0·06 per cent.) between 30 and 39 mg.; and 6 below 30 mg. In only one case was the patient in hypoglycaemic convulsions at the time blood was taken. These cases belonged to no special disease group. In only 19 cases were conditions present usually considered to be associated with hypoglycaemia. These included 7 cases of malnutrition, 4 of epilepsy, and 3 of probable hyperinsulinism. Hart and Lisa conclude: "Either spontaneous hypoglycaemia is not a common condition or routine fasting blood sugars are not reliable guides to its occurrence."

In many cases of hypoglycaemia the causative factor cannot yet be definitely stated. It seems therefore better at present to undertake no rigid classification, and the cases will only roughly be subdivided into (i) those of true hyperinsulinism, associated with tumour of the islets, either benign or malignant, (ii) cases not associated with hyperinsulinism, and (iii) cases in which the cause of the hypoglycaemia is uncertain.

Hypoglycaemia of such types has been termed "spontaneous," as contrasted with that induced by overdosage of injected insulin.

Cases Associated with Tumour of the Islets. The first definite case was reported by Wilder, Allan, Power, and Robinson in 1927. The patient exhibited marked hypoglycaemia. His condition was inoperable and became progressively worse until half-hourly doses of glucose were necessary to prevent convulsions. Blood sugar analyses included figures below 0·03 per cent. Post-mortem examination revealed a carcinoma of an islet with metastases in the liver. An extract of these carcinomatous metastatic nodules was made; injected into an animal, it produced insulin action. A similar case has very recently been reported from the same clinic (Power, Cragg and Linden), in which also an extract of the liver metastases produced an insulin-like effect. Similar cases have been reported elsewhere (*e.g.*, Lemaire; Thalhimer and Murphey) though without biochemical examination of the metastases. Such cases demonstrate the fact, now becoming well recognized, that malignant tumours of an endocrine tissue function by producing the endocrine principle of that tissue, so that hyperactivity results.

Howland, Campbell, Maltby and Robinson reported a case in which the patient exhibited convulsions and coma associated with hypoglycaemia. They operated and removed a small carcinoma arising from islet tissue. The convulsive attacks and the hypoglycaemia disappeared. Breslin reported in 1945 that this patient was still alive fifteen years after the operation.

McClenahan and Norris described similar symptoms in a negro ; the condition proceeded to fatal termination ; at autopsy an adenoma was found originating in islet tissue. In numerous other

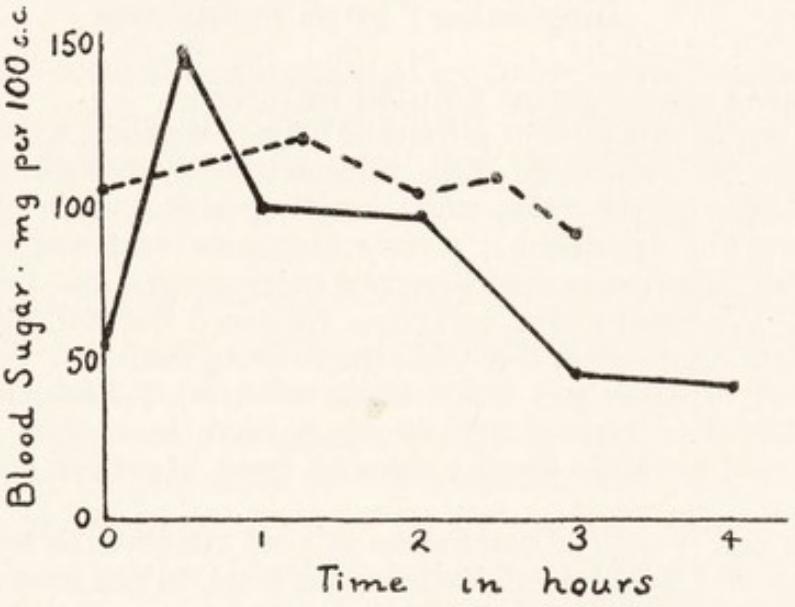

FIG. 26. Hyperinsulinism. The continuous line represents blood sugar values after administration of 50 grams of glucose. Prior to the test the patient had been fed a high carbohydrate diet for a week, while food was withheld for twelve hours immediately prior to the sugar meal. At subsequent operation a small adenoma of an islet of Langerhans was removed. The dotted line represents a similar sugar tolerance curve taken six months later. (After Fraser, Maclay and Mann, Quart. J. Med., 1938, vii, 115.)

cases operation has given complete relief. The tumours are more frequently benign than malignant, though Judd and Rynearson consider them to be either malignant or pre-malignant, and Keating and Wilder, on account of this tendency to malignancy and metastasis, advise operation.

Fig. 26 shows sugar tolerance curves before and after removal of an islet adenoma.

Multiple islet adenomata are sometimes present (cf. Whipple and Frantz ; Kerwin, Conn and Conn).

Frantz in 1940 listed 96 cases of tumours of islet tissue found at operation or at autopsy. Meyer, Amtman and Perlman in 1941 found in the literature 71 cases in which the diagnosis was made pre-operatively, and confirmed at operation, and added another. Their analysis of these cases is interesting :

Benign adenoma :	Successfully removed	38
	Removed without remission of symptoms	1
	Patient died postoperatively . .	8
Malignant tumour :	Successfully removed	16
	Patient died postoperatively . .	4
	Inoperable ; gross metastases . .	5

The following cases present unusual features :—

Ballinger reported a case of a man of fifty-five years, who at exploratory operation was found to have tumour masses involving the liver, pressing on the portal vein, and invading the lungs. The patient recovered from this operation. A liver functional test was normal. His hypoglycaemic symptoms steadily grew more severe and he died a few weeks later. At autopsy the pancreas appeared normal, save for some apparently enlarged islets, but metastases were found in almost all the other internal organs, and since these resembled islet tissue it was concluded that the original tumour must have been that in the liver (which included necrotic tissue) derived from aberrant islet tissue in the liver.

Flinn reported a case of carcinoma of islet tissue with metastases to the liver, which at autopsy showed that at least 50 per cent. of the liver tissue was replaced by islet cell tissue.

Kerwin reported an acute case of fatal hyperinsulinism due to multiple islet cell tumours. The patient passed into continuing coma eight days after onset of the first symptoms, and died eight days later. The diagnosis was missed because the patient did not respond to administration of glucose. The islet tumours contained 30 units of insulin per gm. tissue. The brain showed congestion, oedema, haemorrhage, and nerve cell degeneration in mild degree.

(Klein and Ligternik have reported two unusual cases of cerebral damage, one following insulin shock therapy, the other in a case of diabetes markedly sensitive to insulin. The abnormal sequelae began with a prolonged state of coma, of three and of six days respectively. In the first case most of the intellectual functions were regained, but infantile behaviour persisted. In the second case rational thinking and reasoned action were not regained.)

Malignant islet tumour is not always associated with hyperinsulinism. Sailer and Zinninger have reported the case of a woman aged forty-eight, with a history of symptons during the previous two or three years like those of duodenal ulcer. At operation a malignant islet cell tumour was removed. At no time had there been hypoglycaemic symptons, while glucose

tolerance tests had been normal. Subsequently there was local recurrence with metastases.

Conn and Conn carried out detailed preoperative and post-operative metabolic studies on a woman aged fifty-nine, who was found at operation to have three islet adenomas, which were successfully removed. The studies led to the following conclusions :

There was an over-combustion of carbohydrate, both in the postprandial and postabsorptive state, very marked on a normal diet. After removal of the tumours, the rate of carbohydrate combustion became normal, whence it may be concluded that in hyperinsulinism there is a continuous excessive secretion of insulin.

When the rate of combustion of carbohydrate had been depressed to normal level by low carbohydrate intake, the continuing post-absorptive hypoglycaemia was due to excessive inhibition of hepatic glycogenolysis (the liver actually contained much glycogen).

Variations in the antecedent diet affected the glucose tolerance curve, but to a lesser degree than with normal persons.

Daily injection of adrenaline was a useful adjunct for the hyperglycaemia which it produced, which was not accompanied by increased combustion of sugar, while the excessive inhibition of hepatic glycogenolysis was partly counteracted.

Adrenal cortical extract in relatively large doses produced no anti-insulin effect, and its clinical use as an antagonist to insulin is impracticable.

Hypoglycaemia not Associated with Hyperinsulinism. The second most important cause of a recurrent hypoglycaemia is *liver deficiency*. The prime factor here is inability to store sufficient glycogen as a carbohydrate reserve.

In 1929 Nadler and Wolfer reported a case exhibiting marked hypoglycaemia and convulsions ; at subsequent autopsy the liver was found to be riddled with carcinoma. Crawford reported a case of a negro with primary carcinoma of the liver ; his blood sugar showed marked fluctuations ; he frequently passed into coma with a blood sugar of 0·025 per cent. His sugar tolerance curve was normal in type but depressed ; the maximum reached after ingestion of 100 grams of glucose was only 0·10 per cent.

Judd *et al.* have reported two cases of marked spontaneous hypoglycaemia associated with decrease of hepatic function and a cirrhotic condition of the liver.

In milder degree liver deficiency seems responsible for hypo-

glycaemia associated with "recurrent vomiting" in children, through some degree of fatty degeneration (Josephs), or with phosphorus poisoning (McIntosh), or with acute yellow atrophy of the liver (Feigl and Luce), or in chloroform poisoning in dogs (Bodansky). Lowered blood sugar also occurs along with parenchymatous changes in the liver caused by arsphenamine, by hydrazine, or by the fungus *Agaricus bulbosus* (Philipps). The occasional cases of hypoglycaemia seen in pernicious vomiting of pregnancy (Cammidge) are also probably traceable to undue depletion of liver glycogen during the pregnant state.

Hypoglycaemia of Uncertain Cause. (*a*) *Hypoglycaemia Possibly Associated with Hyperplasia of Islet Tissue.* In a number of cases, where exploration did not reveal a tumour, resection of a portion of the pancreas has been performed, in belief that hyperplasia of the islets was responsible for the hypoglycaemia. Overactivity of the islets due to hyperplasia is difficult to demonstrate, and the earlier surgical efforts were not definitely beneficial. More recently, in cases in which the greater part of the pancreas has been removed, sugar tolerance was undoubtedly improved (cf. Graham and Hartman ; Berry).

In this connection it is interesting to note that in at least 2 cases of hyperinsulinism due to islet cell adenoma which could not be found by exploration, total pancreatectomy has been performed with apparent benefit ; only moderate insulin dosage (30 units daily) was subsequently needed (Waugh *et al.*).

(*b*) *Hypoglycaemia in Young Children.* Gray and Feemster reported in 1926 the case of a premature child born of a diabetic mother, which exhibited somewhat low blood sugar and died on the third day. Autopsy showed apparent hypertrophy and hyperplasia of the islets. In a similar case Randell and Rynearson removed a living child by Caesarean section, and kept it alive by sugar administration. At birth the mother's blood sugar was 0·28 per cent., that of blood from the umbilical cord was 0·19 per cent., and that of the baby's blood 0·04 per cent.

Hartman and Jaudon have reviewed 286 cases of hypoglycaemia in the St. Louis Children's Hospital over a fifteen-year period, and draw the following conclusions : Hypoglycaemia not infrequently occurs in normal new-born infants during the first four or five days of life, and in them seems to be due to an imperfectly developed regulatory mechanism which creates a state of relative hyperinsulinism. At the same period the children of diabetic mothers may show a more severe condition, with, sometimes, development of convulsions and collapse. This is probably due to increased

physiological hyperactivity of the islets (from the hyperglycaemic maternal stimulus) rather than to hypertrophy or hyperplasia. It can be controlled in emergency by adrenaline or intravenous glucose, with the prophylactic use of supplemental milk and carbohydrate feeding immediately after birth. The natural tendency to hypoglycaemia in the newborn is intensified by adrenal or intercranial haemorrhage.

During the first few hours of life the blood sugar concentration of normal infants fluctuates greatly. Immediately after the cord is cut it falls to between 30 and 60 mg. per cent. (without signs of hypoglycaemic shock) and then rises above normal, only adjusting in some days to normal levels (Zondek and Wolfsohn).

On the other hand, a case of pregnancy complicated by hyperinsulinism in the mother has been reported (Le Winn), in which the child was apparently normal (while the pregnancy reduced the sugar tolerance of the mother).

Rector and Jennings, from a study of eleven cases, consider that the rare occurrence in children of hypoglycaemia with recurrent convulsive manifestations is usually found between the ages of one and three years, and is due to a functional hepatic disorder of intermittent character, associated with a temporary depletion of the glycogen reserve, and in most cases is amenable to conservative treatment. Intravenous glucose abolishes the convulsions and a diet high in carbohydrate prevents their recurrence. (Graham and Hartman's case, a girl only twelve months old, exhibiting only 18 mg. per cent. capillary blood sugar, and benefiting from resection of most of the pancreas, would seem to indicate that not all hypoglycaemias in this age group derive their hypoglycaemia from the same cause.)

(*c*) *Hypoglycaemia Associated with Various Conditions.* Hypoglycaemia, sometimes sufficiently recurrent to produce persistent symptoms, has been associated with severe burns (Greenwald and Eliasberg), premature labour (Petterson), adrenal insufficiency, including Addison's disease (Anderson ; Rabinowitch and Barden), pituitary tumours (J. Wilder), menstruation (Harris), chronic infections, recurrent bilious attacks, neurasthenia, etc. (Cammidge, Erklentz).

The hypoglycaemia in Addison's disease is slight. That which sometimes occurs in hypopituitary conditions is usually not accompanied by symptoms, but Mogensen has reported typical spontaneous hypoglycaemia in a case of Simmonds' disease. In von Gierke's disease the hypoglycaemia is symptomless, and

symptomless hypoglycaemia may also be present in myxœdema (Wauchope).

Hypoglycaemic symptoms have been reported in a nursing mother; the symptoms disappeared on weaning (Stenström). Widmark found that there is a fall of blood sugar during the milking of cows, and during lactation of healthy women. It has been suggested that the physical exhaustion of Marathon runners is due to the hypoglycaemia which certainly is present in some of them (Levine, Gordon and Derick).

An association between anginal pain and hypoglycaemia seems possible; Sippe published a study of five cases which he regarded as hypoglycaemic angina of the cardiac type. In such cases effort produces precordial pain and a feeling of exhaustion, both relieved by rest. The pain and exhaustion may occur some time after the exertion (and not immediately as in angina pectoris).

In cases of renal glycosuria, especially with very low kidney threshold, the extra loss of sugar resulting from this can apparently sometimes lead to hypoglycaemic symptoms (Wauchope), which become more definite if carbohydrate intake is restricted (Wilder).

Association of Hypoglycaemia with Abnormal Mental States. Shih-Hao and Hisao-Chien, in reporting a case with symptoms of insulin shock, suggested the desirability of determining blood sugar values in hysterical attacks, since some of these might possibly be due to hypoglycaemia.

Of a number of cases of chronic hypoglycaemia reported by Cammidge, seven exhibited convulsive attacks. Of these four had been believed to be mild epileptics, two had been diagnosed as cases of Ménière's disease, and one had been reported as a victim of secret alcoholic excess, although actually a total abstainer. Their inco-ordination was abolished by raising their blood sugar. Roth has reported three cases exhibiting severe hysterical attacks; one progressed to an epileptiform state, which proved to be due to hypoglycaemia. McGovern's case showed frequent attacks of amnesia and coma, often accompanied by convulsions of epileptoid type. During the convulsions the blood sugar fell to 0·03 per cent. Treatment with carbohydrate every hour warded off attacks for a period of eighteen months.

Of particular significance is the psychiatrist's report in a case reported by Finney: "If it were not for the fact that there is a very striking lowering of the blood sugar, and that the taking of carbohydrate aborts the attack, my feeling would be that these attacks were certainly hysterical." The possibility that hysterical conditions of varying degree may be due to hypoglycaemia

(whatever the cause of that hypoglycaemia) cannot be lightly disregarded.

A case with visual hallucinations and mild but definite catatonia has been reported by Greenwood. Gray and Burtness stress headache, often of the migrainous type, as a condition associated with a blood sugar level between 60 and 90 mg. per 100 c.c. Such headache is completely or partly relieved by frequent carbohydrate meals and has been reproduced by induced hypoglycaemia.

Gilmour and Walton have reported a case of islet adenoma, verified at operation, in which the symptoms were first thought due to an intercranial lesion, a view supported by the findings of a ventriculogram and raised globulin content of the cerebrospinal fluid.

Aitken drew attention to marked residual mental deterioration occasionally noted after operation, and possibly due to prolonged malnutrition of brain tissue (cf. p. 162).

That the neurological manifestations of hypoglycaemia are due to complex factors of which the hypoglycaemia is but one is suggested by the observation of Hrubetz that administration of phenobarbital along with insulin to rabbits prevents development of convulsions, although the hypoglycaemia is produced as usual.

Wilder stresses the occurrence of a nervous hypoglycaemia. The patient is emotionally unstable. He may be hungry and weak at meal times, but, if no meal is taken, the hunger and weakness disappear in an hour or two. Moreover, the morning fasting blood sugar is not abnormally low.

Hill and Sargant have reported an investigation of a young man charged with matricide, who had an abnormal personality associated with a tendency to hypoglycaemia (not due to hyperinsulinism), and on whom, presumably as the result of this investigation, the verdict was "guilty but insane." Apparently in this case hypoglycaemic symptoms might set in with but a very slight degree of lowering of the level of blood sugar.

Differential Diagnosis of the Cause of a Hypoglycaemia. Wilder considers that with a good history and careful examination cases of hypoglycaemia which depend on disease of organs other than the pancreas can usually be properly diagnosed. The difficult task is to distinguish between nervous hypoglycaemia and true hyperinsulinism.

Whipple (quoted by Wilder) uses three criteria for hyperinsulinism, (i) a postabsorptive blood sugar level of less than 0·050 gm. per 100 c.c., (ii) symptomatic attacks of hypoglycaemia

which occur only when the patient is fasting, and (iii) relief of the hypoglycaemic symptoms by administration of glucose, preferably intravenously and without the patient's knowledge of what is injected.

The Mayo Clinic, according to Wilder, employs three somewhat similar criteria : (i) Normal health and evidence of stability of the autonomic nervous system prior to the first episode of hypoglycaemia ; (ii) postabsorptive levels of blood sugar less than 0·060 gm. per 100 c.c. ; (iii) intolerance to the fasting state (especially before breakfast).

If these conditions be present hyperinsulinism is considered probable and operation desirable.

Wilder considers the glucose tolerance test of little value in the diagnosis of hyperinsulinism, and results from injection of adrenaline unreliable.

Gray and Burtness have suggested an " insulin tolerance test " for hypoglycaemia, in which after a twelve to sixteen hours' fast intravenous injection of 0·01 unit of insulin per kg. body-weight is given. This idea is based on Collip's concept that the effect of parenteral administration of any endocrine principle is inversely proportional to its concentration in the body and thus theoretically applies only to cases of hyperinsulinism, and not to all cases of hypoglycaemia. The authors claim that diabetic patients show a greater fall of blood sugar below the fasting value then do normal persons, and hypoglycaemic patients a lesser fall than normal. They state that patients experience no discomfort during this test. From a few tests carried out under my direction I am unable to corroborate the last statement. Fraser supports the test. Baudouin states that injection of insulin into myxoedematous patients gives curves of the hypoglycaemic type, which are changed to normal type by thyroid administration.

Treatment of Hypoglycaemia. If the comparatively rare hyperinsulinism is diagnosed, then, because of the danger of ultimate malignancy (cf. p. 165), operation seems desirable. If, at successful operation, benign islet tumour is found and removed, a permanent cure is probably achieved. The possibility of multiple adenomata should be remembered, although they are rare.

Dietary treatment of cases of tumour can only be palliative, but where tumour can be excluded, dietary treatment of the hypoglycaemic condition must be depended on. This especially applies to the commoner nervous type.

Early treatment advocated increasing the carbohydrate in the diet, and increasing the number of meals. Later a high fat diet

was advocated, with the idea of depressing insulin function (cf. p. 142). Still more recently a high protein diet is being used, since gluconeogenesis from protein is a slow, steady process. The Mayo Clinic *régime* uses a normal diet except that protein intake is increased to 2 gm. per kg. body-weight per day. Patients are warned to curtail physical exertion, or to protect themselves with additional food (cf. Wilder).

Abrahamson suggests that there may be a reciprocal relationship between bronchial asthma and diabetes mellitus ; in asthmatic attacks there is a tendency to hypoglycaemia. Treatment of asthmatic patients with low-carbohydrate high-fat diet and frequent small meals gives marked benefit. He admits that not all patients with hyperinsulinism have asthma.

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The Use of Insulin in Non-diabetic Conditions

Glucose-insulin therapy is of proved benefit in numerous non-diabetic conditions, through the stimulation of appetite induced by insulin. Some of the claims presented in the literature undoubtedly require confirmation.

Excellent results have been obtained with non-diabetic tuberculous patients, the majority of whom, even in severe cases, show increase of appetite and gain of weight and strength (cf. Allen ; Banyai and Jurgens). Many cases of malnutrition have benefited (cf. Metz ; Short), but Freyberg thinks the benefit is due to suggestion. It is of

benefit in congestive heart failure and especially with patients with intractable angina pectoris. The opinion has been advanced that anginal pain is related to faulty carbohydrate metabolism in heart muscle, which is corrected by the insulin (Smith ; cf. however, the association of anginal pain with hypoglycaemia, p. 170).

Insulin promotes the fattening of chronically thin people to optimal weight. A dose of, at maximum, 10 units, given thrice daily twenty to thirty minutes before meals, leads to rapid gain of weight, increased well-being and less nervousness, and thus acts as an admirable tonic. The gain in weight is demonstrably due to actual increase in fat deposits, the fat cells becoming enlarged (Blotner).

Insulin-glucose is of value in combating acidosis, recurrent vomiting and acute intestinal intoxication in children (Gillespie), and the acidosis developing in prolonged narcosis produced for therapeutic purposes in certain types of mental disease (Quastel and Ström-Olsen). It is said to be a useful adjunct in the treatment of drug addition (Braun ; Chen) and peptic ulcer (Jones). Good results in coeliac disease have been claimed by several writers (cf. White).

In 1935 Sakel published his method of treating cases of schizophrenia by repeatedly introducing hypoglycaemia to the stage of convulsions by injections of insulin. Very many papers have appeared during the past four years, dealing with Sakel's method. The general conclusions seem to be that the treatment is distinctly beneficial, although the degree of persistence of the cure and the extent to which it exceeds spontaneous remissions still need careful evaluation. It definitely decreases the period of hospitalization (cf. James *et al.* ; Conwell and Karth). Protamine zinc insulin is relatively inefficient for such treatment (Goldman).

Recently several papers have drawn attention to undesirable results following insulin shock therapy. The case of Klein and Ligternik has been mentioned (p. 166). Proctor and Easton have reported a case of prolonged severe coma. Weil has reported the case of a twenty-year-old male in good physical health, who, shortly after the termination of a hypoglycaemic state, suffered from an acute cardio-vascular collapse which was followed by apparent cessation of heart action. The patient was resuscitated by two intracardiac injections of adrenaline.

Robinson has reported good results in six out of nine cases of acute alcoholic psychosis, achieved by similar shock treatment.

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CHAPTER VI

THE STEROID HORMONES AND RELATED COMPOUNDS

SINCE the hormones of the adrenal cortex and the gonads (including that of the corpus luteum) are closely related chemically, since at least one hormone, progesterone, is elaborated by two glands (corpus luteum and adrenal cortex), and since the precise source of several of the excreted products, including some with endocrine activity, is not yet determined, it is convenient to list all the more important of these compounds before considering the glands which produce them.

Reichstein and Shoppee list 28 compounds which have been isolated from the adrenal cortex. Few of these possess physiological activity. Selye, in his recently published "Encyclopedia," lists nearly sixty steroids stated to have been isolated from the adrenal cortex, or the gonads, or urine of various species of animals, non-pregnant or pregnant, normal or pathological, or human placenta; frequently a compound has been obtained from several sources. Other such compounds will almost certainly be isolated.

The majority are undoubtedly either degradation products of hormones, or intermediate compounds or bye-products produced during the formation of hormones.

Only the apparently more important compounds are listed in this chapter. These include those which definitely possess physiological activity, or excretory products of definite metabolic interest. In addition one or two synthetic compounds with physiological activity are included, and certain related sterols and vitamins, to illustrate their relationship to the steroids.

The constitutional formulae of those compounds marked with an asterisk will be found at the end of the chapter.

The androgenic and progestational compounds and their derivatives are all derivatives of androstane (whose formula is shown), and many of the compounds from the adrenal cortex can be regarded as derived from *allo*-pregnane (whose formula shows the conventional numbering of the carbon atoms). The oestrogenic compounds can similarly be regarded as derived from oestratriene (see its formula).

By convention it is understood that when valency bonds to hydrogen atoms or hydroxyl groups are given in continuous line, they are regarded as above the plane of the ring concerned, and when such valency bonds are represented by dotted lines, the hydrogen or hydroxyl is regarded as below the plane of that ring. Whenever hydroxyl groups replace one of two hydrogen atoms linked to one carbon atom, two stereoisomers are possible. The indices α and β are employed to indicate two isomers in which the hydroxyl groups are respectively below and above the plane of the ring.

Hydroxy (alcoholic) and ketone groups in the compounds are designated by the suffixes "-ol" and "-one," preceded by the number

of the carbon atom to which they are attached. Numbers following the sign Δ indicate the position of double bonds. Where the linkage is between carbon atoms not consecutively numbered, both numbers are given.

In each sub-division of the following list the compounds are arranged in alphabetical order. The common name at present in use, where there is one, is given first. For purposes of reference a number of the earlier names or terms applied to these compounds are given separately, in parentheses, with cross-references.

Sterols

**Cholesterol*, $C_{27}H_{46}O$, a compound of great metabolic importance, can be regarded theoretically as, and is probably actually the parent substance in the organism of cholic acids of the bile, of vitamin D_3 (through dehydrocholesterol) and of the hormones and other steroids of the adrenal cortex and gonads. There is now some evidence in support of this view. When cholesterol "labelled" by incorporating in it deuterium (heavy hydrogen) was fed to dogs, the cholic acid in the bile subsequently contained deuterium (Bloch, Berg, and Rittenburg). When such deuterio-cholesterol was fed a woman in the eighth month of pregnancy the pregnanediol glycuronide from her urine contained such a proportion of deuterium as to indicate that most of such pregnanediol was derived from cholesterol (Bloch). Cholesterol can be synthetized in the mammalian organism, but is at least partly obtained from food of the diet.

**Stigmasterol*, $C_{29}H_{48}O$, obtained from soya bean oil, is valuable as the parent substance used in the commercial preparation of progesterone.

**Ergosterol*, $C_{28}H_{44}O$, obtained from ergot, when irradiated, yields a mixture of compounds from which calciferol has been isolated.

Vitamins, etc.

Vitamin D_3, $C_{27}H_{43}OH$, the naturally occurring vitamin, has been obtained from tuna oil, and prepared from cholesterol.

**Vitamin D_2, calciferol*, $C_{28}H_{43}OH$, has been isolated from the irradiated products of ergosterol.

**Dihydrotachysterol* (A.T.10), $C_{28}H_{45}OH$, is prepared from tachysterol, another irradiation product of ergosterol, and has properties intermediate between those of vitamin D and the parathyroid hormone (cf. p. 102).

Steroids

(*A*) *Androstane derivatives.*

("A" (Wintersteiner), see allo-pregnanolone.)

**Adrenosterone*, $C_{19}H_{24}O_3$, is Δ^4-androstene-3, 11, 17-trione, and a 17-keto-steroid. It has been isolated from the adrenal cortex and has slight androgenic properties.

Aetio-cholane-3(α)-ol-17-one, or 3-α-hydroxy-aetio-cholane-17-one, $C_{19}H_{30}O_2$, is an inert compound, present in normal human male and female urine, and in that from cases of virilism.

Allopregnanediol, or allopregnane-3(β)-20-(α)-diol, or 17(α)-[1(α)-ethyl]-androstane-3(β)-ol, $C_{21}H_{36}O_2$, is an inert compound which has been isolated from bull's urine and the urine of pregnant women, mares and cows.

Allo-pregnanolone, $C_{21}H_{34}O_2$, is 17(α)-[1-ketoethyl]-androstane-3(β)-ol. It has been isolated from ox adrenals, sow ovaries, and the urine of the pregnant woman, mare and sow. It has very slight oestrogenic activity. It is precipitated by digitonin.

Androstane-3(β)-11(?)-*diol*-17-*one*, $C_{19}H_{30}O_3$, has been isolated from the adrenals and is a 17-keto-steroid. It has very slight androgenic activity.

**Androstane*-3, 17-*dione*, $C_{19}H_{28}O_2$, a 17-keto-steroid, has been isolated from the testes of the pig. It has slight androgenic activity.

*Δ^{11}-*Androstene*-3(α)-*ol*-17-*one*, $C_{19}H_{28}O_2$, a 17-keto-steroid, has been isolated from the urine of a patient with an adrenal cortical tumour. It is inactive.

$\Delta^{3,5}$-*Androstadiene*-17-*one*, $C_{19}H_{26}O$, has been isolated from urine of cases of Cushing's syndrome. It is very slightly androgenic. Selye suggests that it may be an artefact.

**Androstenedione*, or Δ^4-androstene-3, 17-dione, $C_{19}H_{26}O_2$, a 17-keto-steroid, has been isolated from the adrenals, and is slightly androgenic.

**Androsterone* (cis-androsterone), or androstane-3(α)-ol-17-one, $C_{19}H_{30}O_2$, a 17-keto-steroid, has been isolated from male and female human urine, from the urine of the pregnant woman and pregnant cow, from that of the bull, of human castrates (of both sexes), of the ox, of hysterectomized women, of women with adrenal tumour, and (as the sodium sulphate ester) from urine of a patient with a Leydig cell tumour. It possesses marked androgenic activity. It is not precipitated by digitonin.

(" *B* " (Kendall), see corticosterone.)

**Corticosterone*, $C_{21}H_{30}O_4$, Kendall's " B " compound and Reichstein's " H " compound, is Δ^4-pregnene-11, 21-diol-3, 20-dione, or 17(α)-[1-keto-2-hydroxyethyl]-Δ^4-androstene-3-one-11(β)-ol. It has been isolated from the adrenals and has marked corticoid activity.

11-*Dehydrocorticosterone*, Δ^4-pregnene-21-ol-3, 11, 20-trione, $C_{21}H_{28}O_4$, is Kendall's " A " compound, and has been isolated from the adrenal cortex. It is corticosterone, with a keto- instead of an alcohol group at C^{11}. It possesses corticoid activity.

**Dehydro-iso-androsterone* (dehydro-androsterone, transdehydro-androsterone), $C_{19}H_{28}O_2$, is Δ^5-androstene-3(β)-ol-17-one, a 17-keto-steroid. It has been isolated from normal human urine of both sexes, urine of human castrates (both sexes), urine of patients with an adrenal tumour and Cushing's syndrome, urine of the cow, the ox, and the pregnant mare. It has androgenic, and very slight oestrogenic properties.

**Desoxycorticosterone*, 11-desoxycorticosterone, 21-hydroxy-progesterone, Reichstein's " Q " compound, is Δ^4-pregnene-21-ol-3, 20-dione, or 17(α)-[1-keto-2-hydroxyethyl]-Δ^4-androstene-3-one, $C_{21}H_{30}O_2$, and has been isolated from the adrenals. It has marked corticoid activity, and slight progestational, oestrogenic, and androgenic activity.

(" *E* " (Kendall), see 17-hydroxy-11-dehydrocorticosterone.)

(" *F* " (Kendall), see 17-hydroxy-corticosterone.)

(" *Fa* " (Reichstein), see 17-hydroxy-11-dehydrocorticosterone.)

(" *G* " (Reichstein), see adrenosterone.)

(" *H* " (Reichstein), see corticosterone.)

17-*Hydroxycorticosterone*, Kendall's " F " and Reichstein's " M " compound, $C_{21}H_{30}O_4$, is 17(α)-[1-keto-2-hydroxyethyl]-Δ^4 androstene-3-one-11(β), 17(β)-diol. It has been isolated from the adrenals and has marked corticoid activity.

17-*Hydroxy*-11-*dehydrocorticosterone*, Kendall's " E " and Reichstein's " Fa " compound, $C_{21}H_{28}O_5$, is 17(α)-[-1-keto-2-hydroxyethyl]-Δ^4 androstene-3, 11-dione-17(β)-ol. It has been isolated from the adrenals and has corticoid activity.

**Isoandrosterone* (transandrosterone), $C_{19}H_{30}O_2$, is androstane-3(β)-ol-17-one, a 17-ketosteroid. It has been isolated from male and female human urine, and has slight androgenic activity. It is precipitated by digitonin.

(*Luteosterone A*, see allo-pregnanolone.)

(" *M* " (Reichstein), see 17-hydroxycorticosterone.)

(" *N* " (Reichstein) is allopregnane-3, 21-diol-11, 20-dione, inert.)

**Pregnanediol* (or pregnanediol-3(α), 20(α), or 3 (trans) dihydroxy-pregnane), $C_{21}H_{36}O_2$, is 17-(α)-[1(α)-hydroxyethyl]-aetio-cholane-3(α)-ol. It has been obtained from urine of the pregnant woman, cow, mare, sow and monkey, from urine of the bull, the ox, and human castrates (both sexes). From urine of both pregnant and non-pregnant women it has been obtained as the sodium glycuronide. It is physiologically inactive.

**Pregnane*-3, 17, 20-*triol*, $C_{21}H_{36}O_3$, is 17(α)-[1(?)-hydroxyethyl]-aetio-cholane-3(α), 17(β)-diol. It has been isolated from women's urine and from that of women with adrenal tumour. It is physiologically inert. It is not precipitated by digitonin.

**Progesterone*, $C_{21}H_{30}O_2$, is Δ^4-pregnene-3, 20-dione, or 17(α) [1-keto-ethyl]-Δ^4-androstene-3-one. It has been isolated from the ovaries and the adrenals. It has progestational activity, and some corticoid activity.

Pregnenolone, $C_{21}H_{32}O_2$, is 17(α)-[1-ketoethyl]-Δ^5-androstene-3(β)-ol. It has been isolated from testes by Ruzicka and Prelog. It has very slight progestational activity (Mason (2)).

**Pregneninolone*, pregneninonol, ethinyltestosterone, or anhydro-hydroxyl-progesterone, $C_{21}H_{28}O_2$, is 17(β)-ethynyl-Δ^4-androstene-3-one-17(α)-ol. It is a synthetic compound, with very slight androgenic activity, some oestrogenic and marked progestational activity.

(" *Q* " (Reichstein), see desoxycorticosterone.)

**Testosterone*, $C_{19}H_{28}O_2$, is Δ^4-androstene-3-one-17(α)-ol. It has been isolated from bull testes, and has powerful androgenic properties.

(*Transandrosterone*, see isoandrosterone.)

(*Transdehydroandrosterone*, see dehydro-iso-androsterone.)

B. *Oestratriene derivatives.*

(*Dihydrofollicular hormone*, see α-oestradiol.)

(*Dihydromenformone*, see α-oestradiol.

(*Dihydrotheelin*, see α-oestradiol.)

(*Dihydroxyoestrin*, see α-oestradiol.)

**Equilenin*, $C_{18}H_{18}O_2$, is $\Delta^{1,3,5:10,6,8}$-oestrapentaene-3-ol-17-one. It has been obtained from urine of pregnant mares, and is oestrogenic.

**Equilin*, $C_{18}H_{20}O_2$, is $\Delta^{1,3,5:10,7}$-oestratetraene-3-ol-17-one. It has been obtained from urine of pregnant mares, and is oestrogenic.

(*Follicular hormone*, see oestrone.)

(*Follicular hormone hydrate*, see oestriol.)

Hippulin, from urine of pregnant mares, is isomeric with equilin and has similar activity.

(*Ketohydroxyoestrin*, see oestrone.)

**α-Oestradiol*, dihydrofollicular hormone, dihydroxyoestrin, dihydrotheelin, dihydromenformone, $C_{18}H_{24}O_2$, is $\Delta^{1,3,5:10}$-oestratriene-3, 17-(α)-diol. It has been isolated from sow ovaries, horse testes, urine of pregnant women, and pregnant mares, and human placenta. It is powerfully oestrogenic. It is precipitated by digitonin.

**β-Oestradiol*, the corresponding compound with 17(β)-ol, has been obtained from the urine of pregnant mares. It is much less active than the alpha-compound, and is not precipitated by digitonin.

**Oestriol* (follicular hormone hydrate, trihydroxyoestrin, theelol), $C_{18}H_{24}O_3$, is $\Delta^{1,3,5:10}$-oestratriene-3, 16, 17-triol. It has been isolated from the urine of pregnant women free and as the glycuronide, from human placenta, and from pussy willows. It has oestrogenic properties, and is somewhat less active than oestrone.

**Oestrone* (follicular hormone, theelin, ketohydroxyoestrin), $C_{18}H_{22}O_2$, is $^{1,3,5:10}$-oestratriene-3-ol-17-one. It has been isolated from the urine of pregnant women and mares, from male human urine and that of the stallion and bull, from human placenta, horse testes, cattle adrenals, and palm kernels. It has also been isolated from pregnant mare's urine conjugated as the sulphate. It has marked oestrogenic properties.

(*Theelin*, see oestrone.)

(*Theelol*, see oestriol.)

(Trihydroxyoestrin, see oestriol.)

Artificial Oestrogens. Masson (1) has recently reviewed the literature describing these synthetic compounds, and he lists 221 showing some degree of oestrogenic activity. Most of them have a structural configuration showing some resemblance to that of the natural oestrogens. The most active are hexoestrol, diethylstilboestrol, and dinoestrol (cf. Chapter VIII).

Masson lists only two compounds possessing adrenal cortical activity, and their activity is negligible. These two are benzoyl carbinol (alpha-hydroxyacetophenone) and 3′ (hydroxyacetyl)-4-hydroxy-α, β-diethyl-stilbene.

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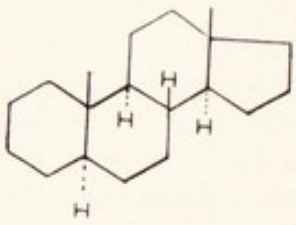
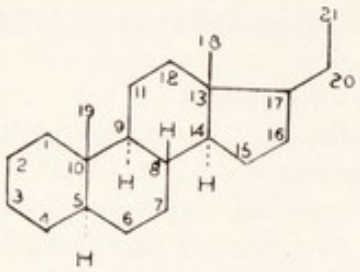
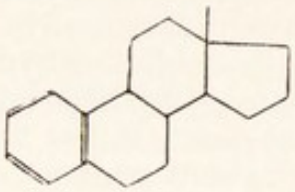


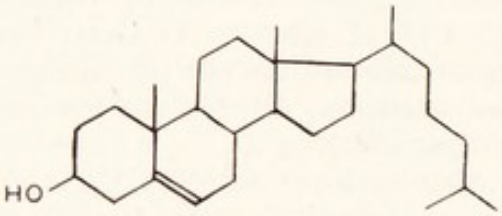
Androstane



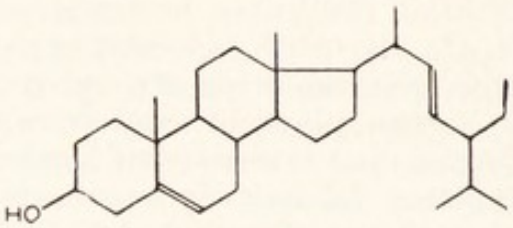
Allo-pregnane (showing numbering of the carbon atoms)



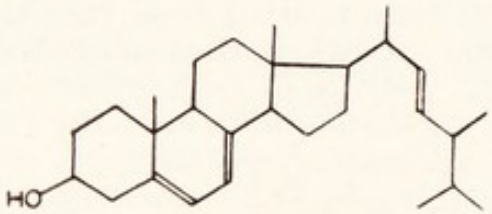
Oestratriene



Cholesterol



Stigmasterol



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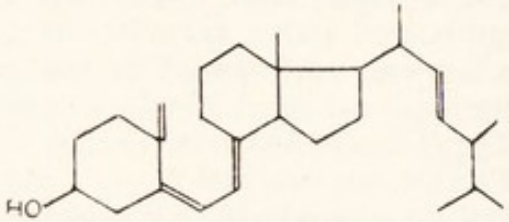
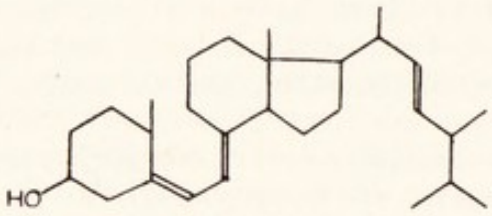
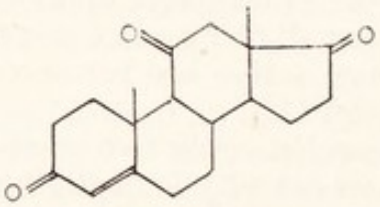


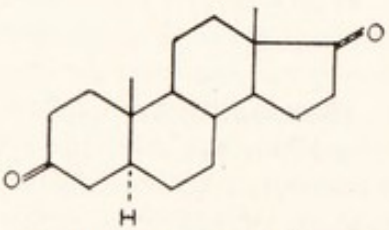
Calciferol (D_2)



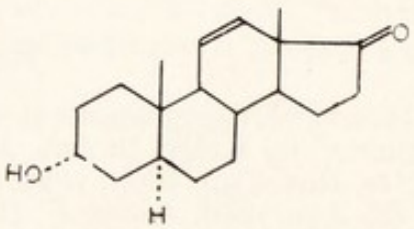
Dihydrotachysterol



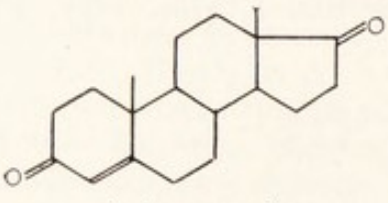
Adrenosterone



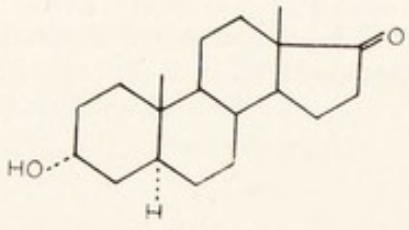
Androstane-3, 17-dione



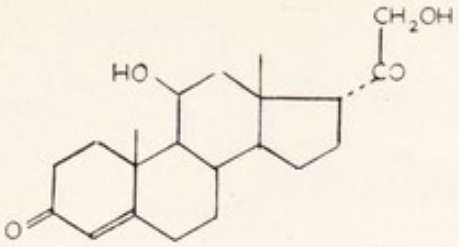
$\Delta^{\prime\prime}$-Androstene-3 (α)-ol-17-one



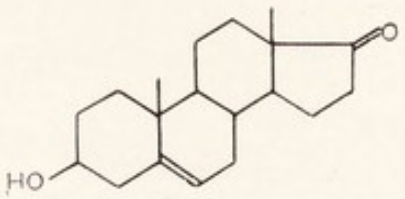
Androstenedione



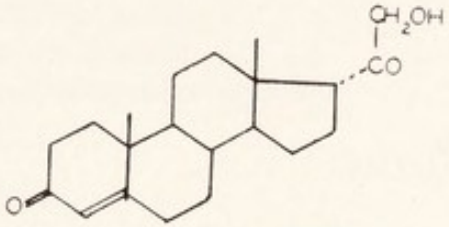
Androsterone



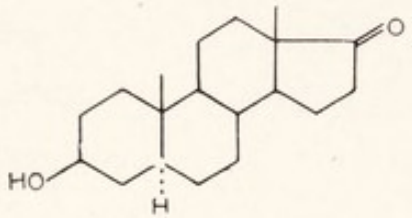
Corticosterone



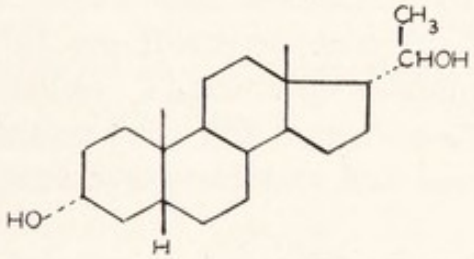
Dehydro-iso-androsterone



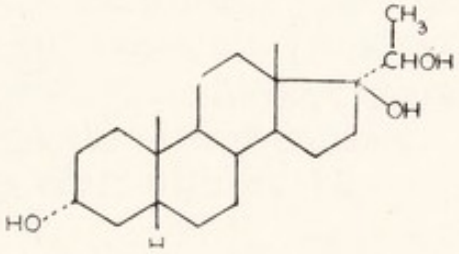
Desoxycorticosterone



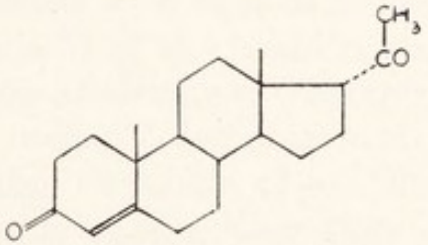
Isoandrosterone



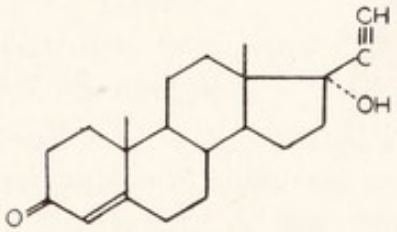
Pregnanediol



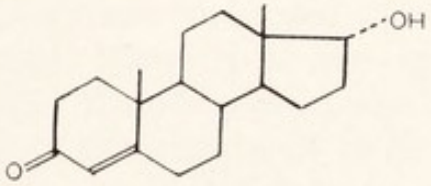
Pregnane-3, 17, 20-triol



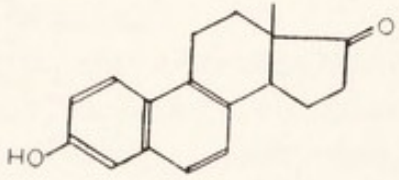
Progesterone



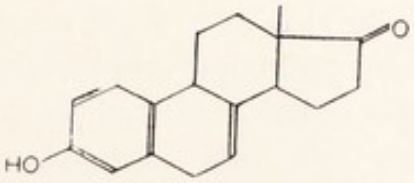
Pregneninolone



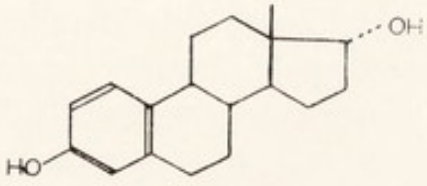
Testosterone



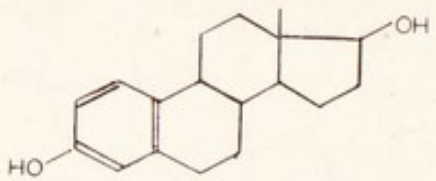
Equilenin



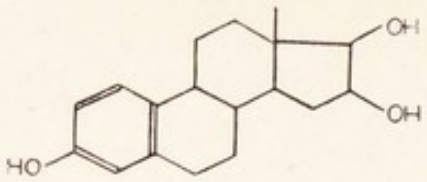
Equilin



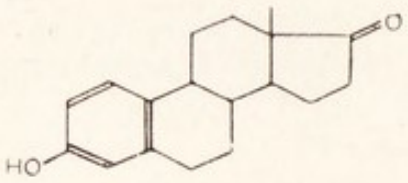
α-Oestradiol



β-Oestradiol



Oestriol



Oestrone

CHAPTER VII

THE ADRENAL GLANDS

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The adrenal medulla and its normal function 187
Abnormal function of the adrenal medulla 193
The adrenal cortex 197
Addison's disease 211
Hyper-cortico-adrenalism. 225

INTRODUCTION

THE paired *adrenal* or *suprarenal* glands are composed of two distinct types of tissue, which in mammals constitute respectively their *cortex* and *medulla.* In elasmobranch fishes these tissues exhibit no form of union; transition stages are found in the amphibia. There is no evidence to prove that the approximation in mammals is not fortuitous, although that seems unlikely. The comparative anatomy has been fully dealt with by Vincent and others.

" Accessory cortical bodies " are found in varying numbers and positions. Their total mass in mammals is relatively small when contrasted with that of the adrenal cortex itself.

The cells of the medulla stain with chromic acid, and from this reaction are termed " chromophile " or " chromaffin." " Chromophile bodies " (also termed " paraganglia ") are found closely adjoining the chain of ganglia in the sympathetic nervous system. In elasmobranch fishes they constitute the whole of the chromophile tissue, but in mammals they are accessory bodies. Some part of the carotid body and the whole of the abdominal chromophile body are composed of chromophile cells.

Cortical tissue is of mesoblastic origin, but chromophile tissue originates from a certain section of the sympathetic structure and thus may be considered to be of nervous origin. Gross section of the human adrenal shows three chief layers, a greyish-white or silvery-grey medulla, surrounded by an intermediary yellow- or dark-brown zone, which is again surrounded by a yellowish-grey peripheral layer, the cortex. The widths of these three zones show wide variations, especially in different age groups. Microscopically the cortex exhibits three strata, the glomerular (external) zone, the fasciculate, and the reticulate (adjacent to the medulla). There is no sharp demarcation between them. The specific cells

of the cortex have been described as "clear" and "dark," according to their appearance after staining with iron-haematoxylin. This may not reveal more than a difference in functional activity. They contain typical mitochondria and are characterized by presence of lipoid granules. In the reticulate zone pigment granules are responsible for its brownish-yellow colour (Vincent; Goldzieher).

Zwemer, in agreement with previous investigators, finds that the cortex grows from without inwards, new cells being formed at the periphery, and cells being destroyed in the reticular zone. The glomerular cells arise from indifferent cells resembling those of connective tissue, and transform to the specific, lipide-rich, spongiocytes. As the cells secrete, the ratio of nucleus to cytoplasm is greatly decreased. Lipide material is probably extruded from the cells in droplet form. Acute demand causes discharge of material from mature cells. Prolonged demand stimulates formation of new cells. (Cf. also Salmon and Zwemer; Bennett.) It will be shown in Chapter IX that the adrenal cortex is under control of an adrenotrophic hormone of the pituitary. The Golgi apparatus, particularly in the cells of the fasciculate zone, becomes shrunken after hypophysectomy, and is restored by injections of extracts rich in the adrenotrophic hormone, while injection of these extracts into normal animals causes hypertrophy of the Golgi apparatus (Reese and Moon; cf. also Miller and Riddle).

The medulla consists of "a solid cell-mass permeated by sinus-like blood vessels. . . . There can be little doubt that the materials (secreted by the cells) find their way directly into the blood within the blood spaces. The cell-protoplasm contains chromophile granules which vary in size and amount in different cells. These cells are stained brown with chromic acid and its salts" (Sharpey-Schafer).

Howard has described the presence of an "X" zone in the cortex of the young mouse and rat and that of the human foetus. It may provide a hormone with androgenic function. In mice it disappears at puberty but persists following castration, and hypertrophies in the male castrate. Administration of testosterone prevents this hypertrophy (Deanesley and Parkes). However, Gersh and Grollman have adduced some evidence against any androgenic function, and Ingle considers that the physiological importance of the X zone remains in doubt.

The embryonic development has been described by Rabin. The cortex develops from the splanchnic mesoderm. The medulla and chromophile bodies develop from the primitive cells of the sympathetic ganglia (the sympathogonia), and originally from the neural crest. In the late stages of fœtal life the sympathogonia

differentiate into ganglion cells and *phaeochromocytes* and it is the latter which have the peculiar property of staining brown with chromic acid.

Ingle states that there is no known nervous control of the functional activity of the adrenal cortex. Its innervation has been frequently described, but Swinyard has reported that the cortex cells of the cat and of man are without neural connections.

The innervation of the medulla is of preganglionic type, fibres arising from at least the sixth to the sixteenth segment of the spinal cord (in the cat), and passing without synaptic interruption to the cells they innervate. The greater splanchnic nerve conducts most of these fibres to the gland, where they form a network in the connective tissue, penetrate the cortex (without innervating it), and end in intimate relationship with the cells of the medulla, each fibre being associated with a definite number of cells (Young).

In most species of mammals the adrenal cortex of the female is larger than that of the male, and since administration of oestrogens causes hypertrophy, while administration of androgens may cause some regression in size, this difference in size may be associated with difference in level of androgens and oestrogens in the two sexes. It is not known whether the functional activity of the cortex of the female is greater than that of the male (cf. Ingle).

Staining reactions show that the adrenal gland is rich in ascorbic acid ; the fascicular region is richest, the medulla and glomerular zones contain less (Glick and Biskind).

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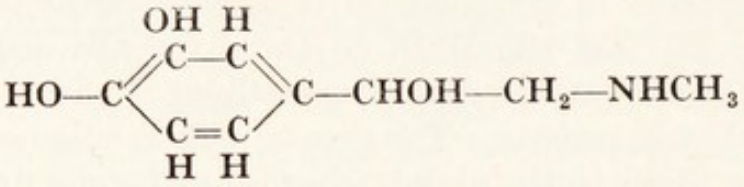
THE ADRENAL MEDULLA AND ITS NORMAL FUNCTION

It was early recognized that extracts of the adrenal medulla produced a powerful pressor effect when injected intravenously

into animals, while such extracts contained a powerful reducing substance and gave several specific colour reactions (an emerald green or blue colour with ferric chloride, and a rose red colour with chlorine or bromine water). In 1901 the chemical work of many investigators culminated in the isolation by Aldrich and Takamine, independently, of the compound *adrenine*, $C_9H_{13}NO_3$, which was subsequently shown to have the constitution



and to be responsible for the various activities of the extracts. Natural adrenine is laevo-rotatory. The dextro-compound has only one-fifteenth its activity (cf. Cori and Welch). Adrenine (so-named by Sharpey-Schafer) is frequently termed *adrenaline*, and (by those who object to the latter term because of its use for a pharmaceutical preparation of the compound) *epinephrine*.

Formation and Destruction of Adrenine. The close chemical relationship of adrenine to tyrosine suggests that the latter is its parent substance. According to Schuler, tyramine is probably formed from tyrosine by decarboxylation in the kidneys, and is then transferred to the adrenals and transformed to adrenine. Holtz has proved that tyramine is formed in the kidneys. Devine has shown that in the bullock adrenal phenylethylamine is the probable precursor. Vinet has suggested that the stages are tyrosine to dihydroxyphenylalanine, to dihydroxyphenylethylamine (in the kidney), to adrenine (in the adrenal medulla).

Adrenine is stabilized in the blood and tissues by such compounds as glutathione and ascorbic acid, which prevent its rapid irreversible oxidation by molecular oxidation and by the cytochrome-cytochrome oxidase system in the tissues (cf. Cori and Welch).

Adrenine is inactivated *in vivo* by conjugation as sulphate; this is evidenced by markedly augmented excretion of organic sulphates following administration of adrenine to the rabbit (Richter; Deichman). Cori and Welch believe that the enzymes chiefly concerned in the physiological inactivation of adrenine are the cytochrome-cytochrome oxidase system (which leads to formation of an unstable indole derivative, adrenochrome), and amine oxidase, which produces methylamine from adrenine.

Histological Demonstration of Adrenine Secretion. Cramer treated resting adrenal gland with osmic acid vapour, stating that adrenine

becomes visible as granules in the medullary cells. When he stimulated the gland to activity these granules were seen to be expelled into the veins of the gland, giving a clear demonstration of internal secretion. By this procedure it was shown that exposure to cold, asphyxia and ether anaesthesia each stimulate secretion.

The Secretion of Adrenine. The preganglionic fibres in the splanchnic nerves which pass to the adrenal medulla (cf. p. 187) produce, when stimulated, either acetyl-choline or a compound with its pharmacological action which stimulates the cells of the medulla to secrete adrenine. Stimulation of the splanchnic nerves, or injection of acetyl-choline after physostigmine (which inhibits the esterase that inactivates acetyl-choline) leads to (increase of) liberation of adrenine from the medulla. Such increased production has been demonstrated in the experimental animal as following a variety of stimuli, such as a state of rage or fear, muscular activity, asphyxiation, haemorrhage, hypoglycaemia, excessive heat or cold, inhalation anaesthetics, etc. On the other hand, section of the splanchnic nerves diminishes the output. (Cf. Cori and Welch.)

The Actions Produced by Adrenine. Injection of adrenine produces numerous effects which parallel those resulting from stimulation of some one or other sympathetic nerve, so that the actions of adrenine, and those of various other compounds related to it chemically, are termed sympathomimetic. Of the various sympathomimetic actions which adrenine produces, the most striking are constriction of arterioles leading to increased blood pressure, and effects on carbohydrate metabolism.

When adrenine is injected intravenously, after a very short latent period the blood pressure rises (the degree of rise showing some proportionality to the dose injected), and then rapidly returns to normal. Whether adrenine be injected or liberated from the adrenals, to reach the arterioles of the systemic circulation it must traverse the right heart, pulmonary circulation, and left heart. The coronary vessels of the heart behave anomalously and are dilated by it, while the arterioles of the lungs are relatively insensitive to it. Dilatation of the coronary vessels provides increased oxygen for the additional work of the heart during the period of increased blood pressure.

The smooth muscle of the arterioles is supplied with sympathetic nerve fibres ; presumably adrenine acts on some receptor substance in the muscle fibre or at the myoneural junction ; the precise point of action has not been determined.

Constriction of the arterioles, especially in the splanchnic area,

results in increased resistance to circulation of blood, causing rise in pressure. This is followed by increase in cardiac intake and output and in rate of blood flow. (Cf. Cori and Welch.)

The vascular system of man is more sensitive to adrenine than is that of other species. Thus rise of blood pressure in man is caused by constant intravenous injection of only 0·00005 mg. per kg. per minute of adrenine, while the dog, cat and rabbit require 0·0005 mg., and the rat 0·001 mg. In man subcutaneous injection of 0·5 or 1·0 mg. of adrenine is usually followed by a rise in systolic blood pressure (though the diastolic pressure often decreases), in pulse rate, and in volume of respiration ; the effect is maximal after thirty minutes and disappears in one or two hours. In laboratory animals such subcutaneous injections do not affect blood pressure. (Cf. Cori ; Cori and Welch.)

Injection of adrenine, or increased output of adrenine from the adrenals, produces along with the elevation of blood pressure a heightened level of blood glucose and lactic acid and an increase in the basal metabolic rate. Our knowledge of the effects on carbohydrate metabolism is largely due to the work of Cori. Cori and Welch have recently summarized that knowledge. These actions are relatively more pronounced than the effect on blood pressure, since subcutaneous injections into dogs, cats and rabbits, while without effect on blood pressure, cause hyperglycaemia and glycosuria. Continuous intravenous injection of adrenine into man at the rate of 0·00005 mg. per kg. per minute produces not only the rise in blood pressure already mentioned, but all the three metabolic effects listed above, and the minimal rate of injection needed to increase blood pressure also increases blood lactic acid.

Adrenine accelerates the rate of enzymatic conversion of liver and muscle glycogen to glucose and lactic acid respectively. In both tissues glycogen is converted by the same series of changes to the hexose phosphate glucose-6-phosphate. The liver possesses a phosphatase which hydrolyses this hexose phosphate to glucose and phosphate, but muscle does not contain this phosphatase, and produces lactic acid by another mechanism, instead of glucose. Adrenine facilitates one of the early stages of the conversion ; its action is therefore common to both liver and muscle.

The lactic acid, when produced in unusual amount under the action of adrenine, in part reaches the systemic circulation, is removed by the liver, and reconverted to glycogen. If the adrenine effect is prolonged this mechanism assists in maintaining the store of liver glycogen, and thus, indirectly, in maintaining the

hyperglycaemia. Such hyperglycaemia does not, in itself, involve increased oxidation of carbohydrate.

It has been mentioned that hypoglycaemia acts as a stimulus to increased output of adrenine from the adrenal medulla; hence, through the action of adrenine, such hypoglycaemia tends to correct itself.

Oxygen consumption is increased following injection of adrenine, not only in the fasting animal, but also in the postabsorptive and in the glucose-fed animal. This effect has been termed by Boothby and Sandiford the calorigenic action of adrenine. The increase in metabolism from adrenine action has not been fully explained, but may be in part due to extra expenditure of energy in the reconversion of lactic acid to glycogen. (Cf. Cori and Welch.)

Normal Function of the Adrenal Medulla. It was for long a subject of controversy as to whether adrenine was continuously secreted into the circulation, or whether there was an intermittent stimulation through nervous excitation through the splanchnics, resulting from emotional excitement, pain, or other such causes. From the latter view came the idea of Cannon's emergency theory of adrenine action. Since even such minor exercise as walking calls forth a definite output of adrenine (Cannon and Britton) the difference in view-point is of little more than theoretical interest. It can be concluded that, as a result of an almost continuous series of minimal stimuli, adrenine is almost continuously secreted in minimal amount. The physiological significance of such secretion is probably small. Removal of the adrenal medullae or denervation of the adrenals or complete sympathectomy does not lead to appreciable functional disturbances in an experimental animal kept in a normal environment.

As an emergency mechanism secretion of increased amounts of adrenine has obvious advantages.

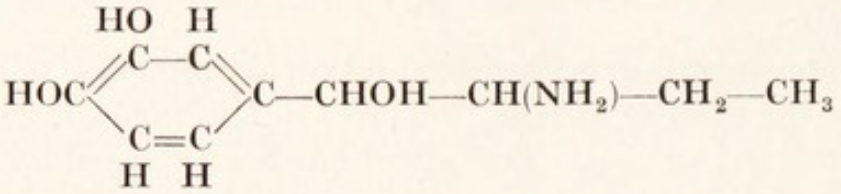
The same mechanism, as a secondary process, is probably responsible for the hyperglycaemia in nicotine poisoning and that which occasionally follows the smoking of tobacco (Lundberg), and, in part, for the hyperglycaemia and glycosuria often associated with hyperthyroidism. In certain states of emotional tension in mental patients glucose tolerance curves show a delayed return to normal fasting values and this effect is traceable to the action of adrenine (McCowan and Quastel).

The prolonged hyperglycaemia and increase in blood lactic acid following the Claude Bernard piqûre of the floor of the fourth ventricle are due to increased output of adrenine (Cori and Welch).

Therapeutic Uses of Adrenine. Adrenine, because of its vasoconstrictor action, has various therapeutic uses, as in allergic diseases, asthmatic attacks, and angioneurotic glottis oedema. Intracardiac injections of the hydrochloride have given spectacular results in resusci-

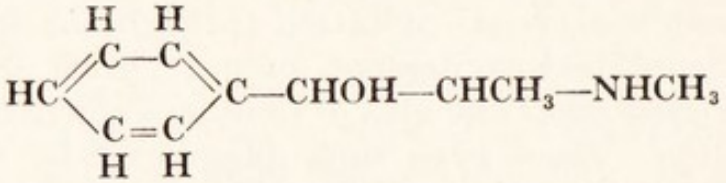
tating persons in whom heart-beat has apparently ceased, through drowning, carbon monoxide poisoning, or accidents of anaesthesia (cf. Cori and Welch).

Ethyl - nor - suprarenine. 1-(3, 4-dihydroxyphenyl)-2-amino-1-butanol (hydrochloride), resembles adrenine, but lacks the power



to raise the systolic blood pressure, tending to lower the diastolic pressure and increase the pulse rate. Administered intravenously it has only one—one hundred and twentieth the toxicity of adrenine. It is more effective than adrenine in acute asthma (Tainter *et al.*).

Ephedrine, a laevo-rotatory compound obtained from the Chinese drug Ma Huang, is effective by mouth or injection. Its action



resembles that of adrenine, being less intense but more prolonged. It has been used successfully in treatment of asthma, etc.

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ABNORMAL FUNCTION OF THE ADRENAL MEDULLA

It has been mentioned that absence of the adrenal medulla does not materially affect the experimental animal which is not subjected to strain (cf. p. 191). This may be in part due to presence of the accessory chromophile bodies (cf. p. 185). In any event there is little sound clinical evidence of disease entities in which the symptoms are attributable to deficient production of adrenine. Goldzieher has reviewed the favourable evidence.

Hyperfunction of the adrenal medulla, with chronically increased functional activity, might be expected to produce a persistently heightened blood pressure, with some degree of hyperglycaemia. This condition is occasionally seen in presence of tumours of chromophile tissue. These hyperfunctioning tumours, however, usually produce *paroxysmal hypertension*, in which, from time to time, the (diastolic) blood pressure rather suddenly rises from normal to 200 or more mm. of mercury, with various acute and distressing symptoms, and, after a variable but relatively short time, sinks back to normal. Probably between fifty and sixty cases of this syndrome have been reported, most of them authenticated by the finding of a tumour at operation or autopsy. The subject has been reviewed by, amongst others, Rabin, Donzalet, and Keating and Kepler.

The condition was first recognized at post-mortem by Robert in 1899, was first diagnosed during life by Vaquez and Donzalet in 1926, and was first successfully treated by surgical intervention by C. H. Mayo in 1927.

The onset of the syndrome is usually, but not always, insidious, the attacks of hypertension gradually increasing in severity and in frequency. An attack commences with tachycardia, the rise of blood pressure is accompanied by shivering and pallor, and followed by palpitation, rapid pulse, perspiration and cyanosis of the extremities. Nausea, vomiting and tremor may be present. A hemiplegia may ultimately develop, some degree of albuminuria is not uncommon in the later stages, and the untreated patient ultimately dies in an acute attack or in coma. At autopsy a varied pathology is found, with a tumour of one or the other adrenal medulla, or, more seldom, of one of the accessory chromophile bodies.

These tumours consist of abnormal proliferations of mature phaeochromocytes, and are variously termed "chromaffin tumours," "paragangliomata," and *phaeochromocytomata*. (Other groups of tumours arising from the adrenal medulla, neuro-

blastomata and ganglioneuromata, are derived from cells comprising the nervous or non-specific elements of the adrenal medulla).

The phaeochromocytoma or paraganglioma is usually benign, perfectly encapsulated, and does not give rise to metastases. It may be as large as an orange. The cellular structure is like that of the normal adrenal medulla, and, histologically, suggests active secretion.

Shipley's case is fairly typical. A woman aged twenty-six suffered from paroxysmal attacks of hypertension of increasing frequency, while severe occipital headaches became an increasingly troublesome symptom. Between attacks her blood pressure was 120/90 ; during attacks it rose to 219/110, and even higher. Diagnosis of adrenal tumour was made ; there was no clue to indicate which gland was affected. Exploration showed the right adrenal involved, and this was removed at subsequent operation. Convalescence was stormy. Ten months later she was entirely free from symptoms, with normal blood pressure. The tumour weighed 115 grams, measured $9 \times 7 \times 3{\cdot}5$ cm., and was completely encapsulated. Macroscopically, it was a tumour of the medulla, microscopically a phaeochromocytoma.

In a case reported by Kelly *et al.*, in which the blood pressure varied from 90/70 between attacks to 280/160 or similar figures in attacks, palpation of the right kidney suggested tenderness, and at operation a large tumour 10·5 cm. in diameter was removed ; there was a fringe of cortex at the lower border. The tumour was filled with necrotic material and apparently many haemorrhages had taken place into it. Its total weight was 240 grams ; one half of it yielded 120 mg. of crystalline adrenine. The patient made a complete recovery.

Hicks has described a case in which a tumour—a phaeochromocytoma—was discovered at post-mortem examination attached to an adrenal by a short fibrous pedicle through which it received its blood supply. Extract of the tumour, injected intravenously into a dog, produced a marked pressor effect. The patient had not exhibited hypertension. In a similar case reported by Rogers hypertension was present.

Nettleship has compared the effect of an extract of a medullary tumour with that of various concentrations of aqueous solution of adrenine on the blood pressure of a cat, and estimated that the tumour contained 67 mg. of adrenine as compared with an average amount from the two adrenals of a normal person of about 8 mg. Beers *et al.* have demonstrated presence of a pressor substance,

presumably adrenine, in the blood of a patient during a paroxysmal crisis.

Biskind, Meyer and Beadner in 1941 reviewed the 29 cases in the literature (including one of their own) in which a tumour was removed by surgery. The list shows that the greatest incidence occurs in patients between the ages of twenty-five and forty-five years, that the condition is commoner in women than in men, and that the right adrenal is more often affected than the left. The tumour was extra-adrenal in only four cases.

Since the operative risk is considerable, preoperative determination of which adrenal is affected is obviously most desirable when possible. In the series of cases reported localization was effected by various means. In eight cases a mass was palpated in the flank, giving presumptive localizing evidence. In some cases, although there was no palpable mass, massage over the suspected adrenal produced a typical paroxysm. The ordinary abdominal roentgenogram may be of little value, although a very large tumour may produce sufficient displacement of the viscera to indicate its presence. Intravenous pyelography is not as satisfactory as retrograde pyelography. Perirenal pneumograms were made in five cases; positive results were obtained in four.

Seven of the 29 verified cases did not show typical paroxysms. These seven exhibited respectively: (i) attacks of suffocation (tumour of the gall-bladder was suspected); (ii) periodic discomfort, nausea and dizziness—with a mass, slowly enlarging, under the right costal border; (iii) blood-pressure 156/106 mm.—with a palpable mass; (iv) precordial palpitation, and diastolic blood pressure varying from 160 to 190 mm. (a palpable mass was present, which proved to be a *malignant* tumour); (v) atypical paroxysms—with a palpable tumour in the left upper quadrant; (vi) variations in blood pressure from 120/78 to 290/120 mm., a basal metabolic rate of + 61 per cent., and no palpable mass; (vii) blood pressure of 182/106 mm., with a large palpable mass in the right upper quadrant of the abdomen.

Postoperatively, shock was an important feature in 18 cases, of which 15 were severely shocked and four died. It was treated as for surgical shock, with, in addition, administration of adrenine in eight cases, intravenously and subcutaneously, while in a few cases adrenal cortical extract or desoxycorticosterone acetate was given as supplemental therapy.

In addition to the four patients who died in shock, one died thirty days later from bronchopneumonia, and one two years

later from metastases from the only malignant tumour in this series. Of the remainder at the time of the review twelve were alive and without symptoms, two still had symptoms or blood pressure variations, and the remaining nine were presumed to be alive.

McCullagh and Engel recently reported two cases, both of which showed a constantly elevated basal metabolic rate, illustrating that effect of adrenine on basal metabolism already referred to (p. 190). The result of a urea clearance test in both was much above 100 per cent. Paroxysms of hypertension were not present, but rather a persistent hypertension. One patient recovered completely following removal of a phaeochromocytoma, both basal metabolism and urea clearance becoming normal. The second case was complicated by a severe diabetes, a thyroid adenoma, and some evidence of hyperthyroidism (including apparently the raised basal metabolism). The adrenal syndrome was not suspected. The patient died following a subtotal thyroidectomy at which a colloid goitre with ruptured cyst was removed. At autopsy a phaeochromocytoma of the right adrenal was discovered. It was concluded that the hypermetabolism was due to this tumour.

In a case of malignant tumour of the adrenals reported by King the tumour was found to contain typical chromophile cells, which were also present in some of the many metastases, but the patient had exhibited normal blood pressure.

In 1942 McGavack *et al.* reported the eighth case of " malignant paraganglioma " of the adrenal medulla. The patient's blood pressure was normal (114/80 mm.). The tumour weighed 930 gm. There were widespread metastases to skull, vertebrae, ilea, hips, tibiae, fibulae, ribs, lungs, pleurae, liver and skin.

McGavack stresses the absence of bouts of paroxysmal hypertension in these malignant cases. As has been already stated, these primary malignant tumours arise from sympathetic ganglion cells or their derivatives (neuroblastoma, etc.). They have been termed the " Pepper type " or the " Hutchison type " of tumour, according to whether they metastize to liver or skull (Keating and Kepler).

Although some of the recorded cases show a persistent hypertension, and others, not operated on, may develop it, it by no means follows that hypersecretion of adrenine is to be considered a common cause of hypertension or of arteriosclerosis. The evidence in favour of its being a possible cause has been set out by Goldziecher (cf. also Green).

From histophysiological studies of medullary changes in various diseases, Drake, Hibbard and Hellwig conclude that the adrenal medulla can play a *rôle* in the early stages of hypertension.

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THE ADRENAL CORTEX

Introduction. The experimental animal survives the removal of one adrenal and the medulla of the second gland, but complete adrenalectomy is in most species rapidly followed by a train of specific symptoms and death, and these effects must be attributed to deficiency of the hormones of the adrenal cortex. The period of survival varies, depending upon the surgical technique, in which frequently a two-stage operation is performed. With the best technique dogs survive, on the average, eight or nine days, and at a maximum about fifteen days ; cats have an average survival of eleven days, although Stewart and Rogoff recorded a survival period in one cat of thirty-two and a half days. Rats seem more resistant to double adrenalectomy, perhaps because of more frequent presence of accessory cortical bodies.

After complete removal of the adrenals the animal (dog or cat) recovers from the operation in a few hours, and then appears normal for some days, except for some loss of appetite. Variable symptoms then ensue, including nausea, vomiting, and bloody diarrhoea. The animal becomes stupid and quiet, and shows weakness and uncertainty of movement. The body temperature begins to fall, and the apathy and weakness increase. The asthenia becomes marked, the animal tires on the least exertion, and exhibits extreme prostration. Some animals (especially rabbits) exhibit convulsions of the hypoglycaemic type. Finally occur dyspnoea, heart weakness, and death. (Cf. Vincent ; Banting and Gairns ; Kendall.)

Biedl showed in 1919 that removal of the corresponding " interrenal body " in elasmobranch fishes produced similar changes, and his results were later confirmed by Kisch. There occur persistent balling of the skin chromatophores, so that the animals take on a dirty-grey colour, slowing of respiration, muscle weakness, shortening of the body musculature, hypersensitiveness to oxygen scarcity, and death. Injection of acid extract of interrenal tissue delays death for hours and the effect is specific. Maes has shown corresponding changes in the adrenalectomized frog.

There seems to be an unusual mechanism of survival in the ground squirrel. Groat found that it would survive adrenalectomy if its food intake could be maintained, and this occurred if the animal were allowed to drink 1 per cent. sodium chloride solution. It will be shown later that such increased intake of sodium chloride has a general beneficial effect in adrenal deficiency (p. 206). However the animal, so treated, is unable to survive a fast of any duration. But after a period, which in females is at least fifteen days, the sodium chloride solution may be replaced by water, and the animal will continue to eat normally, although it cannot survive a fast until at least three or four months have elapsed since the adrenalectomy. Subsequently there is no evidence of adrenal insufficiency. Thus two adrenalectomized animals survived a fourteen-day fast as well as did normal animals.

This apparently complete recovery is due, in females, to the appearance and growth of adrenocortical-like tissue in the ovary. The cells cytologically resemble cells of the post-secretory zone of the cortex, and seem exactly like the cells in the accessory cortical bodies occasionally present in this species. They are not normally present in the ovaries of the ground squirrel. (Small cortical bodies have also been found long after adrenalectomy in one female and three males, near the kidney ; they were considered to have arisen by metaplasia of fibroblasts.)

Groat states that this development of adrenocortical cells does not occur in the ovary of the rat.

The progressive phenomena occurring in the adrenalectomized dog or cat are accompanied by definite metabolic changes in the following sequence : increased excretion of sodium and chloride, accompanied by decreased blood plasma sodium and chloride, increased plasma potassium, blood urea, and non-protein nitrogen, and slight increase of plasma protein ; a varying degree of hypoglycaemia ; decreased plasma volume (to an anhydraemia) accompanied by decreased rate of blood flow and a general dehydration ; fall of blood pressure, and decrease of basal metabolic rate.

The same series of phenomena occur when the maintenance treatment of doubly adrenalectomized animals by potent adrenal cortical extracts is stopped.

Hartman *et al.* (2) state that adrenalectomy in dogs and cats leads to a decrease in blood plasma albumin, and an increase in globulin.

It has been mentioned (p. 187) that there is no evidence that

the functional activity of the adrenal cortex is under nervous control. There is definite evidence that it is under the control of the adrenotrophic hormone of the anterior pituitary (cf. Chapter IX). Atrophy of the cortex rapidly follows hypophysectomy, and can be prevented, or the cortex restored, by adequate injection of potent preparations of the adrenotrophic hormone.

The enlargement of the adrenals which occurs in acute starvation in the experimental animal, and has hitherto been considered a hypertrophy (cf., *e.g.*, Tepperman, Engel and Long ; Goldzieher) has now been shown to occur only just prior to death, and to be a pathological change in the adrenal cortex, probably in the nature of a hydropic degeneration. The similar enlargement from B-complex deficiency is probably due to a similar change (Cameron and Carmichael).

Preparation of Active Extracts. The successful preparation of concentrated potent extracts of the adrenal cortex only occurred

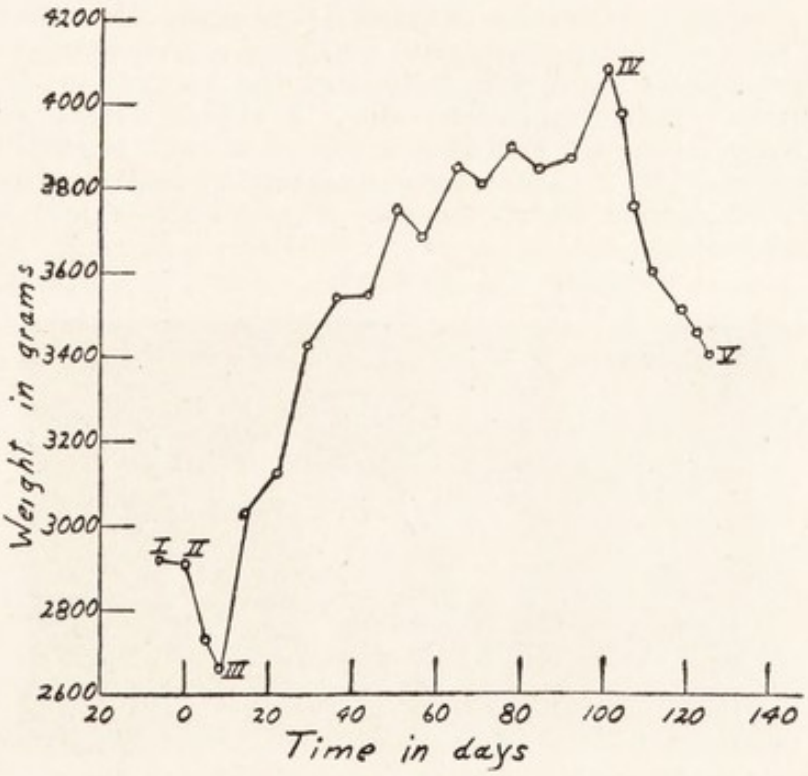

FIG. 27. The weight chart of a bilaterally adrenalectomized cat treated with an active extract of the cortico-adrenal principle, following the exhibition of severe symptoms of adrenal insufficiency. I. Right adrenal removed. II. Left adrenal removed. III. Animal prostrate ; treatment begun. IV. Treatment discontinued. V. Death from adrenal insufficiency. (From Pfiffner and Swingle, Endocrinology, 1931, xv, 338.)

when it was recognized that the essential biological test for activity was the prolongation of life of an adrenalectomized animal (cat

or dog). Potent extracts were first prepared by Stewart and Rogoff, Hartman and his colleagues, and Swingle and Pfiffner, and later by many others. Various methods were employed. Thus

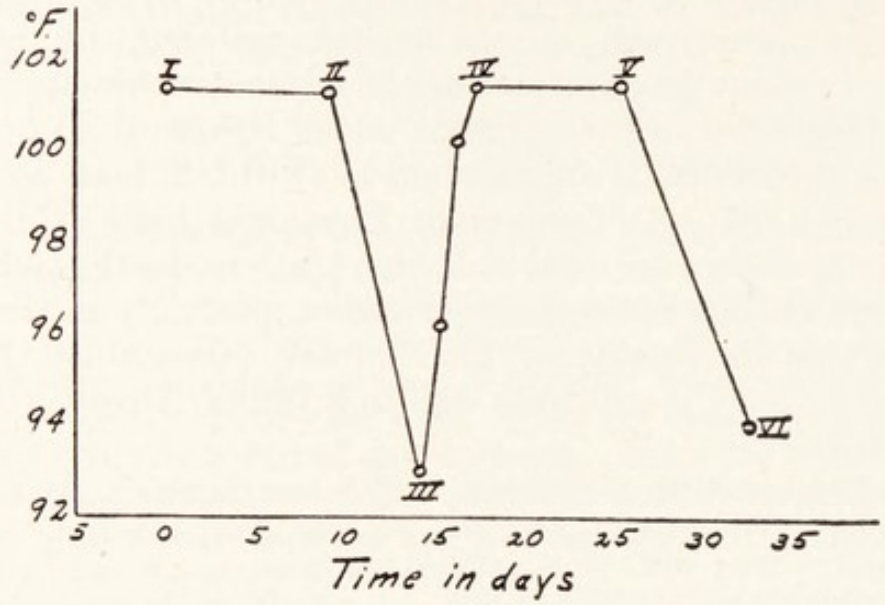

FIG. 28. Rectal temperature chart of a bilaterally adrenalectomized cat treated intraperitoneally with an active extract of the cortico-adrenal principle following the exhibition of severe symptoms of adrenal insufficiency. I. Second adrenal removed. II. No symptoms. III. Prostrate; treatment begun. IV. No symptoms. V. Treatment discontinued. VI. Animal prostrate (died of adrenal insufficiency). (From Pfiffner and Swingle, Endocrinology, *loc. cit.*)

FIG. 29. Bilaterally adrenalectomized female and male dogs about one year after operation. Both animals had been repeatedly brought into a condition of adrenal insufficiency by temporary discontinuance of the injections of adrenal cortex principle. (From Swingle and Pfiffner, Medicine, 1932, xi, 389.)

Swingle and Pfiffner prepared their early concentrates by extraction of the adrenals with ethyl alcohol, and subsequent treatment of the extract with benzene and alcohol, discarding residues, then distribution between 70 per cent. alcohol and petroleum ether,

transference of the alcohol fraction to 95 per cent. alcohol, filtration through permutit (which removes adrenine) and transference to water.

Such preparations will keep completely adrenalectomized animals alive for an indefinite period, and in completely normal condition. Mineral metabolism is restored to normal, the high blood urea falls to normal, normal body temperature is restored. The asthenia is one of the last symptoms of deficiency to disappear.

Some of the effects of deficiency and replacement therapy are illustrated in Figs. 27 to 29.

Intraperitoneal injections act rapidly. Cats in extreme pre-terminal prostration definitely improve in fifteen to thirty minutes. Convulsions (if present) are abolished, and the animals attempt to sit up. Within an hour they may walk about and appear almost normal. Within two hours they may take food. For complete restoration they need in the first twenty-four hours extract equivalent to between 0·125 and 0·25 gm. of fresh whole adrenal gland per kg. body-weight, representing at least 2,000 times the amount of extract obtainable by similar procedures from a normal cat's adrenal (Britton *et al.*). Once recovery has been effected a much smaller maintenance dose is adequate though still one much in excess of the amount obtainable from the animal's glands.

Such extracts are also effective by mouth, but considerably larger dosage is necessary. (Fresh or desiccated adrenal gland is also active by mouth, though the relative activity is low ; it has toxic effects unless the medulla is completely removed.)

Large excess of cortical extract is non-toxic. When the extract is administered to the normal animal there is, initially, a decreased excretion of sodium and chloride and a slight increase in excretion of potassium. After repeated injections this effect is no longer produced (Hartman *et al.* (1)).

It was at first considered that the extracts contained one specific adrenal cortical hormone, for which Hartman proposed the name *cortin*. He himself showed later that there were at least two hormones, one of which he termed the " salt factor," and still further work by many investigators has proved that the adrenal cortex contains a number of compounds with definite physiological actions, and that more than one type of action is exhibited.

The Hormones of the Adrenal Cortex. Numerous studies have been made of the compounds present in the adrenal cortex, largely by Kendall, Reichstein, Wintersteiner, and their respective

TABLE I

Physiologically Active Compounds Obtained from the Adrenal Cortex

Chief activity.	Name.	Amount obtained from 1000 lb. adrenal glands.	Empirical formula.	Alphabetical label.		
				of Reichstein.	of Kendall.	of Wintersteiner.
		mg.				
Corticoid						
	Corticosterone	180	$C_{21}H_{30}O_4$	H	B	—
	11-dehydro-corticosterone	330	$C_{21}H_{28}O_4$	—	A	—
	Desoxycorticosterone	trace	$C_{21}H_{30}O_2$	Q	—	—
	17-hydroxy-corticosterone	< 100	$C_{21}H_{30}O_4$	M	F	—
	17-hydroxy-11-dehydrocorticosterone	340	$C_{21}H_{28}O_5$	Fa	E	F
Androgenic						
	Adrenosterone		$C_{19}H_{24}O_3$	G	—	—
	Androstane-3, 11-diol-17-one		$C_{19}H_{30}O_3$	—	—	—
	Androstene-dione		$C_{19}H_{26}O_2$	—	—	—
Progestational						
	Progesterone		$C_{21}H_{30}O_2$	—	—	—
Oestrogenic						
	Allopregnanolone		$C_{21}H_{34}O_2$	—	—	A
	Oestrone		$C_{18}H_{22}O_2$	—	—	—

colleagues. As related in Chapter VI, at least twenty-eight crystalline compounds have been isolated and their constitution determined, and the list is not yet complete. These compounds are all steroids. Most of them are devoid of physiological activity, and of the remainder, which alone will be considered here, several exhibit activity which is not typically associated with adrenal cortical function.

Different investigators labelled many of these compounds alphabetically before their constitution was determined, but unfortunately did not choose the same labels, so that for some period the literature was confusing. Table I is taken in part from papers by Reichstein and Shoppee, and by Kendall (1942); the list of systematic names, and the constitutional formulae of the compounds, are given in Chapter VI.

The amounts listed in Table I as obtainable from 1,000 lb. of adrenal glands are probably no guide to the actual amounts of the compounds present in the glands (cf. Kendall).

Some idea of the methods used in the separation of these compounds is given in Kendall's recent description. The whole extract of the adrenal cortex is divided into two fractions by repeated distribution between water and benzene. Both phases contain active compounds.

When the benzene is removed and replaced with isopropyl alcohol, 11-dehydro-corticosterone separates in from twenty-four to forty-eight hours. If the residual solution be concentrated, corticosterone crystallizes out after some days. The residual mother-liquor contains a number of steroids, chief among which is allo-pregnane-3 (β), 21-diol-11, 20-dione (Kendall's " H " and Reichstein's " N " compound), to which no common name has yet been given, and which apparently is physiologically inert.

The aqueous solution is extracted with chloroform, which removes several steroids including 17-hydroxy-11-dehydro-corticosterone. After all such steroids, as far as has yet proved possible, have been removed by crystallization, the chloroform solution still contains very active material, usually referred to as the " amorphous fraction ".

The compounds which exhibit as their chief activity an action associated with the known functions of the adrenal cortex can be divided into two groups.

Group I compounds have regulatory action of the blood electrolytes (Kendall terms it the renal function). The group includes desoxycorticosterone, and a compound present in the amorphous fraction, which exhibits strong activity of this type.

Group II compounds control carbohydrate metabolism (and incidentally increase resistance to stress, toxic substances, and shock). This group includes only those hormones which have an oxygen atom attached at carbon atom 11. There are four, corticosterone, 11-dehydro-corticosterone, 17-hydroxy-corticosterone, and 17-hydroxy-11-dehydro-corticosterone. There is some evidence that a mixture of these compounds such as occurs in the whole extract of the gland (and presumably in its secretion) is much more active than the summation of effects of corresponding amounts of the individual crystalline compounds, suggesting some synergistic action (cf. Kendall).

Compounds of Group I are usually considered to have little or no effect on carbohydrate metabolism, and those of Group II to have only slight effect on the blood electrolytes.

Kendall considers that the electrolyte-controlling activity (renal function) of the amorphous fraction is much greater than that of desoxycorticosterone, but Ingle (2) believes that this is not proved, and that they have activities of the same order.

The remaining compounds of Table I have slight or no corticoid activity. The three with androgenic activity, according to Reichstein and Shoppee, have not yet been proved to exist as such in the completely fresh adrenal gland.

Progesterone has, in addition to its marked progestational activity (cf. Chapter VIII), a slight but definite degree of corticoid activity, of the Group I type (cf. Reichstein and Shoppee).

Allopregnanolone has very slight oestrogenic activity (cf. Selye).

Oestrone (p. 234) was isolated by Beall from adrenals, and is probably in part responsible for the oestrogenic activity of the adrenal cortex.

(Lowenstein and Zwemer claim to have isolated two new very active compounds from aqueous extracts of the adrenals; one of these is considered to be possibly composed of a radical of ascorbic acid combined with a reduction derivative of adrenosterone.)

The exact number of hormones produced in the adrenal cortex cannot yet be stated. The compounds whose predominating activity is associated with sex function (as progesterone and oestrone, important products of the ovaries) may or may not be incidental by-products in the adrenal metabolism. It has been suggested that some of them may have a *rôle* in early sex development (cf. p. 260); in adrenal cortical tumour and hyperplasia they definitely exert an effect (cf. p. 413).

The two distinct types of activity of the compounds in Groups I and II suggest that there may at least be two specific hormones. That the adrenal cortex should elaborate four distinct Group II hormones with practically the same physiological action seems

unlikely and one is inclined to agree with Hartman that the four crystalline compounds so far isolated may be stable derivatives of a less stable compound, the true hormone. (For the approximate quantitative effects of the compounds cf. Ingle (4) .)

Functions of the Adrenal Cortex. As judged by the effects of adrenalectomy, and those produced experimentally by administration of adrenal cortical extracts and crystalline compounds derived from them, the cortex has multiple functions, though in all probability its primary functions are few, and distortion of these reveals numerous effects that in reality are secondary. Long (1) lists three groups of functions : (*a*) control of electrolytes and water metabolism ; (*b*) control of carbohydrate and protein metabolism, including the working capacity of muscle ; and (*c*) provision of a mechanism of resistance to various stresses, such as those caused by bacterial toxins, histamine, shock, water intoxication, low temperature, and low oxygen pressure.

Wider functions have been suggested, to which suggestions a valuable critical review by Ingle (2) acts as a useful corrective.

Thus Hartman stresses regulation of permeability of the capillaries (and thereby regulation of blood volume) and of tissue cell membranes in general (and thus of fluid shifts in the organism). Ingle considers that the evidence for a specific effect on membrane permeability is indirect and unsatisfactory.

Hartman and others list control of growth as a function (since adrenalectomy retards growth). This, however, is generally considered to be a non-specific effect (cf. Kendall), and Ingle attributes it to reduction in food intake through loss of appetite, and general physiological abnormalities, rather than to any intimate connection between cortical function and growth processes.

Hartman speaks of regulation of sulphur metabolism, with perhaps specific control of glutathione. Evidence of such specific effect seems lacking.

Control of the nervous system has been suggested, which may be in part direct (since the psychoneural disturbance in Addison's disease—a hypocorticoadrenalism—sometimes precedes the asthenia and other signs and symptoms of the disease). The evidence favouring direct control seems slight.

Hartman believes that the adrenal cortex produces a compound associated with lactation, which he terms *cortilactin* (cf. Spoor, Hartman and Brownell). This view finds little support from others and is not confirmed by the work of Hurst, Meites and Turner.

Selye (2) finds that those steroids with hormonal action (whether this be associated with adrenal cortical function or not) act as anaesthetics when injected in such a manner as to produce a rapid high concentration in the blood. This obviously is a pharmacological but not a normal physiological effect.

Thymic involution seems due to some hormone of the adrenal cortex. Administration of corticosterone to the experimental animal produces

thymic atrophy rapidly (cf. Kendall). From clinical data there seems to be some relationship between cortical hypofunction and enlargement of thymus and lymphoid tissue. Adrenalectomy in both male and female rats produces an increase in the weight and a true hyperplasia of the thymus (Papela). When adrenalectomized male rats are maintained for forty-five days by sodium chloride (see below) thymic involution does not occur (Reinhardt and Holmes) indicating that such control of the thymus is through the Group I compounds of the cortex. The sex hormones also cause atrophy of the thymus and lymph nodes in the rat. The mechanism is unexplained (Ingle).

When the Group II compounds are administered to normal rats, there results atrophy of the adrenal cortex itself; Group I compounds do not produce this effect (Kendall).

The relatively great importance of the control of electrolytes is illustrated by the fact that the lives of adrenalectomized animals can be prolonged by daily injections of sodium chloride solution (without endocrine administration). Kendall *et al.* state that adrenalectomized dogs may be maintained in normal condition by continued administration of sodium chloride, plus sodium citrate or carbonate, and adequate glucose, and without other therapy, and that if the potassium intake be kept low such animals can even be carried through a reproductive cycle.

The control of electrolyte distribution is usually considered to be by direct action on the kidneys, and on the tubules of the kidneys, but this assumption does not rest on finite evidence nor is the mechanism of the action known (cf. Ingle (2)).

Desoxycorticosterone is at least six times more effective than corticosterone in maintaining a normal level of blood urea (cf. Kendall).

Loeb *et al.* have found that overdosage with desoxycorticosterone can reduce the blood plasma concentration of potassium so greatly that paralysis results.

Long (2), reviewing the mechanism of action of adrenal cortical hormones on carbohydrate and protein metabolism, considers that while the exact mechanism is not yet understood, two processes are influenced, the oxidation of glucose in the peripheral tissues, and the formation of carbohydrate from amino-acids or their residues after deamination. (He points out also that certain changes in inorganic metabolism are involved in these effects, such as increased potassium and phosphate excretion which accompany increased rate of gluconeogenesis.)

Some of the evidence leading to such conclusions may be briefly referred to.

Long, Fry and Thompson showed that pure corticosterone, or large doses of adrenal cortical extract, produce glycosuria in partially depancreatized rats.

In adrenalectomized animals there is a decrease in the formation of carbohydrate from protein, as evidenced by the accompanying reduction of urinary non-protein nitrogen. Such animals are abnormally sensitive to insulin. Treatment with cortical extracts or with any one of the Group II compounds reverses these changes ; the carbohydrate stores can be increased above normal by such means, both in the intact and adrenalectomized animal (Long, Katzin and Fry).

Ingle (1) claims that normal rats can be made markedly diabetic by administration of excess of 17-hydroxy-11-dehydro-corticosterone, while both normal and adrenalectomized animals, treated with Group II compounds, become abnormally resistant to insulin given in convulsive doses (Grattan, Jensen and Ingle).

Muscle efficiency, as displayed in adrenalectomized rats maintained with cortical extracts, depends on the Group II compounds (Ingle, quoted by Kendall).

According to Lewis *et al.* adrenalectomized rats lose the ability to synthetize glucose from lactic acid, pyruvic acid, and alanine, and administration of cortical extract or of 17-hydroxy-11-dehydro-corticosterone restores this function.

Reinecke and Kendall have shown that corticosterone, dehydrocorticosterone, and 17-hydroxy-11-dehydro-corticosterone facilitate the deposition of glycogen in the liver of the fasting rat, while desoxycorticosterone does not produce this effect.

Claims have been made that the adrenocortical hormones are useful in treatment of shock, but such claims cannot be upheld. Ingle (3) has summarized the evidence and concludes " No convincing evidence has been forthcoming to show that any of the cortical hormones will protect animals or patients having undamaged adrenal glands against naturally occurring forms of shock." In certain unnatural conditions such as potassium poisoning and water intoxication these hormones possibly increase resistance.

Some additional effects of adrenalectomy. Over 80 per cent. of adrenalectomized rats die when submitted to a temperature of 39° C. and high humidity for four hours. Desoxycorticosterone acetate affords complete protection. (Hermanson and Hartman.) Adrenalectomized rats show marked diminution of gastric secretion and the gastric juice tends to resemble that in achlorhydria. Sodiumchloride and desoxycorticosterone do not restore a normal gastric juice but whole cortical extract does, so that the effect appears due to lack of the compounds of Group II (Tuerkischer and Wertheimer). The adrenalectomized rat maintained on sodium chloride for twenty days has a subnormal plasma albumin concentration (Leathem).

Output of adrenocortical hormones. This is undoubtedly relatively large. Study of blood from the adrenal veins by the Selye-Schenker cold test suggests that the daily output from both adrenals of a 10 kg. dog is equivalent to the amount in 17 kg. of beef adrenals (Vogt). The concept of a high steroidal turnover in the adrenals is supported by the finding of up to 0·86 gm. of neutral 17-ketosteroids in twenty-

four-hour specimens of urine of patients with tumours or hyperplasia of the adrenal cortex (Engstrom, Mason and Kepler). More work in this field is needed.

Alarm reaction. This term is due to Selye (1). He has observed in experiments, chiefly on the rat, that if the organism is subjected to an unusual and severe but non-specific stimulus (such as continued exposure to temperatures just above freezing-point, handling of the intestine, or poisoning with sub-lethal doses of such compounds as atrophine or morphine), a " general adaptation syndrome " develops, which can be divided into two or three stages.

Between the sixth and twenty-fourth hour after application of such a stimulus there is rapid involution of the thymus and lymph glands, spleen and liver, loss of cortical lipides and chromophile substance from the adrenals, accumulation of transudates in pleura and peritoneum, decrease of muscular tone, drop of body temperature, and ulcer formation in the digestive tract. Urine output is decreased, and hypoglycaemia and hypochloraemia appear.

Subsequently, the adrenal cortex enlarges, regaining lipide granules, and the medullary chromophile cells become distended with vacuoles. Blood sugar and chloride return to normal values. Later on the gonads become atrophic, degranulated basophile cells appear in the anterior pituitary, the thyroid tends to become hyperplastic, and secretion of milk ceases in the lactating animal.

Under continuous stimulation, if the stimulus be not too severe, the experimental animal builds up a resistance, so that ultimately the appearance and functions of the organs return practically to normal. But with still further treatment, after from one to three months the animal loses this resistance, hypoglycaemia and hypochloraemia return, and the animal finally succumbs in a stage of exhaustion.

Selye considers that the phenomena exhibited by these non-adrenalectomized animals are due to a state of relative cortical insufficiency. Ingle (2) comments : " But cortical insufficiency can also be regarded as another means of causing non-specific damage to the organism. From this standpoint the secondary symptoms of cortical insufficiency may be regarded as an alarm reaction rather than to assume that any alarm reaction is a state of relative cortical insufficiency. Although it is very probable that under certain conditions of stress the cortex is incapable of meeting the functional requirements for its hormones, thus making symptoms of damage more likely to occur, it has not been proven that a state of functional cortical insufficiency is an essential condition for the manifestation of the alarm reaction. In either partially depancreatized or normal rats, changes which are similar in some respects to those of the alarm reaction can be induced by the administration of large amounts of either cortical extract or of 17-hydroxy-11-dehydrocorticosterone. The pathologic changes occurring during the alarm reaction cannot be prevented by treatment with cortical principles, although in some experimental situations resistance can be increased."

Experimental nephrosclerosis in the rat has been studied by Selye and his co-workers. They state that there are two types of action, " renotropic " and " nephrosclerotic." The first is purely stimulative and is mainly characterized by hyperplasia and hypertrophy of the

tubular cells. Nephrosclerotic action is more damaging, with hyalinization of the renal glomeruli and arterioles, as well as the formation of hyaline casts which obstruct the tubular lumina. It is produced by *overdosage* of desoxycorticosterone, or injections of saline suspensions of the anterior pituitary of cattle (the latter produce the renotropic action also). Animals are sensitized to nephrosclerosis by unilateral nephrectomy and a high intake of sodium chloride.

Experimental nephrosclerosis is usually accompanied by *periarteritis nodosa* in extra-renal blood vessels.

Simultaneous administration of thyroxine greatly accentuates the nephrosclerotic action of desoxycorticosterone, but not the renotropic action of methyl testosterone.

Administration of ammonium chloride is highly effective in preventing some of the more serious toxic effects of overdosage with desoxycorticosterone, but does not significantly affect its therapeutic use. This antagonistic action of the ammonium salt is also effective against the action of the crude anterior pituitary extract on heart, adrenals and kidneys.

A higher carbohydrate, lower protein diet also confers resistance against experimental nephrosclerosis.

Selye suggests that intoxication with excessive amounts of endogenous cortical hormones of the Group I type may play a *rôle* in clinical nephrosclerosis with renal hypertension, periarteritis nodosa, and perhaps also in some of the manifestations of rheumatic fever, and that it might prove useful to test the efficacy of ammonium chloride in such diseases, while its use might permit more extensive therapeutic use of desoxycorticosterone acetate (cf. Selye (4)).

Harrison has been entirely unable to confirm Selye's results and concludes that desoxycorticosterone is not a factor in the causation of arthritis in rats, but that infection is intimately concerned in the etiology of nephrosclerosis and of rheumatic cardiac lesions while low air temperature may possibly be an additional factor. Selye (5) claims that Harrison's results are invalid because but few animals were used, but it is quite evident that further independent experimental support is necessary before Selye's conclusions can be generally accepted.

While, as has been indicated, the production in the adrenal cortex of small amounts of compounds with functions associated with the sex glands is of little or no significance in the normal adult animal, there is evidence that the adrenal cortex does exert some control of gonadal functions. According to Carr and Connor, adrenalectomy produces in male rats loss of libido and potency, and degeneration of the seminiferous tubules, and in the majority of female rats there result suppression of the oestrous cycle and atrophy of the ovaries (cf. also Martin ; Corey and Britton), which can be restored by homotransplants of adrenal cortex (Martin) or injections of cortical extracts (Corey and Britton ;

Britton and Kline). Similar effects are seen in patients with Addison's disease.

It may be assumed, until adverse evidence is forthcoming, that any control of the gonads by the adrenal cortex is indirect.

Assay of Adrenal Cortical Hormones. Early methods of assaying extracts were devised before the multiple nature of adrenal cortical function was realized. Various devices have been used, such as maintenance of adrenalectomized animals, as judged by body-weight and blood non-protein-nitrogen (cf. Pfiffner, Swingle and Vars), response of the muscle of the adrenalectomized rat to short stimuli (Everse and de Fremery), and to prolonged stimulation (Ingle (1)).

Obviously any satisfactory method of assay will need to measure both of the major cortical effects, that on electrolyte regulation (sodium retention), and that on carbohydrate and protein metabolism (perhaps by measurement of gluconeogenesis, or of glycogen deposition in the starved rat).

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ADDISON'S DISEASE

Introduction. Two classical studies of Addison's disease have been presented, that of Addison himself in 1855, and the monograph of Rowntree and Snell published in 1931 (which includes Addison's original paper). Valuable recent papers are those of Loeb, and of Thorn (with comments by Wilder, Thompson, and Cleghorn). These authoritative presentations form the bases of the present account.

Addison's disease is the chronic condition of hypocorticoadrenalism in human beings which corresponds to the acute condition produced in animals by double adrenalectomy. It differs quantitatively through the gradual onset of the disease and the incomplete degree of hypofunction, and qualitatively in some proportion of cases through presence of another disease, such as tuberculosis, responsible for the damage to the adrenals.

The disease is slightly commoner in men than in women, and is commonest between the ages of thirty and fifty years.

Classical Addison's disease is infrequent in children. Some 45 cases appear in the literature, as reviewed by Rosin and Friedman, of whom only half a dozen were under ten years of age. Rosin and Friedman report the case of a seven-year-old boy.

The onset is usually, but not invariably, insidious; this is especially true of tuberculous patients. A respiratory infection, often diagnosed as influenza, may mark the beginning of the illness. Rowntree and Snell suggested that this may not be influenza at all, but in reality an acute initial phase of Addison's disease.

The duration of the disease before modern treatment was usually between six months and two years, although a case has been recorded in which symptoms were only exhibited for eighteen days before death of the patient, while some chronic cases survived several years. The patients were invalids throughout the course of their illness.

Modern treatment really commenced with the application to himself of oral adrenal therapy by Dr. A. L. Muirhead in 1920. The value of salt therapy was discovered a little later. When potent adrenal cortical extracts became available, their therapeutical use in Addison's disease proved so beneficial as to suggest at first that the disease was conquered. Subsequently a lesser degree of optimism seemed more fitting. The synthetic production of desoxycorticosterone acetate at moderate cost proved another forward step of great value, and its utilization in pellet form has still further eased the life of the Addisonian patient.

While the present status and prognosis of this patient is not as good as that of the diabetic, let alone that of the hypothyroid patient, great progress has been made, and if the still unknown active compounds of the cortex can be isolated, and if corticosterone or some other of its group of compounds can be synthetized cheaply, still more benefit will accrue to the patient.

Signs and Symptoms of the Disease. Addison listed "anaemia, general languor and debility, remarkable feebleness of the heart's action, irritability of the stomach, and a peculiar change in the colour of the skin." To these must be added loss of weight and decrease in blood pressure. The pigmentation and the arterial hypotension are two outstanding physical signs.

Thorn, Dorrance and Day found the presenting symptoms in 158 cases to be weakness and fatiguability in all, pigmentation in 94 and anorexia in 91 per cent.

The *pigmentation* is usually brownish, but may vary from negroid to amber and blue-grey; the depth of colour varies still more. The distribution may be diffuse or blotchy. The hands and arms, face and neck, and areas subjected to pressure or friction are especially affected. Areas normally pigmented have the pigmentation accentuated. The colour of the hair often

darkens. The lips are usually dark, and dark patches are seen in the mucous membranes of the mouth which are regarded as especially characteristic. Jet black freckles are common. However, on the one hand some cases of Addison's disease exhibit no pigmentation, and on the other care must be observed in diagnosis, when necessary, to exclude racial pigmentation. The mechanism whereby this pigmentation is produced is as yet completely unexplained.

Patients with Addison's disease, when first seen by a physician, almost invariably exhibit *hypotension*. Under emotional stimuli the blood pressure may rise to normal level or even higher, but during crises (*vide infra*) it falls to low levels and a picture of dehydration and shock is presented. Many of the symptoms and complications of the disease are secondary to that " remarkable feebleness of the heart's action " stressed by Addison, with the resulting hypotension and poor circulation.

Asthenia, subjective and objective, mental as well as physical, is a cardinal symptom and often the first to appear. It fluctuates, being worse after periods of physical or mental activity.

The *gastro-intestinal manifestations* include anorexia, nausea and vomiting, gaseous distension, and occasional periods of intense diarrhoea (although there is a greater tendency to constipation). Stomach and intestinal ulceration is often found (it has also been observed in adrenalectomized animals). There is occasionally frank haemorrhage. Hypochlorhydria is common and achylia frequent.

The digestive disturbances are responsible for the marked *loss of weight*. There is no noticeable emaciation, though muscle tissue atrophies.

The patient is unduly sensitive to cold and to pain stimuli. There is marked lack of resistance to infection, exposure, stress, and drugs.

Course of the Disease. It is usually steadily progressive, though striking remissions and exacerbations may occur. In the exacerbations, the *crises*, hypotension and gastrointestinal symptoms are pronounced, the blood volume is often markedly diminished so that the blood is thick and viscid, and there is clinical evidence of dehydration. Death may occur in such crises.

Failure may be gradual, with increasing asthenia, to a state of complete exhaustion, or termination may be characterized by persistent nausea and vomiting and cerebral symptoms, or there may be sudden collapse after exercise or during a mild infection. In many cases the manner of death resembles that seen in the

experimental animal after adrenalectomy. In some cases the patient dies in hypoglycaemic coma. (Cf. Anderson and Lyall; Welty and Robertson.)

Etiology of the Disease. Typical signs and symptoms rarely become manifest until extensive destruction of functioning adrenal cortex tissue has occurred (Thorn). Tuberculosis and atrophy are responsible for this destruction in the majority of cases. Syphilis is among the causes of an atrophy. A case of amyloidosis of the adrenals, associated with tuberculosis of other tissues, has been reported by Mendel and Saibil.

According to both Thorn and Wilder, while tuberculosis is still the commonest single etiological factor responsible for adrenal damage, yet the number of cases without tuberculosis seems to be relatively increasing. Cragg (reported by Wilder), reviewing thirty recent necropsies, found adrenal tuberculosis in twelve, carcinoma in two, atrophy (without evidence of tuberculosis or other disease) in fifteen, and no definite cause in one. Cawadias stresses the possibility of cancer as cause, and considers that fever is often characteristic of such cases of Addisonian adrenocortical cancer.

Cleghorn points out that active tuberculosis in tissues other than the adrenals can contribute to the death of patients with Addison's disease.

Marañon thinks that there may be a racial factor, and that the disease is relatively commoner in Spain.

Clinical and Laboratory Findings. The *body temperature* in uncomplicated cases is usually decreased (97° to 98° F.); it does not fluctuate markedly. In presence of active tuberculosis the temperature may be above normal. There may be a considerable rise in temperature two or three days before death.

Respiration is usually normal, but becomes markedly irregular in crises and in the advanced stage of the disease. Air hunger may be complained of, and sighing respiration sometimes develops.

The *urine volume* remains at low normal, except in advanced stages of the disease, when it is markedly diminished. Its specific gravity tends to be low, and, in the later stages, to be fixed between 1·008 and 1·012. *Albuminuria* in traces or larger amounts is frequent; *glycosuria* is absent in uncomplicated cases. Hyaline and granular casts are common, but pus cells and erythrocytes, when present, are usually due to concomitant tuberculous lesions in the kidney or urethra. *Creatinuria* is not uncommon, but since it is usually present in conditions involving muscular atrophy, it is of no special significance.

Renal insufficiency, partly due to circulatory asthenia, is often present in crises and in the terminal stages. The urea clearance test may indicate such insufficiency even in presence of normal blood non-protein nitrogen. Nephrosis and tubular atrophy are frequently seen at autopsy.

As already mentioned, *hypochlorhydria* is usually present; *achlorhydria* is frequent.

The *basal metabolic rate* is usually within normal limits, but falls when there are marked nausea and vomiting, and in crises.

Blood Findings. Plasma *sodium* is decreased, and plasma water and volume also, in somewhat lesser degree. Plasma *potassium* is increased. There may be increased non-protein nitrogen, inorganic phosphorus, and sulphate.

Hypoglycaemia is frequently present—disturbances in carbohydrate metabolism vary greatly in intensity. (It has already been mentioned that death may occur in hypoglycaemia.)

In addition, the patient occasionally exhibits hypercalcaemia and increase of plasma phosphatase; the cause of neither has yet been ascertained.

The *respiratory quotient* in fasting conditions tends to be above normal (cf. Thorn *et al.*).

Diagnostic Tests. By lessening the sodium chloride intake in the diet of a patient suspected of suffering from Addison's disease (and in absence of pigmentation, or with dark-complexioned patients, diagnosis is sometimes difficult), it is possible to produce symptoms of Addisonian crisis. This test, due to Wilder, is not without danger and may have been the cause of death (cf. Lilienfeld; Garvin and Reichle). Obviously it should only be employed in hospital and when a proved potent adrenal cortical extract is available in emergency (cf. Snell). A positive result may not be shown for three or four days (Parker).

A less dangerous test which seems to yield good results is the so-called "water test" of Robinson, Power and Kepler. It involves two procedures, based on (i) delayed excretion of additional intake of water by the Addisonian patient, and (ii) increased excretion of chloride, but relative retention of urea by such patients. Two procedures are carried out, simultaneously, though the second is unnecessary if the first gives a negative result. The test is based on the fact that in Addison's disease rapid ingestion of water is not followed by a corresponding increase in urine secretion, while the urinary concentrations of sodium and chloride remain relatively fixed (Reforzo-Membrives, Power and Kepler).

Procedure 1. The day preceding the test the patient eats three ordinary meals but omits extra salt. He is requested not to eat or drink anything after 6 p.m., but up to this time he may drink water as desired. At 10.30 p.m. he empties his bladder and the urine is discarded. All urine which is voided from then on, up to and including 7.30 a.m., is collected. The volume of this urine is measured, and the urine saved for chemical analysis. Breakfast is omitted. The patient is asked to void again at 8.30 a.m., and then he is given 20 c.c. of water per kg. body-weight (9 c.c. per lb.), which should be drunk within the forty-five minutes. He should then empty his bladder at 9.30, 10.30, 11.30 a.m., and 12.30 p.m. To eliminate the effects of exercise and posture on urinary secretion he is kept at rest in bed except when up to void. Each specimen is kept in a separate container. The volume of the largest of the four specimens is measured.

Some patients with Addison's disease excrete so little urine that they are unable to void more than once or twice during the entire morning. In such a case the amount of urine excreted per hour may be calculated, though frequently this is unnecessary because of the very low output throughout the morning.

Conclusions : (*a*) *If the volume of any single hourly specimen voided during the morning is greater than the volume voided during the night, the result of the test is considered negative, indicating the absence of Addison's disease.*

(*b*) If the volume of the largest hourly specimen voided during the morning is less than the volume voided during the night, the result is inconclusive ; *Addison's disease may or may not be present.* In this case the second procedure is necessary.

Procedure 2. Blood is drawn while the patient is still fasting, and the plasma is analysed for urea and chloride. The specimen of urine voided during the night is also analysed for urea and chloride. The four determinations, and the volume determinations of procedure 1, are applied to the following equation :

$$A = \frac{\text{Urine-urea (mg. per cent.)}}{\text{Plasma-urea (mg. per cent.)}} \times \frac{\text{Plasma-Cl (mg. per cent.)}}{\text{Urine-Cl (mg. per cent.)}} \times \frac{\text{Volume of largest hourly day specimen of urine (c.c.)}}{\text{Volume of night urine (c.c.)}}$$

Conclusions : If " A " is greater than 30 the patient probably does not have Addison's disease. If " A " is less than 25 the patient probably has Addison's disease, provided that nephritis can be excluded.

Robinson, Power and Kepler found values of " A " in Addison's disease ranging from 1 to 20, in various fatigue states (in which Addison's disease was not present) from 42 to 348, in two cases of renal disease 16 and 19, and in other organic disorders 33 to 301.

Note. Patients who have already been treated with desoxycorticosterone acetate or potent adrenal cortical extracts must have such therapy discontinued for at least two days. If the discontinuance leads to typical Addisonian crisis the test is obviously not needed.

Treatment of Addison's Disease. The close parallel so obvious between the signs and symptoms and clinical and laboratory findings in the patient with Addison's disease and the adrenalecto-

mized animal obviously indicates that the treatment which proves most beneficial to the animal is the treatment best suited to the patient. The armamentarium therefore consists of salt therapy, desoxycorticosterone acetate, and, until such time as one or more of the compounds controlling carbohydrate metabolism (and typified by corticosterone) are available in quantity and in reasonably cheap form, use of potent adrenal cortical extracts.

Treatment should aim at restoration of the patient to a life of normal activity. Before considering what is now becoming routine treatment, some less usual methods may be mentioned.

Thorn thinks that patients who show remission of the disease to the extent of being able to discontinue specific therapy for awhile probably have had some degree of regeneration of adrenal cortical tissue. Since the adrenal cortex is controlled by the adrenotrophic hormone of the anterior pituitary, and atrophies following removal of this stimulus by hypophysectomy, administration of pituitary adrenotrophic preparations might be expected to benefit Addisonian patients. Thorn states that so far no striking benefit has been observed following such therapy, perhaps because of insufficient dosage.

Transplantation of human normal adrenal glands to patients with Addison's disease has been attempted. Thorn states that at best it has only been of temporary value. Katz and Mainzer, writing in 1941, found only five cases of successful transplants in the literature in patients who indubitably had Addison's disease, success being judged by observations over periods of five months to a year. They reported a sixth case. An adrenal gland of a patient in the same blood group who had just died was grafted into the abdominal muscle of a patient with severe Addison's disease. Results as observed over a period of fifteen months were excellent. Symptoms of adrenal insufficiency were only noted under conditions of marked exertion or during temporary infection.

Thorn classifies patients with Addison's disease into three groups, as follows :

Group A. Patients who need only extra sodium chloride, or low potassium intake, or both.

Group B. Patients who need sodium chloride, and in addition, at frequent intervals, administration of hormone to prevent relapses.

Group C. Patients who need continuous hormone therapy.

The treatment of crisis is specific and needs separate consideration.

Patients in Group A have frequently first manifested symptoms of the disease during the course of an intercurrent infection or a gastro-intestinal upset. Following subsidence of such complications, they frequently improve to such an extent as to need sodium chloride only. In addition to that normally in the food,

the dosage varies from 5 to 20 gm. daily. Gastric irritation is lessened if it be taken with food, or as enteric-coated 1-gm. tablets.

Some additional patients may be added to this group if their potassium intake be restricted.

Sodium citrate has been advocated along with chloride (since these patients excrete sodium faster than chloride). Thorn considers it unnecessary in absence of demonstrable renal insufficiency. Wilder considers it useful.

The patients in Group B have low hormonal needs. They may be maintained many months in good condition with 5 to 15 gm. of sodium chloride daily, with supplemental hormone therapy when this is indicated by occurrence of undue fatigue or nausea. At such times Thorn recommends use for a few days of one of three types of therapy : (*a*) large doses of adrenal cortical extract by mouth (corresponding to 400 to 1,200 gm. of adrenal gland daily), or (*b*) two or three injections per day of 1 c.c. of aqueous cortical extract (corresponding to 100 to 150 gm. adrenals daily), or (*c*) one daily intramuscular injection of 1 to 2 mg. of desoxycorticosterone acetate in oil.

Most patients in Group C can be satisfactorily treated with either (*a*) 2 to 3 c.c. of adrenal cortical extract injected two to three times daily, plus 5 to 15 gm. sodium chloride, or (*b*) one intramuscular injection of 2 to 5 mg. of desoxycorticosterone acetate in oil, with or without 2 to 5 gm. of sodium chloride, or (*c*) pellets of desoxycorticosterone acetate (one of 125 mg. for each 0·5 mg. of injected hormone required for maintenance) with or without sodium chloride, or (*d*) some suitable combination of these.

The criteria for adequate therapy are restoration of normal weight, blood pressure and plasma electrolytes. If marked improvement does not follow addition of 9 to 12 gm. of sodium chloride to the regular diet, supplemental hormone therapy is probably necessary. The maximum increase in blood pressure may not be attained for from four to sixteen weeks.

In patients past middle life a dosage of more than 3 mg. of desoxycorticosterone acetate may impose too great a load on their cardiovascular system, and if more is given their activity should be restricted.

Oral Administration of Hormone. This, according to Thorn, has two disadvantages : (i) Three or four times as much is required of these costly preparations by mouth as by injection ; (ii) There is no assurance of uniform absorption, since the Addisonian patient is so liable to gastrointestinal disturbances. Thompson places the relative effective-

ness of oral administration at a still lower level, and considers that it is not practicable at present.

Very recently several investigators have found that desoxycorticosterone acetate dissolved in propylene glycol (1 mg. per drop) is rapidly absorbed if given sublingually, dosage being regulated according to need (cf. Anderson, Haymaker and Henderson ; Turnoff and Rowntree ; Thorn *et al.*).

Restriction of potassium is undesirable, and sodium citrate should not be given, *when desoxycorticosterone is administered* (Wilder).

Pellets of Desoxycorticosterone Acetate. Pellets should only be used after a patient has been balanced by injection for at least a month and the maintenance dose for that patient determined.

Obviously the amount of the hormone absorbed from a pellet will depend on its surface area, and therefore on its size and shape, and also obviously the amount absorbed will change over a period of time, with the diminishing size and altering shape of the pellet. McCullagh, Lewis and Shively have recently published a valuable study of the rate of absorption of such pellets. They find that when 75 mg. cylindroids (8 mm. high and 1·5 mm. radius) are implanted in the lateral chest wall, 2 or 3 inches below the axilla (using local anaesthesia), the rate of absorption varies from 0·14 to 0·35 mg. per pellet per day. The size and shape of the pellet considerably modifies the absorption rate. Supplemental sodium chloride therapy lessens the necessary daily requirement, and its withdrawal provides an easy means of overcoming the effects of hormone overdosage (as oedema), while increased dosage of sodium chloride is frequently needed towards the end of the life of a pellet.

Dietary Carbohydrate. As long as the patient receives and absorbs adequate carbohydrate in readily available form, and provided the blood pressure, plasma volume and electrolyte balance have been restored to normal, he may live comfortably without the hormone-factor of the adrenal cortex which controls carbohydrate metabolism. However, whenever the carbohydrate requirement is increased, or its intake is lessened, as in starvation, fever, infection or gastrointestinal disturbance, since the patient is unable to furnish himself adequately with glucose by gluconeogensis from protein, hypoglycaemia (with fatal outcome) may ensue unless carbohydrate is given parenterally or (whole) adrenal cortical extract is given in large doses (Thorn).

Complications of Treatment. In rare instances complications such as anaemia, hypoproteinaemia, phlebitis, hypertension, renal disease, or cirrhosis of the liver limit the amount of desoxycorticosterone therapy which may be given, because of the excessive sodium, chloride and water retention accompanying adequate therapy (Thorn).

McGavack stresses the necessity of considering the cardiac condition during therapy. Any existing cardiac damage may be increased by excessive salt or water ingestion, severe curtailment of intake of potassium, or overdosage with adrenal cortical hormones. There may be accompanying muscular weakness,

anasarca, hypoproteinaemia, and hypertension. Such effects are avoided by controlling electrolyte therapy when blood and urine sodium and potassium values approach normal, making administration of vitamin B_1 a standard part of the therapeutic *régime*, using cardiac mensuration as an index of treatment, and avoiding excessive dosage of hormone. McGavack (2) states that the changing size of the heart can be used within definite limits as an index of the respective amounts of sodium and desoxycorticosterone acetate that can be employed safely. Cardiac measurements can, in general, be maintained within normal limits by maintaining the ratio

(Sodium, grams) $\times$ (Desoxycorticosterone acetate, mg.) $=30$ to 45.

the actual figure for any individual patient being very constant (cf. also McGavack and Babcock).

Use of sesame oil as medium for injection occasionally leads to unfavourable reactions—localized redness, pain and tenderness. A different oil, or pellets, can be substituted.

Overdosage (of desoxycorticosterone) may lead to excessive oedema and to hypertension, and, if continued, to pulmonary oedema (especially if there was pre-existing myocardial damage or prolonged invalidism), and sometimes (through low plasma potassium) to symptoms of muscular weakness suggestive of familial periodic paralysis (cf. Thorn).

Treatment of Crisis. The patient may be first seen in crisis, or may proceed to crisis through inadequate treatment, or through complications such as infection when routine treatment becomes inadequate. Thorn recommends rather hard and fast rules in treatment of crisis, but Thompson points out that these are inappropriate, since severity and duration of crisis vary, and treatment must be adapted to the individual.

Immediate intravenous infusion of large volumes (up to two or more litres) of *hypertonic* saline (containing 5 to 10 per cent. glucose, and relatively large amounts of cortical extract) is usually given for the first day or two, with, if necessary, subcutaneous injection of desoxycorticosterone acetate in oil as well. Fluids are given by mouth as soon as tolerated, and the treatment is slowly tapered off towards the routine maintenance dosage as the patient recovers. (Wilder considers that desoxycorticosterone should not be used in crisis.)

Treatment with androgens. Claims have been made that testosterone therapy is moderately successful in increasing strength and energy of patients with Addison's disease (cf. Talbot, Butler and MacLachlan; Williams *et al.*).

Prognosis. This is steadily improving. Thus Cleghorn has reported the results of 12 cases treated with desoxycorticosterone over periods varying from five to twenty-two months. Four were sufficiently recovered to follow their former occupations. Two others were unable to work, but enjoyed considerable, if restricted activity. Four others required supplemental treatment with cortical extracts and were invalids. One, in remission, needed no extra salt or other therapy except during an infection. One was dead.

Firor reports even better results with 17 patients treated with 125 mg. pellets of desoxycorticosterone acetate. Some have already had a second implantation. At the time of report all were in good health after four to nine months' treatment, although one patient apparently showed a partial regression. All had gained weight and all but two were engaged in active work. None had lost all pigmentation.

There are numerous similar reports in the recent literature.

In agreement with the unknown causation of the pigmentation its complete disappearance under any treatment so far available has only rarely been observed.

I am indebted to Professor H. P. Himsworth and to his patient for the details of one of the best results of the modern treatment of Addison's disease, and for permission to use them. The patient, himself a physician, developed the disease in 1936, at the age of thirty-one, and came under the care of Professors T. R. Elliott and Himsworth. Himsworth reported the case in 1939, as presenting an exceptionally severe condition, needing a daily injection of 25 c.c. of adrenal cortical extract ("Organon") and 20 gm. of sodium chloride for maintenance. "But on such a dose for the last eighteen months he has been remarkably well. He can drive 200 miles a day by car, in Switzerland he was able to ski and climb 3,000 feet up an easy mountain, and he has recently held a responsible if not arduous post of daily routine work. His clinical condition is not, however, uniformly stable at this relatively high level, and is always liable to remission as a result of mild infections."

The patient himself, writing in May, 1945, stated that in 1939 he settled in South Africa for the sake of the warmer climate, and in October of that year had his first implant of 50 mg. of desoxycorticosterone acetate (DOCA). "Within a week I was enjoying my food and asked for a second helping for the first time since the disease started." In December he recommenced practice, in 1940 was married, and he has since practised his specialty

without hindrance from his health. He wrote " During the last six years I have suffered no ill-health beyond a rare cold, say, once a year. . . . I have received implants of DOCA of increasing size, and at greater intervals. The last one, of 200 mg., was implanted last November and will, I hope, last from nine to twelve months as previous tablets of 125 mg. (sent me through the courtesy of Dr. Thorn of Johns Hopkins and Dr. Ralli of New York) lasted from six to eight months. . . . In addition to implantation I have a weekly injection of 10 c.c. Cortin or Eucortone, and 1 c.c. of DOCA in oil. In hot weather or if I perspire freely I take a teaspoonful of sodium chloride mixed with a fruit drink, otherwise I take no salt beyond that used in cooking or at the table. . . . Following a suggestion of Dr. Ralli in 1938 I have supplemented an ordinary full diet with vitamin C and the B complex. . . . I have given all the details I think relevant, as life is now a source of pleasure to me and not a burden to be borne."

His South African physician reported at the same time the following data : objectively there were no physical signs ; blood pressure, 110/80 ; cardiac rate, 90 ; urine, normal ; weight, constant at 195 lb. ; *no pigmentation* (the italics are mine) ; and the final comment : " If one did not know of your previous history of Addison's disease, it would not, as you are now, be possible to diagnose it clinically."

This seems to be one of the rarer cases in which pigmentation has disappeared. Answering my inquiry on this point, Professor Himsworth wrote that this patient, when first seen, had marked pigmentation. " On admission his general tint was a café-au-lait colour. On this background moles and freckles stood out as dark sepia dots. There was increased pigmentation of the nipples, median line below the umbilicus and the genitals. On the forehead and left cheek there was an irregular dirty brown smudge. The lips had irregular patches of pigmentation on the external surface. No pigmentation was seen in the mouth by a careful search." He adds that he inclines to the view that the pigmentation of the mucous membrane is the last to appear and the first to go. He thinks this case is the longest survival. The deaths of some of his other patients are attributable to their own ignorance. " I cannot get it into their heads that they must attend regularly for a check-up, irrespective of how well they are feeling. The result is they go on feeling well, decide they will come up to hospital next month when it is more convenient, and in that month suddenly plunge into a crisis. I am beginning to believe

that as far as DOCA inplants are concerned, Addison's disease should be treated by the calendar rather than by the patient's feelings."

The above case has been dealt with in some detail, since it illustrates that, provided a patient is educated to the vicissitudes of the disease and able to co-operate fully, there really is a possibility of prolonged life and usefulness even in severe cases.

According to van Zwanenberg, Addison's disease is aggravated by pregnancy and the prognosis for both mother and child is bad. He reported the results in 13 cases. In two the disease appeared to develop in the puerperium ; one of them died in three weeks. Concerning the other 11, the baby was born dead in 6 cases and the mother died after labour in 6 cases. He considers that the best course is to allow the pregnancy to continue, with adequate treatment by cortical extract both before and after labour.

Recent Unusual Cases. Rushton, Cragg and Stalker report a case of spontaneous hypoglycaemia, with markedly increased sensitivity to insulin. Hyperinsulinism was suspected. No tumour of the pancreas could be found, but at autopsy both adrenal cortices were found atrophied in extreme degree.

Butler, Ross and Talbot reported the case of a new-born infant who showed slight increase in pigmentation. On the thirteenth day anorexia, nausea and vomiting developed, with impending collapse ; intravenous glucose and saline revived the infant. Both laboratory studies and clinical findings indicated Addison's disease, and administration of cortical extracts was necessary to maintain good health. The genital organs were large, and urinary output of oestrogens and androgens was above normal. The case was considered to be one of abnormal activity of the X zone (cf. p. 170), with inefficiency of the remainder of the cortex.

Wilkins and Richter report the case of a sexually precocious three-year-old boy, who ate (by choice) large amounts of sodium chloride since the age of one year, and who died when placed on routine hospital diet. Shortly prior to death blood sodium was found to be low, and non-protein nitrogen high. At post-mortem it was found that there was hyperplasia of the X zone, and marked diminution of the rest of the cortex. This case is reminiscent of Richter's experiments which demonstrated that adrenalectomized rats drank sodium chloride solution in preference to water.

Locket has reported a case of what appeared to be Addison's disease, complicated by severe normocytic, normochromic anaemia, steatorrhoea, and melanuria. Pernicious anaemia, idiopathic steatorrhoea, and sprue were ruled out. The patient responded fairly well to pellets of desoxycorticosterone acetate.

Cause of Pigmentation in Addison's Disease. Spoor and Ralli point out that several investigators have reported slight to moderate degrees of melanosis in animals following adrenalectomy. They themselves found that when black rats are fed a diet deficient in the filtrate factors of the B complex vitamins achromotrichia is produced and there is a decrease in the extractable melanin of the skin. Adrenalectomy at this stage results in an increase in such extractable melanin, but the

increase does not occur if the rats are treated with desoxycorticosterone acetate. Hence occurrence of the pigmentation of Addison's disease would seem to be due to deficiency of that type of hormone.

Use of Adrenal Cortical Hormones in Other Conditions. Goldman, Markham and Schaffer state that pemphigus involves the adrenals, and patients with this disease exhibit fundamental alterations in salt and water metabolism. They claim that a case of acute pemphigus was benefited by treatment with desoxycorticosterone acetate.

The possible use of cortical hormones in shock has been referred to (p. 207). Loeb has dealt with some of the apparently favourable literature. Desoxycorticosterone is certainly useless in shock; corticosterone has a possible beneficial effect (cf. Sevringhaus's review). Keating, Rynearson and Power state that there is no evidence that preoperative administration of desoxycorticosterone will prevent surgical shock, nor is there evidence that shock, as encountered among surgical patients, is associated with acute adrenal cortical insufficiency.

Hartman has dealt with various conditions—other than Addison's disease—in which administration of adrenal cortical hormones is possibly of value.

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HYPER-CORTICO-ADRENALISM

Conditions in which, through tumour or hyperplasia of the adrenal cortex, there is evidence of hyperfunctioning of the cortex, do not present a picture the opposite of that seen in Addison's disease, but one rather of distorted gonadal action, in which hirsutism is usually present, and which is frequently associated with Cushing's syndrome. Since this syndrome is common to tumour of the basophile cells of the anterior pituitary and tumour of the adrenal cortex, it will be discussed later (cf. Chapter XII).

However, since hirsutism is so marked a feature of this syndrome, it may be mentioned here that some evidence is accumulating that growth of axillary and pubic hair is normally under control of the adrenal cortex, rather than of gonadal hormones (cf. Albright, Smith and Fraser). Kepler, Peters and Mason have reported a case of Addison's disease with pubic and axillary alopoecia, but with normal menses.

Dijkhuizen and Behr report the deaths of four infants, three males and one female, following symptoms of a gastrointestinal stenosis disorder. Autopsy in three cases showed hypertrophy of the adrenals ; the literature contains records of a few similar cases. It was suggested that there is increased cortical activity in such cases.

However, any such hypertrophy may merely be a secondary response to some one of numerous kinds of stimuli and may in itself be without special significance (cf. Tepperman, Engel and Long ; Sarason).

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CHAPTER VIII

THE ENDOCRINOLOGY OF REPRODUCTION

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INTRODUCTION

THE endocrine differences between the two sexes are quantitative, rather than qualitative, so that it is desirable to make the closest comparison between them, rather than to consider them separately. Moore wrote recently "Animals are not selectively and exclusively male and female, but are intermixtures of both potentialities in which usually one set of characters predominates. Without a clear dominance of one set of characters the animal becomes an intersex or hermaphrodite." This set of characters is due to the dominant effect of certain hormones acting on a specific genetic constitution.

Since these hormones cannot be said to produce exclusively male or exclusively female effects, and since both sexes elaborate hormones appearing to produce effects associated with both sexes, the complexity of the endocrine factors governing sex is obvious.

More than one endocrine compound is essentially (but not necessarily exclusively) associated with "maleness," and more than one endocrine compound is essentially (but not necessarily exclusively) associated with "femaleness." The naturally occurring compounds, and synthetic compounds with like properties, are termed respectively *androgenic* and *oestrogenic*. The testes are the principal but not the sole source of androgens, and the ovaries are the principal but not the sole course of oestrogens. As has been seen in Chapter VII, the adrenal cortex produces compounds with androgenic, and compounds with oestrogenic properties, and, as will be seen, the placenta also produces oestrogenic compounds.

Development of endocrine knowledge concerning sex and reproduction awaited recognition of suitable test procedures. These were ultimately based on certain changes produced by castration (as the comb changes in capons), and others associated with the female sex cycle (as changes in the vaginal walls of female

animals during the cycle). Before these are considered it is desirable to review briefly the normal development of the gonads in mammals (for more detailed accounts such monographs as those of Frank, Parkes, or Robson must be consulted).

In the earliest stage of gonadal development of the human embryo no histological sex differentiation is as yet possible ; the tubular system is bisexual. Sex is first distinguishable in the third week of embryonic life (13 mm.) by appearance of the " testis cords " in the male. In embryos of both sexes Wolffian (male) and Müllerian (female) ducts develop equally for a while ; subsequently the development of one predominates, and that of the other lags, and finally is only represented by vestigial remains. Sexual differentiation in mammals is exemplified by (i) the gonad itself—ovary in the female, testis in the male, (ii) the accessory reproductive organs—(corpus luteum), uterus, vagina, clitoris, and mammary glands in the female, seminal vesicles, prostate, penis, in the male, and (iii) the secondary sex characters, markedly diverse in different species, and characterized in human beings by distribution of hair, by voice, and by a relative enlargement of the capacity of the pelvis in women.

The ovary can be considered as divisible into a superficial or cortical, and a deep or medullary layer. The latter consists of a highly vascular, highly cellular stroma of connective tissue, in which follicles are embedded along with the results from their degeneration or maturation. In addition, in many species, blocks or groups of epithelial cells are present, the " interstitial tissue " of the ovaries. In the human ovary the presence of this interstitial tissue has not been clearly demonstrated (and current opinion does not associate such interstitial tissue with ovarian hormones). The external layer of the cortex, single low cylindrical germinal epithelium continuous with the peritoneal epithelium, covers the tunica albuginea, an ill-defined layer of connective tissue containing some unstriped muscle fibres. From the epithelium epithelial cords grow into the substance of the ovary, and subsequently break up into small nests of " primordial follicles," some of them subsequently becoming enlarged to form the primitive ova. Each follicle consists, from without inwards, of the theca externa, the theca interna, and the follicular epithelium which carries the ovum. As the follicle matures it extends inwards until it reaches some size, but eventually also projects outwards, bulging the surface of the ovary. The cavity within this mature Graafian follicle is filled with a viscous liquid, the liquor folliculi. At birth the human ovary contains some thousands of primordial follicles and a few growing Graafian follicles.

From birth to puberty the ovaries slowly increase in size. With the approach of puberty the Graafian follicles become greatly enlarged, and eventually rupture, discharging their ova. Following such rupture the point of rupture closes, the cavity fills with blood, and is subsequently invaded by connective tissue. The follicular epithelium multiplies and its cells enlarge. They acquire more and more lipide material, which, in bovine and human ovaries, is coloured orange or yellow from the presence of a trace of carotene (with some xanthophyll), whence the name *corpus luteum*. In many other species, including the rat and mouse, the corpora lutea are not yellow in colour.

If the discharged ovum is unfertilized, after a short period involution and obliteration of the corpus luteum set in. If, however, the ovum is impregnated and becomes embedded in the uterus (or abnormally elsewhere) the corresponding corpus luteum enlarges still further, to involve about a third of the ovary, and persists throughout pregnancy.

The majority of the Graafian follicles fail to reach complete maturity and rupture, but undergo atresia at some stage short of this. Such follicles are finally entirely absorbed or else are metamorphosed into corpora lutea atretica and finally small corpora albicantes. The atresia seems to be associated with definite stages of the oestrous cycle.

Abruptly, with the first ovulation, occurs the first sexual cycle, the first *oestrus*. Characteristic changes occur in the uterus and vagina. Primates and other mammals exhibit some differences in the cycle. In the lower mammals it can be divided, using the nomenclature of Heape, into :

1. *Anoestrus*, the quiescent or resting stage of ovary and uterus (absent of course from the first cycle) ;
2. *Prooestrus*, the coming on of " heat," in which occur maturation of follicles in the ovary, and turgescence of the uterus and vagina, with certain endometrical changes in the uterus ;
3. *Oestrus*, the period of heat and of desire, during which ovulation takes place in the ovary ;
4. *Pregnancy*, or return to *anoestrus*.

In polyoestrus animals, in which the cycle is repeated several times during the breeding season, oestrus is followed by periods of recuperation and growth, *metoestrus* and *dioestrus*, and these again by prooestrus.

In the immature female rat and mouse the external orifice of the vagina is closed by a " plate," a thin wall of cells, which is ruptured during the first cycle by enlargement of the vagina. In the guinea-pig a corresponding membrane is regenerated after each period of oestrus.

In primates, if pregnancy does not take place, *menstruation* occurs. In the turgescent uterus a rapid necrosis of its functional layers is accompanied by haemorrhage.

Ovulation in the rabbit and ferret only follows copulation. " Pseudo-pregnancy " can be induced by sterile mating with a vasectomized male. Ovulation is then followed by development of normal corpora lutea, modification of the uterine mucosa, and hypertrophy of the mammary glands (conditions typical of the early stages of actual pregnancy). Pseudo-pregnancy is probably due to a nervous reflex set up through copulation, and acting through the anterior pituitary to produce ovarian development and formation of corpora lutea. When pseudo-pregnancy is produced by similar procedure in the rat and mouse, the lives of the corpora lutea are prolonged and the next oestrus delayed.

The testes of most species of animals show no corresponding cycle of changes, nor do their functions call forth any cyclical change in the secondary sex glands of the male. In certain species with only one sexual season in the year, or even two, as voles, shrews, and hedgehogs, cyclical changes do occur.

The internal secretion of the testis is generally believed to be associated with the *interstitial cells* or *cells of Leydig*, epithelium-like cells

associated with the intertubular connective tissue, and forming conspicuous isolated groups of cells in man.

According to a recent report by Okkels and Sand, the nerves of the human testis are far more numerous than hitherto assumed. A great number of these nerves make contact with the Leydig cells. Near the hilum these cells may occupy a perineural situation. In the deeper layers of the tunica albuginea intraneural Leydig cells may be found. Inside the parenchyma nerve fibres may interpenetrate groups of Leydig cells. Neurofibrils may end by touching individual Leydig cells. This intimate relationship between nerves and Leydig cells seems to be established at puberty.

Okkels and Sand suggest that the function of these nerves is secretory and perhaps related to a special area of the hypothalamus concerned with the whole complex of the sexual processes. They point out that also "the possibility exists of a biological mechanism by which the neurotrophic Leydig cells may influence the testicular nerves by means of a special secretion. The nerves could thus transmit centripetal stimuli which might explain the psycho-sexual phenomena associated with the influence of the sex hormones on the central nervous system."

Marshall has critically reviewed present knowledge of the causes determining sexual periodicity in mammals and birds, and the relationship of the internal sex rhythm to seasonal changes and external environmental phenomena in general. These often—especially exposure to sunlight (and probably to the ultra-violet rays of that light)—act enteroceptively through the nervous system and probably through the hypothalamus upon the anterior pituitary, and through it upon the gonads. Marshall concludes "in all the higher animals sexual periodicity, while conditioned by the environment, is regulated in its successive phases by the combined integrative action of the nervous and endocrine systems."

Castration and Implantation. Much early information was gained concerning the functions of the gonadal hormones by study of the effects of extirpation and of grafting. Such experiments afforded information of great value concerning the hormonal control of the secondary sex organs and characters.

The experiments of Nussbaum on the frog in 1912 produced reasonable evidence that the sex characters of the male are controlled by a specific hormone of the testis. In the breeding season of these amphibians a thickened pad of skin develops on the first digit of each forelimb of the male, associated with increased muscular development of the limb. This development is preparatory to his prolonged copulatory embrace of the female. Nussbaum showed that if the male is castrated the thickened pad and the increased muscular development do not occur, but that if a piece of testis is introduced into the dorsal sac of such a castrate, then mating changes ensue normally. The absence of nervous connections from such a graft indicated that the effect was due to a testicular hormone (cf. Vincent).

In the young male rat, four to six weeks old, the penis is short and thin, with undeveloped corpora cavernosa, the prostate is scarcely visible, and the seminal vesicles are very small. In the adult rat the penis is relatively long and wide, and can be easily protruded, the corpora cavernosa form its proximal part, the prostate is a relatively large, lobular organ, and the vesicles are similarly large and filled with a coagulable secretion. If castration is performed at the age of four to six weeks the adult castrate shows scarcely any change in the sex apparatus from the period of castration. The effect of castration on male mice is very similar. Corresponding changes have been observed in the guinea-pig, rabbit, and dog (cf. Lipschütz).

The precise effect of castration on man, practised throughout the centuries, has only within recent years received exact study from the physiological standpoint. Much information was gained by studies of the Skopecs, a Russian religious sect who practise castration in the first decade of life. Following such early castration the adult castrate has small and under-developed penis, prostate, and seminal vesicles. Masculine distribution of hair does not develop. The beard is absent. The limitation of hair in the pubic region is feminine. Obesity may or may not be present. The larynx is an enlarged infantile larynx, and the voice of the prepuberal boy persists throughout life. The skeleton shows some characteristic changes. Growth of the long bones persists beyond the usual time ; the castrate tends to be tall through disproportionate length of leg. The general intelligence is not specially influenced, but apathy is a characteristic feature. Post-puberal castration produces less marked effects (cf. Lipschütz).

Observations on the results following castration in different species of mammals indicate that, wherever specific structures are associated with sex, castration affects their growth. Castration in young stags leads to non-development or arrest of development of antlers, according to the age at castration. But in eland and in horned cattle, where both sexes possess horns so that these are not related to sex differentiation, their growth and development are not affected by castration (Vincent).

Ovariectomy in the female leads to corresponding changes. In young rats, mice, guinea-pigs, and rabbits, the uterus and vagina remain infantile. The mammae remain undeveloped. The sex-cycle does not occur.

In women observations are available almost exclusively following post-puberal castration, and are less accurate and uniform. In all cases, however, atrophy of the uterus and vagina takes

place, and menstruation ceases. Such castrated women usually gain weight through deposition of fat. Certain of these changes are comparable with those observed at the climacteric.

Generally speaking, gonadal implants tend to restore the secondary sex organs of castrated animals to normal function.

Extirpation and implantation experiments in birds are of some importance in the present connection, since certain of the results have been employed as biological tests, especially for the testicular principle. Fowls have been chiefly used. Different races show considerable variation in results. Much of our present accurate knowledge is due to Pézard and Goodale.

Castration of young cockerels at the age of three months leads to a characteristic development of comb, wattles, and barbles, which remain small, bloodless, and thin, infantile rather than feminine. The spurs are not influenced. The plumage is not greatly changed. The capon becomes somewhat larger and heavier than the normal bird, but the increase in weight is mainly due to the laying down of more fat (whence the ancient practice of castrating fowls). Castration in the hen leads to the development of a comb similar to that of the capon, and the acquiring of " male " plumage, which, however, more closely resembles that of a capon than of a normal cock. Thus removal of either testes or ovaries results in production of a neutral bird (cf. Lipschütz).

Vaginal Smear Tests. Early studies by Moran and Lataste, Heape, L. Loeb and others suggested that distinct cyclical changes occur in the vaginal walls of animals. In 1917 Stockard and Papanicolaou published a complete account of the changing types of cells found in vaginal smears of the guinea-pig during the course or oestrus. In 1920–22 Long and Evans showed that the same series of changes take place in the rat, and Allen and Doisy quickly applied these changes as a test to measure endocrine potency of ovarian preparations. The following account is taken from Stockard's review.

In the guinea-pig the period of oestrus lasts about twenty-four hours and occurs very regularly every fifteen to seventeen days. Throughout the twenty-four-hour period fluid is abundant in the vagina. For the first six to twelve hours (during which period the female will accept the male), the fluid is a fairly clear, frothy mucus. It gradually increases in quantity until it fills the lumen of the vagina. During the second stage, two to four hours, the fluid presents a cheesy appearance, and during the third stage, five to ten hours, it slowly becomes more liquid and serous. A fourth stage is also differentiated, in which there may be slight

bleeding. Following this period of sexual activity the "vaginal closure membrane" grows over the vaginal opening (a change specific to the guinea-pig). If this membrane be broken during the dioestral period the vagina is found to contain only a scanty amount of slimy fluid, poor in cells.

Smears prepared from the vaginal fluid at the different stages show such characteristic differences in appearance as to be diagnostic of the exact sexual state of the animal.

In the first stage the mucous fluid contains an abundant mass of cells, of a squamous type and showing considerable plasmolysis with bent and wrinkled cell-membranes. Their nuclei are very small and pycnotic; the protoplasm has degenerated and does not stain well; it exhibits a reticular structure. These cells, derived from the wall of the vagina, predominate over all others at this stage.

Towards the end of the first stage and at the beginning of the second there are also present some elongate, cornified cells, without nuclei, which are desquamated from the more external portions of the vagina. They stain decidedly red with haematoxylin and eosin, while the commoner type appear merely grey.

FIG. 30. Dioestrous smear: leucocytes in stringy mass. × 40.

FIG. 31. Pro-oestrous smear: chiefly nucleated epithelial cells with an occasional leucocyte. × 40. Present thirty-five to forty hours after first injection.

FIG. 32. Oestrous smear: non-nucleated cornified epithelial scales. × 40. This type usually appears within forty-eight hours after the first injection and is a certain criterion of the positive action of an extract.

FIG. 33. Flat, cornified elements of the oestrous smear stage. × 250. Eosin stains these cells a brilliant red. Although the site of the former nucleus is apparent, all basophilic staining reaction has been lost.

FIG. 34. Early stage of leucocytic infiltration (metoestrum). × 40. Few nucleated epithelial cells have appeared as yet.

FIG. 35. Late stage of the metoestrum. × 40. Enormous numbers of leucocytes, some cornified scales (in the centre of the field), and many nucleated epithelial cells.

During the second period the enormously increasing number of cells in the fluid causes its cheese-like consistency. These cells are derived mainly from the vaginal wall, and are healthy epithelial cells, as contrasted with the plasmolyzed cells of the first stage. The nuclei show only slight signs of degeneration. The protoplasm stains well. The second stage corresponds in time with the rupturing of the Graafian follicles and discharge of the ova.

While leucocytes are in smears of the first and second stages, in the third stage they predominate to such an extent that the

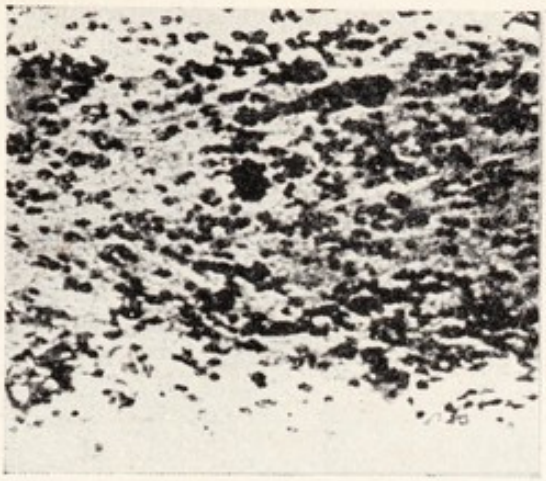
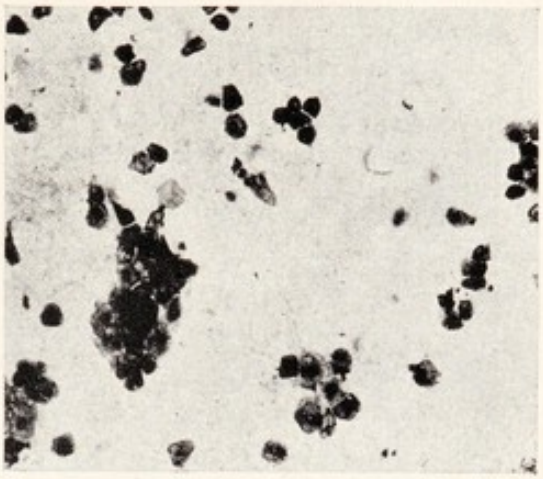


FIG. 30.



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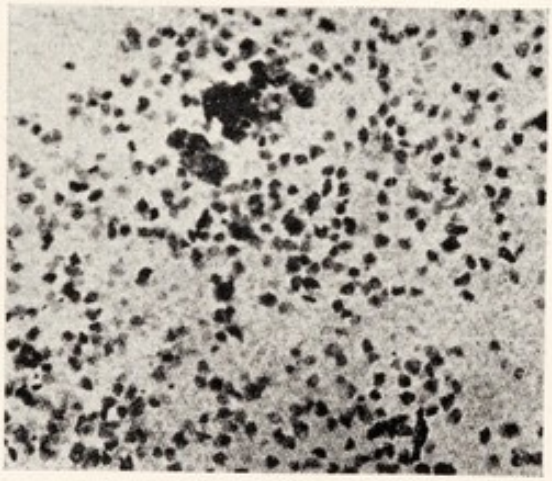

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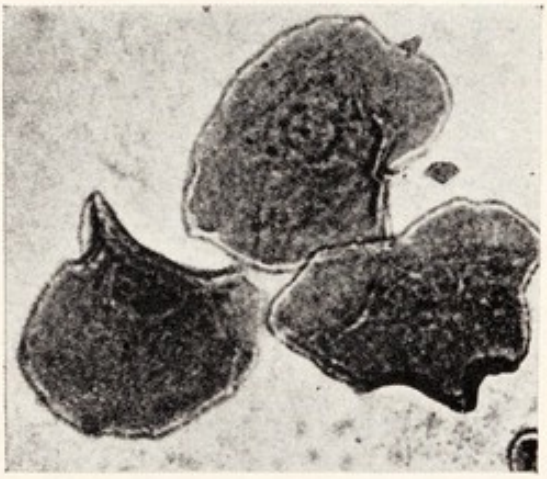

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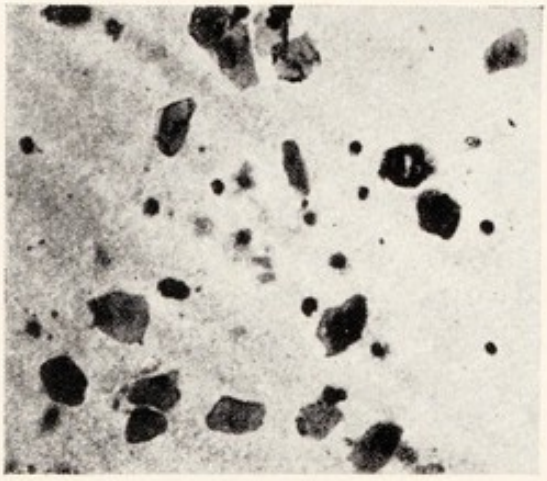

FIG. 34.

FIG. 35.

PLATE II : Vaginal smears of artificially induced oestrus in spayed rat. (From Allen, Doisey, *et al.*, Am. J. Anat., 1924–25, XXXIV, 169–171.) (For legends see p. 232.)

[*To face p.* 232.

epithelial cells become isolated from each other and each is surrounded by a number of leucocytes. These appear to dissolve or digest the epithelial cells. The fluid thus becomes more serous.

The fourth stage presents a similar appearance ; sometimes red blood cells are present from a slight haemorrhage.

Fluid obtained during the dioestral period shows gradual changes from the fourth to– just before new oestrus—the first stage.

Different investigators have examined the vaginal discharge in the mouse, rat, monkey, opossum, cow, and rabbit, and all have found a strikingly uniform correlation between the particular cellular composition of the vaginal smear, and the several stages in the process of follicular growth and ovulation.

Papanicolaou first definitely showed the existence of some degree of rhythmicity of the human vaginal smear.

The importance of the vaginal smear test lies in the correlation. Immature animals and castrates do not exhibit the vaginal cycle. Its induction by injection of ovarian extracts constitutes a positive test for the efficiency of those extracts. The test has the additional advantage that the castrated animal need not be sacrificed but can be used repeatedly. The cycle in the mouse and rat is only of four to six days' duration, so that these animals are particularly suitable for the test.

The vaginal smears of an artificially induced oestrus in the spayed rat (Allen and Doisy's procedure) are shown in Plate II. Figs. 30–35.

The proliferative process due to oestrogenic stimulation is itself responsible for the changes in the vaginal smears. As Rubenstein has pointed out, as the vaginal mucous membrane increases in thickness its superficial cells grow further and further away from their blood supply and undergo the same essentially degenerative process (cornification) that occurs in the skin. Consequently the degree of cornification seen in the smears indicates the progress of the proliferative process.

Early Work on Reproductive Hormones. *Oestrogenic Hormones.* In 1923–24 Allen and Doisy succeeded in obtaining an oestrogenic concentrate from fresh follicular liquor of sows' ovaries, fractionating between lipide solvents and water, and finally obtaining a fraction which induced oestrus in spayed rats and rabbits. They showed that a concentrate, similarly active, could be obtained from whole ovaries and from placenta. Later, Zondek and Aschheim found that urine of pregnant women and of pregnant mares is a rich source of such oestrogenic material.

At first it was believed that only a single compound was respon-

sible for the oestrogenic activity, and numerous names, such as oestrin, folliculin, and progynon, were given to this hypothetical compound by different investigators. Since the preparation in crystalline form of more than one active compound, such names have been almost completely discarded.

Crystalline *oestrone* was obtained independently and almost simultaneously by Doisy (August, 1929), Butenandt (October, 1929), and Dingemanse (1930) from the urine of pregnant women (cf. Fig. 36).

Doisy termed it *theelin*. In 1930 Marrian isolated a second active compound from the same source ; Doisy obtained it a little

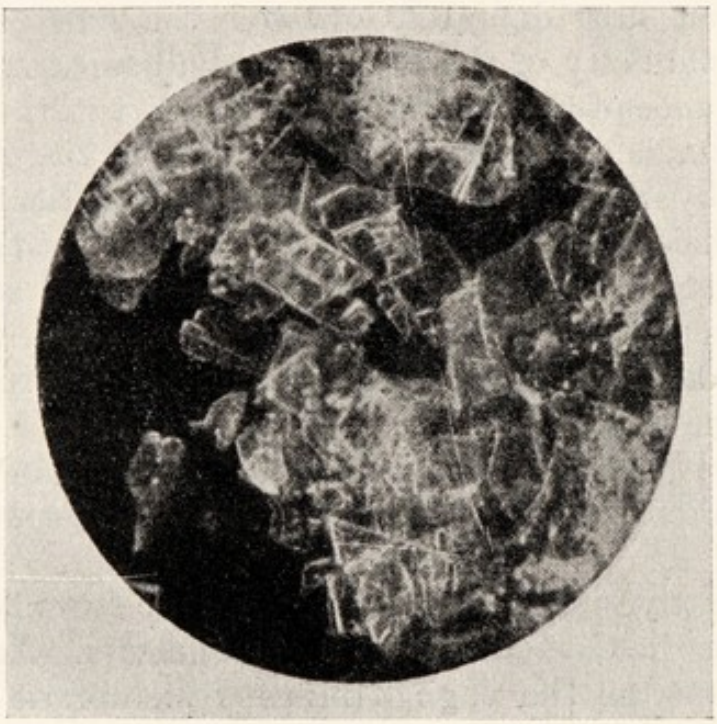

FIG. 36. Crystallized oestrone from acetic ether. (From Butenandt, Zeitschr. physiol. Chem., 1930, cxci, 127.)

later. This compound, *oestriol*, was termed *theelol* by Doisy, and differs from oestrone by the elements of a molecule of water. The terms *oestrone* and *oestriol* are based on a formal nomenclature which applies to a whole series of such compounds, and are now generally used. In 1935 Doisy showed that the still more active compound *oestra-di-ol*, already synthetized, was naturally present in ovarian tissue.

Hormone of the Corpus Luteum. Association of the corpus luteum with endocrine function was first suggested by Prenant and von Born. Fraenkel adduced some experimental evidence which supported this view ; he showed that removal of the corpus luteum of the rabbit leads, in early pregnancy, either to

absorption of the foetuses or early expulsion. Later work by numerous investigators confirmed the view that the corpus luteum is an endocrine gland.

Results of experimental removal of the corpus luteum suggested that it normally inhibits ovulation during pregnancy, and that if it is removed during pregnancy, abortion will occur in some, though not in all species.

Evidence obtained by Loeb and others, working with the guinea-pig, rabbit and bitch, demonstrated that the corpus luteum secretes a substance which sensitizes the uterus (so that it will then respond to mechanical stimuli by formation of decidual tissue).

In addition to the three functions thus suggested by this experimental evidence (inhibition of ovulation, sensitization of the uterus for implantation of the ovum, and maintenance of pregnancy) some evidence was obtained that the corpus luteum took part in the development of the mammary glands (cf. Parkes).

Early accurate work on the corpus luteum indicated that its hormone is extractable by lipide solvents. Such extracts produced changes typical of early pregnancy and pseudo-pregnancy in the uterus of castrated rabbits, and also continuance of life and normal development of the embryos of rabbits castrated during pregnancy. The hormone was variously termed progestin (Allen), corporin (Hisaw), the beta-factor (Wiesner), lutin (Clauberg), and luteosterone (Slotta). In 1934 this substance was obtained in crystalline form independently and almost simultaneously by four groups of investigators, Butenandt and his co-workers, Slotta, Ruschig and Fels, Allen and Wintersteiner, and Hartmann and Wettstein. The question of priority, of secondary importance, has been dealt with fairly by Hohlweg and Schmidt. The name " progesterone " has been agreed upon.

Hormones of the Ovum and Placenta. The presence of oestrogenic material in placenta was demonstrated early. Japanese workers (Hirose, Murata and Adachi) obtained evidence that it also contained a substance which produced numerous corpora lutea in rabbits, in a manner simulating the action of anterior pituitary implants (cf. p. 336). Wiesner obtained placental extracts with similar properties, and Collip (1) developed these studies still further.

Collip showed when an acetone extract of human placentae is acidified, addition of excess of alcohol fractionates it into two parts containing different hormones. The precipitate, purified by repeatedly re-dissolving it in water and re-precipitating with

alcohol, gives finally a preparation which produces the pituitary-like effects already described, and which, when injected into immature rats nineteen to twenty-one days old, produces oestrus in three to five days. Collip termed the active compound in this material the *anterior-pituitary-like*, or A-P-L principle. A-P-L behaves as a protein, has not been crystallized, and has not yet been obtained in definitely pure condition. It must be administered by injection to be effective.

The alcoholic filtrate from A-P-L is concentrated by removal of alcohol, then acidified and extracted with ether. *Emmenin*

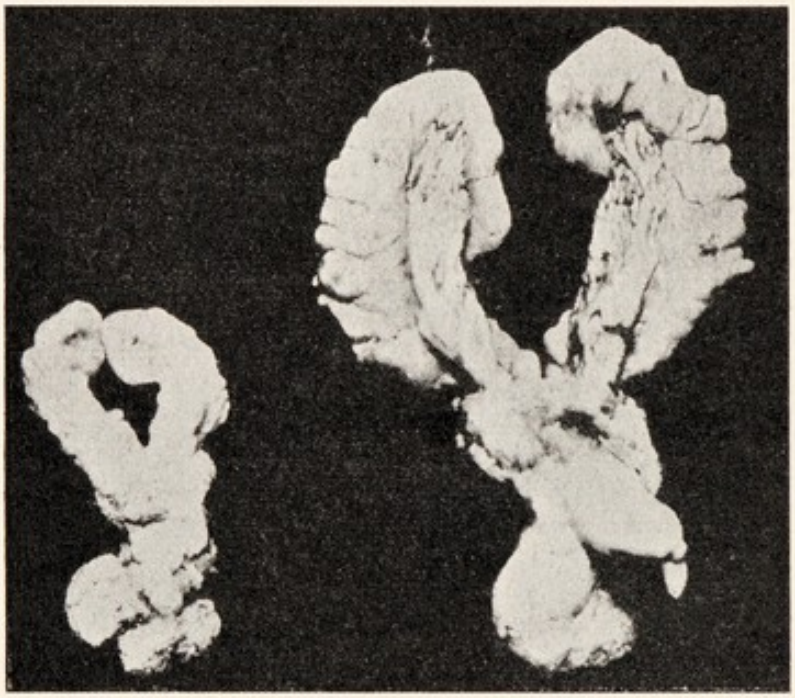

FIG. 37. Seminal vesicles and prostate of control (left) and experimental adult rat (right) after injection of the anterior-pituitary-like principle (the equivalent of 15 grams of placenta) administered daily except Sundays for forty-two days. (From Collip *et al.*, Can. Med. Assoc. J., 1931, xxiv, 201.)

remains in the aqueous phase, while some oestriol is present in the ether extract, and has been obtained in crystal form (Collip (2); Browne), and its identity definitely established. Collip showed that when the emmenin fraction was autoclaved in acid solution it became ether-soluble, suggesting that it is an ester of oestriol (Collip, Browne and Thomson). Later work suggests that it may be a glycuronide.

Emmenin is effective orally, as well as by injection. It rapidly produces oestrus in immature rats, but produces no definite changes in the ovaries. It has no effect on the cycles of normal adult rats, or on the normal course of pregnancy or lactation. It has practically no effect on adult castrates. It thus differs from

oestrone in this respect and in its apparently greater effectiveness by oral route.

The A-P-L principle also affects the male animal. Marked enlargements of the accessory genital structures are produced, especially of the seminal vesicles and prostate gland (cf. Fig. 37). The weight of the testes is not much affected. Function, rather than hypertrophy, is stimulated (Collip).

As already stated, oestrone is present in the urine of pregnant women in relatively large amount. Collip (1) succeeded in separating concentrates from urine which appeared to correspond with emmenin and the A-P-L principle, and from the former he obtained crystals of oestriol.

The early work of Zondek and Aschheim on pituitary extracts showed that these possessed gonadotrophic properties. They considered that two hormones were present in these extracts, which they termed *prolan A* and *B*. (These are the FSH and ICSH of the pituitary, cf. p. 336.) In 1927, having found that similar preparations from urine of pregnant women were markedly gonadotrophic, they assumed that these were pituitary hormones, prolans. This is now known not to be the case. Pituitary gonadotrophic hormones are excreted, especially in urine of post-menopausal women but only in relatively small amount.

Hamburger suggested that the anterior-pituitary-like hormone obtained from placenta and from the urine of pregnant women be termed the *chorionic gonadotrophic hormone*, and it is now generally termed *chorionic gonadotrophin*. Since it is produced by chorionic tissue derived from the ovum, it can truly be regarded as the primordial hormone. It is concentrated from urine in various ways; essentially the treatment consists of precipitation from acid urine with alcohol and purification of the precipitate by extraction with ether, re-solution in water, and re-precipitation with alcohol. A water-soluble preparation is obtained. It has not yet been obtained in crystalline form.

Hormones of the Testes. The biological tests usually employed for the concentration of the endocrine principle have been the prevention of atrophy of the prostate and seminal vesicles in castrated rats and mice, and the production of comb-growth in capons. Koch summarized the earlier work. McGee, working under his direction, conclusively demonstrated in 1927 that a benzene extract can be prepared from testes which causes comb-growth when injected into capons. Later work showed that the same, or some similar principle is present in the urine of men, and in traces in bull's blood. Extraction with lipide solvents is an essential feature in the preparation of concentrates from testes

or urine. Butenandt was the first who definitely obtained crystals of an androgen from urine, and determined its constitution ; he termed it *androsterone.* Subsequently *testosterone,* much more active, was isolated from bull testes.

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HORMONES ASSOCIATED WITH REPRODUCTION AND RELATED COMPOUNDS

Introduction. These hormones form two entirely dissimilar groups of compounds : (i) the gonadotrophins and prolactin, proteins, and (ii) the androgenic and oestrogenic hormones, and progesterone, steroids. In addition there are a number of steroids possessing androgenic or oestrogenic activity in some degree, which may or may not be regarded as true hormones, and others, without physiological activity, but of importance in so far as their existence throws any light upon the metabolism of the hormones.

Various esters of the natural hormones have been prepared ; only those of therapeutic importance will be mentioned.

Many synthetic steroids have been prepared, of which a number show androgenic or oestrogenic activity, usually slight. Only one or two are of therapeutic importance.

A group of synthetic " hormones," non-steroid in character, is becoming of considerable therapeutic importance and needs special consideration.

The close chemical relationship between the various steroid hormones, especially the androgens, progesterone, and those associated with adrenal cortical functions (cf. Chapter VII) naturally results in several of them possessing secondary hormonal activities, vicarious, and probably of little importance in the normal functioning of the organism. Thus the androgen testosterone, in sufficient dosage, exhibits progesterone-like properties (cf. Corner ; Greene and Burrell), while progesterone in adequate amount exhibits androgenic properties (cf. Greene *et al.*). Desoxycorticosterone (p. 203) exhibits progestational activity (cf. Leathem and Crofts). Such vicarious activities will not be further considered here.

Some chemical notes on the steroids are given in Chapter VI.

The Gonadotrophins and Prolactin. It will be shown in the next chapter that the anterior pituitary produces two gonadotrophic hormones, whose function is to control the development and work of the gonads, and also prolactin, which has several functions. They are all proteins, and have all been obtained in pure or almost pure condition.

The *follicle-stimulating hormone*, FSH, causes growth of follicles in the ovary, and development of seminiferous tubules in the testes.

The *interstitial-cell-stimulating hormone*, ICSH, augments the action of FSH, their combined effect leading to the production of the sex hormones of the ovary and ovulation. ICSH also stimulates development of luteal tissue and corpora lutea, but the additional stimulus of *prolactin* is needed before the corpora lutea can produce progesterone.

In the male ICSH stimulates the interstitial tissue of the testes to secrete androgen.

Prolactin is essential for actual secretion of milk in the mammary glands, and seems also responsible for development of maternal behaviour in mammals.

The *chorionic gonadotrophin* is produced primarily by some part of the fertilized ovum, immediately after it becomes embedded in the uterine wall, and subsequently from the corresponding foetal part of the placenta, and continues to be produced from this

source until detachment of the placenta, either at normal parturition or at abortion. Much of it is excreted in urine.

Collip's purified preparation from placenta behaved as a protein. Bischoff and Long prepared a concentrate from urine of pregnancy which appeared to contain only a single gonadotrophin. Gurin, Bachman and Wilson, by preliminary adsorption on benzoic acid, and extraction with aqueous acetone or 50 per cent. alcohol, obtained highly purified preparations which indicated that the gonadotrophin behaved chemically as a mucoid (hexosamine and acetyl and apparently galactose radicals were present).

When preparations of chorionic gonadotrophin either from placenta or from urine of pregnancy are injected into female laboratory animals (rabbit, rat, mouse, etc.) they produce effects on the ovaries practically identical with those produced by the pituitary gonadotrophin ICSH (maturation of follicles ; formation of corpora lutea). But if tested on the hypophysectomized animal these results do not ensue. The chorionic gonadotrophin, injected into male animals, stimulates an increase in size and number of the interstitial cells of the testis.

Newton has recently marshalled the evidence in favour of the production of this hormone by the placenta, and against its production by the anterior pituitary.

Pituitary implants from pregnant women appear to possess no gonadotrophic activity, although their urine is rich in chorionic gonadotrophin. Urine from cases of hydatidiform mole and of chorionepithelioma is still richer in it, although, especially in the latter condition, there is no known association with increased pituitary activity.

The results of Kido's experiments are very suggestive. He has shown that when human chorionic villi are transplated to the anterior chamber of a rabbit's eye, a positive test for chorionic gonadotrophin (presence of haemorrhagic follicles) is shown by the rabbit's ovaries, and if that rabbit's urine is injected into a second rabbit its ovaries also show a positive test (cf. Newton).

Very striking also are the results of Gey, Seeger and Hellman. They cultured placental tissue obtained at hysterectomy from a three-months' pregnant woman in a medium of 40 per cent. human cord serum, 10 per cent. beef embryo extract, 10 per cent. balanced salt solution, and 40 per cent. chicken plasma. Using the Aschheim-Zondek pregnancy test on twenty-one-day-old rats, they found that placental cells produce a substance which behaves like chorionic gonadotrophin, and, when cultured for over two months, still retain this power, which possibly resides specifically in the Langhans' cells. They also found that a hydatidiform mole, similarly cultured for a month, produced the same effect. Similar experiments with foetal pituitary tissue gave negative results.

As indicating the association of chorionic gonadotrophin with the ovum itself, there is evidence that when fertilized human ova two or three weeks old are implanted into rabbits, haemorrhagic follicles are

produced in their ovaries. Chorionic gonadotrophin appears in human female urine very shortly after nidation of a fertilized ovum, that is, as soon as material from the ovum can possibly reach the maternal circulation. It is thus detectable by the Friedman pregnancy test within a few days after a missed period. The amount rapidly increases during the first two months of pregnancy, then falls to a lower level, but persists until the placenta is completely detached at parturition or at abortion.

Extraction of placenta shows the maximum of gonadotrophin two to three months from the onset of pregnancy. It is paralleled by simultaneous high levels in blood and urine at this time (Bickenbach ; cf. Boycott and Rowlands).

The nature of the action of chorionic gonadotrophin strongly suggests that its normal function is to maintain an active corpus luteum, and thus a constant supply of progesterone for maintenance of the uterus of pregnancy.

A gonadotrophin appears in the urine of the pregnant chimpanzee between the 25th and 35th day of gestation, and disappears between the 100th and 130th day. A gonadotrophin is present in the urine of the pregnant monkey for one week only, between the 18th and 25th days (Hartman). Whether there is any species difference between these gonadotrophins has not yet been ascertained.

A gonadotrophin is present in the foetal part of the pig's placenta, while another is sometimes present in cow's urine between the 38th and 150th days of pregnancy (cf. Newton).

Equine Gonadotrophin. This definitely distinct gonadotrophin is present in the blood serum of the pregnant mare and is not excreted in the urine. Cole found that the greatest concentration is usually between the 60th and 75th day following breeding in the pony, and between the 70th and 80th day in draft mares and thoroughbreds, also that there seemed to be an inverse relationship between body size and hormone content, ponies yielding at the maximum period 200 to 400 International Units per c.c., thoroughbreds and draft mares varying from 12 to 100 I.U. per c.c.

Day and Rowlands report that it appears in the serum of pregnant ponies between the 30th and 47th day after ovulation, and quickly reaches a maximum, which is maintained between the 60th and 75th days, the hormone almost completely disappearing from the blood by the 110th day. At time of maximum concentration the blood of a Shetland pony contained 352 I.U. per c.c., and those of four out of six Welsh ponies 150 to 185 I.U. per c.c. ; the other two gave much lower values.

Day and Rowlands state that weekly withdrawal of blood to the extent of 10 per cent. of the total volume, for four weeks, has no

effect on the course of the pregnancy nor on the concentration of hormone in the serum.

Cole and Goss find, distributed over a part of the endometrium in apposition to the chorion, specialized structures which they term "endometrial cups," and which contain 4 to 12 I.U. of gonadotrophin per mg. fresh tissue; they elaborate a secretion into the uterine space containing 50 to 314 I.U. per mg. fresh secretion. They conclude that these cups (and not the chorion) are the chief source of equine gonadotrophin.

The activity of this hormone is greater than that of chorionic gonadotrophin, in that its action resembles the combined actions of the two pituitary gonadotrophins. Concentrated preparations have been made by Cartland and Mason, Rinderknecht, and Cole *et al.*; the last, apparently the most concentrated, seemed to contain but one active substance.

The Natural Steroid Hormones and Related Compounds. Present knowledge of the sources of the chief compounds in this group has been indicated in Chapter VI and is set out in tabular form in Table II (cf. also Doisy; Pincus and Pearlman).

TABLE II

Sources of the Chief Sex Hormones and Related Compounds

Source	Compounds isolated
	Androgenic compounds
Bull testes	Testosterone
Pig testes	Androstanedione
Adrenals	Adrenosterone, allopregnanolone, androstane-diol-one androstene-dione
Normal human urine (both sexes)	Androsterone, dehydroisoandrosterone, isoandrosterone
Castrate human urine (both sexes)	Androsterone, dehydroisoandrosterone, isoandrosterone
Bull urine	Androsterone, dehydroisoandrosterone
Ox urine	Androsterone
Urine of women with virilism	Androsterone, dehydroisoandrosterone, isoandrosterone
Pregnancy urine (women)	Androsterone
Pregnancy urine (cows)	Androsterone, dehydroisoandrosterone
Pregnancy urine (mares)	Dehydroisoandrosterone
	Oestrogenic compounds
Horse testes	α-Oestradiol, oestrone
Sow ovaries	α-Oestradiol, oestrone
Cattle adrenals	Oestrone
Human placenta	α-Oestradiol, oestrone, oestriol
Male human urine	Oestrone
Human pregnancy urine	α-Oestradiol, oestrone, oestriol
Stallion urine	Oestrone
Mares' pregnancy urine	α-Oestradiol, oestrone, β-oestradiol, equilin, hippulin, equilinin
	Compound with progestational activity
Ovaries (corpus luteum)	Progesterone
Adrenals	Progesterone
	Inactive compounds (partial list)
Bull's urine	Pregnanediol, allopregnanediol,
Normal woman's urine	Pregnanediol, allopregnanediol, pregnanetriol
Pregnancy urine (woman, cow, mare)	Pregnanediol, allopregnanediol
Castrate urine (woman, man, ox)	Pregnanediol
Urine of woman with virilism	Pregnanetriol

Examination of Table II reveals a number of interesting anomalies.

Testosterone, the most potent androgen known, has so far only been isolated from bull testes. It is *assumed* to be the chief or sole androgenic hormone of the testes of other species, but this is still only an assumption. *Androstanedione* from pig testes has by comparison but slight androgenic activity.

α-Oestradiol, the most potent natural oestrogen, has been isolated from sow ovaries and from human placenta, but also from stallion *testes*, which also have yielded the next most potent oestrogen, *oestrone*, and have not yet yielded a crystalline androgen. Oestrone has also been obtained from the adrenals. (Thayer, Doisy and Doisy have recently shown that β-oestradiol, prepared from mare's urine, is a true oestrogen, although its activity is slight.)

Oestriol has so far only been obtained from human material, and *equilin*, *hippulin*, and *equilinin* from urine of the pregnant mare, indicating at once that the metabolism of the oestrogens differs in different species.

Presence of compounds in the urine of castrates indicates that they cannot be wholly formed in the gonads, or wholly formed from compounds produced in the gonads, though it would be wrong to conclude that the total source of such materials is extra-gonadal.

Evidence will be adduced that pregnanediol is a degradation product of progesterone, yet, since it is also present in the urine of bulls, of the ox, and of male and female human castrates, it is not completely associated with the corpus luteum (nor is progesterone itself).

The four androgens which have been isolated from the adrenals have relatively slight androgenic activity.

The difference in action between different androgens seems to be quantitative rather than qualitative, and the same is true of the oestrogens, although there is some evidence that their effects vary quantitatively in different species (*vide infra*).

The general actions of androgens and oestrogens have been mentioned. Androgens control and maintain the development of the penis, seminal vesicles, and prostate, and the variations in body conformation, voice, hair distribution, and so on, generally referred to as the male secondary sex characters.

Oestrogens control and maintain the development of the uterus and vagina, and mammary glands, and the corresponding variations in body conformation, voice, hair distribution, etc., generally referred to as the female secondary sex characters.

Progesterone produces certain changes in the uterus and vagina, following oestrogenic stimulation.

Hair Growth. While the pattern of hair distribution seems generally to be under the influence of the dominating sex hormone, whether that be androgenic or oestrogenic, some clinical evidence has been quoted (Chapter VII, p. 225) that axillary and body hair growth is not entirely under control of the hormones of the gonads. Emmens has studied body hair growth in rats and finds that castration does not affect it in either sex, that administration of androgens has no effect on it, but that oestrogens slow the growth. Hooker and Pfeiffer find that oestrogen retards growth of hair, but that androgen protects against this action.

Effects on General Metabolism. The androgens produce other than purely sex effects, though such other effects may be only secondary. Testosterone propionate administered to healthy young men tends to reduce the output of urea and creatine, and of potassium and phosphate and to increase the output of creatinine, organic acids, and acetone bodies (Butler *et al.*). Similar results have been obtained with eunuchoids (cf. Kenyon).

Testosterone has induced growth in height in undergrown underdeveloped boys, and growth of boys during the adolescent growth spurt and in precocious puberty of certain types is due in all probability to androgens of the testes.

Oestradiol benzoate induces reduction in urinary nitrogen, inorganic phosphorus and sodium excretion in sexually underdeveloped men and women, but the necessary dosage to produce this effect is large, so that it is not certain that it is a physiological manifestation of ovarian function (cf. Kenyon). It increases the plasma calcium and inorganic phosphate of normal, parathyroidectomized, and hypophysectomized pigeons (Riddle *et al.*).

Effects on the Pituitary. Oestrogen injected into rats of both sexes initially causes enlargement of the pituitary and apparently stimulates production of gonadotrophic hormones. Chronic treatment, however, apparently depresses pituitary activity since it leads to atrophy of the gonads (cf. Marrian and Butler ; Deanesley). The synthetic compound stilboestrol and the natural oestrogens produce identical effects (Wolfe and Brown). Androgen is relatively less effective than oestrogen in depressing the gonadotrophic activity of the pituitary, and produces even less effect on the pituitary of the male than on that of the female (Koch).

Effects on the Gonads. Selye and Collip found that when oestrone is administered to hypophysectomized rats whose ovaries were maintained in normal condition by administration of anterior pituitary extract, enlargement of the ovaries was produced, indicating direct action of oestrogen on the ovary.

Administration of oestradiol causes testicular atrophy, which,

however, can be prevented by administration of large doses of testosterone (Selye).

Reports of damaging action of testosterone on the testis are somewhat conflicting.

Wamman, Reese and Koneff state that injections of testosterone propionate into young, mature male rats produce degeneration of the tubules of the testis, which is more pronounced with lower doses. The Leydig tissue becomes subnormal, and more so at higher dosage. Selye reports similarly.

Wells, using the ground squirrel as test animal, found that continued treatment with large doses of testosterone or its propionate severely injured the interstitial cells, but did not reduce the number of spermatozoa nor apparently damage the germinal epithelium. He considered that the action was produced through the pituitary, by inhibiting output of ICSH, but not of FSH.

Moore and Morgan employed the opossum as test animal, and could obtain no definite evidence of any damaging effect of such treatment, between birth and maturity of the animals.

While some difference of effect in different species is not unlikely, such extreme differences do not seem probable.

Dehydroisoandrosterone, pregnenolone, and certain related synthetic compounds exhibit spermatogenic activity, as evidenced by maintenance of spermatogenesis in hypophysectomized male rats (cf. Masson (1)). (Administration of pregnenolone is said to lessen fatigue (Hoagland.)

Effect on the Symphysis Pubis. Hisaw and his co-workers claim to have obtained a concentrate from corpora lutea residues freed from progesterone, which showed the specific effect of relaxation on the symphysis pubis of the guinea-pig which in 1926 had led Hisaw to postulate a specific hormone *relaxin* (cf. also Albert and Money).

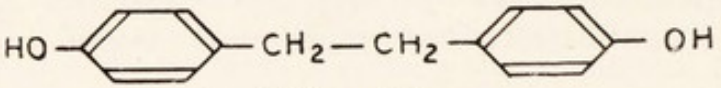
Esters of Natural Steroid Hormones. For therapeutic purposes esters such as testosterone propionate, oestradiol benzoate, oestradiol dipropionate, ethynyl oestradiol, etc., have proved of much value. They tend to give slightly decreased but much more prolonged action than corresponding amounts of the natural hormones. Methyl testosterone has the advantage of being relatively much more effective than testosterone when administered orally.

Synthetic Steroid Hormone. *Pregneninolone*, or *ethinyltestosterone*, or *anhydro-hydroxy-progesterone* (cf. Chapter VI) is relatively very active orally, and has marked progestational activity (about one-tenth that of injected progesterone). It is thus a valuable and

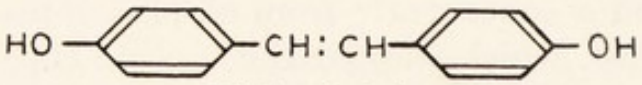
much cheaper therapeutic substitute for progesterone. It has, in addition, slight androgenic and oestrogenic properties.

Synthetic Non-steroid Oestrogens. These have been especially studied by Dodds and his collaborators. They have found active oestrogens among the derivatives of diphenylethane and diphenylethylene. Anol (p-hydroxy-propylenebenzene) and 4 : 4′-dihydroxydiphenyl also have oestrogenic activity, so that evidently the phenanthrene nucleus is not essential for such activity. The most potent compounds they have so far obtained are *stilboestrol* and *hexoestrol.*

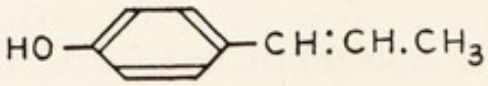
Stilboestrol (diethyl-stilboestrol, and, in full, 4 : 4′-dihydroxy-$\alpha\beta$-diethylstilbene) has an activity three times as great as that of oestrone (and almost comparable with that of oestradiol) and the additional therapeutic advantage that it is relatively more effective than either of these when administered orally. Its action is similar to that of oestrone on the uterus of the ovariectomized rat, on the mating reaction, on the vagina and uterus of immature rats, and on nipple growth in the guinea-pig (but it shows less action on the mammae than does oestrone). Its esters behave similarly to those of the natural oestrogens, the effect being slightly lessened, but prolonged. The dipropionate is especially effective



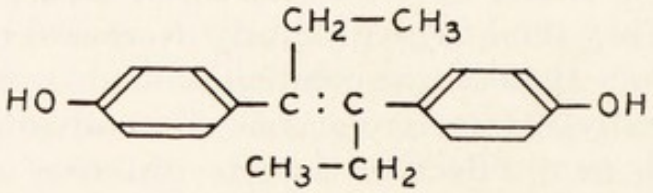
Diphenylethane



Diphenylethylene



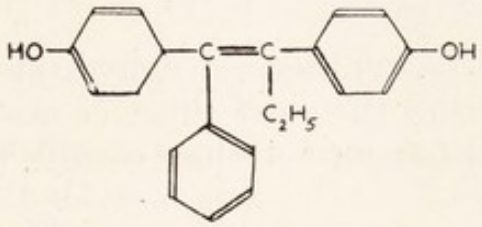
Anol



Stilboestrol

Dodds claims that hexoestrol (4 : 4′-dihydroxyphenyl-$\gamma\delta$-n-hexane) is more active than stilboestrol, while dinoestrol has similar activity (cf. Masson).

X-ray measurements of the molecular size and shape of stilboestrol and oestrone indicate configurational similarity (cf. Fraenkel-Conrat) which might explain their similarity of action, yet, as Emmens points out, oestrogenic activity does not seem necessarily to depend on such configurational arrangement, since it is exhibited in marked degree by α-phenyl-β-ethyl-stilboestrol. He thinks that all compounds exhibiting marked activity may be



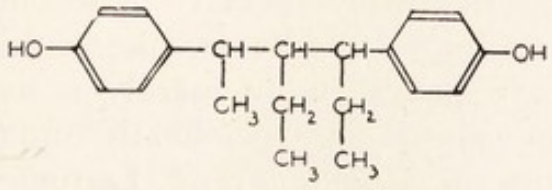
α-Phenyl-β-ethyl-stilboestrol

regarded as having a phenanthrene nucleus or a skeletal arrangement simulating it.

(By contrasting the minimal dosage needed to produce effects by direct application to the uterine wall, and by injection, Emmens differentiates between oestrogens and what he terms *pro-oestrogens*, compounds which are converted by the organism into oestrogens, and which are therefore much less effective by direct application. He finds that compounds of the stilboestrol series are pro-oestrogens unless they have hydroxyl groups in the 4 : 4′ positions, and two side chains each of at least two carbon atoms.)

v. Euler and Adler have shown that the corresponding α-β-dialkyl stilbene quinones have good oestrogenic activity.

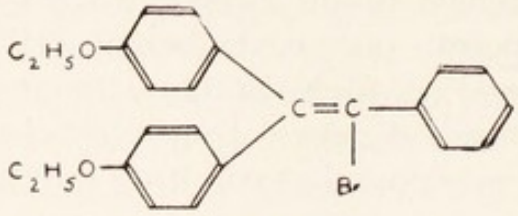
A compound of similar type, but not belonging to the stilboestrol series, is " octofollin " (benzoestrol), which has activity of the same order as stilboestrol, and is a 2, 4-di(p-hydroxyphenyl)-3-ethylhexane (cf. Blanchard *et al.* ; Murphy ; Talisman).



Benzoestrol

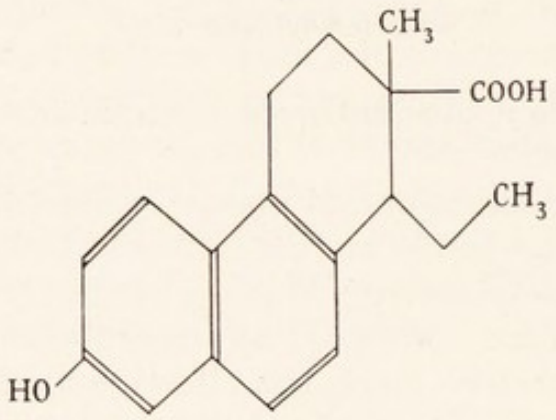
Robson and Schönberg have prepared a synthetic oestrogen which, though it must be administered in considerably higher dosage than stilboestrol to produce threshold effects, in still higher dosage has the marked advantage, as tested on mice, of greatly prolonged

action. This compound (D.B.E.) is αα-di(p-ethoxyphenyl)-β phenyl-bromo-ethylene.



"*D.B.E.*"

Miescher *et al.* have synthetized dehydrodoisynolic acid, which Schopp claims is one of the most effective oestrogens available for oral use. Joël has reported excellent results with it.



Dehydrodoisynolic acid

Laqueur's X-substance. Laqueur believes, and Deanesley and Parkes, and others have supported his view, that testicular tissue contains a still unknown X-substance, which is neither androgenic nor oestrogenic, but materially enhances the activity of testosterone, although not needed to activate it. It is stated to be also present in liver, adrenals, ovaries, wheat seedlings, and urine, and is lipide-soluble. It has been purified to the extent that a 0·5 mg. daily dose is definitely effective in accentuating the action of testosterone on rats. It behaves like a highly unsaturated fatty acid, and may prove to be merely a naturally occurring metabolite, and not a compound specifically functioning to enhance androgenic activities (cf. Koch ; Freud, Laqueur and Mühlbock).

Comparison of Activities of Androgens and Oestrogens. Tests are based on some one or other of the various effects produced by the androgens and oestrogens. At present there is considerable confusion in the results that have been obtained by different investigators. Use of different species of animals, use of different effects for comparison, and variations in methods of dosage, all

seems to affect results to the extent that it is impossible to make any clear cut statements that one androgen or oestrogen is more or less active than another androgen or oestrogen by some definite ratio. This is well exemplified by the comparisons of oestrogens recently collated and extended by Sondern and Sealey. Results based on production of oestrus in spayed rats and mice are shown in Table III. Sondern and Sealey's own results, giving the dosage to which 50 per cent. of twenty or more adult castrated animals respond, are shown in Table IV, while their further results using

TABLE III

Dose of Oestrogen Producing Oestrus in Spayed Animals

Oestrogen	Adult spayed rats		Adult spayed mice		Report by
	Subcutan. Administr.	Oral Administr.	Subcutan. Administr.	Oral Administr.	
Oestradiol					
(in glycol) .	—	—	0·025	1·1	Emmens.
(in oil) .	1·0 R.U.	60–75 R.U.	—	—	Rowe & Simond
Oestrone					
(in water) .	2·5	—	2·5	—	Hain & Robson
	0·33–0·5	5·0–6·6	0·06–0·07	—	Rowe & Simond
	0·6	—	—	—	Dodds, Lawson & Noble
(in glycol) .	—	—	0 1	—	Emmens
(in oil) .	3·3	—	0·9	—	Hain & Robson
	1·0 R.U.	40·0 R.U.	—	—	Rowe & Simond
Oestriol					
(in water) .	1·0–1·35	2·5–3·0	—	—	Rowe & Simond
(in glycol) .	—	—	1·1	3·0	Emmens
(in oil) .	1·0 R.U.	10·0 R.U.	—	—	Rowe & Simond
Stilboestrol					
(in water) .	0·25	—	—	—	Dodds, Lawson & Noble
in propylene)	—	—	0·1	0·4	Emmens
(in oil) .	0·35	1·0	—	—	Dodds, Lawson & Noble

other methods of test are shown in Table V. All figures are for micrograms except when marked " R.U." (rat unit).

Tables III to V indicate that statements as to comparable activity can only be made for a specific effect and a specific method of administration. Only a few generalizations seem proper. Of the natural oestrogens oestradiol is the most effective by injection, oestriol orally. Stilboestrol given orally is about as effective as oestradiol given subcutaneously. Oestriol, orally, is approximately

TABLE IV

Dosage of Oestrogen Producing Oestrus in Fifty per Cent. of Spayed Animals

Oestrogen	Rats			Mice		
	Subcutan. administr. (S)	Oral Administr. (O)	Dosage Ratio O/S	Subcutan. Administr. (S)	Oral Administr. (O)	Dosage Ratio O/S
Stilboestrol.	1·7	2·75	1·6	0·07	0·35	5
Oestriol .	27	85	3·1	1·5	3·5	2·3
Oestrone .	3·0	225	75	0·085	9·0	105
Oestradiol .	1·8	175	97	0·015	7·5	500

TABLE V

Comparison of Oestrogens by Various Methods, using Rats

Method	Oestradiol	Oestrone	Oestriol	Stilboestrol
Minimum significant uterine weight change				
(Subcut. admin.) .	0·05	0·2	0·05	0·015
(Oral admin.) .	0·5	1·0	0·05	0·03
Maximum average uterine weight *				
(Subcut. admin.) .	2·0 (40 mg.)	7·0 (46 mg.)	1·0 (22 mg.)	2·0 (65 mg.)
(Oral admin.) .	6·0 (46 mg.)	8·0 (45 mg.)	6·0 (31 mg.)	1·5 (49 mg.)
Initial vaginal oestrus				
(Subcut. admin.) .	0·10	0·035	0·05	0·025
(Oral admin.) .	0·25	0·5	0·25	0·10

* The average weights produced are given in parentheses.

as effective in producing initial changes in the uterus as is stilboestrol, but its maximum effect is less.

It is by no means certain that even these rough generalizations can be applied to the larger mammals, including human beings. This is indicated by observations on the relative toxicity of the oestrogens (*vide infra*).

A further illustration of the difficulty in contrasting oestrogens by different tests is furnished by comparisons of stilboestrol and hexoestrol. Dodds has stated that, as judged by the vaginal smear method (using small animals), stilboestrol is two and a half times as active as oestrone, while hexoestrol is roughly ten times as active as oestrone, *i.e.*, four times as active as stilboestrol. Bishop *et al.* reported that the two have about equal potency. Yet Freed

finds that, as tested on menopausal patients, hexoestrol is only about one-fifth as active as stilboestrol.

Similar criticisms as to comparative activity apply to the androgens. It is certain that testosterone is much more active than androsterone, which is more active than dehydroisoandrosterone ; most of the other androgens have much less activity.

Relative Toxicity of Natural and Synthetic Oestrogens. When stilboestrol was first used clinically some suspicion arose that it was potentially a dangerous drug, largely on account of the nausea and vomiting experienced by some proportion of patients using it. However, there seems to be no doubt that its relative toxicity is no greater than that of oestradiol, while clinical experience indicates that hexoestrol and " octofollin " are less liable to produce nausea and vomiting.

Within the past year or two several papers have appeared dealing with the toxic effects of very large doses of these oestrogens.

MacBryde, Castrodale, Helwig and Bierbaum find that excessive overdosage to dogs (male or female), whether it be of oestrone, oestradiol benzoate, or stilboestrol (in equivalent dosage) produces fatty degeneration and hydropic degeneration of the liver, hyperplasia in the bone marrow, predominantly of the myeloid elements, and leucocytosis and fall in thrombocytes in the peripheral blood ; in some cases the platelets disappear entirely, with moderate decrease in red blood cells and haemoglobin (cf. also Castrodale *et al.*).

Tyslowitz and Dingemanse report that an aplastic anaemia (not prevented by simultaneous injection of liver extracts) develops after a latent period of one to three weeks in normal dogs of both sexes, and in castrated female dogs, after treatment with large doses of oestrone, oestradiol benzoate, or stilboestrol. They state that the most striking effects are fall in the red blood cells, reticulocytes and thrombocytes, and the occurrence of granulocytopenia after an initial leucocytosis. The bleeding time is prolonged. At first the anaemia is hyperchromic, later normo- or hypochromic.

When daily injections of 5 mg. of oestradiol benzoate in 1 c.c. of olive oil are given until the onset of severe symptoms, the fatal dose lies between 8 and 16 mg. per kg. body-weight, and a fatal effect is produced by injection for sixteen to forty days. The toxicity of stilboestrol is no greater. But daily injections of 1 mg. of either oestradiol benzoate or stilboestrol have proved harmless over a nine months' period.

Testosterone or testosterone propionate does not produce anaemia even when given in amounts twice as large as those of

the oestrogens over several months, but, when given simultaneously with oestrogen, does not prevent the toxic effects of the latter.

Vollmer and Gordon found that oestradiol benzoate lowers the red blood cells in castrated female rats, while testosterone propionate raises the count in rats of both sexes and in castrated females after hypophysectomy has produced an anaemia. Androgens increase the haemoglobin and red blood cell content in the blood of man (McCullagh and Jones).

There is, however, a marked species difference in the toxicity of the oestrogens. Tyslowitz and Hartman find that large doses produce no effect on the blood picture of the rhesus monkey. Karnaky states that prolonged massive doses of stilboestrol produce no harmful effect on women ; in pregnant women no nausea is produced by dosage below 500 mg. per day.

In any case it is to be stressed that the toxic results produced in dogs are with dosage much greater than that employed in human therapy.

The Metabolism of the Sex Hormones. *The Androgens.* Although testosterone so far has only been isolated from bull testes, it is customary to assume that it is *the* male sex hormone. Weakly androgenic androstanedione, isolated from pig testes, is probably of no great significance.

Administration of testosterone to patients or normal men results in marked rise in urinary excretion of androsterone, isoandrosterone, and inert aetio-cholanolone-3(α)-17, and the first and third of these also in the male chimpanzee (Fish and Dorfman), though, curiously, Horwitt *et al.* find that such administration to pregnant, but not to non-pregnant female monkeys, also leads to urinary excretion of androsterone, while Schiller, Dorfman and Miller, giving a fairly large dose of testosterone propionate to an eighteen-year-old normal girl, recovered from the urine androsterone and aetiocholanolone in greater degree than from men.

Any severe metabolic disturbance other then hypergonadism, or the virilism associated with an adrenal cortical tumour, results, sooner or later, in a decrease in urinary androgen excretion. Human castrates of both sexes excrete androsterone and dehydroisoandrosterone (cf. Table II), while in cases of adrenal cortical tumours there may be a strikingly increased excretion of dehydroisoandrosterone (Callow), *or* of isoandrosterone (Hirschmann). It can be concluded that androsterone and isoandrosterone are derived both from testosterone and from adrenal compounds, dehydroisoandrosterone possibly only from the latter (*cf.* Koch (2)).

When methyltestosterone is administered to patients, increased

urinary excretion of androgens does not follow ; its catabolic path must differ from that of testosterone.

The liver seems to inactivate both testosterone and methyltestosterone, the former more efficiently (Burrill and Greene ; cf. Krichesky, Benjamin and Slater). The products of this inactivation are unknown.

All androgens in fresh male human urine are present in conjugated form (McCullagh and Osborn), and since hydrolytic methods partially decompose some of them it is doubtful whether more than an approximation to the true values is at present possible.

The following list of figures, from Koch (2), gives such approximate values for various species. It will be noted that human beings excrete relatively much more than other species (chiefly as androsterone and dehydroisoandrosterone). All values are given in terms of androsterone. Some values for oestrogens (as oestrone) are included. It is to be noted that the excretion of androgens is reckoned in milligrams, that of oestrogens in micrograms.

Men (25 to 35 years)	3–10 mg. androgen per day ; 5–15γ of oestrogen.
Women (23–24 years)	3–10 mg. androgen per day ; 18–36γ of oestrogen.
Eunuchoids (av.)	2·2 mg. androgen per day ; 2·6γ of oestrogen.
Boys (6½ to 10 years)	0·07–0·2 mg. androgen per litre.
Girls (8 to 10 years)	0·18–0·2 mg. androgen per litre.
Male chimpanzees	0·3–1·3 mg. androgen per litre.
Female chimpanzees	0·2–0·8 mg. androgen per litre.
Stallions	0·1–0·8 mg. androgen per litre.
Bulls	$<$ 0·1 mg. androgen per litre.
Rams	0·4 mg. androgen per litre.
Rats	0·1 mg. androgen per litre.

The Oestrogens. Doisy showed that 1 kg. of sows' ovaries contain 0·014 mg. of α-oestradiol and 0·010 mg. of oestrone, while cow's ovaries do not appear to contain oestrone (cf. Westerfield, Doisy *et al.*). It is usually considered that *the* hormone of the ovary is α-oestradiol, though the assumption will rest on a securer foundation when this compound has been isolated from the ovaries of several species. Smith and Smith have obtained some evidence that the human ovary can convert oestradiol into oestrone, and also oestrone into oestradiol.

The presence of oestradiol and of oestrone in stallions' testes (and their absence from urine of geldings) is so far without explanation, as is also the formation of oestrone in the adrenals.

The isolation of oestradiol and oestrone from human placenta, the continued presence of oestrogens in blood and urine of pregnant

women following ovariectomy, and the prompt fall in their excretion following delivery, indicate that oestradiol and oestrone are actually produced in the human placenta for functional purposes, and not merely stored there.

By various experiments with animals and with human castrates it has been estimated that human ovaries produce about 0·4 mg. of oestrogen (calculated as oestrone) daily, and about 10 mg. during the usual normal menstrual cycle (cf. Doisy). The daily excretion of oestrogens in the urine of non-pregnant women has been given (p. 253).

The relative amounts of oestradiol, oestrone and oestriol respectively present in human placenta and excreted in human pregnancy urine, are, according to Doisy, 0·038, 0·035, and 0·140 mg. per kg., and 0–0·6, 1–3 and 10–30 mg. per twenty-four hours. Such figures emphasize the relative importance of oestriol as the chief human excretory product. Pincus and Pearlman estimate that the placenta produces in late pregnancy 12 to 50 mg. of oestrogen daily.

Oestrogens are inactivated in the liver (Burrill and Greene). Stilboestrol and hexoestrol are said to be more resistant to hepatic inactivation than are the natural oestrogens (Lipschütz *et al.*).

Oestrone is excreted as a conjugated sulphate in the urine of pregnant women and pregnant mares (Schachter and Marrian ; Butenandt), as also in that of stallions (Jensen, Larivière and Élie), and it is reasonable to assume that it is present in this form in the urine of non-pregnant women also. Oestriol is excreted as a glycuronide ; it has been isolated as sodium oestriol glycuronide from pregnancy urine (Cohen, Marrian and Odell).

However, at the mid-interval of the menstrual cycle there is a sudden appearance of free oestrogen in the urine, possibly due to its liberation in the follicular fluid from the ruptured follicle at ovulation, and peritoneal absorption and excretion too rapid to permit complete conjugation. Free oestrogen is also present in slight amount just before the onset of menstruation (Palmer).

Some of the varied pathways of oestrogen degradation—which may differ in different species—are indicated in the following statements (cf. Doisy ; Pincus and Pearlman ; Schiller).

When α-oestradiol is administered to ovariectomized-hysterectomized rabbits they excrete oestrone and β-oestradiol ; hence the rabbit needs neither ovaries nor uterus to bring about these changes.

When α-oestradiol or oestrone are given either normal, ovariectomized, or ovariectomized-hysterectomized monkeys, they excrete

both ketonic and non-ketonic oestrogens ; absence of ovaries and uterus therefore does not essentially modify the processes.

α-Oestradiol administered to a man resulted in excretion of oestrone ; oestrone gave oestriol.

Oestriol has so far only been obtained from human placenta and human urine.

Two oestrane-diols have been isolated by Marker from urine of non-pregnant women ; they were not found in urine of pregnant women, suggesting some difference in oestrogen metabolism in the two states.

Pincus has carried out a number of interesting experiments which led him to conclude : (i) oestradiol is converted into oestrone in animals with functioning ovaries ; (ii) oestrone is converted into oestriol in animals with functioning uterus ; (iii) oestriol cannot be converted into oestrone or oestradiol ; (iv) progesterone facilitates the conversion of oestrone to oestriol and increases the amount of oestrogen excreted.

However, these experiments were carried out with animals for which there is no definite proof that they can form oestriol. Doisy points out that the conclusions are based on colorimetric methods, insufficiently checked by bioassay, and that re-examination of the subject is desirable.

Cantarow *et al.* state that in the dog, and perhaps also in woman, bile is an important medium of excretion of both endogenous and exogenous oestrogens, and that while the liver inactivates oestrogens, this is probably not a rapid process.

Progesterone is excreted by women in urine as sodium pregnanediol glycuronide (Venning and Browne) during the latter half of the menstrual cycle and during pregnancy. They found that its excretion commences within forty-eight hours of ovulation, and ceases twenty-four to forty-eight hours before menstruation commences. According to Wilson, Randall and Osterberg, the average daily excretion of pregnanediol is 5 to 10 mg. during the first four months of pregnancy, and then this rises sharply to an average of 25 mg. in the fifth month, and then slowly to an average of 54 mg. in the ninth month, although there are large variations in the actual figures for different women. Their results suggest that during the first four months of pregnancy the corpus luteum is responsible for the progesterone, and subsequently the placenta. (The glycuronide is conjugated with the hydroxyl group at the third carbon atom (Heard *et al.* ; Huebner *et al.*).

Veitch, Malone and Everitt obtained 40 to 50 mg. of pure crystalline pregnanediol per litre between the second and eighth month of pregnancy.

The amount of pregnanediol excreted does not account for all

the progesterone formed in the body, or administered. Venning and Browne showed that when all the normal mechanisms for progesterone formation are operating (as in the luteal phase of the menstrual cycle or in early pregnancy) there is maximum recovery of administered progesterone as pregnanediol. When progesterone is injected in such cases 20 to 55 per cent. can be recovered as sodium pregnanediol glycuronide, while when the latter itself is injected only 43 to 58 per cent. is recovered, indicating that pregnanediol is largely catabolised further. There is some evidence that it is decomposed in the liver (Leblond).

Progesterone also gives rise to much smaller amounts of allopregnanediol, epi-allopregnane-3-ol-20-one, and epi-pregnane-3-ol-20-one (Marker, Kamm and McGrew) and probably other inert excretory products (cf. Pincus and Pearlman). Its excretion as glycuronide seems limited to women.

Bloch by feeding cholesterol tagged with deuterium to an eight months' pregnant woman has obtained suggestive evidence that it is the precursor of progesterone and pregnanediol.

Table II records that pregnanediol is present in urine of the bull, of normal women, of pregnant women, cows, mares and sows, of castrate women and men, and the ox. Elder could not obtain it from urine of the pregnant chimpanzee.

Though the corpus luteum is the chief normal site of production of progesterone, and the uterus is probably the normal site of most of the pregnanediol excreted in urine, neither corpus luteum nor uterus is essential to its production, though uterine endometrium facilitates its formation (for it is excreted by amenorrhoeic patients following large doses of progesterone, especially if the endometrium has been stimulated by oestrogen (Venning and Browne).

Pregnanediol is excreted by hysterectomized women (Venning and Browne) and by man (Buxton and Westphal) following large doses of progesterone, and also, in small amount, normally (Fish and Dorfman ; Huschmann). Castrates and the bull normally excrete pregnanediol ; in them it must be produced from other sources than progesterone of the corpus luteum and placenta. But it must be remembered that progesterone is also a product of the adrenal cortex (cf. p. 204). In the bull the urinary prenanediol seems to be associated with a functioning testis, since the steer excretes none in detectable amount (Marker).

Horwitt *et al.* have shown that oral administration of desoxycorticosterone to two men and one woman with Addison's disease, to a hypogonadal man, and to an ovariectomized chimpanzee,

resulted in urinary excretion of pregnanediol; the maximum amount isolated was 3 per cent. of the desoxycorticosterone given. They consider that this helps to explain its presence in small amounts in male urine, etc., since desoxycorticosterone is a normal adrenal product.

The two synthetic products anhydrohydroxyprogesterone (Allen *et al.*) and pregnenolone (Pearlman and Pincus), when given orally to man, result in the excretion of pregnanediol.

Additional Note. Various toxic compounds are conjugated in the liver and subsequently excreted through the kidneys as sulphates or glycuronides, the process being regarded as a *detoxication*. It scarcely seems logical to consider similar conversion of compounds whose action is physiological as a detoxication, and it is probably more proper to regard such conversion as a mechanism by which the body lessens, for functional reasons, their degree of activity, and perhaps facilitates their excretion.

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THE INTEGRATION OF ACTIONS OF THE HORMONES ASSOCIATED WITH REPRODUCTION

Introduction. It is the purpose of this section to trace out the integrated control of the organs of reproduction, especially in the female animal, by the hormones of the pituitary and of the gonads themselves, whereby the whole mechanism becomes one co-ordinated pattern.

It has been mentioned early in this chapter that histological sex differentiation is possible at a very early stage in embryological life. Such development is probably under genetic and not under endocrine control, for no definite evidence has been produced that the determination of sex is in any way conditioned by hormones.

From the period of this differentiation each sex calls for separate treatment. In this volume the phenomena in woman will be stressed, those in the lower mammals being introduced chiefly from the light they throw upon human phenomena. Any application of data for the lower orders of mammals to primates must be made with caution, because of the difference between the oestrus cycles of the former and the menstrual cycle of primates.

Sex Development and Reproduction in the Female Animal and particularly in Woman

Events Preceding Ovulation. Experiments on rats indicate that ovarian follicles can develop to a diameter of 200μ to 300μ in absence of the pituitary, but not beyond this stage (cf. Hisaw and Astwood). Pituitary control commences therefore at an early stage of development.

Such control is general throughout animals. Even in some of the more primitive insects (orthoptera) development of oviducts and of ova, though not of spermatozoa, has been shown to be under the control of the corpora allata, which in certain respects resemble the pituitary of vertebrates (cf. Scharrer).

A certain degree of maturity is needed before the gonads become responsive to gonadotrophins (cf. Pfeiffer), but, as FSH and ICSH stimuli gradually increase, some proportion of the Graafian follicles enlarge, with potential production of oestrogen, and ultimately, at the onset of puberty, the stimulation is sufficient to lead to rapid growth of a number of follicles, with resulting rapid increase in the output of oestrogen, and finally one or more of these follicles rupture—the actual number varying in different species, with discharge of one or more ova. The site of production of the ovarian hormone is most probably the theca interna of follicles of all sizes (Corner).

Nathanson, Towne and Aub have shown that between the ages of three and seven years both boys and girls excrete a small and constant amount of oestrogens and also of keto-steroids in urine. (It seems probable that these are largely derived from the adrenal cortex.) From eight to eleven years of age the excretion of oestrogens by girls increases, and about one and a half years before the menarche it becomes cyclic, the intensity of the cycles gradually increasing. Nathanson and his co-workers detected pituitary FSH in the urine of girls as early as eleven years of age, but consider that its non-detection still earlier may be due to inefficiency of the method used. Hence the menarche in girls is the culmination of an endocrine development commencing about five years before puberty.

Experiments on rats indicate that increased level of ICSH production is needed to produce pre-ovulatory swelling of the ovaries and ovulation, and must be maintained during formation of corpora lutea (Pfeiffer).

The actual rupture of a follicle seems due to the increased osmotic pressure of its own fluid contents (Smith *et al.*). Its ovum is slowly extruded in an oozing mass of fluid (Reynolds). The process seems to need no nervous control, for it can occur in apparently normal fashion in the experimental animal after all nerve connections to the ovary have been severed, and has occurred in transplanted ovaries of many species. Yet potential nervous influence, producing for example delay in ovulation, cannot be entirely disregarded (Hinsey).

The increased output of oestrogen prior to puberty is accompanied by accelerated development of the accessory sex organs. Pfeiffer suggests that their tissues become more sensitive to

oestrogenic stimulation, but the increase in production of oestrogen which has been shown to occur seems in itself an adequate explanation.

In the young girl, with increased production of oestrogen commencing at about her eighth year, commence also the development of the female pelvis, the breasts, and pubic hair, in that order (Fluhmann); growth of the infantile uterus is stimulated.

At the time of ovulation the infundibulum of the apposed Fallopian tube is alternately exposed to each side of the neighbouring ovary, and ciliate movements assist the transfer of ova to the tubes (cf. Reynolds; Burdick, Whitney and Emerson).

Sequelae to Ovulation. Following ovulation, the ruptured follicle is transformed into a corpus luteum (cf. p. 227) whose specific lutein cells are probably responsible for the production of progesterone.

Appearance of heat in the rat marks the beginning of luteal activity and secretion of progesterone, although there is then no luteal tissue in the follicles but only early luteal changes in the follicular walls (cf. Hisaw).

The unruptured Graafian follicles continue to produce oestrogenic hormone. Corpora lutea of certain species produce oestrogen also, and this is not surprising, since these corpora lutea contain both epitheleoid layers of the follicular wall. The corpora lutea of the sow yield 60 to 80 rat units of oestrogen per kg. fresh tissue, those of women 2,000 to 3,000 or more rat units per kg. (Curtis). This continued production of oestrogen indicates concurrent need for oestrogenic activity along with that of progesterone.

If the ovum is not fertilized, then in the lower species of mammals there is a return to anoestrus (or metoestrus, dioestrus, and again prooestrus), while in primates the menstrual cycle is completed by menstruation.

Thus in the young girl, following the first ovulation, the first menstruation occurs, to be followed by others at irregular but decreasing intervals, until cycle follows cycle with a moderate degree of regularity. Not infrequently the early cycles do not include ovulation (cf. p. 270).

Events in the Menstrual Cycle and in Corresponding Cycles in Lower Mammals. *Uterus.* The growth of the uterus and its maintenance depend on continued oestrogenic stimulation. (Following ovariectomy and following the menopause the uterus atrophies; administration of oestrogen prevents the atrophy. Cf. Reynolds.)

The oestrogenic hormone prepares the uterus and Fallopian

tubes for the stimulation of progesterone which follows the first and each succeeding ovulation, being responsible for the *pre-ovulatory* growth of the uterus. The principal effects produced are a generalized hyperaemia, followed by increased growth of the endometrium, with mitoses in glands and epithelium of this tissue. The tubes are similarly effected. During this pre-ovulation period in woman and the female monkey the uterus contains little or no glycogen (cf. Reynolds ; Allen).

When, following ovariectomy and the ensuing uterine atrophy oestrogen is injected, these changes occur within a few hours, and are accompanied by increased oxygen consumption.

Progesterone is responsible for the post-ovulatory changes in the uterus ; oestrogenic stimulation must precede its action or there will be no response to it. For normal post-ovulatory development concurrent progesterone and oestrogen stimulation seem necessary, although excessive oestrogenic stimulation prevents proper endometrial response to progesterone (Reynolds).

Progesterone produces secretory changes in the endometrium, still further augments its blood supply, and, by some mechanism still unknown, causes deposition of glycogen (for nutritive purposes), especially in the most superficial glands (Reynolds).

The uterus undergoes the same type of change in primates as in the lower mammals. The basal layer of its endometrium responds to oestrogen, generating, and in each new cycle regenerating, a functional layer, which is subsequently converted by action of progesterone to a receptacle suitable for a fertilized ovum. If no fertilized ovum nests within it the functional layer is cast off and the cycle finished by menstruation.

Van Dyke and Chen found that fresh uterine mucosa of the macaque monkey contained in the pre-ovulatory period 0·3 per cent., and in the presence of a functioning corpus luteum 0·53 per cent. of glycogen. Zondek and Stein found for human uterine mucosa the respective values 0·1 and 0·25 to 0·55 per cent.

The actions of oestrogen and of progesterone are directly on the cells of the uterus. Very minute doses of crystalline progesterone introduced directly within the lumen of the uterus of the rabbit (previously sensitized with oestrone) produce the characteristic progestational proliferation of the endometrium (McGinty *et al.*)

Vagina. The changes in the vaginal epithelium, as indicated in the smear and due to the effect of oestrogen, have already been dealt with (p. 231). Mucification of the vaginal epithelium may be due to synergistic action of balanced amounts of oestrogen and progesterone (cf. Wintersteiner and Smith). The cyclical changes

in the smear are much less pronounced in primates than in rodents.

Papanicolaou has reviewed the variations in vaginal smears in different species quoting Corner's 1923 work on Macacus rhesus monkeys, in which it was noted that during menstruation the smears contain erythrocytes, epithelial cells and leucocytes, in the first half of the intermenstrual interval there were relatively few epithelial cells and many leucocytes, while at the end of this half there was a sharp drop or even total disappearance of leucocytes ; during the second half of the interval there was increased desquamation of epithelial cells. (In subsequent work Corner could find no difference in the smear changes in ovulatory and non-ovulatory cycles in the monkey.)

Papanicolaou found the following changes in the smear of the human female. During the menstrual phase there were numerous erythrocytes, abundant polymorphonuclears, mononuclears were conspicuous, and towards the end of the phase there was a leucocytic exodus. During the following eight to twelve days there was a leucopenia. Epithelial cells showed an increasing tendency to cornification, and the cornified cells were usually nucleated. At the presumed time of ovulation there was a sudden increase in the number of leucocytes. Cornification was pronounced. Subsequently the smears showed great variation, as between proportion of leucocytes and cornified cells.

While, therefore, as in the monkey, there is definite evidence of a cyclic variation, it is not clear cut, and interpretation is more difficult than with rodents (cf. also Rubenstein).

Experimental administration of oestrogen causes a lowering of the *p*H of the vaginal fluid of monkeys, while subsequent treatment with progesterone leads to a rapid rise of *p*H (Dow and Zuckerman). The corresponding changes in glycogen content suggest that the *p*H is determined by the extent of the production of lactic acid (cf. Wintersteiner and Smith).

Motility of Fallopian Tubes and Uterus. Reynolds stresses the patterned co-ordinated muscular activity in tubes and uterus initiated by oestrogen. Contraction waves commence in the myometrium of the tubes and spread to the uterus. When these effects are produced in the experimental animal an initial hyperaemia, due to the oestrogen, is followed by a latent period which is not increased by increase of dosage, and is followed by the contraction waves. Progesterone inhibits this rhythmic motility, and quiescence of tubes and uterus sets in at variable periods after ovulation in different species.

Dickenson's results from rectal palpation of women (quoted by Reynolds) show the same patterned co-ordination. Motility of the uterus is greatest during maturation of the follicle when oestrogen output is about maximal. It subsides to quiescence as the corpus luteum is formed and produces progesterone, and it shows a

secondary increase in activity just before menstruation (when progesterone output is decreasing). The human uterus is highly sensitive to progesterone ; this is exemplified by the specific relief a minute dose affords in most cases of " after-pain " (cf. p. 294).

Fate of Ova. Fertilization of ova must occur within a relatively short period after their liberation, or does not occur at all. The time-limitation is due to the short life-period of spermatozoa at body temperature, one or two days (cf. Knaus), and early changes in the outer surface of the ovum, which becomes enveloped by a layer of protein nature, and so is rendered impermeable to spermatozoa (Reynolds).

Whether fertilized or unfertilized, ova pass down the tubes, at first rapidly uner the influence of the rhythmic contractions, then more slowly, when progesterone from the newly formed corpora lutea has inhibited the motility. A definite time is needed for each species, to permit adequate preparation of the uterus for nidation. Thus if motility of the tubes, in rabbits and mice, is unduly increased by injection of oestradiol, passage of fertilized ova can be accelerated, but they thereupon disintegrate in the fluid of the unprepared uterus (cf. Evans).

Adequate daily doses of testosterone propionate cause retention of blastocysts in oviducts of mice, apparently through a progesterone-like effect (Burdick *et al.*).

Passage through the tubes lasts three days in the monkey, after which the fertilized ovum remains six days in the uterus " bathed in the nutritive juices furnished by the maternal glands " (Hartman). The time periods in women are probably about the same.

Under normal conditions the unfertilized ovum dies during passage, and passes out of the uterus. The fertilized ovum, after a period varying with the species, penetrates the surface of a uterine endometrium properly prepared for its reception by progesterone.

Mammary Glands. The oestrogenic hormone stimulates the early development of the mammary glands, probably by direct action, for MacBryde has shown that application of oestrogen in ointment directly to human breasts stimulates their growth, and that if the treatment be confined to one breast the growth is limited to that breast.

Lyons and Sako have produced similar results in young male rabbits by inunction with oestrone, and Speert also obtained similar results with male rhesus monkeys.

Hair Distribution. The female pattern of hair distribution is at least largely due to oestrogenic action (cf., however, p. 244). This specific pattern develops precociously in young girls with granulosa-cell tumours which produce oestrogen (p. 298), while no abnormal distribution occurs in women with anovulatory cycles (p. 270), so that it does not appear to be in any way under the control of progesterone.

Other Secondary Phenomena. The deep reddening and swelling of the " sexual skin " (covering the external genitalia) of monkeys is the result of oestrogenic stimulation, and has been produced in ovariectomized monkeys and baboons by injections of oestrogens ; it is maximal at the time of ovulation (Fluhmann).

The nasal mucosa of the intact monkey responds to oestrogen in a specific manner, especially in the middle and inferior conchae, which exhibit reddening and swelling. In normal animals this nasal activity occurs cyclically and pre-menstrually. A similar phenomenon occurs in women (Mortimer, Collip, *et al.*).

Some curious observations have been made by Hamilton, which indicate that tanning of the skin by ultraviolet rays of sunlight is due to the production of some colourless precursor which needs the presence of gonadal hormones for a photograph-like " development," both androgens and oestrogens being effective.

Menstruation. Certain types of bleeding must be clearly differentiated from menstruation. So-called mid-interval bleeding of women and female monkeys, the pro-oestrous bleeding of the bitch and the oestrous bleeding of the cow occur at about the time the Graafian follicle reaches full development and ruptures. In addition, both bitch and cow, and also the guinea-pig, exhibit some bleeding which in point of time corresponds to the menstruation of primates (Fluhmann).

The bleeding at the end of anovulatory cycles in women and monkeys can be described as pseudo-menstruation for the sake of distinction, though, as far as is at present known, only histological examination of the uterine endometrium prior to such bleeding definitely enables it to be differentiated from true menstruation.

Hartman (3) has recently reviewed the subject of menstruation (cf. also Fluhman). Present knowledge is largely due to the work of Markee, who made intraocular grafts of uterine endometrium in the Macacus monkey. In the first part of the menstrual cycle, under oestrogenic stimulation, such grafts showed a rhythm of alternate vasodilatation and vasoconstriction of certain areas ; at the time of ovulation vasodilatation was marked. One to five days prior to menstruation stasis occurred, with regression of the

mucosa. Such stasis is apparently caused by resistance in the spiral arteries. Then four to twenty-four hours before the haemorrhage there was a constriction of the spiral arteries resulting in marked blanching of the graft, necrosis of the tissues, dilatation and rupturing of small arteries, increasing size of haematomata, and finally escape of free blood.

Regression must be rapid to result in haemorrhage. Lack of ovulation does not change the course of events appreciably. Hartman considers that progesterone has nothing to do with the cause of menstruation though it can modify its course. Deprivation of oestrogen is the prime cause; deprivation of progesterone as well can shorten the flow.

This is probably not quite the complete story. Administration of progesterone just prior to menstruation delays it (cf. Wintersteiner and Smith). During surgical operations in women excision of a recently formed corpus luteum results in menstrual bleeding within forty-eight hours, but if, following such excision, progesterone is injected, menstruation does not occur for seventy-two hours or even much longer (Morgan and Davidson). Massive doses of oestrogen do not have this effect (Wiesbader, Engle and Smith).

Menstruation is undoubtedly under nervous influences to some extent. Emotional states, such as fear of pregnancy and anxiety, may inhibit the menstrual flow in women (Theobald), but the channel of influence, whether through the anterior pituitary, the ovary, or the uterus itself, is not yet known (cf. Hinsey).

Any who have had reasonably large experience with the Friedman pregnancy test must have encountered a number of cases where report of a negative result when communicated to an unmarried woman previously exposed to risk of pregnancy was rapidly followed by menstruation, and this time-sequence occurring two or more weeks after a missed period seems too definite to be attributable to chance. In such cases there seems no reason to suppose that ovulation was delayed, and one must conclude that the second stage of the cycle was unduly prolonged through some nervous control associated with anxiety.

In the anovulatory cycle menstruation occurs after the usual time interval and since there is no progesterone production, must be associated with diminishing output of oestrogen.

Surgical removal of a granulosa-cell tumour—which produces oestrogen—is followed by profuse menstrual bleeding within forty-eight hours (cf. p. 300). Genital haemorrhage of the new-born, with accompanying enlargement of uterus and breasts, can be similarly accounted

for, the latter being due to stimulus of maternal oestrogenic hormone, and the bleeding to sudden arrest of that stimulus at birth (cf. Fluhmann).

It has been shown that the pituitary is not an immediate factor in the production of menstrual bleeding. Wilson and Kurzrok report two cases of women in whom the secretory endometrium persisted beyond the sixth day of a scanty menstruation. They consider that a special " bleeding factor," postulated by various investigators, does not exist, and that the time of occurrence of menstrual bleeding depends both on the stimulus (or cessation of stimulus) of the ovarian hormones, and the reaction of the endometrial blood vessels to it, the latter being a potentially variable component, not properly synchronized in their two cases.

Gillman has carried out careful studies on the female baboon, whose perineum is a sensitive indicator of effects of the female sex hormones, oestrogen producing turgescence and progesterone (following or along with oestrogen) producing deturgescence. If progesterone is administered in sufficient dosage its withdrawal is followed by bleeding. By repeated injection of progesterone during the turgescent or first part of the cycle it is possible to prolong the cycle ; by early withdrawal of progesterone the cycle can be materially shortened. Bleeding follows withdrawal of progesterone much more rapidly than withdrawal of oestrogen.

Length of the Cycle. It has been pointed out that in the adolescent girl the early cycles are irregular and prolonged. Amenorrhoea is not uncommon during the summer months. After regularity has been established it is never absolute. Haman recently reported on the length of the cycle in 2,460 cycles in 150 normal women of ages varying from nineteen to forty-two years. The extremes were ten and fifty-five days, the average length 28·4 days, but only 15 per cent. of the total number were twenty-eight-day cycles.

Time of Ovulation. Ogino, and Knaus, independently, from accurate studies of menstrual histories of many women, and correlation of occurrence of pregnancy with known times of coition, drew the conclusion that ovulation must occur about fourteen or fifteen days before the next expected period, and that in order that pregnancy can result coition must occur a little prior to, or just following, ovulation.

These conclusions were apparently supported by the results of ingenious experiments by Knaus on women (in which uterine contractions were recorded by means of inserted balloons kept under low pressure). He had previously shown that in pseudo-pregnancy in the rabbit—the post-ovulatory stage—the uterus will not contract following injection of pituitrin, and believed he was able to show the same refractoriness of human uterine muscle following ovulation. These experiments have been frequently repeated by others, with varying results. Henry and Browne cannot confirm them. However, other very definite facts support the views of Ogino and Knaus.

Views that ovulation occurs at a definite time during the cycle support the theory of a so-called " safe period " in women, during which coition cannot lead to pregnancy, and therefore have an important bearing both on avoidance of pregnancy and on the induction of pregnancy in some proportion of apparently sterile women. Latz and Reiner have recently published an analysis of the careful records of twenty-four women, who first used the sterile periods to avoid pregnancy, and later cohabited in fertile periods and conceived. Studies of 11,249 cycles in 1,000 women, varying from 15 to 41 days, and including 49,356 intercourses without conception resulting, led to the definite conclusion that ovulation takes place fifteen days before onset of the next menstruation.

C. G. Hartman has carried out a series of important studies on female monkeys, and has demonstrated that the menstrual cycle so closely resembles that of women that conclusions about one species may reasonably be applied to the other. Thus, for example, in the young adolescent monkey the length of cycle is very variable, as it is in young girls. In older monkeys, as in women, there is less time-spread, the average length of the cycle being four weeks in both, though individual monkeys show even less regularity than individual women.

The time of ovulation in monkeys can be accurately detected by rectal palpation, and occurs on the average on the thirteenth day of a twenty-eight day cycle, that is, fifteen days before the next expected period. In almost all animals studied ovulation occurred between the eighth and sixteenth days of the cycle. Hartman concludes that in the monkey there is an absolutely safe period during which conception cannot occur ; the potentially fertile days are from the eighth to the twenty-first of the cycle.

More recently van Wagenen has published results in close agreement with those of Hartman. Ovulation in the monkey occurred on the ninth to the eighteenth days of the cycle, and most frequently on the eleventh to fourteenth days. Successful (forty-eight hour) mating (placing in a cage with a male) occurred most frequently when commenced on the tenth and eleventh days.

Hamilton, Barnes and Dodds have recently listed the cases in which human ova were recovered at a very early stage, and in which the menstrual histories of the women were sufficiently known to permit conclusions as to the time of ovulation. The findings are shown in Table VI (cf. also Rock and Hertig).

Admitting the impossibility of predicting the definite length of any cycle until its completion, these figures nevertheless indicate that ovulation occurs during a rather restricted time-period.

The electrical potential of the body, measured from finger-tip to finger-tip of each hand, changes at the mid-interval (Burr). Rock showed that when laparotomy was performed on a patient just after this change had occurred a fresh ovulation was found—

TABLE VI

Time of Ovulation as Calculated from Recovered Ova

Observers	Day of Cycle on which Ovum was obtained	Estimated Age of Ovum	Length of Menstrual Cycle	Estimated Time between ovulation and next Menstruation
Lewis . . .	22nd	Possibly 1 day	Preceding cycle 35 days	14–15 days
Pincus and Saunders				
Case 1 . .	19th	Possibly 2 days	About 28 days	12 days
Case 2 . .	20th	Possibly 2 days	26–30 days	9–13 days
Hamilton *et al.*				
Case 1 . .	17th	Not more than 12 hours	Formerly 28 days. Preceding cycle 30 days	14 days
Case 2 . .	16th	Possibly 1–2 days old	28 days	14–15 days

on the fourteenth day of the cycle ; Burr has recorded a similar case.

Temperature studies lend further support to ovulation at such a period (see p. 280).

Browne and Venning's findings concerning the initial time of excretion of pregnanediol (p. 255), and data pertaining to the occurrence of mid-interval pain and mid-interval haemorrhage, are all in good agreement with the view that the time of ovulation is limited to within a relatively short interval during the cycle.

D'Amour has studied twenty menstrual cycles of five normal subjects, using several methods concurrently. He concludes that the sudden increase in pituitary gonadotrophic excretion at the mid-interval is the effect most indicative of the exact time of ovulation. Such a peak was present in eighteen of the twenty cycles (the remaining two were judged by other criteria to be anovulatory). The range of time was narrow : one on the 13th, eight on the 14th, six on the 15th and three on the 16th day preceding onset of menstruation.

Reynolds has undoubtedly expressed the views of the majority of investigators in this field : " The occurrence of ovulation . . . for cycles of average length (twenty-eight to thirty days) . . . is generally from the twelfth to the eighteenth day. Of course it is inevitable that variations occur, due to diversity of the length of cycles in most individuals."

It has been pointed out, however, that emotional influences are

undoubtedly able to extend the interval between ovulation and the end of the cycle, by a mechanism still unknown (p. 266).

Though certain experimental data indicate that slight luteal activity can precede ovulation (cf. p. 261, and Smith, Smith and Schiller), the amount of progesterone produced must be minimal, and almost certainly quite inadequate to lead to output of pregnanediol in definitely detectable amount, so that conclusions drawn from the time of initial excretion of pregnanediol are not invalidated.

Reciprocal Control by Pituitary and Ovarian Hormones. The control of ovarian function by the pituitary gonadotrophins is recognized and has been dealt with. There is also some evidence that the two gonadotrophins of the anterior pituitary are reciprocally controlled by the oestrogenic hormone, which, towards its peak of production, is believed to depress output of FSH and possibly increases output of ICSH (cf. Pfeiffer). Ovulation and regression of follicles lead to lessened production of oestrogen, and this is still further lessened in women, along with progesterone, when the corpus luteum regresses. Inhibition of the pituitary is thereby removed, so that renewed stimulus of FSH again causes renewed production of oestrogen by other newly enlarging follicles, the reciprocal control thus producing cycle after cycle.

It has been mentioned that experimental chronic stimulation by oestrogen leads to atrophy of the pituitary (p. 244), so that it is reasonable to assume that the chronic physiological stimulation which must occur during most of the cycle leads to an increasing depression of pituitary activity. Further experimental proof of this effect is still needed. Experiments with rats have shown that testosterone suppresses FSH and increases output of ICSH from the pituitary (Hellbaum and Greep).

Anovulatory Cycles. In the monkey anovulatory cycles are the rule during the summer months—the non-breeding season, and are frequent after pregnancy and lactation (Hartman). Seasonal amenorrhoea occurs in young female baboons and chimpanzees during the winter months, apparently through failure in initiation of follicular development (Young and Yerkes), but is more common in adolescent girls in the summer months. There is also evidence that in girls anovulatory cycles are not uncommon. In cases where early coition is frequent, yet pregnancy is not usual until several years after the menarche, fertility gradually increasing (cf. Fluhmann).

In anovulatory cycles the endometrium remains in the preovulatory stage, and curettage towards the end of the cycle detects the condition. There are no clinical manifestations, and, as already mentioned, the lengths of such cycles and of bleeding

periods are normal. The cause of failure to ovulate is not definitely known, but may be lack of appropriate pituitary stimulation (cf. Fluhmann).

Anovulatory cycles in apparently normal women are by no means uncommon (cf. Rubenstein), and are frequent during the post-partum period. In a recent study by Lass, Smelser and Kurzrok of 194 cycles of forty-seven women, all initially nursing but with regularly occurring menses, 106 were found to be anovulatory and eighty-two ovulatory as judged by endometrial biopsies. In some cases the studies were carried beyond the stage of weaning ; the type of result was the same. It was found that the time of appearance of the first ovulatory cycle in these women was irregular, and further that occurrence of an ovulatory cycle does not predispose to another ovulation in the succeeding cycle.

The Menopause. Permanent cessation of menstrual cycles occur in women in middle life and may well be due, as Zondek suggests, to exhaustion of suitable ovarian follicular material. With the cessation of ovarian response to pituitary stimulation, through lack of follicles to respond or to respond normally (Watson *et al.*), there is a fairly rapid cessation of oestrogenic output, with resulting atrophy of the uterus and corresponding changes in the vagina (cf. Fluhmann).

The Cycle of Pregnancy. The fertilized ovum passes down a Fallopian tube in the same way as does an unfertilized ovum, and reaches the lumen of a uterus prepared for nidation by the combined action of oestrogen and progesterone, and well stored with glycogen ; after a period of some days, varying with the species, the ovum embeds itself in the endometrium. In woman and the female chimpanzee implantation is interstitial, in the monkey superficial (Hartman). With this embedding the long cycle of pregnancy commences.

In primates the ovarian cycle is in abeyance during pregnancy, presumably through chronic oestrogenic stimulation of the anterior pituitary and resulting depression of its gonadotrophic function. Ovarian follicles grow and mature, but do not as a rule ovulate.

In the rhesus monkey there may be one or two abortive cycles which seldom reach the stage of bleeding. Two cases of women with bicornate uteri have been reported, in whom periodic bleeding during pregnancy was observed. The lower species of animals show variations. The oestrous cycle continues in the rat, and some stages of it occur in the guinea-pig. Ovulation can be induced experimentally in the mouse without abortion following. It occurs spontaneously in the mare, while in the cow follicles tend to enlarge, with occasional oestrus (cf. Snyder).

During pregnancy in the rabbit both tubes and uterus remain quiescent for a long period, and activity of the tubes no longer spreads to the uterus, which does not exhibit spontaneous motility until late in pregnancy (Reynolds).

Following embedding of the fertilized ovum the corpus luteum persists and enlarges. If ovariectomy is performed before the implantation has taken place, then gestation terminates in all species (that have been studied), and this must be attributed to removal of the corpus luteum and consequent cessation of maintenance of the uterus by progesterone. Subsequent to implantation the need for this continued stimulus seems to vary in different species. Snyder has reviewed the evidence. In the guinea-pig once implantation is complete, removal of the corpus luteum does not necessarily lead to abortion. In the cat ovariectomy at the forty-sixth day of pregnancy results in abortion, but at the forty-ninth does not. In women ovariectomy at the thirty-fourth day, and in the female rhesus monkey at two months (Hartman (2) says twenty-five days), does not necessarily lead to abortion. In the mare and female donkey there is no corpus luteum present in the latter part of pregnancy. On the other hand, in the opossum, rabbit and mouse the corpus luteum is essential throughout pregnancy.

In the rat abortion or resorption invariably occurs following ovariectomy. Zeiner finds that the average period before such abortion is eighty hours, and if the ovariectomy is performed in two stages, to lessen shock, the average period is lengthened to 108 hours.

As long as the corpus luteum is present it continues to produce progesterone. Biological tests have demonstrated the presence of that compound in the corpora lutea of sows until the last ten days of gestation (cf. Evans).

The sharp rise in excretion of pregnanediol in human pregnancy urine at the fifth month and the abrupt cessation in its excretion at parturition suggests that progesterone is formed in the human placenta (cf. p. 255), and gives a rational explanation for the non-occurrence of abortion, following a not-too-early ovariectomy. The same type of explanation may hold for other species, but further evidence is needed (cf. Reynolds).

The placenta contains appreciable amounts of chorionic gonadotrophin from an early stage, and it is usually considered that one of the chief functions of this gonadotrophin is to maintain the corpus luteum as long as necessary. In addition the placenta contains amounts of oestrogens much greater than that produced by the ovaries ; their functions presumably include both maintenance of the uterus and depression of the pituitary. The

placenta also contains glycogen, which it stores presumably under the influence of progesterone.

Growth of the uterus during pregnancy is not only due to a combination and alternation of hormonal stimuli, but also to the distension stimuli of growing foetuses and their placentae, of combined foetal and uterine origin (Reynolds).

Duration of Pregnancy. This is to some extent under experimental control. Delay can be caused in mice by suckling young, or by injection of progesterone, and in rats by injection of extracts of the anterior pituitary. Such delay results in a parallel delay in development of the foetuses and in parturition (Snyder). If rabbits, normally at term on the thirty-second day, are injected with chorionic gonadotrophin on the twenty-fifth day, ovulation is induced, with production of fresh corpora lutea, and parturition is delayed to the fortieth day. That this delay is due to the progesterone from the fresh corpora lutea is shown by the fact that injection of pure progesterone will also cause it (Heckel and Allen). The foetuses continue to grow and remain alive for three days past normal term, then die, but the placenta still functions after their death, so that onset of labour cannot be due to changes in the foetus or the placenta, or to mechanical distension of the placenta (Snyder; Koff and Davis).

Parturition. It will be shown in the next chapter that oxytocin of the posterior pituitary causes uterine contraction *in vitro*. It therefore seems possible that oxytocin may be a normal factor in induction of parturition. There is as yet lack of completely convincing evidence in support of this view, and it has even been shown that in the experimental animal parturition can occur after hypophysectomy. Yet it has also been shown that the oxytocic activity of the blood is depressed during pregnancy but is increased above normal at term (Caroca and Konef), while free oestrogen appears to sensitize the uterus to the action of oxytocin, and free oestrogen, instead of its esters, becomes available just before parturition (cf. Bell and Robson). Furthermore, just before parturition the excretion of oestriol in human urine decreases and that of oestrone increases (cf. Freud, Laqueur and Mühlbock) and Smith *et al.* suggest (2) that this increase of oestrone is the determining factor leading to onset of labour. Palmer has recorded a case which showed a marked rise in excretion of free oestrogen before abortion at the fourteenth week.

Reynolds considers that the actual mode of contraction of the uterus in labour does not resemble that induced by oxytocin. Perhaps effects of the true posterior pituitary hormone (cf. p. 321) and of oxytocin are not precisely identical.

Russell states that pitressin of the posterior pituitary, another possible artefact of the single hormone, is twenty-five times more

powerful in its effect on human uterine muscle than oxytocin, while the latter is ten times more powerful than pitressin when tested on the virgin guinea-pig uterus. He finds no difference in the reactivity of strips of muscle cut from the uterus before and after delivery.

Hain claims that labour is not associated with a rise in excretion of free oestrogen, but that prior to delivery there occur fluctuations in hormone output suggesting some extraneous controlling factor.

According to Lyon there is a marked decline in the excretion of pregnanediol for several days before labour, suggesting that the concentration of progesterone may be insufficient to maintain pregnancy. This may be related to such fluctuations of oestrogen since according to Smith *et al.* (3) there is evidence that administration of stilboestrol stimulates secretion of progesterone in pregnancy.

The Mammary Glands. Throughout pregnancy these glands are subjected to continuous oestrogenic stimulation, as a result of which, with the probable added stimulus of progesterone and prolactin of the anterior pituitary they develop to the stage of storage of secretory products. Lactation does not occur till parturition, when it is induced through stimulus of prolactin; this stimulus is enhanced by nervous reflexes set up through the act of suckling (cf. Robson; Selye and McKeown; Pfeiffer; Reece and Leathem).

But administration of synthetic oestrogens produces copious lactation in some proportion of maiden heifers and dry cows (Folley and others).

Experiments with guinea-pigs, and treatment by stilboestrol of young women with primary amenorrhoea, have shown that the pigmentation of nipples and areolae is the result of oestrogenic stimulation. The effect is not produced after the menopause, but pregnancy is normally associated with it (Davis *et al.*).

Sex Development in the Male Animal, including Man. It has already been stated that up to the age of seven years there is little difference between the excretion of oestrogens and androgens by girls and boys. Subsequently a difference is perceptible; girls excrete more oestrogens, boys more keto-steroids (including androgens), and this increased excretion of keto-steroids becomes especially marked after eleven years of age, when the secondary sex characters begin to appear. The follicle-stimulating hormone can be detected in the urine of boys between the twelfth and thirteenth year, and its late detection may be due to the lack of delicacy of present methods of detection. As in girls, so also in boys, the endocrine development which leads to sexual maturity begins to be evident in the excretory products about five years before puberty (Nathanson, Towne and Aub).

It has been pointed out that pituitary FSH controls the sperma-

togenic elements and ICSH development of the interstitial cells of the testes, and the results just quoted indicate that such development commences several years before puberty. As a consequence development of penis, prostate and seminal vesicles ensues, along with the characteristic secondary changes indicating maleness.

There is some evidence that descent of the testes to the scrotum is under control of the androgenic hormone.

Martin replaced rat testes by paraffin pellets inserted into the tunica albuginea cavity. Some days later it was found that the artificial testes ascended towards the inguinal canal or the abdomen. Testosterone propionate was injected, and after ten to fifteen days of treatment the "testes" completely descended to the scrotal pouch. Somewhat similar results were obtained with monkeys.

There is no evidence of cyclical fertility in man, and he remains fertile for a longer period than his counterpart. Men may experience a "menopause" characteristic but less marked and more delayed than that of women.

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DISEASE STATES ASSOCIATED WITH REPRODUCTIVE HORMONES

Introduction. These disease states cannot be dealt with as systematically as those associated with other hormones. There is not a simple hypogonadism or hypergonadism for each sex. Results in women of too much or too little production of proges-

terone, and of too much or too little chorionic gonadotrophin are theoretically possible. There is the added complication, which must not be forgotten, that each sex produces both androgens and oestrogens.

In many instances the patient has to be treated for a condition, such as amenorrhoea or sterility, instead of a definite disease. The cause of the abnormal condition calls for careful analysis of possibilities, and unless it can be shown to be probably an endocrine cause, endocrine treatment is usually not called for. In certain conditions, however, as will be seen, endocrine therapy seems to have a definite beneficial effect, even if the application be purely pharmacological, rather than replacement therapy.

It would be difficult therefore to frame an ideal classification. That used here is merely convenient. It is also felt that, from the endocrinological point of view, some advantage is gained by dealing with corresponding conditions in the two sexes in close conjunction.

A few notes are given here on some of the available diagnostic tests, and on general treatment and the endocrine preparations available for replacement therapy.

Notes on Diagnostic Tests. These are often useful in controlling treatment, as well as for diagnostic purposes.

Tests for Oestrogens. Biological tests are available for blood and urine, based on the original Allen-Doisy test with rats. For blood two somewhat differing techniques are available, due respectively to Frank and to Fluhmann (cf. Fluhmann). They both need a considerable amount of blood, so that a series of tests on the same patient seems undesirable ; further, the results they yield are not entirely in agreement when carried out on the same patient. Chemical tests for oestrogens are not yet available.

Tests for Progesterone. Measurement of the excretion of sodium pregnanediol has become established as a measure of progesterone formation and therefore of degree of corpus luteum function. It must be remembered, as Hamblen has pointed out, that conclusions from the degree of excretion of the glycuronide as to the extent of function of the corpus luteum assume that there is a normal uterine endometrium, a normal liver function (to form the glycuronide), and a normal kidney function (to excrete it). It must also not be forgotten that other tissues besides the uterine endometrium can transform progesterone to pregnanediol (cf. p. 256).

Methods are also available for estimation of free pregnanediol, and Wooster has critically reviewed their relative usefulness.

Curettage of the endometrium gives accurate knowledge as to the functioning or non-functioning or absence of the corpus luteum.

Haskins has recently applied the intrauterine technique (direct application to a rabbit's uterus, after priming with oestrogen) devised by McGinty, Anderson and McCullough, to measurement of pro-

gesterone in blood of pregnant women, and claims that it is very delicate.

Tests for Androgens. Chemical methods for measurement of the 17-keto-steroids are available (p. 413). These steroids include the excretory androgens and their measurement gives a clue to androgenic activity. There are numerous methods, most of them too recent to have been thoroughly evaluated. It is to be hoped that a simple standard procedure can be agreed on, capable of being carried out as a routine test by the ordinary hospital laboratory.

Test for the Pituitary Gonadotrophin FSH. Klinefelter, Albright and Griswold have adapted Heller and Heller's test, in which the hormone is precipitated from urine by addition of eight volumes of alcohol, and injected into mice. They claim that the test will distinguish between a normal and a decreased level of excretion of the follicle stimulating hormone.

Tests for Chorionic Gonadotrophin. The Zondek and Aschheim test for pregnancy, using mice, and the Friedman modification, using rabbits, are in reality not tests for pregnancy, as is usually considered, but tests for the chorionic gonadotrophin, and therefore yield positive results with urines from cases of pregnancy, incomplete abortion, hydatidiform mole, and chorionepithelioma (as well as with certain cases of teratoma of the testicle in man). They are remarkably accurate, as is also the corresponding test depending on extrusion of ova in the cloaca of the South African clawed toad, *Xenopus laevis* (Shapiro and Zwarenstein ; cf. Weisman and Coates) though the use of the latter is limited by the availability of that species of toad. Aschheim has recently modified the original mouse test, though the time required is not shortened.

Frank has published a useful modification, carried out with rats and giving results within twenty-four hours. It appears to have about the same degree of accuracy.

(McCullagh and Cuyler have dealt with " false positive " Friedman tests, which they have obtained in a number of conditions where neither pregnancy nor any evidence of chorionic tissue was present, including sixty-nine of 360 tests on men. They have obtained such results in a number of endocrine conditions, and consider that in absence of chorionic tissue such positive tests can be considered as a qualitative measure of excessive activity of the anterior pituitary. Their percentage of false positives in women is much greater than that obtained in most laboratories, but their definition of a positive result is not that usually employed for diagnostic purposes for pregnancy.)

The numerous other tests, chemical and biological, for which claims have been made during the past few years that they are diagnostic of pregnancy, have fortunately been shown to be thoroughly inaccurate with sufficient rapidity to prevent much harm from their use. Thus the so-called " colostrum test " (in which a small drop of diluted colostrum from breasts of normal primipara twenty-eight or more weeks pregnant is injected intradermally on the flexor surface of the forearm, and is supposed to give with non-pregnant women an enlarging wheal surrounded by a red areola and persisting at least an hour) gives, according to Allen and Donaldson, only 54 per cent. accuracy with pregnant women, and 88 per cent. accuracy with non-pregnant women, and is

therefore practically valueless. The "histidine" test is also quite unsatisfactory (Davey and Daley).

In pregnancy pregnanediol continues to be excreted, indicating a persisting production of progesterone. Based on this Guterman has devised a colour reaction test for pregnanediol in urine ; for this he claims 92 per cent. accuracy in a series of 248 cases, and a greater degree of accuracy than was obtained in simultaneous Friedman tests. However, he wrongly interprets results of the latter, which is a test for functioning chorionic tissue and not for pregnancy *per se ;* its greater accuracy, when properly interpreted, is well established. Greenhill recommends the Guterman test as useful in detecting cases of threatened abortion in time to administer progesterone as preventive measure.

The Vaginal Smear Test. Papanicolaou's study of the human vaginal smear has been referred to (p. 263). He has recently (1946) reviewed its use in research and in diagnosis. The preparation and staining of specimens is relatively easy, but he points out that the interpretation is rather difficult, and special training is necessary.

Papanicolaou and Shorr used it to check the effect of oestrogenic treatment at the menopause, and Rubenstein found it useful in determining the proper treatment of menstrual disturbances in adolescent girls. Hall claims that the test is useful in the prevention of abortion and miscarriages by indicating when progesterone should be administered to correct too marked an oestrogen phase ; by its use he has prevented such accidents in all but three of 141 cases.

(The use of the test has been extended to detect carcinoma of the uterus, this being an exfoliative lesion, and detached cells, mixed with desquamated cells of normal epithelium, being recognizable. Papanicolaou (2) says that the test is useful for this purpose, but is still not as dependable as biopsy and curettage. Meigs *et al.* consider that it is a useful preliminary test, permitting rapid examination of large numbers of women. But a negative test does not exclude cancer, and a positive test requires corroboration from a biopsy before surgery is indicated. In 1,015 tests they found a diagnostic error of 4 per cent.

Mack has proposed a new method for studying vaginal smears, based on the iodine-glycogen reaction.

A cotton applicator is inserted in the vagina and twirled lightly against the vaginal wall. The cotton end is then rolled lengthwise over the surface of a clean glass slide, this rolling giving a uniformly thick film of cells. The film dries almost immediately. Staining is accomplished by laying the slides face down over a shallow dish containing Lugol's solution. Iodine vapours rising insensibly from the solution

stain the glycogen-containing cells in two or three minutes, permitting immediate microscopic examination. Such stains fade in twenty-four to forty-eight hours, but restaining can be carried out repeatedly as necessary, the same intensity being produced.

Mack classifies the depth of staining into four grades : (i) Complete glycopenia ; smears contain only small yellow cells, and amorphous cellular débris. (ii) Somewhat greater abundance of epithelial elements. Some glycogen is seen as irregular brown deposits at the cell margins, or scattered irregularly through the cytoplasm, giving the cells a mottled appearance. Small numbers of diffusely stained brown cells may be present, with many glycopenic yellow cells. (iii) More epithelial cells, larger and more regular. The diffusely stained cytoplasm has a light brown colour. Yellow cells are also present in abundance. (iv) This grade is easily recognizable by almost exclusive presence of large, flat, deeply stained brown iodophilic cells, present singly or in large clumps. It represents maximum oestrogenic effect and corresponds to the smear of the normal proliferative (follicular) phase.

A Temperature Test. Within the last two or three years a number of papers have appeared dealing with variations of the waking-temperature in women throughout the menstrual cycle and in pregnancy, and drawing some important conclusions concerning ovulation, pregnancy, etc. As long ago as 1904, Van de Velde showed that in normal woman the body temperature is relatively low during the first half and relatively high during the second half of the menstrual cycle. The recent work has been summarized and extended particularly by Martin, Tompkins, Nieburgs, Barton and Wiesner, and Halbrecht.

To carry out the test the normal subject or the patient, following explicit instructions, takes her temperature each morning immediately upon awakening, and at about the same time, after a restful night's sleep. The measurement may be oral or rectal, but is preferably vaginal, and obviously must be one alone of these in any series of measurements. The measurement must be immediately charted. A constant climatic environment, absence of infection, etc., are obviously necessary conditions for the proper interpretation of the test.

From numerous studies with many women, and usually with a number of cycles of each woman, and with frequent endometrial biopsies as guide to interpretation, the following conclusions seem justified.

The normal " waking-temperature " cycle in fecund women is biphasic, with a change from relatively low to slightly higher temperature at the time of ovulation. At this time there may be a sudden slight drop in temperature preceding the rise, while there may be a rather sharp drop in temperature just prior to menstruation (cf. Nieburgs).

Experimentally it has been shown that injection of oestrogens

does not affect the waking temperature, but injection of progesterone causes a slight rise resembling the spontaneous shift at time of ovulation (Barton and Wiesner).

Anovulatory cycles are monophasic, and if such monophasic cycles are checked by biopsy in the latter part of the cycle, only

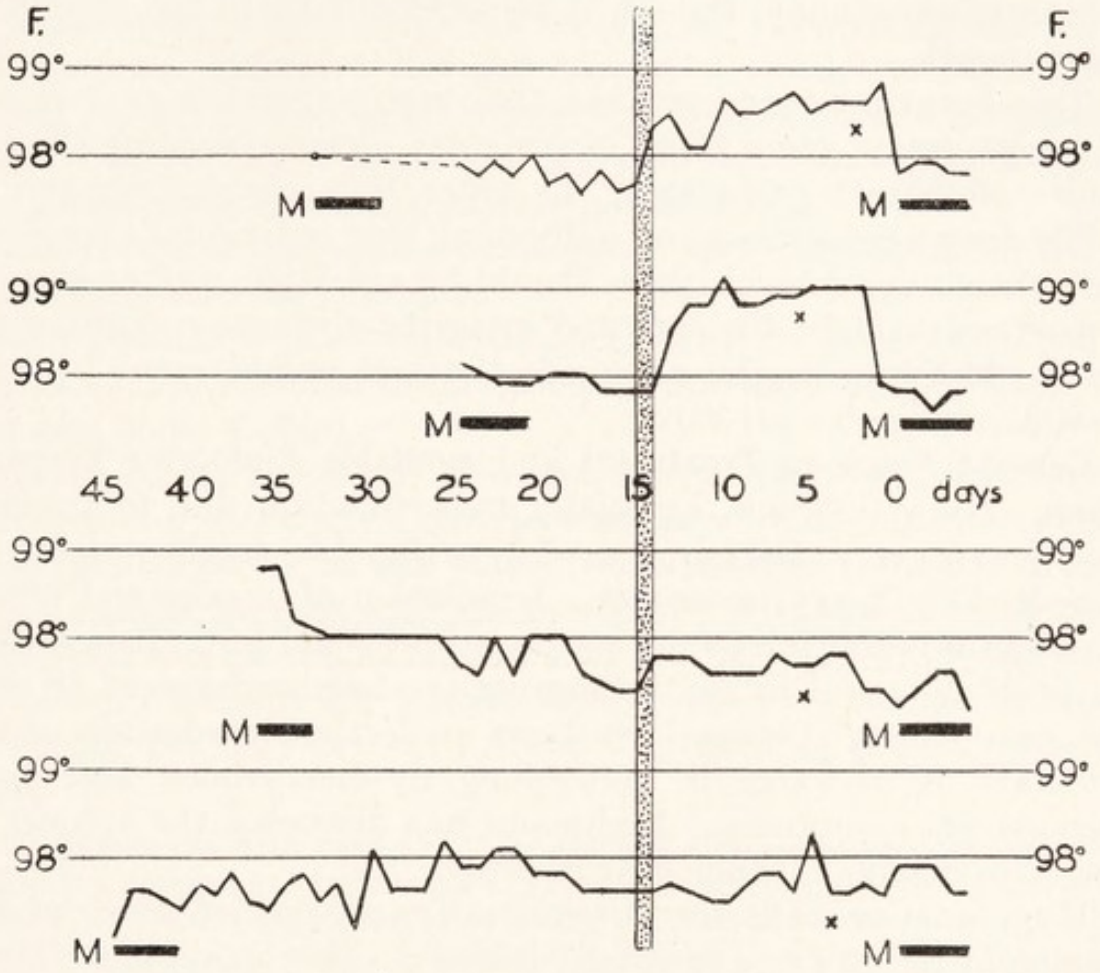


FIG. 38. Daily temperature charts throughout a menstrual period of four women. *M*, menstrual period. *X*, time at which endometrial biopsy specimen was taken. Time reckoned in days from the following menstrual period. The upper two curves are "biphasic" and the biopsy showed secretory epithelium, indicating that the cycle was ovulatory. The lower two curves are "monophasic," and the biopsy only showed proliferative epithelium, indicating an anovulatory cycle. Data from Figs. 1, 3, 5, and 7, Martin, Am. J. Obst. Gynec., 1943, xlvi, 53.

proliferative epithelium is found (Martin; cf. Fig. 38). The test is therefore of value in detecting anovulatory cycles as a potential cause of sterility (Martin), and also, with normal cycles, in ascertaining the time of maximum fertility for those who wish to conceive, and the unsafe period for those who don't (Tompkins).

The relatively higher temperature persists after conception, so that a change to the lower temperature, or a persistent lower

temperature, excludes the diagnosis of pregnancy (Barton and Wiesner) and the test can thus be used as a suggestive sign of early pregnancy, the " poor man's Friedman test " (Tompkins). Halbrecht diagnoses pregnancy when the higher temperature shows no tendency to fall twenty days after the initial rise. He states that this higher temperature usually persists to the fifth month of pregnancy, though it sometimes falls in the second or third month.

This temperature record has also been suggested as a means of investigating some types of irregular uterine bleeding (Tompkins : Nieburgs). Obviously, in order that conclusions can be safely drawn concerning any individual, that individual's temperature chart over several cycles should be available, and even more important must be the care and integrity given to compiling the chart. If these can be assumed, the test would seem to have considerable potential value.

General Notes on Treatment and available Endocrine Preparations. Hyperfunction, especially hyperfunction due to tumour, calls for surgery. Mild degrees of hyperfunction might possibly be benefited by X-ray treatment. Irradiation of ovaries and uterus is potentially dangerous during their functional life. It is said to be possibly useful in controlling uterine haemorrhage at or near the menopause. Claims have been made that irradiation of the pituitary is of value in controlling dysmenorrhoea and post-menopausal symptoms. Fluhmann has discussed the subject in the conservative manner that it needs.

Hypofunction calls for administration of one or more of the numerous natural and synthetic hormones now available. These include the following :

Natural oestrogens and derivatives : α-oestradiol, its benzoate, dipropionate, and ethinyl ester ; oestrone ; oestriol and " emmenin " ; a mixture of " equine conjugated oestrogens," frequently and incorrectly termed " sodium oestrone sulphate."

Synthetic oestrogens and derivatives : (diethyl-)stilboestrol, stilboestrol dipropionate, stilboestrol monomethyl ether ; hexoestrol ; dinoestrol ; benzoestrol.

Androgens : testosterone ; testosterone propionate ; methyltestosterone.

Progesterone and anhydrohydroxyprogesterone (or pregneninolone, or 17-ethinyl-testosterone).

Gonadotrophins : pituitary gonadotrophins, chorionic gonadotrophin, equine gonadotrophin.

These compounds have been given a multitude of trade names.

Unless each trade name is accompanied by a clear indication of the actual nature of the preparation (which is not invariably the case) the wholesale drug house supplying such preparation is scarcely crediting the physician with the adequate knowledge of endocrinology needed for its employment.

When pure compounds are employed, dosage should be in milligrams. Effective dosages expressed in international units based on assays with small laboratory animals tend to be astronomically large ; these large figures create an illusion that dosage is very high instead of being merely physiological.

The " equine conjugated oestrogens " are standardized in terms of sodium oestrone sulphate.

The gonadotrophic preparations are still necessarily defined in terms of international units based on standard preparations and rat assays (cf. Collip).

In an earlier section of this chapter (p. 248) the difficulty was stressed of making any clear-cut statements that one androgen or oestrogen is more or less active than another by some definite ratio, results varying with the method of test, and of administration, and the species of animal used for testing. From the point of view of therapy for human beings, assay on human beings is probably the only certain method of obtaining definite information.

Experiments with rats and mice suggest that α-oestradiol is the most effective natural oestrogen when given by injection, oestriol when given orally, and also that stilboestrol orally is about as effective as oestradiol, subcutaneously (p. 249). It has further been pointed out that hexoestrol tested on laboratory animals, seems more potent than stilboestrol, but assayed on menopausal patients, it appears a much weaker drug (p. 250). The following statements still further illustrate the difficulties in drawing definite conclusions between the various oestrogenic compounds.

Mack (2), using iodine-stained vaginal smears in menopausal women as test method, finds that (*a*) oestriol is less effective orally than an equal weight of oestrone, (*b*) oestradiol given orally is equal in effect to an equal weight of oestrone in oil, and (*c*) stilboestrol, orally, produces a greater effect than an equal weight of oestrone or of oestradiol, though its effects fluctuate more.

Greene states that, as tested on menopausal women, oestradiol benzoate is less effective, milligram for milligram, than oestradiol dipropionate. Soule states, in similar tests, that ethinyl oestradiol is the most active oral oestrogen he has used.

Freed and Greenhill find that injections of oestrone crystals suspended in water give more prolonged relief in menopausal cases than oestrone suspended or dissolved in oil.

Turner, Davis and Hamblen claim that the potency of " sodium oestrone sulphate," as judged by production of hormone-withdrawal

bleeding in women with functional amenorrhoea, is the same, milligram for milligram, as stilboestrol.

Choice of some of these compounds for therapy has to be governed to some extent by production or non-production of undesirable reactions. Several, given orally, produce gastro-intestinal disturbances such as nausea and vomiting in some proportion of patients, and it seems impossible at present to make any definite statement as to which is least objectionable from this point of view. Good claims have been made for hexoestrol (cf. Karnaky ; McElroy, Snyder and Clark), for ethinyl oestradiol (cf. Watson ; Soule ; Groper and Biskind ; Salmon *et al.*), for stilboestrol monomethyl ether (cf. Geschickter and Byrnes ; Elden), and for the " equine conjugated oestrogens " (Neustaedter, and many others). No compound, natural or synthetic, seems definitely perfect in this respect, but the patient who responds badly can be treated by injection or by implantation of pellets.

A number of methods of administration are available, and no conclusion can yet be drawn as to the most desirable, though pellet implantation has obvious advantages in many cases ; sublingual administration does not seem to be particularly advantageous for most patients.

Most of the steroid compounds and derivatives may be given by injection, though a number are designed especially for oral use.

The following are effective orally : oestradiol, oestrone, oestriol, emmenin, ethinyl oestradiol, " equine conjugated oestrogens," stilboestrol, hexoestrol, stilboestrol monomethyl ether, anhydrohydroxyprogesterone, methyltestosterone.

The following have been found to be effective when given sublingually, although effective control of dosage has perhaps not been so clearly demonstrated : oestradiol in propylene glycol-alcohol (Salmon and Geist ; Hall ; Joël), stilboestrol in propylene glycol (Castrodale, Loeffel and MacBryde), anhydrohydroxyprogesterone (Joël), testosterone in propylene glycol-alcohol (Lisser, Escamilla and Curtis ; Hurxthal), and methyltestosterone as tablets (Joël), or in glycol (Lisser, Escamilla and Curtis). Oestradiol, so given, is said to be as effective, milligram for milligram, as oestradiol benzoate by injection (Hall). Stilboestrol in propylene glycol, while possibly equivalent, milligram for milligram, with the same compound taken orally, produces nausea much more frequently (Castrodale, Loeffel and MacBryde). The dosage of testosterone needed for sublingual administration is two or three times that required when given by pellet implantation (Hurxthal). Salmon and Geist in 1940 drew attention to the possible toxic effect of prolonged administration of propylene gylcol, and it is not certain that such possibility has yet been definitely excluded.

Testosterone has been given effectively by inunction (Tager and Shelton ; Fleischer and Kushner). By this method also control of dosage is probably less efficient.

Implantation of pellets has been employed usefully with a number of steroids. Where implantation therapy is used, it is obviously important to determine the rate of absorption, which is of course the actual effective dosage. Warwick and Parkes found that progesterone is absorbed from large tablets implanted subcutaneously at an average rate of about 20 per cent. per month, so that 50 mg. tablets supply about 10 mg. per month. Greenblatt and Hair have obtained identical results, although they find that after three or four months the proportion absorbed tapers off.

Foss has reviewed the literature on implantation therapy with oestrone, oestradiol and its esters, and testosterone, and has measured their rates of absorption in a number of human subjects. He states that, employing flat discs or cuboids implanted in the anterior abdominal wall, oestrone is absorbed at an average rate of 0·18 mg. per day (in different persons the range was from 0·06 to 0·41 mg. per day), oestradiol about twice as fast; testosterone propionate tablets of 190 mg. lost 0·85 per cent. of their weight per day. Four 50 mg. tablets of testosterone in the same subject lost 1·18 per cent. of the total weight per day. Tablets of progesterone weighing 25 mg. lost 1·31 per cent. of their weight per day, a result not in very good agreement with that of Parkes and Warwick. Bishop and Folley recommend cast pellets of testosterone, which are uniformly absorbed at a predictable if changing rate. In general, it is agreed that the absorption of all such pellets is proportional to their surface area.

Foss remarked that tablets of testosterone propionate, testosterone and progesterone tend somewhat to slough out; those of oestrone and oestradiol do not do so.

The results with oestrone suggest a rather wide potential variation in rate of absorption. Howard and Jewitt found fairly large variations in absorption of testosterone propionate. More measurements of this kind seem very desirable, especially with tablets of definite size and shape.

Intersexuality (**Intersex**; **Pseudohermaphroditism**). This has recently been the subject of a monograph by Cawadias; he defines it as a morbid exaggeration of a normal process. Sex is ante-natally determined by the genes, but they act in part through the gonads. The gonads of each sex carry vestigial remains of the other. The characteristics of each can be inhibited or exaggerated.

Cawadias classifies intersexuality into various types, which have no clear-cut demarcation between them. (1) In the *gonadal* type the normal balance of male and female elements is upset. A virilizing tumour of the ovary is an example of this. (2) In the *genital* type there is variable degree of malformation of the external and internal reproductive organs, due to an embryological fault. (3) In the *morphological* type the secondary sex characters and bodily conformation resemble those of the opposite sex. An endocrine agency is responsible, as is illustrated in the virilism in

women due to adrenal cortical tumours. (4) In the *psychological* type the disturbance does not so much affect the physical organism as it does mental phenomena as temperament and emotion. Cawadias stresses the importance of the mild intersex changes, rather than those leading to actual pseudohermaphroditism or hermaphroditism.

Experimental work has been largely directed to produce embryological faults by hormones. The work of Greene and Ivy, and similar work by others suggests potential mechanisms for the production of intermediate sex forms. When pregnant female rats are injected with oestrone or oestradiol just prior to birth of young, the female offspring develop hyperspadias, which indeed can be produced in the new-born young themselves by injection of minute doses into them. Male offspring are not affected.

When pregnant female rats are injected with testosterone, the female offspring show either arrested development of the vagina, or become free-martins, exhibiting structures resembling prostate and seminal vesicles; development of structures from the Müllerian duct tends to be inhibited; development of structures from the Wolffian duct tends to be stimulated. Male offspring are not affected.

Large doses of testosterone transform the ovaries of young female rats towards the male type of gonad, with production of atrophy and development of numerous epithelial tubules (Selye).

Injection of oestrogen into the incubating eggs of the fowl, or into ring dove females thirty hours before one of their ova would break from the ovary, can produce intersex or sex-reversal in the developing male embryo (cf. Riddle and Dunham).

Pseudohermaphroditism has been produced experimentally in the monkey by van Wagenen and Hamilton. When pregnant females were treated for a long time with large injections of testosterone (5 to 20 mg. daily) genetic female foetuses developed as pseudohermaphrodites and exhibited anomalies which closely resembled those in human female pseudohermaphrodites. They had male external genitalia, with a penis-like phallus containing the urethra lying cephalad to a well-formed scrotum. The uterus, uterine tubes, and upper vagina were normal in structure and position. The vagina ended in the dorsal wall of the prostatic urethra, and bore a striking resemblance to a prostatic utricle. Prostate glands were present and as large as those of a control male. They surrounded the vagina and had developed as outgrowths of the urogenital sinus, both above and below the Müllerian tubercle.

One foetus, a genetic male, was but little affected.

Gynaecomastia can be considered as a partial intersexual phenomenon in man, due to incorrect androgen-oestrogen balance. Maliniac distinguished between true gynaecomastia, due to endocrine imbalance, and pseudogynaecomastia (bilateral), a soft, painless adiposis of the breast, usually not responsive to endocrine therapy, but improvable by surgery. In true gynaecomastia patients excrete the usual amount of oestrogen, but androgen excretion may be low (Kenyon *et al.* ; De La Balze).

McCullagh and Rossmiller apparently have produced gynaecomastia in some proportion of male hypogonad patients treated with methyl testosterone.

Klinefelter, Reifenstein and Albright have reported nine cases of a syndrome characterized by gynaecomastia, small testes and aspermatogenesis, without absence of Leydig cells. They think the syndrome supports the view that the testis produces a second hormone, inhibin, postulated some years ago by McCullagh and Walsh, but admit that if it exists its action is oestrogenic in character.

Conditions involving Hypo-oestrogenism in Women. These include the extreme degree of deficiency which follows castration, and which occurs at the menopause, and various lesser degrees of deficiency some of which are not primarily associated with the ovaries.

Castration and the Menopause. Prepuberal castrates are rare among women. The available evidence is in agreement with that derived from experimental castration in young female animals—there is arrest of sexual development, and even some degree of regression. Surgical removal of the ovaries during the reproductive period on account of cancerous or other lesions leads to gradual regression involving all the other sex organs and sex characteristics. Certain subjective symptoms are prominent—nervousness, hot flushes, irritability and fatigue. The earlier this artificial menopause is produced during the reproductive period the severer may be the resulting symptoms. At the natural menopause the same changes occur, more gradually, and at least 50 per cent. of women exhibit the same subjective symptoms (Pratt). They are probably related to increased output of the pituitary gonadotrophins.

Werner has made a careful comparative study of fifty-three castrated women, ninety-six in the menopause and forty-eight having involutional melancholia. He classifies the subjective symptoms as nervous (nervousness, excitability, irritability, headache, etc.), circulatory (hot flushes, tachycardia, vertigo, etc.), and general (lassitude, constipation, menstrual disorders, etc.), and concludes that they are accompaniments of ovarian

hypofunction or non-function, and points out that there is a striking parallelism in the symptoms of the menopause and of involutional melancholia.

There is some evidence that women excrete more androgen at the menopause (Hamblen (2)), though old women only excrete small amounts.

Oestrogenic therapy is strikingly beneficial and is most apparent when given to patients suffering from severe symptoms. Androgenic therapy has also been reported of benefit in some instances.

It will have been seen (p. 283) that the castrate or menopausal woman has proved a most valuable test subject for the various oestrogens, and that a large choice is available for her treatment. Dosage found adequate to cause the disappearance of the severer symptoms should, after such disappearance, be gradually reduced, but a maintenance dose is required for several months or the symptoms recur. A very few patients do not seem to be benefited. The necessary dose of the different oestrogens seems to vary greatly. Their cost also varies greatly.

Eisfelder has made an interesting computation of costs of several of them, for patients in New York. He finds that, from the patient's point of view, stilboestrol given orally is vastly cheaper than the correspondingly effective dose of oestradiol benzoate, administered by injection, and that this is considerably cheaper than oestrone, also administered by injection. Yet, since 22 per cent. of his patients on stilboestrol developed nausea, he considers oestradiol benzoate is the oestrogen of choice. He finds that 1 mg. of oestrone, injected, suffices for four to six days, 1 mg. of oestradiol benzoate, injected, for eight to ten days, and 1 mg. of stilboestrol is needed daily, when taken orally.

Greene and Dorr state that when stilboestrol is properly administered it should not produce unpleasant side reactions. Proper administration entails avoidance of amounts in excess of the individual needs of the patient. The necessary dose varies greatly from patient to patient and cannot be predicted. Initially a small dose should be given, which should be slowly increased until symptoms are relieved. If this be done reactions will not occur. They start with 0·1 mg. orally, daily, which after a week or two is increased to 0·2 mg. daily, if there has been no symptomatic improvement, and there is subsequent similar increase to 0·5 mg., 1·0 mg., etc., until relief is produced. They have found that only twenty-two of ninety-eight patients needed more than 0·5 mg. daily, and none developed undesirable side reactions.

Stoddard and Metzger found that equivalent results were given by 1·0 mg. of oestrone by injection, 0·42 mg. of oestradiol benzoate by injection, and 0·5 mg. of stilboestrol, orally.

Ethinyl oestradiol seems to be effective in much smaller dosage than oestradiol. Salmon *et al.* obtained satisfactory clinical relief with an average daily dose of 0·45 mg. for from four to seven days, and a subsequent maintenance dose of 0·15 to 0·3 mg. daily. Watson recommends similar dosage. Groper and Biskind found that 0·05 to 0·15 mg. daily was effective in twenty-nine of thirty-three patients (cf. also Soule). Wiesbader and Filler state that often 0·025 mg. daily is sufficient.

Very many excellent reports have appeared in the recent literature

concerning " equine conjugated esters," which, it will be remembered, are standardized in terms of sodium oestrone sulphate. The optimal dose appears to be about 1·25 mg. per day in divided dosage for one or two weeks, and subsequently 1·25 mg. every other day, though some physicians recommend a slightly higher dosage (cf. Fried *et al.* ; Gray ; Sevringhaus and St. John). A small percentage of patients exhibit nausea.

Freed, Eisin and Greenhill find that 1·0 to 2·5 mg. of " benzoestrol " given orally daily is effective. McElroy, Snyder and Clark state that the threshold effective dose of hexoestrol is 6·0 mg. daily, by oral administration. Geschickter and Byrnes found that the dose of stilboestrol monomethyl ester usually effective was 10 to 15 mg. in sesame oil, injected intramuscularly once weekly for a month, and subsequently 1 mg. orally each night. D.B.E. is probably not as effective as stilboestrol (Sway ; Greene).

Testosterone propionate by injection, or methyl testosterone by mouth is effective, but relatively large dosage is needed, as 30 mg. of methyl testosterone daily (cf. Berlind) ; this androgenic treatment may be particularly useful in persistent menopausal haemorrage (cf. Black). Christy claims that a synthetic vitamin E preparation is as effective as oestrogen. It has the advantage that it can be used freely with menopausal patients who have neoplastic disease.

Salmon, Geist and Walter have successfully prevented onset of menopausal symptoms after bilateral ovariectomy by implanting pellets (or loose crystals) of oestradiol or its esters. Of 36 cases none showed symptoms at the end of a month, while 62 per cent. of the controls did so. At the end of three months the figures were respectively 3 and 89 per cent. The amount of hormone implanted varied from 15 to 31 mg.

Ault, Hoctor and Werner consider that oestrogenic therapy can practically be regarded as specific in involutional melancholia, and record a series of cases showing 92 per cent. recovery with such treatment. They believe that this therapy is indicated for any woman who, at the menopause, has disturbing mental aberrations, whether mild or severe, and also it is beneficial in relieving distressing symptoms of the climacteric in other types of psychoses. Jones, MacGregor and Tod also report good results in a series of cases of depression at the menopause. Somatic symptoms were relieved in all ; six made good recovery within five months.

Oestrogenic therapy has also been beneficial in treating psychotic disturbances resembling those at the menopause sometimes seen in certain patients following childbirth, and in others with dysmenorrhoea (Adamson ; Schneider).

Kaufmann has established true menstruation in castrated women by combined oestrogenic and progesterone therapy simulating in time that

of the normal cycle. The dosage necessary corresponds to that normally produced in the organism. The results are chiefly of theoretical interest. Neustaedter has obtained similar results, employing in all 120 mg. of oestradiol, and 900–1,200 mg. of anhydrohydroxyprogesterone, in all of six castrates. This further illustrates the usefulness of the latter compound as a substitute for progesterone.

Other Conditions involving Hypo-oestrogenism in Women. *Primary amenorrhoea* is in reality a secondary effect, through non-development of the uterus, through lack of oestrogenic stimulation, presumably through lack of adequate gonadotrophic stimulation to the ovaries. If it is of long standing there is thus arrested development of the uterus, which is frequently small and infantile, and must be stimulated to grow. Kaufmann achieved success in three of five cases, with doses of oestradiol benzoate totalling 200 to 300 mg. or more. Mazer and Israel reported a similar degree of success with similar dosage.

Escamilla and Lisser have reported a striking case of a woman of thirty-four years, married twelve years, with an appearance suggesting primary hypogonadism, with delay of epiphyseal closure and the skeletal disproportion (unduly long extremities) characteristic of pre-adolescent eunuchoidism, mammary glands and breast contours almost flat, adolescent nipples, and sparse pubic and axillary hair (which had first appeared at eighteen years). At first inadequate dosage was given, 0·1 mg. of oestradiol dipropionate hypodermically three times a week. After five weeks this was doubled ; after another month 2·5 mg. were given three times weekly. After still another month this dose was doubled, and within two months of commencing the 5·0 mg. dose the patient's menarche occurred, lasting thirteen days. The dosage was reduced to 5 mg. once a week. Three months later the second menstrual period occurred. Neither flow was considered to be " withdrawal bleeding." Concomitantly the breasts increased in size and there was increase in growth and amount of axillary and pubic hair.

Goldzieher and Adler describe a similar case.

Ornstein produced cyclical uterine bleeding in four cases of Lorain-Levi infantilism with combined oestrogen-progesterone therapy. He found that equine gonadotrophin and a combination of pituitary and chorionic gonadotrophins were ineffective.

On the other hand, Looney treated a case of primary amenorrhoea without evidence of hypopituitarism with equine gonadotrophin. The patient showed no immediate response, but began to menstruate for the first time two years after cessation of this treatment, and continued to menstruate at moderately regular intervals during the following six months. After a further period of amenorrhoea lasting a year, menstruation was again induced by combined treatment with equine gonadotrophin and thyroid.

Secondary amenorrhoea. This may arise from endocrine or from non-endocrine causes. In either case the actual amenorrhoea is due to inadequacy of oestrogenic stimulation to the uterus, how-

ever that inadequacy be produced. Non-endocrine causes are very varied and include malnutrition (including that which occurs in wasting diseases such as severe diabetes and tuberculosis), morphine addiction, alcoholism, Fröhlich's disease, emotional disturbances, change of climate, etc. It is not improbable that in some of these conditions the pituitary is in the line of communication between the primary cause and end result, but the original cause is non-endocrine. Secondary amenorrhoea may also occur in various diseases primarily affecting other endocrine glands than the ovary, such as Simmonds' disease and acromegaly, Cushing's syndrome, hyperthyroidism, etc.

Treatment obviously should depend on the primary cause of the amenorrhoea. In a number of cases success has been claimed following the use of oestrogens alone (cf., for example, Kaufmann, Mazer and Israel). Different schools of clinicians evidence from their writings considerable difference of opinion concerning treatment. In the small number of cases where oestrogenic treatment has seemed to lead to permanent cure, such " cure " may well have been due to the disappearance of whatever primary cause led to the oestrogenic deficiency. Frank, writing in 1937, considered at that time that no useful purpose is achieved by prescribing oestrogen. Novak, writing two years later, thought that in some cases oestrogenic therapy can remedy a quantitative deficiency in the patient.

Kaufmann established true menstrual bleeding in a fairly large number of cases of secondary amenorrhoea by combined oestrogen and progesterone therapy, simulating in time the normal process. Menstruation commenced in most cases on the second day after the last injection of progesterone. After such artificial menstruation had been induced for three consecutive months, if treatment was stopped regular spontaneous menstruation often occurred for several months.

Cinberg recently reported an interesting case. Two uterine bleedings were induced in a girl of seventeen years (whose menarche had occurred four years before, with subsequent six-week periods, ceasing suddenly eight months prior to treatment) by parenteral use of progesterone. A spontaneous, normal menstrual rhythm was not produced. X-ray stimulation to the pituitary and ovary was unsuccessful in establishing menstruation. Combination oral treatment with stilboestrol and anhydrohydroxyprogesterone led to establishment of menstruation, recurring spontaneously at six-week intervals for over six months.

Gray reports good results in several cases following use of equine gonadotrophin.

Hypomenorrhoea, a less common condition than amenorrhoea, is apparently sometimes benefited by prolonged treatment with such oestrogens as oestriol (1·5 to 8 mg. orally daily for three

months) or emmenin in corresponding dosage, or oestradiol benzoate (1 to 2 mg. by injection at four day intervals for three months); normal premenstrual endometrium has been demonstrated in some cases, and normal spontaneous menstruation has followed cessation of treatment (cf. Mazer and Israel).

Oligomenorrhoea is also in itself a manifestation of oestrogenic deficiency; there is some evidence of good effects following prolonged low dosage with such an oestrogen as emmenin (cf. Fluhmann).

Dysmenorrhoea probably does not involve oestrogenic deficiency; only occasional benefit seems to result from treatment with emmenin or oestradiol benzoate, and this may be but temporary (cf. Fluhmann). Hirst *et al.* claim better results. Progesterone is said to give benefit through stopping contraction of uterine muscle (Fluhmann; Reynolds); anhydrohydroxyprogesterone is similarly useful (Soule). Androgen gives temporary relief in some cases (Jacoby and Rabbiner), and equine gonadotrophin also seems of potential benefit (Gray).

Menometrorrhagia associated with an atrophic endometrium (as revealed by study of vaginal smears) is successfully controlled by administration of oestrogen (Rubenstein).

Pharmacological Use of Oestrogens in Various Conditions. In certain disease conditions not necessarily due to oestrogenic deficiency oestrogenic therapy is of proved benefit.

Atrophic rhinitis is benefited by local treatment with oestrogen in corn oil. Intranasal oestrogen insufflation seems to produce some improvement in many cases of *constitutional deafness.* (Cf. Mortimer, Collip *et al.*)

Gonorrhoeal Vulvovaginitis in Childhood. Oestrogenic therapy is definitely beneficial. The basis of the treatment is the epithelialization of vaginal mucous membrane produced, and conversion of an alkaline vaginal fluid to one definitely acid. Oral therapy has been largely used, but vaginal suppositories are also very effective. Mazer and Israel consider that the optimal dose is, in terms of oestradiol benzoate, 0·2 mg. given hypodermically every other day. (Cf. also Brown.)

Stilboestrol is effective. (Cf. Russ *et al.*)

Good results have been reported following oestrogenic treatment of *senile* vaginitis (Jacoby and Rabbiner). Topical application in a lanoline medium is satisfactory (Finkler and Antopol). Oestrogens are also useful in *senile pruritis* in women (Feldman *et al.*); 1 mg. of oestradiol dipropionate subcutaneously once a week is adequate.

In *mazoplasia* (painful and nodular breasts) and nipple-bleeding oestrogenic therapy is sometimes beneficial (Mazer and Israel). It relieves breast engorgement in the early puerperium (Soule and Bortnick). It is distinctly useful in cases of *dead foetus.* Reynolds states that successful removal was effected in ten of a series of twelve cases (cf. Jeffcoate).

According to Rubenstein oestrogen is useful in treatment of *premenstrual headache*, in relatively young women, even with active ovarian function. (This seems to suggest a too rapid cessation of oestrogen production just prior to menstruation as cause of the headache.)

Migraine has sometimes been relieved by emmenin (Blakie and Hossack); Leyton, however, has reported a case in which oestrogen administration precipitated attacks of a migraine which, without treatment, occurred periodically. He found that chorionic gonadotrophin relieved it.

Acne, produced by androgens (Hamilton) is cleared up by oestrogenic treatment (Lawrence and Werthessen).

According to Seley, Vernick and Godman large doses of orally effective oestrogens given to patients with lymphogranuloma venereum who have symptoms of intestinal obstruction may sufficiently dilate the rectal strictures causing such symptoms to render operative interference unnecessary.

Huggins and McDonald state that ethyl oestradiol in low dosage usually arrests the haemorrhage in cases of chronic haemospermia.

Conditions involving Hyper-oestrogenism in Women. Certain ovarian tumours are associated with overproduction of oestrogen. These will be dealt with later.

Kaufmann produced cystic hyperplasia of the uterus experimentally in a castrated woman by chronic overdosage with oestrogen, thereby indicating that such cystic hyperplasia occurring clinically is due to a condition of hyperproduction of oestrogen, and that oestrogenic treatment is contraindicated.

Metropathia haemorrhagia, associated with lack of ovulation and a hyperplastic endometrium, is usually if not always due to hyperoestrogenic stimulation arising from cystic ovaries, granulosa cell tumours, ovarian sarcomata or fibromata, or like causes. (It can be induced experimentally in the female monkey by excessive oestrogenic stimulation.) Excellent results have been obtained in treating this condition with progesterone, 2·5 to 5 mg. or more, spread over several days (Kauffmann); anhydrohydroxyprogesterone is also useful.

In *menometrorrhagia* in adolescent girls, whose vaginal smears were predominantly plaques of cornified epithelial cells with pyknotic nuclei, Rubenstein found that progesterone therapy controlled the bleeding, cessation of therapy being followed by a normal type of bleeding.

Functional uterine bleeding, not associated with a definite lesion, does not respond to this therapy (cf. Gaines, Geist and Salmon); the therapeutic agent of choice seems to be androgen or chorionic gonadotrophin (Richardson) or prolactin (cf. Goldzieher).

Palmer states that the uterine bleeding of normal menstruation, of abortion, of labour, and of menorrhagia, etc., is always associated with

presence of free oestrogens in the urine, suggesting that in each of these cases it is associated with similar physiological processes.

Goldzieher recommends treatment of menstrual disorders with prolactin.

Sheffey warns that endocrine therapy instituted to control uterine bleeding without preliminary examination to exclude organic pelvic disease has far too often resulted in delayed diagnosis of uterine cancer.

Endometriosis can perhaps be regarded as due to hyperoestrogenic stimulation. Hirst considers that intramuscular injection of testosterone propionate is a practical treatment in advanced cases where radical excision is contraindicated or refused.

Conditions involving Deficient Progesterone Secretion. Certain cases of habitual or threatened abortion seem due to lack of progesterone, since good results have been claimed following its use in a number of pregnant women (cf. Fluhmann; Quigley; Hudson and Rucker). Oral anhydrohydroxyprogesterone is apparently as efficient as progesterone (Davis *et al.*). Vaux and Rakoff recommend combined progesterone and oestradiol therapy, for which they claim very good results.

In anovulatory cycles there is of course a marked or total lack of progesterone; treatment will be considered in dealing with sterility.

Pharmacological Use of Progesterone. It gives striking relief in fifteen to twenty minutes in abolishing the after-pains of labour (Reynolds); 1 mg. produced complete relief in forty-eight of fifty-five patients (Lubin and Clark). Henry and Browne do not support this view, but Dr. F. H. McGuinness informs me that in his experience progesterone is definitely of benefit.

It is also useful in treatment of chronic cystic mastitis (mastodynia and adenosis sub-varieties, but not cystic disease) if 5 mg. are administered in oil twice weekly during the last two weeks of one or two consecutive menstrual cycles (Geschickter).

Harding reports that oral anhydrohydroxyprogesterone gave good results in sixty of eighty-two patients with functional dysmenorrhoea.

(According to Lipschütz *et al.* when fibroids are produced in female guinea-pigs by subcutaneous pellets of oestradiol, their growth can be stopped and regression produced by implantation of progesterone. On the basis of these findings Goodman has treated seven patients with uterine fibromyoma with injections of progesterone and considers the results sufficiently promising to warrant further investigation of the treatment.)

Conditions involving Overproduction of Progesterone. Hamblen (1) has reported the case of a patient who exhibited in the last phase of

her cycles ecchymotic lesions, poly-hypermenorrhoea, dysmenorrhoea, and menstrual headache, and excreted abnormally large amounts of sodium pregnanediol glycuronide. Intensive oestrogenic therapy reduced this excretion, and the symptoms disappeared.

Hypoandrogenism in Man. This includes the condition following castration, the so-called male climacteric, and eunuchoidism.

Castration in Man. The effect of castration in the male, as in the female, is to cause persistence of infantile characteristics, or some degree of regression of sex characteristics, according to the age of castration. A study by McCartney of twenty Chinese eunuchs and three Skopecs illustrates the mental tendency of such castrates. He found in them typical dementia praecox or schizoid characters. They exhibited good intelligence and orientation, but were introspective or apathetic. They could talk intelligently but appeared stupid, were methodical but usually not purposeful, and were cold, passive and moody. Some retained sexual function, but without libido. Rowe's studies are in agreement. He wrote : " The male castrate is the victim of a profound mental depression. In his mutilation he sees the loss of all the virile qualities that made him male, and in this loss resides an unhappiness that tinges all the events of life with a sombre hue." He quoted some cases exhibiting a striking psychological effect following demonstration of a partial masculinity, which illustrated the fact that, at least in adult man, successful coitus is more largely due to psychic than to endocrine control.

Castrated men, like old men, excrete only traces of androgens and oestrogens (Kenyon *et al.* ; Freud, Laqueur and Mühlbock).

Injection of testosterone propionate or similar therapy abolishes nervous and vasomotor symptoms in castrates (McCullagh). Foss (1) has reported similar good results in the case of a post-puberal eunuch (whose condition was the result of war injury at the age of nineteen). Foss considers that an initial dosage of 100 to 140 mg. of testosterone propionate, with subsequently about 40 mg. weekly, is probably adequate in such cases. There are numerous similar reports, and equally good results are obtained with methyl testosterone. " The patients are changed from shy apprehensive, depressed individuals, to hopeful, cheerful, interested social beings " (Kearns).

Biskind has described a case in which testicular atrophy supervened on a bilateral herniorrhaphy. Shortly thereafter the patient began to have flushes associated with profuse perspiration. These disturbances occurred approximately every half-hour and the syndrome persisted

for twenty years, becoming in the last year or two of this period increasingly severe, although not more frequent, and almost incapacitating the patient for his work. Under adequate androgenic therapy the flushes and sweating disappeared, but recurred whenever the dosage was reduced below the maintenance level (10 mg. of methyl testosterone taken orally three times a day, or implantation of methyl testosterone pellets to give corresponding dosage).

The Male Climacteric. Werner points out that in women the cessation of menstruation is the visible evidence of the beginning of decrease or cessation of ovarian function; the climacteric syndrome results from the ensuing endocrine imbalance. Probably a much larger proportion of men than of women pass through the climacteric without any evident disturbance. The average age is somewhat later. In 54 men experiencing symptoms the chief were: subjective nervousness (54), diminished potency (49), depression (46), decline in memory and power of concentration (43), decreased libido (4), fatiguability (38), disturbed sleep (35), and irritability (34). Hot flushes were only experienced by 18 and undue sweating by 17.

Werner finds that intramuscular testosterone propionate, 25 mg. three times a week (or three to eight times the dose, if given orally) is effective in promoting a sense of well-being. It should not be given to stimulate potency. When symptoms occur their duration varies from a few months to occasionally, several years.

In the severer cases mental change may gradually transform to a psychosis, for which apparently testosterone treatment is not of much value (cf. Pardoll and Belinson).

Eunuchoidism. This is a condition in which the accessory male organs and characteristics fail to develop properly, through inadequate androgenic stimulation. The hypogonad condition arises usually from insufficient stimulation by pituitary gonadotrophins, but the testes themselves may be directly affected by diseases such as mumps, typhoid fever, new growths, etc. The typical eunuchoid is therefore in a condition of hypogonadism from early life.

Damage to the testes in adult life, as for example through syphilis, can lead to a mild type of eunuchoidism, through regressive changes.

The excretion of androgens by eunuchoids is low normal, or below normal (Kenyon *et al.*).

McCullagh reported that severe prepuberal hypogonad cases treated by injection of testosterone propionate show, in order, penile erections, increase of pubic and axillary hair, growth of

penis, lesser growth of scrotum, and still lesser growth of prostate. The testes apparently do not increase in size. Nocturnal emissions occur, and the volume of semen increases, but it contains no spermatozoa unless they were present before treatment started. The larynx grows and the voice becomes lower. Facial acne occurs and the beard grows.

These results have been confirmed by numerous similar reports in the literature. Methyl testosterone orally seems to be the easiest method of treatment (cf. Kearns).

Pharmacological Uses of Androgens. *Female gynaecological disorders.* For these androgens can scarcely be considered as replacement therapy, nor in all cases can they be considered as effective by counteracting undue production of oestrogen, yet such therapy has proved beneficial in a number of cases. Its usefulness in menopausal states has been mentioned (p. 289). A symposium of Geist, Salmon, and Hamblen, very fully documented, deals with the subject thoroughly. Androgens have been shown to be of benefit in a considerable proportion of cases of functional bleeding (with or without presence of small fibroids), in some cases of premenstrual mastalgia, in the majority of cases of premenstrual tension, and in some cases of dysmenorrhoea, ovulation pain, and endometriosis. It must be employed with care, to avoid such effects of over-dosage as hirsutism, hoarseness, slight clitoral enlargement, and atrophic vaginitis (brunettes with a tendency to hirsutism are said to be more susceptible). Salmon terms these androgenic effects " arrhenomimetic." Hamblen considers that there are few clear-cut indications for use of androgens in rational gynaecological therapy. He lists only certain menopausal cases, and some cases of hypermastia (when treatment should be by local application).

A clue to safe dosage is given in the results of a study by Geist on a series of twenty-five women with normal menstrual cycles. He found that doses of 500 mg. of testosterone propionate per month produced temporary suppression of menstruation, hypoplasia and atrophy of the endometrium, and evidence of oestrogenic deficiency in the vaginal smear. All cases returned to normal after cessation of treatment. Still larger doses sometimes produced hoarseness, hirsuties, acne, and enlargement of the clitoris, though in almost all cases there was spontaneous regression after the treatment was discontinued. Doses of 200 mg. per month produced none of the above effects.

Enuresis in children of both sexes is said to be benefited by androgenic treatment. Methyl testosterone, 10 to 20 mg. orally daily for several weeks, is usually an effective dose and is believed not to produce any lasting undesirable effects (Schultz and Ander-

son). Some proportion of cases of nocturia and frequency in post-menopausal women can also be relieved by androgenic therapy (Greenblatt).

Suppression of lactation can be produced by percutaneous use of testosterone (Fleischer and Kushner). Senile pruritis in men yields to androgenic treatment (Feldman *et al.*). It is claimed that testosterone propionate, 25 mg. twice weekly for eight weeks or more, is beneficial in angina pectoris (Waldman).

Hyperandrogenism in Man. Over production of androgenic hormone in young boys by certain testicular tumours is a cause of sexual precocity, and will be dealt with later.

Dunn has reported two cases of hypersexual males (an adult and an adolescent) who were benefited by stilboestrol therapy.

Endocrine Tumours of the Ovary. Certain tumours of the ovary are developed from cells dating from the early stages of its development. When such cells are disassociated from the developmental stream in the undifferentiated phase of ovarian embryology, a tumour developing from them is non-endocrine in character, a *dysgerminoma* (corresponding to aseminoma of the testis). From elements persisting in the ovary and possessing masculine potentialities an *arrhenoblastoma* can arise. *Granulosa and theca cell tumours* arise from the female mesenchyme and have feminizing effects, the extent of which depends largely on the age at which they occur (Novak (2); cf. Geist and Spielman).

Meigs and Parsons define a granulosa cell tumour as one composed of cells resembling very closely those of the granulosa of the normal Graafian follicle. These tumours may be of any size but are usually that of an orange. They are nearly always unilateral, usually solid, with cystic areas in them. They may occur at any age. All secrete oestrogen, and the presence of undue amounts of oestrogen in the urine of girls exhibiting precocious puberty, or in that of women past the menopause, is suggestive evidence of their presence.

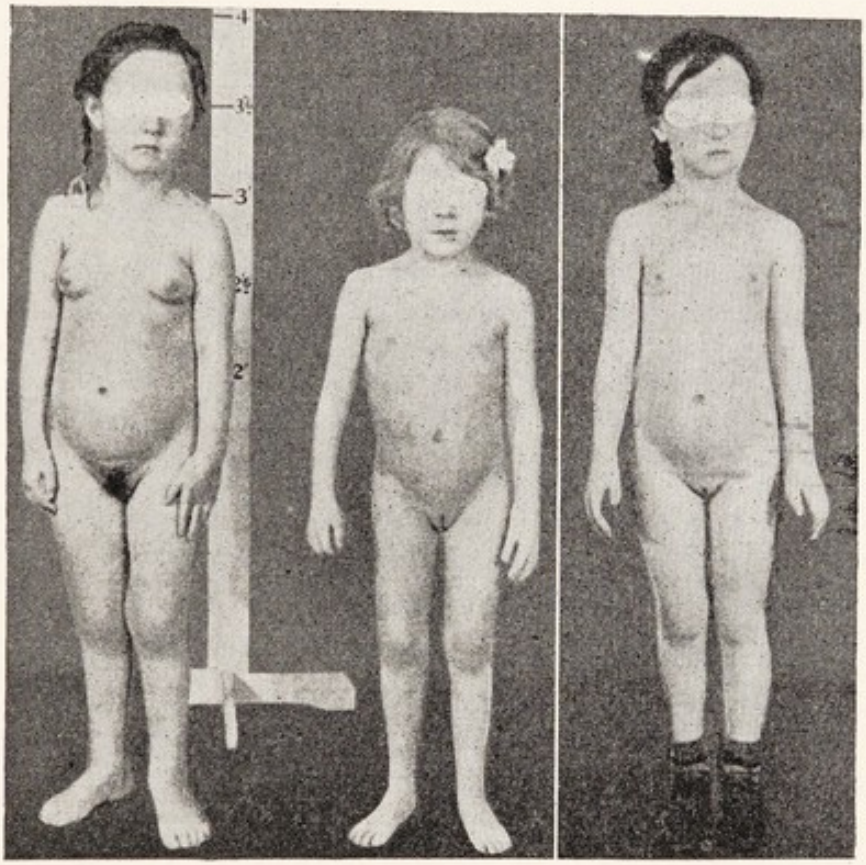
According to Fraenkel, a theca cell tumour (*thecoma*) is formed by direct transition of the theca interna of atretic follicles. These tumours are hard in consistency and yellowish white in colour. They are usually considered to produce oestrogen (Fraenkel's case exhibited virilism). The excessive oestrogen in the reproductive period seems frequently associated with amenorrhoea; in post-menopausal cases it produces irregular and prolonged uterine bleeding (Wolfe and Neigus; Kirschbaum; cf. Banner and Dockerty).

Henderson has reviewed the findings in 30 cases of ovarian

tumours belonging to these two groups. Only one was malignant. He states that granulosa-like cells are present in all theca-cell tumours, and theca-like cells in a number of the granulosa cell tumours. The age incidence for theca cell tumours is later.

The postmenopausal cases included five of carcinoma of the endometrium, and ten of uterine fibroids, suggesting but not proving a causal relationship.

Novak points out that the majority of these tumours occur



A B

FIG. 39. A. Precocious secondary sex characters in a five-year-old girl with a granulosa cell tumour of the right ovary. Precocious skeletal growth as contrasted with that of a normal five-year-old patient. B. Recession of the secondary sex characters, fifteen months after operation. (From Parks, Am. J. Obst. Gyn., 1938, xxxvi, 674.)

during reproductive life, when the effects of increased oestrogen production are inconspicuous or lacking. He thinks that most cases of female sexual precocity are not due to a granulosa cell tumour.

Both types require surgery. In cases of granulosa cell tumour in young girls striking results are obtained. Pregnancy has occurred following removal of a thecoma during the reproductive period ; removal in the post-menopausal period leads to cessation

of irregular bleeding. Novak states that the recurrence rate following surgery is about 30 per cent.

Parks has published an excellent account of a granulosa cell tumour in a young girl.

> The girl apparently developed normally until just over four and a half years, when enlargement of breasts and growth of pubic hair were first observed. Three months later slight menstrual bleeding occurred. After another four months she was admitted to hospital. Her weight then was 51 lb., and her height 46 inches, about the height of an eight-year-old girl. Breasts and nipples were well developed. There was abundant growth of pubic hair, but no axillary hair. The facial expression was more mature than her age. X-ray examination suggested a bone age of at least ten years. Mentality corresponded with age. At operation a right ovarian tumour of granulosa cell type was removed, measuring $8 \times 5 \times 4$ cm. On the second post-operative day a profuse menstrual flow began, which lasted forty-eight hours. (This well illustrates the relationship of pseudo-menstruation to the removal of oestrogenic stimulation.) There was complete recovery, with recession of secondary sex characters within fifteen months (cf. Fig. 39, A and B). Dr. Parks has informed me that on November 4th, 1939 (almost four years after operation) this child was nine years old, weighed $76\frac{1}{2}$ lb., was $51\frac{1}{2}$ inches high, and was the youngest, tallest, and brightest girl in her grade at school. There had been no return of the sexual precocity.

Curtis, Ayre and Foote, and Hodgson, Dockerty and Mussey have reported several cases of young women in whom normal pregnancy occurred a few months after removal of a tumour; evidently prolonged excessive oestogenic stimulation produces no permanent damage to the reproductive system. Hodgson, Dockerty and Mussey record that there were 62 such tumours removed at the Mayo Clinic between 1910 and 1944, constituting 1·63 per cent. of all the ovarian tumours in that period; 37 were post-menopausal and in this group there were four recurrences and three deaths following conservative operation; hence in such cases bilateral oophorectomy and hysterectomy seems advisable. In the younger group there were no recurrences.

On the other hand, Jones and TeLinde have reported three recurrences of granulosa cell tumours, fourteen, twenty and twenty years after the original tumours were thoroughly and satisfactorily removed (respectively at the ages of fifty-six, thirty-nine, and twenty-six years).

The much rarer *arrhenoblastomata* lead to defeminization and masculinization. They are usually considered to originate in certain undifferentiated cells occurring in the region of the rete ovarii (the female homologue of the testis). The clinical manifestations vary. In the extremer cases amenorrhoea results, the breasts flatten and atrophy, a heavy growth of hair appears on face,

chest, abdomen and lower extremities, the contours of the body take on a male appearance, the voice deepens, and the clitoris hypertrophies to penis-like proportions. Usually absence of obesity and striae atrophiae permit differentiation from Cushing's syndrome (cf. p. 418), although a case has been reported which rather strongly resembled that syndrome, with obesity present, but silvery-greyish-white instead of flame-red striae ; differential diagnosis was only definitely made at post-mortem examination (Canelo and Lisser). Milder cases may show only amenorrhoea or amenorrhoea with hypertrichosis.

The tumours are sometimes stated to be benign but are usually considered to be of low-grade malignancy. They may show a resemblance to testicular structure or be atypical. They usually occur between the ages of twenty and thirty, seldom later. The youngest so far reported was in a girl aged fifteen.

Dramatic results usually follow removal of the tumour. McIntyre has reported a typical case.

An unmarried woman, aged twenty-six years, consulted her doctor about a swelling in the abdomen, first noticed a year before. She was admitted to hospital with a diagnosis of probable ovarian tumour, or a pedunculated fibroid of the uterus.

Her menstrual periods, after growing scantier for two years, had ceased altogether for eighteen months. There had been a slight growth of hair for eight years ; during the past year it had become coarser and she now had to shave every day. Her pubic hair had spread to the whole abdomen. The clitoris was greatly enlarged.

There was indication of a large firm tumour, freely mobile and the size of a small football, on the right side. A salpinogram assisted in establishing the diagnosis of a solid right ovarian or broad ligament tumour, probably an arrhenoblastoma. The tumour, removed, proved histologically to be an arrhenoblastoma.

She had an uneventful convalescence. Ten months later she shaved less often, had less hair on face, thighs and upper abdomen, but its distribution was still male. She had regained normal feminine curvatures and had gained weight. The enlarged clitoris had not regressed. Libido was absent (a result stated to be unusual).

Brentnall has described a case of arrhenoblastoma complicating pregnancy. Masculinization became apparent during the third month of pregnancy in a young woman. At term the right ovary was found to be replaced by an arrhenoblastoma, whose removal resulted in disappearance of the masculine changes. The child was apparently a female pseudo-hermaphrodite.

Endocrine Testicular Tumours. *Tumours of the Interstitial cells*, definitely proved to be of endocrine character, are extremely rare. The literature contains accounts of three in boys, associated with sexual precocity, and three in adult men, of which two were malignant.

In 1929 Rowlands and Nicholson reported the case of a nine-year-old boy with premature puberty and a swelling of the left testicle. His history showed nothing abnormal until the age of six, his voice broke at seven, and puberty was established at eight years. At nine years he appeared a fully grown young man of about twice his age, 5 feet tall, powerfully built, with hair on his chest, loins and pubis. His intelligence was above the average for his age ; he was good tempered and not vicious. There were no nocturnal emissions. The right testicle was normal for his age, the left about five times as large. His penis was fully developed.

The left testicle was removed and the tumour proved to be of interstitial cells. Two years later there had apparently been no secondary growths. He shaved regularly and appeared eighteen years old. There had been no retrogression of sex characters but no advance. He had only grown three-quarters of an inch in the two years.

(Sacchi reported a very similar case in 1895, in which excision of a very large left testicle in presence of an atrophic right testicle led to disappearance of the physical signs of precocity. The nature of the tumour was not determined (cf. Weber).)

Stewart, Bell and Roehlke in 1936 reported the case of a sexually precocious child of five, who was normal till four years of age. He was 51 inches high, somewhat tall for his age. His genitals were enlarged to adult size, and pubic hair had appeared but was sparse. There was no hair on face or axilla. His mentality was somewhat precocious ; he was intelligent and well-behaved.

The right testicle was enlarged, with a small, firm tumour. This testis was removed. Fifteen months later pubic hair had disappeared and the penis had regressed slightly in size.

Werner *et al.* reported a third case in 1942, very similar to the second. Both tumours were of interstitial cells.

Budd in 1937 reported the case of an adult man with a testicular tumour associated with gynaecomastia. The latter showed definite regression three months after castration. Thus apparently such tumours in adults can produce oestrogen.

Masson in 1943 published a profound study of two malignant tumours of the Leydig cells in adults. The first case, a man of sixty-two, married and the father of a family, had a testicle the size of a duck's egg, which was removed. The seminiferous tubules had degenerated. The tumour was uninodular and unicentric. The testis contained some normal Leydig cells.

The man's health remained normal for four years, when a growth appeared in the right inguinal region, and increased in size rapidly. Biopsy showed it to be a metastasis of the original tumour. It was removed but the patient developed pleural pneumonia and died. At autopsy several visceral and bone metastases were found.

The second case, a man of thirty-two years, had a left testicular tumour, with a history of marked enlargement for a year. His sexual activity had always been low. The tumour was at first considered to be a hydrocele and fluid was removed several times. Ultimately the left testis was removed. It showed a multinodular and multicentric tumour and contained no normal Leydig cells. The tumour was considered to have arisen from successive generations of interstitial cells, each developing from the mesenchyme, and giving rise to an autonomous nodule.

Nine years later this man had developed extremely large metastases in the liver. He was admitted to hospital and his urine examined for endocrine excretion by Browne. Elimination of gonadotrophins and oestrogenic compounds was but slightly elevated ; excretion of 17-ketosteroids was fifty times the normal amount. The patient lost weight rapidly, and died suddenly from heart failure. At autopsy, besides the huge liver, metastases were found in lungs and skull. The gigantic liver was estimated to be 3 kg. metastases and 2 kg. hepatic tissue.

Masson compares these two apparently different types of tumour with two types which can be produced in certain strains of mice by prolonged administration of different oestrogens (cf. p. 283), and considers that in his second case, as in that of Budd, oestrogen was produced in the tumour cells, and, by a vicious circle, stimulated further development of tumour tissue.

Teratomata of the testis are almost all malignant. The urines of patients with malignant teratomata give positive tests for chorionic gonadotrophin. When excessive amounts of gonadotrophin are excreted the tumour is considered to be a chorion-epithelioma, and the patient usually dies within a year (cf. Hinman).

It is somewhat difficult to understand why tumours which are labelled histologically as carcinoma or adenocarcinoma (as are the majority of these teratomata) can produce chorionic or chorionic-like gonadotrophin, even in small quantities, and no adequate explanation has yet been advanced. However, the views of Gill, Caldwell and Goforth afford a plausible explanation. They consider that these tumours arise from primitive cells which have essentially the same capacity as the developing ovum and that the malignant trophoblastic elements are derived from ectoderm in the same way as the comparable tissue in ordinary pregnancy. The cells from which these tumours arise are multipotential sex cells, normally present in the adult testicle, and are probably spermatogonia. The differential elements in such teratomata are probably not responsible for any hormone production.

Note on Sexual Precocity. Greenhill divides cases of sexual precocity into four groups, but a fifth ((iii) below) must be added. These groups then are :

(i) Sexual precocity associated with adrenal tumours. (This is discussed in Chapter XII.) Females predominate in this group, and most have associated virilism (hirsutism, enlarged clitoris, and marked muscular development). Precocious menstruation is rare.

(ii) Sexual precocity in girls associated with ovarian tumours usually of the granulosa-cell or theca-cell type, but occasionally teratomata or carcinomata. This type has been dealt with. It is the one most curable by operation, but is relatively rare.

(iii) Sexual precocity in boys associated with androgen-producing tumours. This has been dealt with. It is rarer than (ii).

(iv) Sexual precocity associated with lesions of the brain or the pineal gland. This constitutes a heterogeneous group, including cases of ventricular cysts, tumours of the tuber cinereum, tuberous sclerosis of the brain, and especially hydrocephalus and tumours of the pineal. It is the most hopeless from the point of view of treatment.

Gross has dealt particularly with neoplasms involving the infundibulum or floor of the fourth ventricle.

Such precocity usually is seen very early in life. The outstanding features are (i) precocious maturation of the genitalia, which adhere to the sex of the child, (ii) marked development of secondary sex characters, (iii) excessive somatic development, (iv) advance in bone age, (v) in some cases oliguria, in others polyuria, indicating disturbance of water balance, and (vi) minimal or no signs of an expanding intracranial lesion.

In boys the penis and testes are almost of adult size, there is abundant pubic hair, frequent erections, and some occurrence of ejaculation. In girls there is striking development of the external genital organs, hypertrophy of the labia and mons veneris, sparse growth of pubic hair, marked breast development, and onset of menstrual flow.

The mechanism by which such brain lesions produce this marked sexual precocity is not understood. Gross suggests that perhaps a pressure effect stimulates the pituitary to increased activity.

Bing, Globus and Simon collected 177 cases of pineal tumour from the literature. These included 21 cases of precocious puberty ; only one of these was a girl.

(v) The most common type is the " constitutional type " to which Novak has drawn attention, and which occurs only in girls. He has given details of 9 cases of sexual precocity in otherwise normal girls, for which only an explanation on a constitutional or genic basis seems possible. All the nine menstruated before eight years of age, the earliest at fifteen months. For such children avoidance of development of self consciousness or a sense of abnormality is necessary ; in Novak's cases occurrence of early ovulation was demonstrated by laparotomy. They obviously therefore need protection against possibility of insemination. After the age of ten to eleven years they do not differ from other girls.

Endocrine Tumours of the Secondary Sex Organs. *Chorion-epithelioma of the Uterus.* Urine of patients with hydatidiform mole gives a markedly positive (pregnancy) test for chorionic gonadotrophin (p. 278). Following passage of the mole in a

considerable proportion of cases the positive test persists, although quantitatively the amount of gonadotrophin excreted may vary considerably. The continued formation of gonadotrophin depends upon persistence of chorionic tissue in the uterine walls. It is generally recognized that this persisting tissue may be of very varying degree of malignancy, though the precise grading and terminology has not been agreed upon. Williams recently suggested a classification of the condition into three groups: (i) syncytial endometritis or syncytioma (in which there is infiltration with syncytium only); (ii) malignant mole or chorioadenoma (presence of syncytium, Langhans' cells and villi); (iii) chorion-epithelioma (presence of Langhans' cells and syncytium). The last group has a poor prognosis, and it is the case with true chorion-epithelioma which excretes relatively very large amounts of chorionic gonadotrophin.

Carcinoma of the Prostate. While this perhaps scarcely has an endocrine cause, it is apparently accentuated by androgenic stimulus, for it is definitely benefited by castration and by administration of oestrogen. Numerous papers have been published in the past few years (cf., *e.g.*, Chute and Willets; Lane; Smith and McLean), and the subject has been thoroughly reviewed by Huggins, one of the foremost surgeons in this field.

There is a high incidence of tumours of the prostate in man (and in the dog and lion). Unselected autopsies in men over forty years of age reveal benign hypertrophy in 45 per cent., while the incidence of cancer of the prostate in men over fifty lies between 9 and 17 per cent. Many of these cancers are microscopic and remain latent, but others are the cause of death in 5 per cent. of men over fifty in the United States.

Estimation of the acid phosphatase content of blood serum is of diagnostic value.

It has long been known that the blood content of an enzyme, phosphatase, increases in certain bone diseases, and in diseases of the liver, and it has more recently been shown that there are two types of phosphatases, one whose maximum activity is at the slight degree of alkalinity of the body tissues (" alkaline phosphatase "), and which is increased in bone and liver diseases, and another (" acid phosphatase ") whose optimal activity is at *p*H 4·8 to 5·0. Such an acid phosphatase was demonstrated to be present in spleen and kidney tissue of swine and cattle in 1934 (Davies; Bamann and Riedel), and in the human prostate in 1935 (Kutscher and Wohlberg), and shortly afterwards Gutman and his co-workers showed that the blood serum of certain patients with disseminated prostatic carcinoma contains increased amounts of acid phosphatase.

Since the phosphatases are enzymes, amounts of them must be ex-

pressed in empirical units. King and Armstrong's method of estimation is now usually employed and by it normal alkaline phosphatase values are 5–13 units, and normal acid phosphatase values do not exceed 4·5 units, per 100 c.c. blood serum. Values of acid phosphatase above 10 units indicate prostatic cancer (with metastases), although slight increases sometimes occur in other diseases (and Herbert has suggested a possible method of differentiation). Haemolysis of the blood sample must be avoided, since the red blood cells also contain an acid phosphatase. An accompanying increased alkaline phosphatase, in absence of liver damage or clinical evidence of other diseases affecting bone, is probably due to bone damage from metastases.

Huggins recommends perineal prostatectomy in early treatment; if the condition is advanced orchidectomy should be performed, or, if operation is refused or considered dangerous, oestrogen should be administered.

Orchidectomy results in disappearance of pain, usually as early as the second day. There is increased appetite and a gain in weight which is maintained. If the central nervous system has become involved paralysis may disappear. Distressing urinary symptoms may lessen. (Sexual desire and penile erections cease; hot flushes occur and can be controlled by oestrogen.) The prostatic tumour decreases in size and becomes softer; the metastases may or may not regress. The acid phosphatase of blood serum decreases; the alkaline phosphatase may increase for four to eight weeks but should then decrease. If it subsequently rises to high values (indicating a carcinomatosis) prognosis is bad. Prognosis is worse in undifferentiated carcinoma than in adenocarcinoma. With shrunken testes little effect is to be expected from orchidectomy.

Huggins considers that oestrogen is not as effective as orchidectomy (cf. also Emmet and Greene), and that X-ray to prostate and testes is of doubtful value. A case reported by Lane illustrates the degree of improvement which can be produced rapidly by orchidectomy.

The man had widespread bone involvement, the right acetabulum being particularly severely affected. He suffered badly from pain and had persistent flexion deformity of his hip. Orchidectomy gave rapid relief. Free movement was restored to the right hip within a few weeks, and in two months X-ray examination showed unequivocal evidence of retrogression and repair.

Clute and Willets consider that as good results are obtained with stilboestrol as by castration. Moore, Wattenberg and Rose agree, and the majority of recent reports deal with cases treated by oestrogen.

Riches recommends commencing stilboestrol treatment as soon as a positive serum acid phosphatase is reported, with dosage

1 mg. three times daily, increasing by daily increments to 5 mg. three or four times per day. The dose can be reduced later according to progress, the level of the acid phosphatase serving as guide ; the maintenance dose is found to vary from 1 to 10 mg. daily. Good results are to be expected in over 90 per cent. of cases. Duration of the improvement cannot be foretold. Certain side-effects result : enlargement of breasts with pigmentation of nipples, reduction in size of penis and testes, and impotence. Nausea and vomiting are rare, and can be relieved by changing to hexoestrol or dinoestrol.

The beneficial results are proving to be less enduring than was hoped for. Thus Herger and Sauer reported in 1945 that of 130 patients treated with stilboestrol or by orchidectomy or given both treatments 33 were dead from the disease (24 with metastases, 9 without) and 9 were dead from other causes. Of the 33, 18 had survived less than one year (of whom 10 had metastases), 12 died in the second year (11 had metastases) and all were dead within two and a half years. Another 34 were deteriorating in spite of treatment, 21 of them being in the terminal stage. (In 10 of this group castration was performed after stilboestrol proved ineffective ; there was a temporary improvement in 7, of less than six months' duration, and complete failure in 3.) In 37 the response so far has been favourable, but in 20 of these the disease is progressing, so that only in 17 of the total number has the treatment been so favourable that the clinical improvement has coincided with an apparent temporary arrest or regression of the disease.

Huggins (2) has recently reported on 20 cases of disseminated prostatic cancer treated by orchidectomy. Remissions of varying lengths of time occurred in 18. After five years 5 were still alive, of whom 1 had slowly advancing prostatic carcinoma ; the other 4 exhibited no clinical or laboratory evidence of cancer.

Oestrogen-androgen Relationships to Cancer. The relationships illustrated in the previous section seem general. Thus Farrow and Adair have reported that in three women and one man with breast cancer and metastases the condition was made worse by administration of testosterone propionate, while following castration in another man with osseous metastases from cancer of the breast there was relief of pain and diminution of the metastases.

Oestrogen, however, seems in general to have greater carcinogenic potentialities than androgen. Most of present knowledge is derived from animal experiments.

Allen has reviewed the production of tumours in experimental animals after long continued treatment with oestrogenic hormones.

Genital organs are involved primarily, but non-genital tissues are also affected. The uterus may develop cancer of the cervix (in mice) or fibromyomas of the cornua (in guinea-pigs).

The mammary glands are especially susceptible to cancer. In certain inbred strains of mice low tumour-incidence among females is increased by oestrogenic treatment. Males of strains whose females are susceptible to spontaneous mammary cancer may acquire the disease after injection of oestrogen.

The testes of mice respond to oestrogenic treatment by hypertrophy of the interstitial cells. In the A strain of mice unilateral nodules may become large tumours (which are transplantable to other mice if these are treated with oestrogens). The tumour tissue may secrete androgen.

Pituitary hypertrophy and chromophobic tumours of considerable size can be induced in high incidence in mice of certain strains and in rats.

The adrenal cortex may develop tumours after long oestrogenic treatment of mice. Oestrogenic tumours have been reported in albino mice.

Excessive oestrogenic stimulation may lead to cystic hyperplasia of the uterus, metaplastic changes of male accessory organs, lymphatic leucaemia, and hypertrophy of bile ducts.

Bonser and Robson have produced interstitial adenomata in the testes of male mice of the A strain by prolonged administration of triphenylethylene. The more resistant the mice are to this treatment, the more probable it is that when tumours develop they will be malignant and give rise to metastases. Stilboestrol, on the other hand, causes degeneration of the interstitial cells, and formation of new interstitial cells which give rise after several generations to tumours (Shimkin and Grady).

There is evidence that androgens in moderate dosage counteract the carcinogenic activity of oestrogens (Murray ; Nathanson and Andervont ; Murlin).

While the chemical relationship between the steroids and carcinogens such as benzpyrene and methylcholanthrene suggest that some steroids must have carcinogenic potentialities, and while this is fully borne out by the experimental work just quoted, there is no evidence that when used in proper therapeutic dosage there is danger that androgens or oestrogens (including the synthetic compounds) may produce cancer.

Sterility. Of the various causes of sterility only failure to ovulate and sperm deficiency will be considered here.

Failure to ovulate is, in most if not all cases, presumably due to lack of adequate gonadotrophic stimulation, and seems therefore to call for treatment by one or other of the available gonadotrophins. Results of their use are, to date, disappointing. Hamblen, reviewing them critically in 1939, concluded that no definite proof had been adduced that administration of any

available gonadotrophin could call forth complete ovarian response (growth of follicles, rupture of follicles, and formation of corpora lutea) in patients whose ovaries are not responsive to their own endogenous pituitary gonadotrophins.

Much has been hoped from use of the powerful equine gonadotrophin. Yet Davis and Hellbaum, writing in 1943, can draw no more favourable conclusion from its use. They state that it has not proved a panacea. It will augment normal ovarian responses in the human ovary, but it probably will not initiate ovarian activity. They think that the chief hope in the future lies in the preparation of more potent pituitary gonadotrophin concentrates.

Abarbanel and Leathem state that equine gonadotrophin can do more harm than good, and consider that a nutritionally balanced diet plus desiccated thyroid is more rational and effective.

Hamblen and Davis state that "synapoidin," a combination of chorionic and equine gonadotrophins, given intramuscularly, produces poor response in patients with hypo-oestrinism, but good response in those with anovulatory failure, but without hypo-oestrinism (of whom, in their series, 18 per cent. became pregnant).

(Bickers has reported a near-fatal allergic reaction to equine gonadotrophin; he subsequently found that consecutive skin tests in seventy-four women showed five positive reactors.)

Sperm Deficiency. Pullen *et al.* found that no gonadotrophin produced definite improvement, and stated: "The most beneficial therapeutic schedules for seminal inadequacy are hygienic measures, sexual rest, and thyroid substance in appropriate cases." A later report by Davis, Pullen, Madden and Hamblen stresses the lack of definite improvement, whether pituitary or equine gonadotrophin were used alone, or in combination with each other, or with testosterone propionate.

Undescended Testicles. For some years the use of chorionic gonadotrophin in cases of undescended testicles became a vogue. A healthier viewpoint has arisen and is exemplified in the papers of Mimpress, Browne, Wilson, and Rea. Mimpress found the treatment effective in only six of nineteen patients. Browne remarked that the "treatment will not bring down any testes that would not have descended without it, though it hurry the descent." Wilson states that under three years of age the diagnosis of uncomplicated non-descent is uncertain. Spontaneous descent may be awaited till ten years of age, but, unless the testis lies in the superior scrotal position waiting should not be persisted in beyond that age. Hormonal therapy may be used before operative

treatment as a means of determining whether spontaneous descent is possible, but should only be used in the pre-puberal period. It is unlikely to be successful with the unilateral cryptorchid, and will only be successful in those cases which would normally have undergone spontaneous descent at a later date. Operative treatment can be safely carried out after three years of age, and should be completed before puberty, the optimal age for operation being from eight to eleven years.

Rea is of the opinion that the chief value of the endocrine therapy is that it makes it possible to differentiate between those testes which need surgical intervention and those which do not. Such therapy should be delayed till nine to eleven years.

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CHAPTER IX

THE PITUITARY GLAND

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INTRODUCTION

THE pituitary body, like the adrenals, is built up of two unrelated parts, composed of different types of tissue, of which one is typically glandular, the other related to nervous tissue. The two parts come together in foetal life. The embryology and histology have frequently been fully described. The following brief statements are taken chiefly from Bailey's description.

The human pituitary (hypophysis cerebri) is a small organ, averaging about 0·57 gram in weight, and tending towards an ovoid shape. Rasmussen gives its average dimensions as 10 mm. (antero-posteriorly) × 6 mm. (dorsiventrally) × 13 mm. (side to side). It is situated beneath the brain in the sella turcica of the sphenoid bone. "No other single structure in the body is so doubly protected, so centrally placed, so well hidden" (Cushing).

The customary division into two lobes, anterior and posterior, separated by a cleft lined with epithelium, is merely gross. When the posterior lobe is examined microscopically it is itself seen to be composed of two distinct parts, the inner core or *pars nervosa* (or neuralis), an extension from the hypothalamic region of the brain, and an outer lining of epithelium, the *pars intermedia*. This intermediate part is continuous at the stalk which unites the gland with the brain, and at the posterior extremity, with similar cells of the anterior lobe.

The anterior lobe, or *pars distalis* (or *glandularis*), is more homogeneous. From it a thin layer of cells, the *pars tuberalis*, spreads out over a small adjacent area of the base of the brain.

In the foetal stages of development these various parts show a fair degree of parallelism in different mammals; the glands of adults show greater differences. In adult man the epithelial-lined cleft between the two lobes is either obliterated, or persists as isolated cystic cavities. Rasmussen (1) states that the pars intermedia is practically absent in the adult human pituitary,

but Brander finds that it is extremely variable in extent and arrangement.

The pituitary of the adult human female is larger than that of the adult male, due to a larger anterior lobe. It is larger in negroes than in whites. At least in some proportion of cases pregnancy increases the size of the anterior lobe. It decreases in size in man after middle age, but less noticeably so in woman. In both sexes the pars neuralis and pars intermedia increase in size with age.

The anterior portion rises from the ectoderm of the stomodeum just in front of the bucco-pharyngeal membrane as a long evagination (*Rathke's pouch*) which grows upwards to meet the nervous portion ; the apex, applying itself to the surface of the nervous tissue, becomes the pars intermedia. The nervous portion arises as a downward evagination from the floor of the diencephalon, in the region of the tuber cinereum, and becomes almost completely enveloped by the anterior portion. The cavity of this evagination disappears (except in the cat), leaving a funnel-shaped extension of the third ventricle (the infundibulum). The attachment of the epithelial portion to the buccal epithelium becomes attenuated and is finally broken. (Islands of such " anterior-pituitary " cells may occur separately in the pharyngeal wall, or enclosed in the sphenoid bone.)

Engelbach has summarized the divergencies in different mammals: " The three mammalian types of hypophysis are exemplified in the cat, the dog, and man. In the cat, the posterior lobe is hollow and its cavity is in free communication with the third ventricle of the brain. The epithelium of the anterior lobe almost completely surrounds the posterior lobe. In the dog, the body of the posterior lobe is solid, but the neck is hollow and communicates with the third ventricle. As in the first type, the posterior lobe is almost completely surrounded by epithelium. In the third type (man, monkey, ox, pig, and rabbit), the body and neck of the posterior lobe are solid, although traces of a cavity are occasionally found in the neck. The epithelium of the anterior lobe does not spread so far around the neck and spreads over and into the adjacent surface of the brain (Herring)."

In the monkey and probably in man the pars glandularis is supplied by (i) afferent arteries and (ii) afferent (not efferent) portal veins which originate in the region of the stalk from a plexus which surrounds and also penetrates the infundibular stem. The terminal parts of these arteries and veins unite to form sinusoids. The veins from the pars glandularis pass from the lateral pole to the cavernous sinuses. The blood supply of the remaining parts of the pituitary is almost independent of that of the anterior lobe, the vessels entering and leaving by the posterior

pole of the pars neuralis. The blood supplies of the hypothalamus and the pituitary are not linked, so that hormones from the pituitary body do not have immediate access to centres in the hypothalamus (cf. Wislocki and King ; Van Dyke).

Little is known of the origin of nerves controlling the anterior pituitary, though evidence of such control is accumulating. (For example, it is known that light affects the secretion of gonadotrophic hormone in birds and in the ferret, while strong diffuse electrical stimulation causes ovulation in the rabbit (Van Dyke). Fine amyelinated nerve fibres follow the vascular supply to the anterior lobe, branches leaving at intervals to traverse the cellular columns and end between the glandular cells (Bailey). But a large proportion of the anterior lobe seems to be practically devoid of nerve fibres so that Rasmussen (4) rather doubts whether the fibres present have a secretory function and thinks that they are associated with the vascular system.

A tract of nerve fibres originates in the paired supraoptic nuclei of the hypothalamus, and descends the anterior wall of the infundibulum, to spread out in the nervous portion, ending in " tangled masses around the blood vessels and among the cells " (Bailey). In the human pituitary this tract contains at least 100,000 fibres (Rasmussen and Gardner). The function and morphological maintenance of the pars neuralis depend on a normal flow of stimuli to it from the supraoptic nuclei. If they are destroyed, the neural lobe atrophies and ceases to produce its hormones (Van Dyke).

While there is some experimental evidence that in cold-blooded animals the pars intermedia is under nerve control (Van Dyke), Rasmussen (4) states that in the human pituitary large areas of this portion of the pituitary seem to be devoid of nerve fibres, though at least a few fibres end on its cells (while a negligible number pass through it from the neural lobe and end just within the anterior lobe).

It is stated that lymphatic vessels have not been demonstrated in the pituitary.

Microscopically, the anterior portion consists of columns of cells separated from one another by large vascular sinuses and some connective tissue. Two groups are differentiated as *chromophile* and *chromophobe* by the different intensities of their staining reactions. The deeper staining properties of the former are due to granules in their cytoplasm. These granules are of two types. From the presumption that their staining reactions are restricted to acid and basic dyes respectively, they are usually termed *acidophile* and *basophile*. Since they do not show such restricted

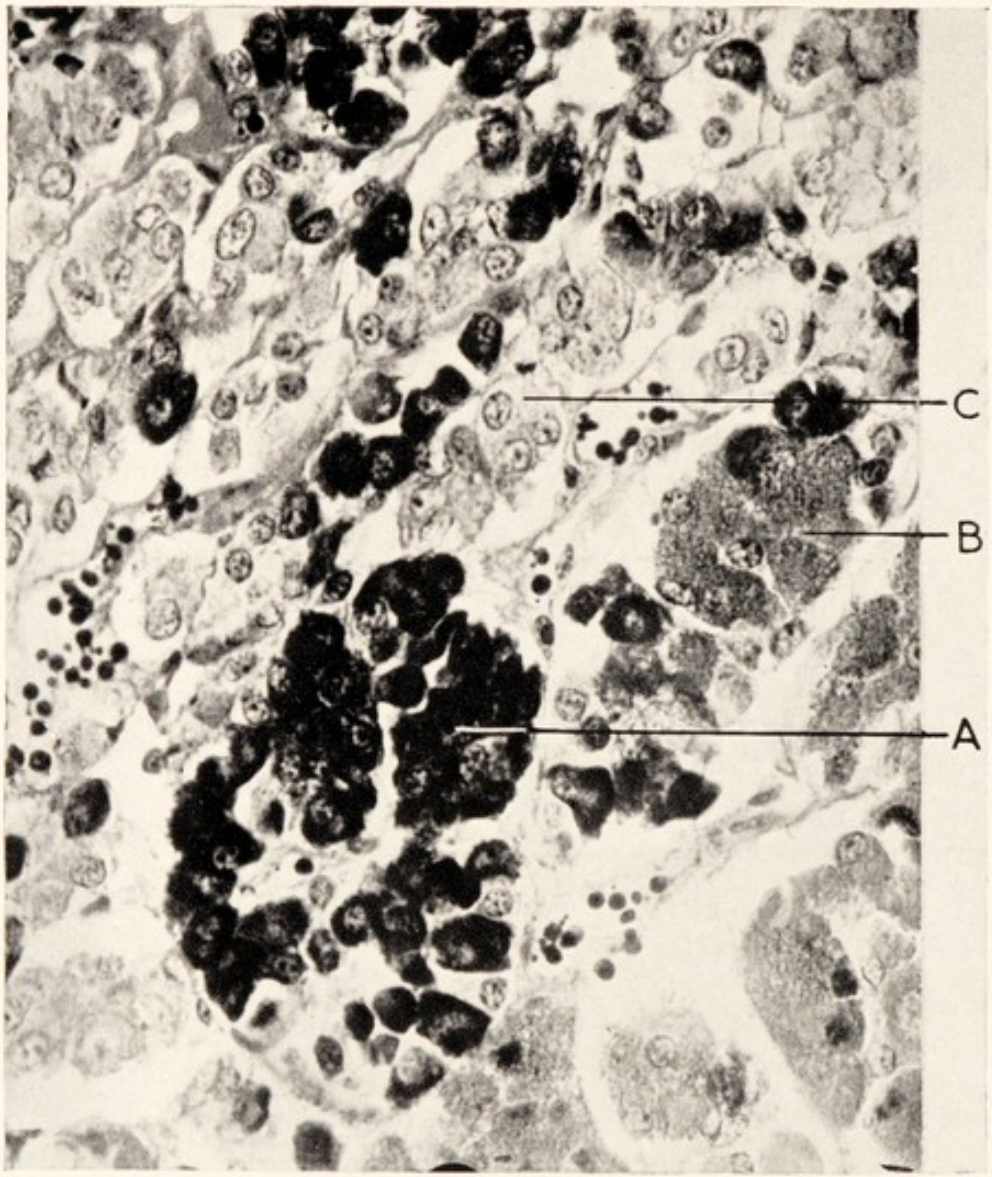

FIG. 40. Section of anterior lobe of human pituitary, stained with aniline blue and acid-fuchsin. *A*, acidophile cells, dark-staining and clustered; *B*, basophile cells (intermediate shade); *C*, chromophobe cells (faint shade). × 400. (Photo-micrograph by Professor William Boyd.)

[*To face p.* 317.

staining properties, Bailey termed them *alpha* and *beta* cells respectively. It is generally considered that no cell contains more than one type of granule.

Fig. 40 reproduces an excellent photomicrograph, kindly furnished me by Professor William Boyd, and which well illustrates the relative distribution of the three types of cells. Koneff describes an adaptation of the Mallory-Azan staining method which he claims gives tinctorial differentiation and shows good cytological detail. By this procedure basophile cells stain blue, acidophile cells orange red, and chromophobe cells are colourless or light grey.

According to Rasmussen (1), the distribution of these three types of cell in the anterior pituitary of man is :

	Extreme Values	Mean Value
Chromophile (Acidophile (Alpha) . .	23 –59	37
(Basophile (Beta)) . .	4·5–27	11
Chromophobe (Neutrophile) . . .	32 –66	52

He finds (3) a very similar distribution in the pituitaries of non-pregnant women (averaging 43 per cent. alpha, 7 beta and 50 chromophobe), while pregnancy causes no significant change. Basophiles, as will be evident, are more numerous in man than in woman. With increasing age chromophobes increase and acidophiles decrease in men ; basophiles increase in women.

Wolfe has presented evidence of cyclic variations in the three types of cells in the rat, dog, and sow, corresponding to the different phases of oestrus.

Certain so-called *cells of pregnancy* and *cells of castration* have been described as occurring in these two conditions (cf. Englebach ; Biggart ; Ellison and Wolfe). While there is evidence for the existence of the latter, Rasmussen has been unable to identify specific " pregnancy cells." The enlargement of the pituitary during pregnancy is not due to hyperplasia of any one of the three types of cells. Special " pregnancy cells " do not occur in the guinea-pig (Kirkman). The changes following gonadectomy in the experimental animal which result in appearance of " castration cells " can be corrected by administration of oestrogens or androgens (Van Dyke). Rasmussen (3) considers that so-called " pregnancy cells " are really highly active acidophile cells.

There is evidence that adrenal cortical deficiency is accompanied by a marked reduction in the percentage of basophile cells. When

large doses of oestrogens or androgens are injected into normal animals basophile cells are depleted of their granules (Van Dyke).

The alpha granules are large and spherical, and usually so close-packed as to obscure all other structural details of the cell. They appear during the third foetal month ; the beta cells appear a little later. The chromophobe cells, for the most part, contain but little cytoplasm.

Biedl suggested that the chromophobe cells are " mother cells " from which both basophile and acidophile cells are derived. This theory has been beautifully proved by Severinghaus. He has shown that the chromophobe cells of the rat's pituitary can be separated into two distinct types by reason of differences in their Golgi apparatus. That of the first type corresponds to the Golgi apparatus of the acidophile cells (a filamentous net), while that of the second corresponds to the Golgi apparatus of the basophile cells (a ring). He can find no evidence of change from the alpha to the beta type, but he shows further, from studies of the pituitaries of castrated rats, that chromophile cells can revert to chromophobe cells. The castration cell has the typical basophilic type of Golgi apparatus.

The nervous portion contains three different cellular elements, typical ependymal cells, mossy neuroglial cells, and larger pyramidal or spindle-shaped cells. The last are peculiar to this tissue, and have been termed pituicytes by Bucy. In the human gland these pituicytes compose the bulk of the tissue of the pars nervosa. They give off fragile processes and often contain greenish-brown granules of pigment, readily stained by neutral red or methyl green. Griffiths (2) states that pituicytes, like astrocytes, are derived from spongioblasts.

The pituicytes, being peculiar to the neural lobe, are frequently assumed to be the cells responsible for its hormones vasopressin and oxytocin (see p. 295). Griffiths (1) has adduced evidence from tissue culture experiments that the pituicytes form a pressor substance. Gersh has furnished evidence of possible glandular nature of what he terms the " parenchymatous cells " of the posterior pituitary, and deduces on histological grounds that they probably produce a pressor substance. These cells are practically identical with Bucy's pituicytes.

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THE POSTERIOR PITUITARY

Oliver and Schafer showed in 1895 that when extracts of the pituitary gland are injected intravenously into animals a marked and prolonged rise of blood pressure results. Howell, shortly afterwards, proved that the effect was due to extracts of the posterior lobe, while Dale found that these extracts also caused contraction of uterine muscle. These extracts also possess both diuretic and anti-diuretic properties. In small dosage a diuretic effect is produced, apparently due to improvement of the general circulation, but larger doses produce an anti-diuretic effect, apparently by direct action on the afferent arterioles of the kidney glomeruli (Adolph).

Thus extracts of the posterior pituitary such as "pituitrin" possess three outstanding properties, (i) ability to raise blood pressure (pressor activity), (ii) ability to produce uterine contraction (oxytocic activity), and (iii) ability to produce diuresis or anti-diuresis under differing conditions (renal activity).

By different fractionation procedures Kamm and his associates, Stehle and Fraser, and Irving, Dyer and Du Vigneaud have separated from such extracts two non-crystalline fractions, one with high pressor potency and only very low oxytocic potency, the other with high oxytocic potency and only negligible pressor activity. No crystalline compounds have yet been obtained, but these amorphous fractions are usually considered as two almost pure hormones. That associated with oxytocic activity was

termed by Kamm *alpha-hypophamine* and is more frequently called *oxytocin* or *pitocin*. The other is similarly named *beta-hypophamine*, or *vasopressin* or *pitressin*.

It is usually considered that the pressor principle is responsible for the action on the kidney, though there is some evidence that during its inactivation by heat the pressor activity is lost slightly more rapidly than its renal action (Heller), and final proof that the pressor hormone is responsible for both activities is still lacking (cf. Irving and Du Vigneaud). Moreover, according to Boyd and Garand, both pitressin and oxytocin possess the renal activity, pitressin being at least ten times but not more than fifty times more active than oxytocin.

The almost pure preparations of the two principles are white or slightly cream coloured amorphous powders, very slightly hygroscopic. They hydrolyse practically entirely to a mixture of amino-acids. Stehle and Trister obtained from the hydrolysate of pitressin tyrosine, cystine, arginine, proline and isoleucine, and from that of oxytocin the same acids, with the exception that leucine replaced isoleucine. A colorimetric test indicated presence of a trace of tryptophane in both. Histidine, glutamic acid, phenylalanine, hydroxyproline, glycine and cysteine were absent.

From ultracentrifuge and dialysis studies and from the sulphur content it is concluded that their molecular weights are between 600 and 2,000, suggesting that they are relatively simple polypeptides (cf. Irving and Du Vigneaud).

The activities of both compounds are destroyed by trypsin but not by pepsin ; they are also destroyed by the enzymes in extracts of various tissues. Tyrosinase completely inactivates the oxytocic principle, but prolinase and arginase do not affect it, suggesting that the phenolic group of tyrosine may be essential to its activity (cf. Irving and Du Vigneaud).

Both compounds are stable in dilute acid solution and decompose in alkaline solution. Kamm considered that they are both basic in character, but recent electrophoretic studies indicate that their molecules are probably amphoteric (Irving and Du Vigneaud).

Evidence in Favour of a Single Hormone. Abel believed that the activities of the posterior pituitary were due to a single compound of large molecular size, and in 1931 MacArthur published some experimental evidence in favour of this view. Recently stronger evidence has become available.

In 1940 Rosenfeld found that purified pressor and oxytocic preparations showed little tendency to sediment in the ultracentrifuge, this suggesting that both compounds were of small

molecular size. On the other hand, when press juice of the posterior pituitary was ultracentrifuged the material responsible for both activities sedimented rapidly, and no definite separation of activities occurred. The rate of separation suggested that the active compound had a molecular weight of from 20,000 to 30,000.

In 1942 an important paper was published by Van Dyke, Chow, Greep and Rothen. They suspended fresh ground posterior lobes in 0·01 normal sulphuric acid, centrifuged off inert material, and salted out with 8 per cent. sodium chloride. The precipitate was further fractionated in various sodium chloride concentrations, and finally a potent and apparently uniform product was obtained, 1 kg. of fresh material yielding 0·7 gm. which had pressor, oxytocic and antidiuretic activities of equal order (as contrasted with those of the original material). The molecular weight, as determined by the ultracentrifuge, was 30,000 ; calculated from the amino-nitrogen value, on the assumption that each molecule contained one free amino-group, it was 26,000. The compound was rich in cystine radicals (16 per cent.). Its activity was but little affected by crystalline pepsin, but was almost completely destroyed by trypsin and chymotrypsin.

Van Dyke pointed out that the material may in reality consist of an inert protein, with adsorbed active compounds ; there is good but not final evidence against this view. Irving and Du Vigneaud consider that the question should be investigated further, before this protein can be accepted as the sole hormone of the posterior lobe (cf. also Fraenkel-Conrat). Potts and Gallagher satisfactorily used permutit to separate vasopressin (adsorbed) from oxytocin (not adsorbed) in aqueous extracts of desiccated posterior lobe, and considered their results adverse to the theory of a single hormone.

The Posterior Lobe as an Endocrine Gland. The facts that vasopressin, oxytocin, and the protein isolated by Van Dyke all possess definite pharmacological properties are beyond dispute. These activities in themselves are not evidence that any of these compounds are hormones, but evidence supporting this view is accumulating. Mention has already been made (p. 293) of Griffiths' tissue culture experiments which suggested that the pituicytes form a pressor substance.

Lim and his colleagues have shown that during the pressor response following stimulation of the central end of the vagus the jugular venous blood contains, in the normal animal, an oxytocic substance, and an anti-diuretic substance. (These are not found,

under like conditions, in the hypophysectomized animal.) Repeated vagus stimulation results in a lessening of the pressor response ; it is re-established by rest. There is a parallel exhaustion and reappearance of secretory granules in the pituicytes (cf. Thomson and Collip).

Haterius and Ferguson, by stimulating rabbits in the region of the infundibular stalk several hours post-partum, produced an increase in uterine activity (both increased frequency and amplitude of contraction) closely resembling the action of oxytocin. This result persisted after spinal transection, section of the splanchnic nerves, and vagotomy, but not after blockage of the pituitary stalk. It seems legitimate to conclude that the posterior pituitary actually secretes a hormone with oxytoxic activity.

The work of Gilman and Goodman in 1936–37 has shown that the tubular reabsorption of water from the glomerular filtrate in the kidneys depends upon the action of vasopressin (or the protein-hormone). If the rate of excretion of water is likely to lead to dehydration, the rate of secretion of the hormone is increased, the rate of tubular reabsorption becomes greater, and water is conserved.

It has been pointed out that the posterior pituitary is under nervous control, receiving stimuli through the supraoptic nuclei of the hypothalamus. This has been amply demonstrated by the work of Fisher, Ingram and Ranson, and others on cats and monkeys, in which it was shown that if this nervous control be lost (as by complete severance of the pars nervosa from the hypothalamus) the kidneys lose their power to concentrate urine, so that polyuria and polydipsia result—an experimental diabetes insipidus—while there is concurrently a retrograde degeneration of the supraoptic nuclei. This also explains how suitable afferent stimuli can inhibit secretion of urine after renal denervation. (See Van Dyke, and Thomson and Collip ; cf. also Gersh and Brooks.)

Conversely, it has been shown that dehydrated rats and cats excrete an antidiuretic substance, unless they have been hypophysectomized, or the supraoptic-hypophyseal tracts have been interrupted (see Van Dyke). Further, dehydration causes definite cytological changes in the pituicytes of the posterior pituitary of the rat (Gersh).

Evidence has been adduced that the supraoptic region of the dog's hypothalamus contains an appreciable amount of an antidiuretic substance, which may be related to that of the posterior pituitary (cf. Melville and Hare).

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DISEASES ASSOCIATED WITH THE POSTERIOR PITUITARY GLAND

From what we know of the actions of the principles extractable from the posterior pituitary, hyperfunction or hypofunction of that lobe should lead to symptoms associated with blood pressure, altered degree of contractility of smooth muscle and abnormality of renal function.

Tumours of the anterior pituitary may damage the posterior lobe, even to the extent of almost complete obliteration (cf. Fig. 52, p. 349). There is some evidence of a resulting decrease in blood pressure (Cushing). Nevertheless, as Cushing has pointed out, lesions of the posterior pituitary, whether of human occurrence or experimentally produced in animals, frequently do not lead to perceptible symptoms.

Diabetes insipidus is the most outstanding abnormal condition which is presumably associated with hypofunction of the posterior lobe. This disease is characterized by the continued excretion of large volumes of a pale urine of low specific gravity, free from sugar and other abnormal constituents. In many patients the only symptoms present are this polyuria and a proportional polydipsia. Others may exhibit weakness and emaciation. At autopsy of such patients lesions of the pituitary gland have been

found. Further, in many cases normal kidney secretion could be restored by continued injections of " pituitrin." Hence it seemed reasonable to conclude that some pituitary lesion caused the condition.

The results of earlier extirpation experiments lent support to this view. Intense polyuria was produced (Cushing ; Houssay). The issue became confused in two ways. Injection of " pituitrin " into an experimental animal sometimes produced diuresis. Damage to brain structures adjacent to the pituitary also caused polyuria. Camus and Roussy were the leading workers in experiments of the latter type.

They demonstrated that ablation of the dog's pituitary produced marked but only transient polyuria, provided the base of the brain was uninjured during the operation, while damage to the base of the brain bordering on the pituitary resulted in marked and persistent polyuria, even though the pituitary was not damaged ; this polyuria was not controllable by injections of pituitary extracts (Camus and Roussy) (cf. also Bailey and Bremer). Delayed adiposity and genital atrophy can occur in these cases.

Even recently Keller claimed that selective destruction of the posterior lobe in the cat and total hypophysectomy in the dog can be brought about without causing diabetes insipidus, while immediate and sustained diabetes insipidus invariably follows total hypophysectomy plus drastic gross infringement of the anterior hypothalamus. He concluded that an extra-hypophyseal mechanism exists in the environs of the anterior hypothalamus, elaborating an anti-diuretic compound. Nevertheless most recent work suggests direct involvement of the posterior pituitary hormone.

Maddock, and later Mahoney and Sheehan, found that application of silver clips at various levels of the hypophyseal stalk in various animals (though not in the monkey) produced a marked and enduring polyuria. Such results at first tended to be interpreted as due to a damming back of some hormone, believed normally to pass to the ventricles from the posterior lobe by this channel, though Cushing pointed out that in such experiments the nerve impulses to the posterior lobe are interrupted, and this has proved to be the actual cause of the polyuria.

Dandy has recently reported a case of persistent polyuria and polydipsia of over eleven years' duration, which followed transection of the hypophyseal stalk in a girl of seventeen during an operation for presumed tumour. Anterior pituitary functions have not been interfered with, and normal pregnancy has occurred.

As already recorded, interruption of the nerve tracts between the supraoptic nuclei and the posterior pituitary results in a persistent polyuria and a consequent polydipsia, the essential features of clinical diabetes insipidus.

On the other hand, complete ablation of the whole pituitary gland usually results in only transient polyuria, and the persistent polyuria produced experimentally can be relieved by ablation of the anterior lobe of the pituitary. Thus some hormone of the anterior pituitary must be functioning normally for the development of true diabetes insipidus (precisely which hormone has still to be determined). The earlier views of Hann (1918) and Richter have thus been confirmed by the recent work of Fisher and Ranson and others. (See Van Dyke ; cf. Dodds (2).)

An interesting case of diabetes insipidus, which adds further confirmation, has been reported by Bernstein. At autopsy it was found to be a case of primary bronchogenic carcinoma, with metastases involving the supraoptico-hypophyseal system.

Good results have been reported in treatment of diabetes insipidus following administration of posterior lobe pituitary powder intranasally (Marble; Canelo and Lisser; Mainzer).

Daily administration of amidopyrone (pyramidon), alternated every fourth day with pitressin, is said to produce good results in the treatment of diabetes insipidus (Kahn).

Injection of pitressin tannate in oil gives relief when injected once in thirty-six hours or less (Greene and January ; Spingarn *et al.*).

Hyperfunction of the Posterior Pituitary (?). Jones has reported a case which presented hypertension, hyperchromic macrocytic anaemia (which responded to liver therapy), achlorhydria, and depressed carbohydrate tolerance. Noble *et al.* obtained from the urine of this patient an extract exhibiting pressor and anti-diuretic activity of vasopressin type. As the patient improved clinically the excretion of pressor-substance decreased. Dodds and his co-workers (see below) have shown that injection of vasopressin can produce achlorhydria, sometimes followed by anaemia. It was hence thought possible that the patient's condition might be due to hyperfunction of the posterior pituitary.

Gastro-intestinal Ulcers. Dodds (1) found that posterior pituitary extracts injected subcutaneously or given orally to laboratory animals, produce severe lesions in the acid-bearing area of the stomach, which last one to two weeks. A profound anaemia is also produced, accompanied by marked leucocytosis. The effect is due to vasopressin in the extracts (Selye, Stehle and Collip). Relatively large dosage is needed, and it is doubtful if these experimental results are significant in considering the etiology of clinical ulcers (cf. Van Dyke).

Hypertension. Griffiths *et al.* claim that certain patients with high blood pressure excrete an antidiuretic compound in the urine. Treated either by irradiation of the pituitary or by repeated injection of pitressin, about half of such cases are benefited, with disappearance of the urinary antidiuretic compound.

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THE INTERMEDIATE LOBE

Extracts of the posterior pituitary gland such as " pituitrin " cause a dispersion of the black pigment granules in the epidermal melanophores of the frog and other amphibia. This effect is not due to a hormone of the posterior lobe ; separation of the pars intermedia from the pars neuralis is not easily effected.

The pars intermedia of the pituitary of fish, amphibia, birds and mammals (including man) elaborates this hormone. Certain fishes, such as the stickleback (*Gastrosteus aculeatus*), bitterling (*Rhodeus amarus*), and the small carp-like *Phoxinus laevis*, develop at the time of spawning a brilliant red colour in the ventral part of the body, and especially in the region of the fins (Van Dyke). According to Zondek and Krohn this is due to a hormone which they term " intermedin," and which is present in an aqueous extract of the pars intermedia. Intermedin is probably identical with the melanophore-dispersing hormone present throughout vertebrates, but final proof of this is still wanting.

Geiling and Lewis showed that cultures of the pars intermedia of the mouse and rat, while they had no effect on blood pressure (showing that vasopressin was absent), had a marked melanophore-dispersing effect when injected into frogs.

In the porpoise (Wislocki) and the whale (Valsö), and probably in marine mammals generally, the pars intermedia is absent ; the melanophore-dispersion hormone is formed by the anterior lobe of the whale (Valsö). Geiling has studied the pituitary of the finback and sperm whales very carefully, in association with MacCallum, Wallen-Lawrence, and Riddle, and has shown that there are only present a large anterior and a smaller posterior lobe, separated by a septum. No pars intermedia could be found. The posterior lobe contains no melanophore principle, but there is a plentiful supply of it in the anterior lobe. The posterior lobe contains the usual amount of vasopressin, but much less oxytocin, and both of these appear to be elaborated in the posterior lobe itself. The anterior lobe contains the gonadotrophic, thyrotrophic, and adrenotrophic principles (cf. pp. 336, 342, 344) but a very low prolactin content.

While in amphibia the melanophore-dispersion hormone produces effects which suggest a possible physiological function, its function in birds and mammals is not at present definitely known. Very active preparations of the melanophore hormone prepared by Stehle are rich in the metabolic hormone of O'Donovan and Collip, a different hormone, probably of the anterior pituitary (cf. p. 346). Landgrebe and Waring prepared the melanophore hormone almost free from anterior pituitary hormones.

Fournier *et al.* claim to have obtained good results in treatment of vitiligo by local injections of melanophore hormone. Sevringhaus (1943 *Yearbook Neurol., etc.*, p. 425) cannot confirm this.

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THE ANTERIOR PITUITARY

Introduction

The anterior pituitary contains only two types of functioning cells, the acidophile and basophile cells. Yet for a considerable period, following the isolation of the first active extracts a little more than twenty years ago, a steadily increasing number of hormones were considered to be products of these two types of

cells. At one time as many as fifteen different hormones were seriously postulated by different investigators (cf. Jensen and Tolksdorf (1)). The existence of the majority of these has not been substantiated, and within the last six or seven years a more rational view has gradually become current.

At the present time six different hormones have been separated, four or five pure or nearly pure, the remainder moderately so. There is no evidence for a seventh. They are all proteins. They may be breakdown products or modified products of a fewer number of compounds formed from these during the processes employed to separate them, though Fraenkel-Conrat seems to consider that this is unlikely.

The six accepted hormones are (i) the growth hormone, (ii) and (iii) two gonadotrophic hormones, (iv) the lactogenic hormone, (v) the thyrotrophic hormone, and (vi) the adrenotrophic hormone. The probable seventh is the metabolic hormone.

The chief difficulty in characterizing the individuality of these compounds rests in their purification from each other. As has been stated, they are all proteins. Only one has (possibly) been crystallized, although even the crystallinity of a protein is an unsatisfactory criterion of its purity. Electrophoretic analysis, observations in the analytical ultracentrifuge, and the determination of solubility curves in suitable solvents, along with constancy of biological activity, are considered the best procedures for determining the degree of purity of protein-hormones. Shedlovsky has recently discussed the application of such criteria.

Experimental methods designed to ascertain the function of the anterior lobe have consisted of extirpation, of implantation, and of injection of extracts, or of the various more or less pure hormones, as these became available.

The earlier extirpation experiments of Paulesco, Cushing, Houssay, and others led, following an initial latent period of varying duration, to fall in body temperature, slow respiration and pulse, limp musculature, coma and death. Houssay noted polyuria in young pups and oliguria in adult dogs (the whole pituitary was extirpated). He further noted that animals which survived for some time showed retardation in both general and sexual development, development of adiposity, and increased tolerance for sugar.

Partial extirpation of the anterior lobe leads to characteristic symptoms of hypopituitarism. Young animals remain small, their milk teeth and their juvenile fat are retained. Their epiphyses do not ankylose. The thyroid enlarges, the thymus persists and

the adrenal cortex thickens. Sexual maturity is markedly retarded. A subnormal temperature is shown and basal metabolism is diminished. Carbohydrate tolerance is increased. Adult animals also show a tendency to gonadal atrophy and obesity (cf. Sharpey-Schafer).

Some clear-cut results have been obtained with amphibia. Smith and Allen showed independently in 1916 that the hypophyseal pit can be located and the minute portion of pituitary tissue removed in frog tadpoles which are only 3 or 4 mm. in length. This operation produces a remarkable change in development. The tadpole acquires a silvery appearance, remains dwarfed, and does not metamorphose. Its thyroid remains reduced in size, also its adrenal cortex, though the medulla is unaffected. Thyroid feeding will not induce complete metamorphosis of such animals.

Selye has developed a rapid and accurate technique for extirpating the pituitary of rats, and Collip, Selye and Thomson found that following such operations the testes of male rats, whether immature or adult, undergo atrophy, with reduction both of germinal epithelium and of interstitial tissue. The epididymus, prostate and seminal vesicles are reduced in size. In adult female rats, hypophysectomized during lactation, there is rapid retrogression of the mammary glands and failure of milk secretion. In immature females the thecal cells of the ovary are transformed to " deficiency cells " (Selye).

Thus from deficiency of pituitary hormones, produced by extirpation, there is evidence that they are concerned, directly or indirectly, with growth, gonadal development, carbohydrate and fat metabolism, thyroid function, and secretion of milk.

Administration of potent pituitary extracts to the normal animal should produce an artificial hyperfunction, partial or complete according to the nature of the extracts. Within recent years it has been shown that the hypophysectomized animal is much more susceptible to such potent extracts than is the normal animal, and is therefore a more useful vehicle for testing them. Oral administration of such preparations is without definite effect.

The Growth Hormone

H. M. Evans and his co-workers showed, in a series of papers commencing in 1921, that injections of potent pituitary extracts into rats produced gigantism. Saline extracts of anterior bovine pituitaries were injected daily into rats for prolonged periods, commencing at the age of fourteen days. Typical results are

shown in Figs. 41–43. Under such treatment female rats have reached a weight of over 700 grams, as compared with controls of 300 grams, and males over 900 as compared with 450 grams. The animals are symmetrically proportioned, with a normal metabolism. The degree of gigantism corresponds to production of human beings 10 to 12 feet high.

Teel and Cushing and their co-workers carried out similar studies on dogs, using an alkaline extract of beef pituitary (which contained several hormones). An experiment on two female bull-

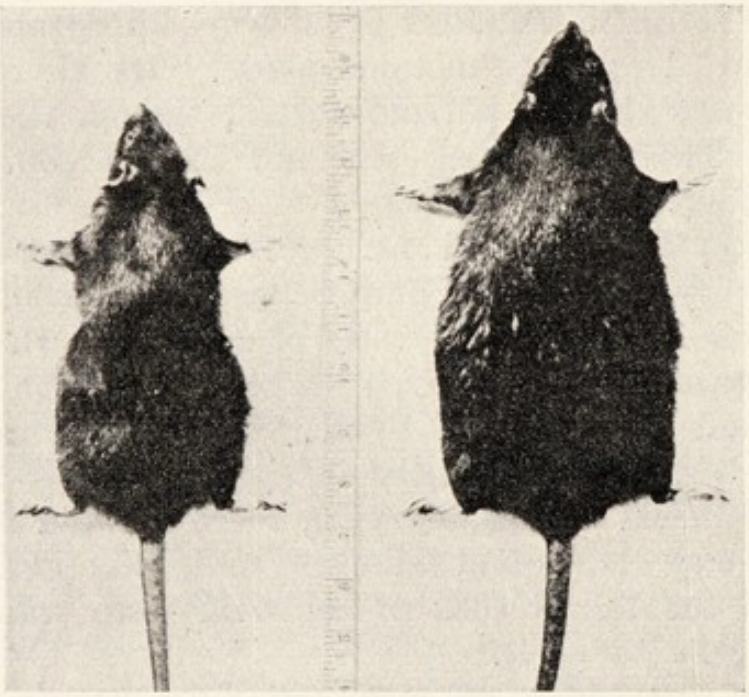


FIG. 41. Photograph at time of autopsy (at somewhat over 400 days of age) of two female rats whose growth curves are shown in Fig. 42. The rat on the right received daily intraperitoneal injections of anterior lobe extract for over a year. The rat on the left is the untreated litter-mate control. (From Evans, Harvey Lectures, 1923–24, p. 212.)

dogs was commenced at seven weeks of age, and continued till the death of the experimental animal. Initially the dogs weighed 4·87 and 5·0 kg. Daily intraperitoneal injections were given the smaller dog for fourteen months, with gradually increasing dosage. The experiment shows perfectly the gigantism, ultimately an enfeebled gigantism, produced by prolonged hyperpituitarism. The changes in appearances are shown in Figs. 44–47.

After three and a half months' treatment the lower jaw and skull in the experimental animal were perceptibly larger than those of the control, the tongue was larger and the animal stood higher. After four months the animal became weak and languid. Muscular movements were poorly controlled. The appetite increased. After six months

sluggishness had increased. Movements were plantigrade rather than digitigrade. Owing to muscular laxity the spine sank beneath the scapulas and the experimental animal, although much heavier, stood less high than the control. The abdomen was large and pendulous.

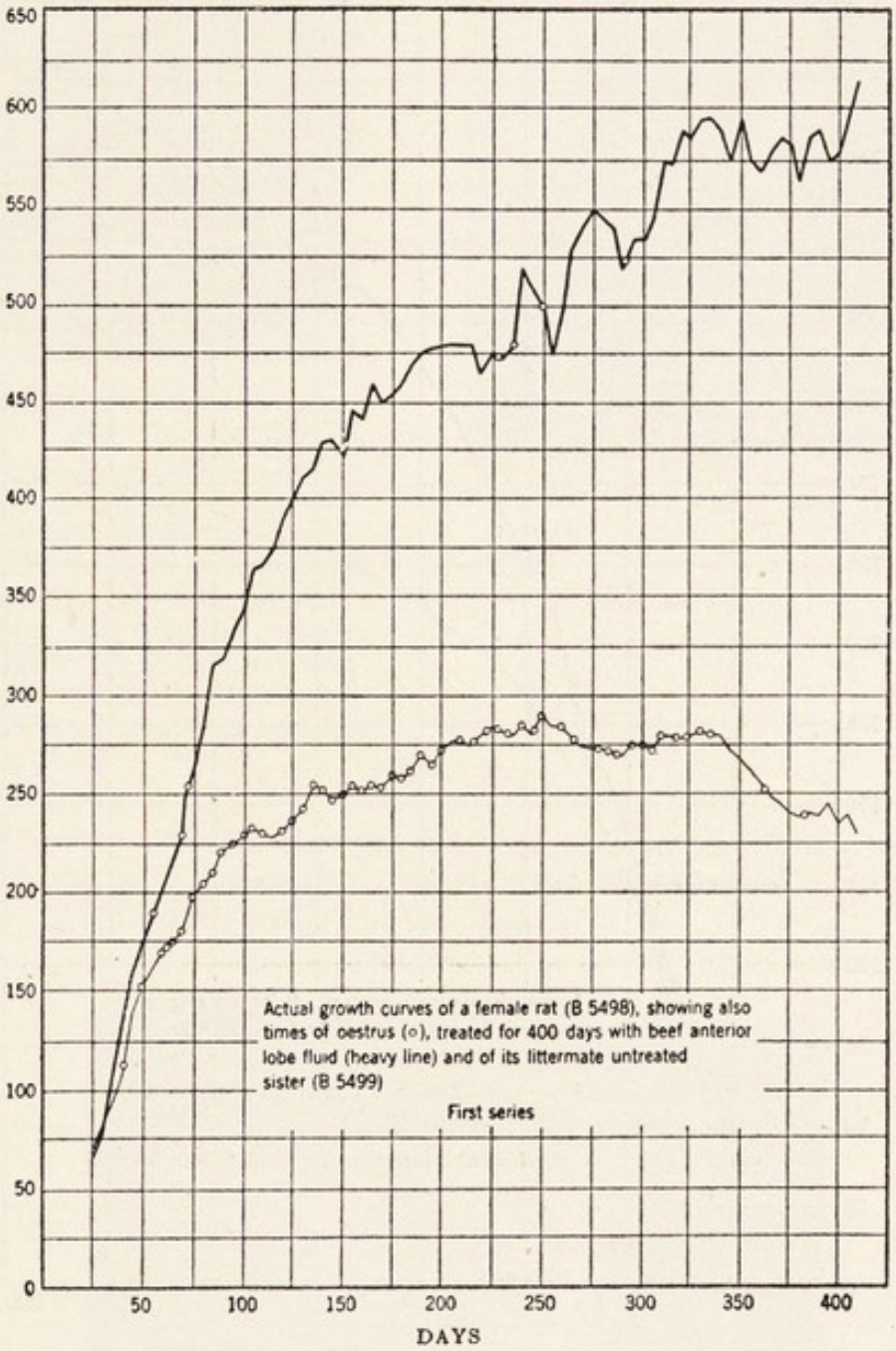


FIG. 42. Actual growth curves of the two female rats shown in Fig. 41. That of the treated rat is given in heavy line. (From Evans, *loc. cit.*)

There was prolapse of the vagina. The animal suffered from stubborn diarrhoea. Blood analyses revealed no striking changes.

After eleven months the udders were abnormally large and colostrum could be squeezed from them. The animal never went into heat, its control sister did so at thirteen months.

After developing polyphagia, asthenia, sialorrhoea, and spontaneous

lactation, the animal died at the end of fourteen and a quarter months' treatment, on a very hot day ; the actual cause of death was myocardial failure and oedema of the lungs. At death it weighed 44 kg., the control 23·5 kg. The control was killed and both were autopsied.

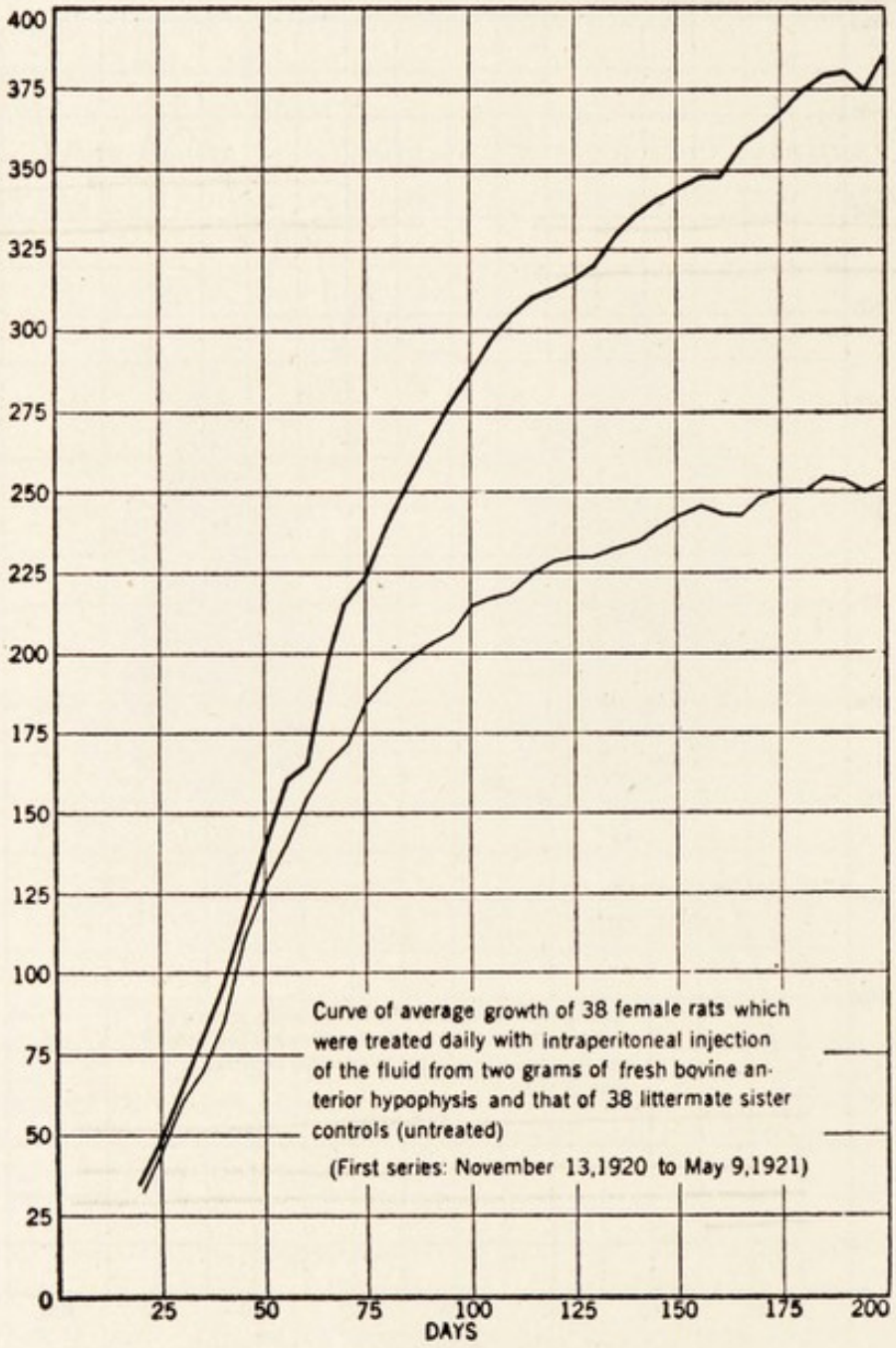


FIG. 43. Curve (thick line) of average growth of thirty-eight female rats which were treated daily with intraperitoneal injections of the fluid from 2 grams of fresh bovine anterior pituitary, contrasted with the curve (thin line) of thirty-eight untreated littermate sister controls. (From Evans, *loc. cit.*)

The experimental animal, as compared with the control, showed absence of fat, disproportionately small and soft musculature, and a generalized splanchnomegaly. The heart and kidneys were enlarged, the liver enormous ; it showed passive congestion and central necrosis.

The thyroid was much enlarged and histologically showed small acini and paucity of colloid. The adrenal cortex showed relative enlargement and contained numerous small adenomas.

FIG. 44. Effect of continued injections of the growth principle of the anterior pituitary. Littermate bull dogs, three months after the beginning of the experiment. The treated animal (on the right) was already slightly larger than the control. Note the enlargement of tongue and paws. (From Putnam, Benedict and Teel, Arch. Surgery, 1929, xviii, 1709.)

FIG. 45. The same two animals eight months later. Treated animal on right. (From Putnam, Benedict and Teel, *ibid.*, p. 1710.)

The ultimate skeletal changes are seen in Fig. 46. The ovaries were large and contained ripe but unruptured follicles. The uterus and vagina were markedly enlarged (cf. Fig. 47).

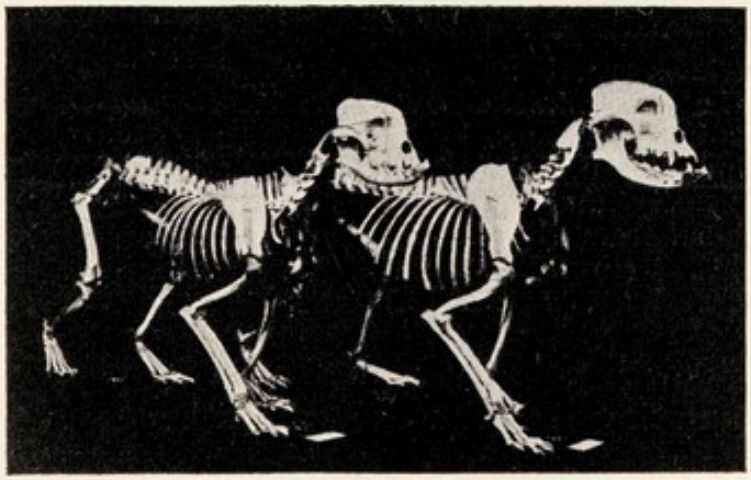


FIG. 46. Skeletons of the treated and untreated animals at the end of the fourteen months' experiment. Treated animal on right. (From Teel and Cushing, Endocrinology, 1930, xiv, 158.)

The pituitary was of the same weight as that of the control.

Cushing's alkaline extract thus produced definite effects on growth, on the gonads, on the thyroid, and on the adrenal cortex.

Evans *et al.* have produced very definite results with hypophysectomized dogs, using an impure growth extract (cf. Fig. 48).

Experiments with mice have shown that the growth principle produces correctly proportioned growth of the whole body, as judged by the relative weights of the chief organs, and the percentage dry weight, fat content, ash content, and calcium and phosphate content of the ash (Wahlberg).

Restoration of normal growth has been demonstrated following pituitary implants into hypophysectomized (dwarf) tadpoles (Allen (1)) and into a strain of dwarf mice (Smith and MacDowell).

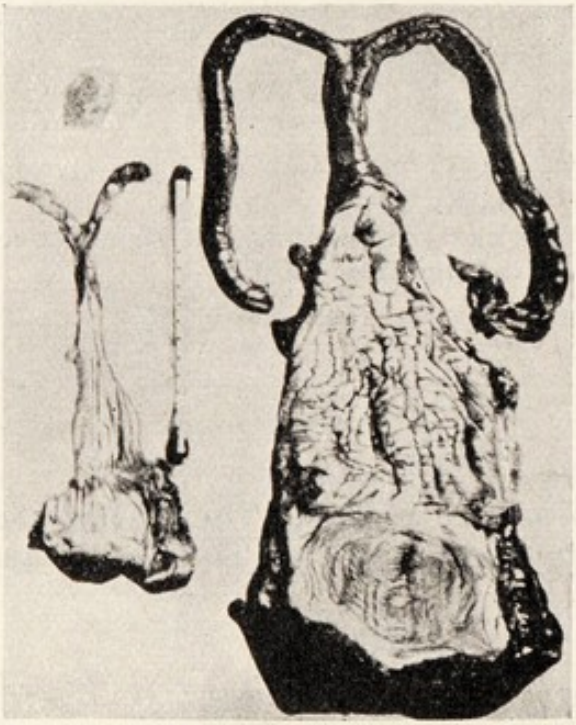


FIG. 47. Vaginae, uteri and left ovaries of the two animals. The vaginae have been laid open by an incision along the anterior wall. Note the rugosity and thickness of the specimen from the treated animal (right). (From Putnam, Benedict and Teel, *loc. cit.*, p. 1719.)

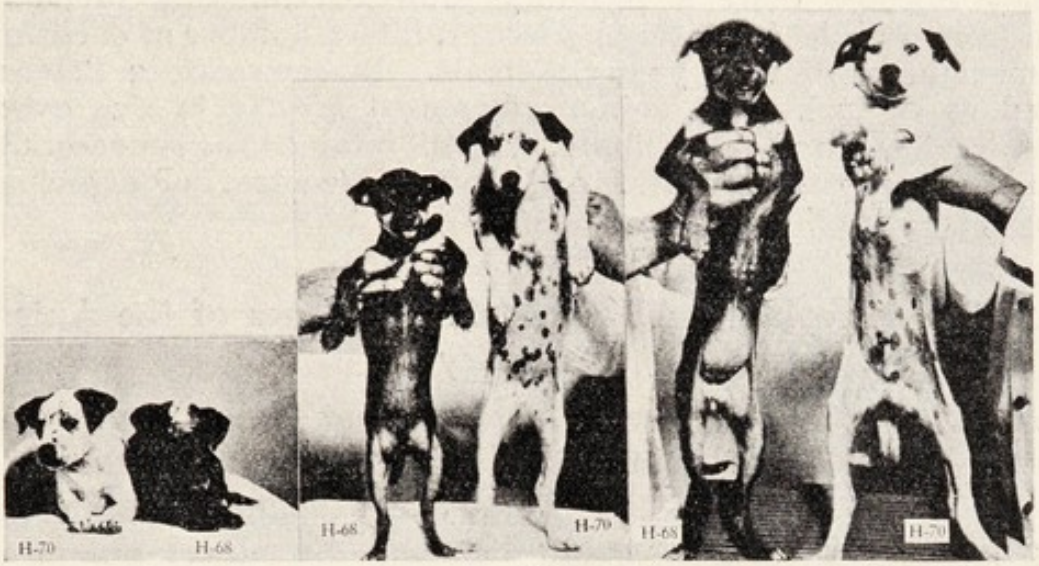
Preparation and Properties of the Growth Hormone. It has been obtained in pure or practically pure condition by Li, Evans and Simpson. From a calcium hydroxide extract of acetone-dried ox pituitaries they selected a globulin fraction containing the hormone, and this was further fractionated with sodium chloride, appropriate manipulation of the *p*H, and precipitation with ammonium sulphate, with final isoelectric precipitation.

The growth hormone is a protein, with a molecular weight of 44,250. The pure preparation has no thyrotrophic, adrenotrophic, gonadotrophic, or lactogenic activity. Its growth potency is destroyed by pepsin and trypsin, and by coagulating its solution by heating to 70–80° C. It is more stable in alkaline than in acid medium.

The pure hormone causes resumption of body growth and increase in the epiphyseal cartilage cells of the tibia in hypophysectomized rats ; the latter effect is regarded as a specific test for it.

It must also be remembered that the ability of an animal to grow does not alone depend on the growth hormone. For example,

Salmon has shown that when rats are thyroidectomized at birth they do not respond to this hormone at all.



A. B. C.

FIG. 48. A. Puppy bitch H-68 was hypophysectomized at eight weeks of age; H-70, litter-mate male control. B. Appearance four weeks later. Injection of growth extract commenced. C. Appearance after two months of injections. (From Evans *et al.*, Memoirs of the University of California, 1933, xi.)

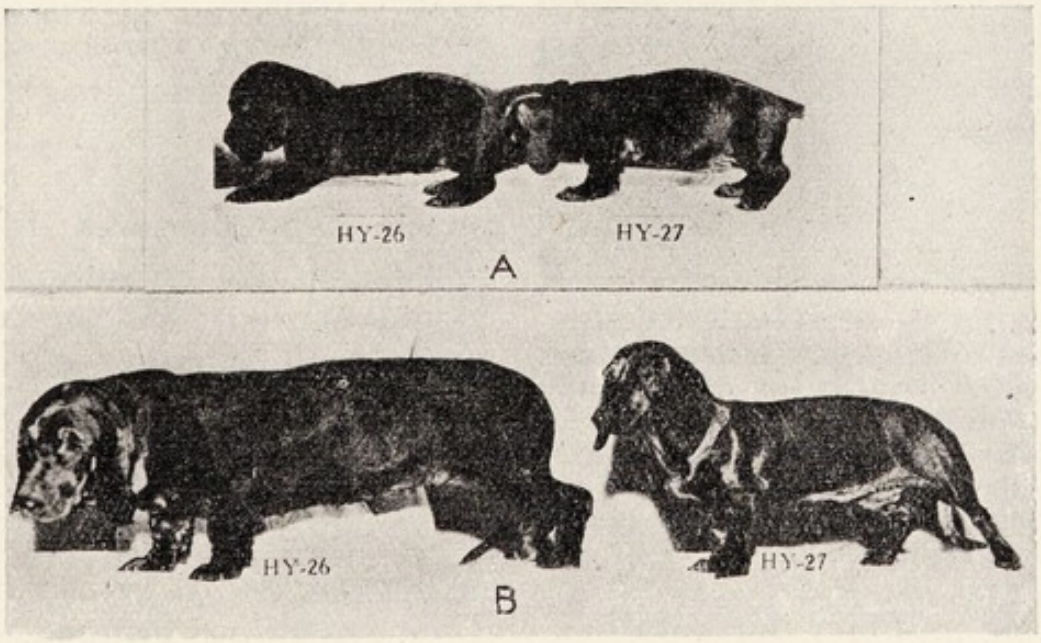


FIG. 49. A. Litter-mate female dachshunds six weeks old. B. The same animals eleven and a half months old. HY-26 had been injected with the growth principle for thirty-five weeks. Note the elongated body, huge head, and redundant skin. (From Evans *et al.*, Memoirs of the University of California, 1933, xi.)

The Achondroplastic Dwarf. Although achondroplasia is usually considered to be associated with the germ-plasm itself, from time to time the theory is advanced that the pituitary may be a causal factor.

Evans and his associates (Evans *et al.*) have ruled out the possibility of pituitary involvement. Among the breeds of dogs the dachshund typifies this distortion of relative lengths of trunk and limbs.

They injected daily a pituitary growth-stimulating preparation, freed from gonad-stimulating hormones, into a number of dachshunds, commencing with very young animals. In each case a litter-mate served as control. The animals increased greatly in size over the controls, gigantism being definite, but still retained the achondroplastic form of the short extremities. A typical pair (control and experimental animal) is shown in Fig. 49.

The Gonadotrophic and Lactogenic Hormones of the Anterior Pituitary

Introduction. Early work showed that daily transplants of pituitary into sexually immature mice and rats produced precocious sexual maturity, as shown by development and mating. The ovaries are enlarged, with superovulation (cf. Figs. 50 and 51), and the uterus and vagina become typical of the adult animal. Testes respond variably, but the secondary sex organs of the male are increased in weight and physiological activity. Such treatment applied to adult female rats produces hypertrophy of ovaries and superovulation, but it seems to produce no apparent effect in adult males. The secondary sex responses are not shown by castrates. Gonadal degradation, which normally follows hypophysectomy, ceases, following pituitary implantation, and the gonads are restored.

FIG. 50. Above. Ovaries of littermate control rat. Weight, 21 mg. Below. Ovaries of experimental rat after thirty implantations of fresh rat pituitary gland over eighteen days. Weight, 340 mg. (From Collip, Proc. California Acad. Med., 1930.)

Zondek postulated two pituitary gonadotrophic hormones, which he termed prolan A and B. His terminology has not been generally accepted, though his hypothesis of two hormones has proved correct. The first, gametokinetic or gamogenic, stimulates male germ cells and ovarian follicles, and is now generally termed the folliclestimulating hormone (FSH). The second stimulates the formation of lutein cells in the ovaries, and the

interstitial cells of the testes, and is termed the luteinizing hormone (LH), or preferably the interstitial-cell-stimulating hormone (ICSH).

These pituitary hormones must be distinguished from the chorionic gonadotrophin of women (cf. p. 234) and equine gonadotrophin (cf. p. 241).

Methods for adequate separation of the two pituitary gonadotrophins have gradually been devised. Present knowledge has recently been summarized by Chow, Fevold, and Fraenkel-Conrat.

Preparation of the Follicle-stimulating Hormone (*FSH, Thylakentrin*). This can be obtained from pituitary glands or from the urine of normal, menopausal or castrated human beings. Urine concentrates have been prepared by precipitation with tannic acid or alcohol and further fractionation, but so far apparently insufficient concentration has been effected to permit chemical characterization. Human and horse pituitaries are relatively rich in FSH and poor in ICSH, but are unavailable in adequate quantities, so that in most studies sheep and hog glands have been used. The most effective method of measuring potency of preparations is the increase of weight of ovaries in the hypophysectomized animal, while absence of corpora lutea in such animals, along with atrophy of interstitial tissue, indicates absence of ICSH from such preparations (Chow).

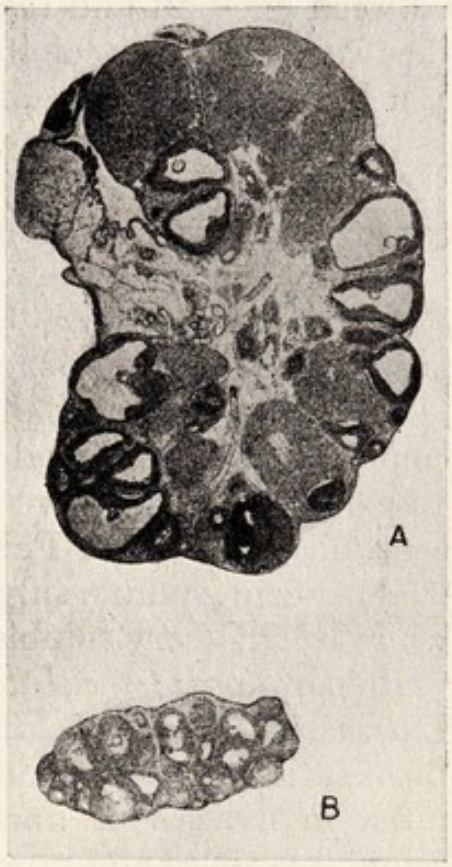


FIG. 51. A. Cross section of ovary of rat. Sexual maturity induced on the twenty-seventh day of life, following four daily transplantations of anterior pituitary lobe of the rabbit. B. Ovary of untreated, litter-mate control. (From Smith and Engle, Am. J. Anat., 1927–28, xl, 188.)

Three of the purest preparations of FSH so far available have been obtained respectively by Greep, Van Dyke and Chow (from swine pituitaries), Jensen, Tolksdorf and Bamman (from sheep pituitaries), and Fraenkel-Conrat, Simpson and Evans (from sheep pituitaries). The preparation from swine pituitaries, according to Fraenkel-Conrat, is less potent, but possibly more free from ICSH than those from sheep pituitaries.

The method of Fraenkel-Conrat and his colleagues may be taken as illustrative of the type of procedure. Acetone-desiccated sheep pituitaries were extracted with 40 per cent. alcohol, and FSH precipitated from the extract by 50 per cent. acetone at *p*H 4·5. It was redissolved and fractionally precipitated several times between one-half and two-thirds saturation ammonium sulphate, then successively precipitated from 33 per cent. acetone at *p*H 4·8, and from 67 per cent. alcohol; finally, less active material was salted out by saturation with sodium chloride at *p*H 4·1.

The potency of the product was such that 6 gamma would cause resumption of follicular growth in the ovaries of hypophysectomized rats.

According to Chow, fresh pituitary glands are preferable to acetone-dried glands, since there is less possibility of denaturation.

The chief difficulty of final purification of FSH rests in the completeness of removal of ICSH. Precipitation at — 6° C. with 40 per cent. alcohol gives a richer ICSH precipitate, but at 55 per cent. alcohol a richer FSH precipitate. ICSH is very insoluble in 20·5 per cent. sodium sulphate buffered with M/4 acetate at *p*H 4·4, while FSH is very soluble in this mixture.

Preparation of the Interstitial-cell-stimulating Hormone (ICSH, Luteinizing Hormone, LH, Metakentrin). Assay methods on which purification has depended have been the production of corpora lutea in ovaries of immature female rats, and the growth of seminal vesicles and prostate in male rats through stimulus of the interstitial cells of the testes, etc.

Fevold has summarized recent attempts at purification in some detail. He states: "In the last two or three years a high degree of purification has been obtained in at least three laboratories. The preparations from two of these laboratories are reported to be pure proteins, as determined by sedimentation in the ultracentrifuge, electrophoretic analysis, and by solubility studies. The product obtained by the third group (his own) appears not to be pure, as judged by these criteria, but seems to exceed those of the others in activity." The actual methods are too complex to be reported here.

Van Dyke and his co-workers used fresh hog pituitaries, the Evans group acetone-dried sheep pituitaries, and Fevold and his co-workers fresh sheep pituitaries. The three different products showed marked differences in the isoelectric point, electrophoretic mobility, and sedimentation constant, the molecular weights of the first two preparations being estimated at 90,000 and 40,000 respectively.

Fevold concludes that if the first two preparations are pure ICSH, then sheep and swine ICSH are different proteins. Chemical analysis of the preparations supports such a view. Evans' sheep preparation yielded 4·5 per cent. mannose, 5·8 per cent. glucosamine, 1 per cent. tryptophane, 4·5 per cent. tyrosine, and 5·4 per cent. cystine. The swine preparations yielded only 2 per cent. carbohydrate, but 3·8 per cent. tryptophane.

The activities of the three preparations seem to have been determined by different procedures which do not permit exact comparison.

The Lactogenic Hormone (*Prolactin, Galactin, Mammotropin*). Riddle obtained by isoelectric precipitation of an acid extract of anterior pituitary tissue a fraction which stimulated development of the crop-gland in male, female, or castrate pigeons. E. I. Evans showed that crude extracts of anterior pituitary produce copious lactation in virgin and in dry goats, and Lyons *et al.* showed the same effect in virgin heifers and in normal bitches. The dependence of lactation on pituitary function is shown by the fact that hypophysectomy of lactating rats stops the lactation, while pituitary extract will produce lactation after hypophysectomy and after castration (Collip, Selye and Thomson). Similar results have been obtained with bitches, while male dogs, after pre-treatment with oestrogens, reacted to alkaline extracts of anterior pituitary by a copious flow of milk (Houssay (1)).

Bates and Riddle obtained a concentrate of prolactin as early as 1935. There is now good evidence that the pure hormone has been isolated.

Preparation of Pure Prolactin. Assays are based on the effect on the crop-gland or on lactation. The following method of preparation (White) can be taken as typical. Beef pituitary glands are extracted with acid-acetone at *p*H 1·5 (Lyons' method). To the extract acetone is added to 92 per cent. concentration, the precipitate is extracted with water, and the extract again precipitated with 92 per cent. acetone, giving crude prolactin, in yield of 1·2 to 1·9 gm. per kg. of original material. This is dissolved in aqueous alkali and the *p*H adjusted to 6·6 in presence of ammonium sulphate (one-twentieth saturation). The adrenotrophic fraction is precipitated and the solution is adjusted to *p*H 5·4. These last two steps are repeated several times, and finally the precipitate (at *p*H 5·4) is dialysed free from salt and dried with acetone, giving 120 to 190 mg. of purified prolactin.

Crystalline prolactin has been prepared from the amorphous preparation by a modification of the method used to crystallize

insulin (and also by precipitation from dilute acetone solution). The product is usually in small hexagonal crystals. The yield is small, and the purity no greater than that of the best amorphous preparations. Recrystallization seems to cause denaturation (cf. White).

The best amorphous preparations are pure and homogeneous, as judged by electrophoretic experiments, solubility studies, and ultracentrifuge analysis.

Chemical and Physico-chemical Properties of the Pituitary Gonadotrophins and Prolactin. FSH is a protein. Proteolytic enzymes digest it, although apparently somewhat more slowly than ICSH. Amylases also destroy its activity, indicating that this is associated with its carbohydrate moiety. It has been termed an albumin (Fraenkel-Conrat) and a glyco-protein (Chow). (Most albumins contain carbohydrate radicals, and the distinction between the two classes of proteins is not rigid.)

ICSH is also a glycoprotein. Ketene destroys the activity of both, probably through acetylation of amino-groups, suggesting that free amino-groups are necessary for their activities. Cysteine also inactivates FSH, possibly indicating that –S–S– linkages are needed for its activity, although other explanations have been suggested (Chow).

Sedimentation studies of prolactin indicate a molecular weight of about 35,000, while calculations from osmotic pressure measurements, and from content of amino-acid radicals, suggest 25,000, a figure which White considers to be too low.

Prolactin yields approximately 5·5 per cent. tyrosine, 1·3 per cent. tryptophane, 3·4 per cent. cystine, 4·3 per cent. methionine, and 8·3 per cent. arginine, and its content of sulphur is relatively high, about 2 per cent. (White, Fraenkel-Conrat). It is digested by both pepsin and trypsin. It is inactivated by ketene and by nitrous acid, indicating that free amino-groups are needed for its activity. Cysteine does not permanently inactivate it.

Biological Properties of the Pituitary Gonadotrophins and Prolactin. Since these three hormones have been obtained in relatively pure form, more definite statements can be made concerning their activities. These have recently been reviewed by Pfeiffer. He considers that a certain degree of maturity is necessary in order that the gonads may become responsive to gonadotrophins.

FSH causes growth of follicles in the ovary, and development of seminiferous tubules in the testis, but does not, alone, stimulate the production of sex hormones. For this, in addition, a small proportion of ICSH is needed. Pre-ovulatory swelling, ovulation,

and corpus luteum formation need a much higher level of ICSH stimulation than that required for maintenance of the interstitial cells of ovary or testis.

The pituitary of the male secretes ICSH at a level too low for luteinization of the ovarian follicles of the female.

Rat experiments suggest that the oestrogen produced in the growing follicle suppresses FSH output and increases ICSH output.

Immediately following mating in the rabbit, FSH, ICSH (and thyrotrophic, and possibly adrenotrophic hormones and prolactin) are released by the pituitary.

ICSH, in addition to the functions already mentioned, stimulates development of luteal tissue and corpora lutea (but does not maintain the corpora lutea). In the male it stimulates the interstitial tissue of the testis, to secret the androgenic hormone.

Neither oestrogen, progesterone, nor prolactin alone is adequate for mammary growth. Oestrogen plus progesterone produce slight development, but for complete development prolactin is required in addition. Conclusive results have been obtained with hypophysectomized male mice (White ; cf. also Lyons). Following parturition there is a sudden increase in the prolactin content of the pituitary, and prolactin is essential for lactation and continued milk secretion (Pfeiffer).

In cattle and goats the artificial oestrogen diethyl-stilboestrol is said to induce both mammary development and copious milk secretion, suggesting a variation in different species (cf. Pfeiffer).

Prolactin is a necessary stimulus for the production of progesterone in luteal tissue (Evans, Simpson and Lyons).

Riddle has found good evidence that prolactin is responsible for the " broodiness " (nesting instinct) in fowls, and the maternal instinct in mammals. He has shown that injection of prolactin into virgin rats leads to definite maternal behaviour—retrieving, cuddling and protection of young in their vicinity, nesting (cf. Riddle and Bates).

Nalbandov states that injection of prolactin into normal mature cockerels inhibits the gonads by shutting off FSH output, so that there results decrease in the weight of the testes and in androgenic activity, and cessation of crowing, treading, etc.

There is some evidence that prolactin promotes growth in the pigeon, though not in mammals (cf. Long).

Folley, Young *et al.*, from comparative studies on different species of mammals, have adduced evidence that prolactin is not the only factor concerned in the galactopoietic action of the anterior pituitary.

The Thyrotrophic Hormone

It has been known for some time that the thyroid gland is affected both by induced hypopituitarism and induced hyperpituitarism. It has been mentioned (p. 329) that removal of the pituitary in frog tadpoles stops thyroid development ; the same operation in young rats leads to atrophy of the thyroid, and in adult toads to flattening of thyroid epithelium and accumulation of colloid. Conversely, implants of anterior pituitary or injections of extracts into salamander larvae or adult toads provoke thyroid hyperfunction.

Loeb and Aron showed independently in 1929 that injection of anterior pituitary extract into guinea-pigs produced thyroid hyperplasia resembling the histological picture in Graves' disease. This focussed attention on a possible thyrotrophic factor of the pituitary, and has been confirmed and extended to other species of mammals and to birds. Thus Schockaert found that daily injections of potent extracts of bovine anterior pituitary into young male ducks produced (besides regression of thymus and hypertrophy of testes) marked and rapid increase in the size of the thyroid which histologically showed heightened activity, and chemically showed rapid decrease of iodine content to a low level. After three weeks' treatment exophthalmos developed ; this disappeared a week after cessation of treatment. Houssay *et al.* made similar studies in dogs. Hypophysectomy led to thyroid atrophy, and, histologically, hypoactivity (without loss of iodine). Injection of alkaline extracts of pituitary led to thyroid hypertrophy and hyperplasia, lowering of iodine content, and increase of blood iodine (even in hypophysectomized animals).

Loss of iodine is paralleled by loss of thyroxine, indicating definite discharge of the thyroid hormone (Foster *et al.*).

The autopsy findings on Cushing's giant bull-dog bitch (p. 333) are in agreement.

Hypophysectomy in rats lowers the basal metabolic rate, which can be restored to normal by anterior pituitary homotransplants, or daily injections of thyroid extract, but not by injections of posterior pituitary extract (Foster and Smith).

In human pituitary deficency disease the basal metabolism tends to be low ; some cases of Simmonds' disease exhibit frank myxoedema (cf. Chapter X). In acromegaly basal metabolism is frequently above normal (cf. Chapter XI). Houssay and Artundo showed that the pituitary affects basal metabolism through the thyroid, since, after thyroidectomy, subsequent hypophysectomy does not affect the basal rate.

Marine produced marked thyroid hyperplasia accompanied by exophthalmos in immature rabbits by daily injections of small doses of methyl cyanide. Thyroidectomized rabbits developed the exophthalmos. Marine considered that inhibition of tissue oxidation due to the cyanide affected some hypothalamic centre which stimulated the anterior pituitary to discharge its thyrotrophic hormone, while at the same time the sympathetic system was stimulated, directly or indirectly, to produce the exophthalmos.

Eitel, Krebs and Loeser showed that when slices of dog's thyroid were suspended in serum saturated with oxygen and at body temperature, addition of a thyrotrophic concentrate produced typical hyperplastic changes, indicating direct action on the thyroid. Thyroid transplants are affected by the thyrotrophic hormone as rapidly as is the thyroid itself, so that the effect is produced through the blood stream and not by a nervous mechanism (Marine and Rosen ; Houssay, Biasotti and Magdalena ; Krayer).

Preparation and Properties of the Thyrotrophic Hormone. Several improved methods of preparation have been published in the past two or three years by Fevold *et al.*, Jensen and Tolksdorf (2), Bosnes and White, and Fraenkel-Conrat *et al.* The purest preparation yet available seems to be that of Ciereszko and White. Their product is so active that one gamma gives a thyroid histological response in the chick. It behaves in the Tiselius apparatus and the ultracentrifuge as a homogeneous product of the relatively low molecular weight of 10,000.

They extracted ground frozen beef pituitaries with 2 per cent. sodium chloride at low temperature and *p*H 7·8. The extract was adjusted to *p*H 4·1 and an equal volume of acetone added, the low temperature being maintained. The precipitate was rejected ; an equal volume of acetone was added to the solution, and the precipitate so produced was extracted with water and the extract adjusted to *p*H 9·0. A precipitate formed and was removed, the solution being then adjusted to *p*H 7·0 and 5 per cent. lead acetate added to complete precipitation. This precipitate was rejected and trichloracetic acid added to the solution to give 0·5 M. concentration. A precipitate slowly flocculated out and was removed. The clear colourless solution which remained was dialyzed and concentrated, to give finally a white solid product, very soluble in water ; the solution gave the usual protein tests and a positive Molisch reaction.

Studies with the various purified products now available indicate that they produce all the effects already described and attributed to the thyrotrophic hormone. The hormone may be a pseudoglobulin. Radioactive iodine studies suggest that it specially controls the rate of iodine uptake by the thyroid and the conversion of diiodotyrosine into thyroxine in the gland (Morton *et al.*).

The Adrenotrophic or Adrenocorticotrophic Hormone

Cushing's syndrome, in which an identical, or almost identical syndrome may be due either to an adenoma of the basophile cells of the anterior pituitary, or to a tumour of the adrenal cortex (cf. Chapter XII) is an indication of a close relationship between the two glands.

Smith (1930) and Evans (1932) showed that following hypophysectomy the rat's adrenals atrophy, while pituitary implants or injections of pituitary extracts restore them. The degenerative changes particularly affect the zona fasciculata and zona reticularis. Pituitary extracts (free from gonadotrophins) produce in these zones an increase in cell cytoplasm and partial recovery of lipoid granules (Evans *et al.*). The adrenal medulla is not affected by hypophysectomy (Houssay *et al.*).

Li, Simpson and Evans have now obtained the adrenocorticotrophic hormone in highly pure condition (cf. also Sayers, White and Long). Its chemical properties differ considerably from those of the other hormones of the anterior pituitary. It is not destroyed by peptic digestion, nor in neutral solution at 100° for two hours. It is stable in hot acid but not in hot alkaline solution. It does not contain cysteine radicals. There is evidence that both free amino and tyrosine groups are essential for its activity. It is rapidly inactivated by trypsin.

It inhibits growth in rats (this effect being antagonized by the growth hormone) and retards bone formation (Evans *et al.*). It elevates the β and γ fractions of plasma globulin (White and Dougherty), perhaps through its involutionary effect on thymus and lymphoid tissue (cf. Dougherty and White ; Reinhardt and Li ; Yoffey *et al.*) ; White and Dougherty conclude that the lymphocytes of lymphoid tissue may be a storehouse of the plasma globulin, controlled by this hormone through the adrenal cortex.

The so-called anti-insulin or glycotrophic action of the pituitary has recently been shown to be due to its adrenotrophic hormone (Jensen, Grattan and Hart), which also produces increase in the arginase content of the liver (cf. Fraenkel-Conrat).

The Adrenocorticotrophic Hormone and Gamma Globulins of Blood Plasma. Injection of adrenocorticotrophic hormone or of corticosterone into normal animals produces lymphatic degeneration, with dissolution of the stored lymphocytes, and at the same time causes an increase in the total plasma proteins, this being largely in the beta and gamma globulin fractions. Using electrophoretic and immunological techniques it has been shown that the lymphocytes contain a reserve store of gamma globulin, and it may therefore be concluded that this is released under control of the anterior pituitary, exercised

through the adrenal cortex. The antibodies of the blood are present in the gamma globulin fraction, and evidence has also been adduced that the rate of antibody release from lymphoid tissue is under pituitary and adrenal cortex control. (Cf. Dougherty and White ; Dougherty, Chase and White ; Kass ; Reinhardt and Li ; White and Dougherty.)

The Metabolic Hormone (?)

There is much evidence associating the anterior pituitary gland with carbohydrate and fat, and even protein metabolism. There is also evidence that a good deal of this metabolic activity can be associated with either the adrenotrophic, growth, or thyrotrophic hormones. It is still a matter of opinion whether their actions leave some activities still unaccounted for, justifying the assumption of a specific metabolic hormone. Many such have been postulated by different investigators ; that one, but not more than one, exists seems possible.

Some of the more striking instances of pituitary association with metabolic processes will be mentioned, along with some part of the evidence for and against a specific hormone.

The acromegalic occasionally exhibits true diabetes mellitus, and more frequently a lowered carbohydrate tolerance (cf. Chapter XI). Hypoglycaemia may be present in human hypopituitary states (Collip), and patients with Simmonds' disease are frequently hypersensitive to insulin (Houssay (2)).

In most vertebrates there seems to be an antagonism between the pituitary and the islets of Langerhans. This has been established by the numerous researches of Houssay (2) and his collaborators, and repeatedly confirmed. Pancreatectomy in the previously hypophysectomized toad does not produce diabetes ; if, then, pituitary tissue is implanted, diabetes ensues. In the hypophysectomized dog (which is markedly sensitive to insulin) removal of the pancreas only leads to a mild diabetes, and such an animal—the " Houssay dog "—may live for many months without specific treatment, though it finally becomes more and more undernourished, extremely cachectic, and dies. The Houssay dog shows exaggerated hyperglycaemic response to a meal, and may exhibit glycosuria. It can be balanced by careful combined treatment with insulin and suitable anterior pituitary extracts, and this balanced animal resembles the pancreatectomized dog balanced with insulin, though its respiratory quotient is higher. It can store liver glycogen.

As with the toad, injections of suitable anterior pituitary extracts into the Houssay dog produce a typical diabetes.

Long (1) showed that the adrenalectomized, pancreatectomized cat and dog, just maintained with adrenal cortical extracts, present a somewhat similar picture, suggesting that at least part of the pituitary effect is mediated through the adrenal cortex. In subsequent work on rats he obtained evidence that functioning adrenal cortical tissue is needed for participation of the anterior pituitary in carbohydrate metabolism. Nevertheless Houssay (2) has found that the diabetogenic effect of anterior pituitary preparations can be demonstrated in the adrenalectomized and almost completely depancreatized dog maintained with only sodium chloride.

It has long been known that alkaline extracts of the pituitary when injected into rats induce ketonuria (Burn and Ling, 1928) and ketonaemia (Hoffmann and Anselmino, 1931).

Young (2) finds that if dogs, cats, or rats, given a daily ration of meat food just sufficient to maintain steady body weight under normal conditions, are injected daily with his diabetogenic extract, there result nitrogen retention (through the laying down of tissue protein), a rise in body weight (and diabetes in the cat and dog). An important effect of the extract appears to be the partial replacement of carbohydrate and protein catabolism by that of fat. Young suggests that the disposition of protein in the body requires the active co-operation of insulin, and thus, in animals susceptible to diabetes, the pancreatic islets are first stimulated to produce excess insulin, and then become relatively exhausted. Under normal stipulation the deposition of new tissue is merely associated with normal growth. He thinks the essential factor in the extract may be the growth hormone. (Cf. Ogilvie.) Conn and Louis postulate a pituitary principle with direct action on the islets.

Young (1) showed a few years ago, and his work has been adequately confirmed (cf. Houssay (2)), that if crude saline extracts of fresh pituitary tissue are injected daily into dogs, cats, or rabbits, these animals within a few days exhibit hyperglycaemia, polyuria, glycosuria and ketonuria. These subside unless the daily injection dose is gradually increased, but if so maintained a continuous diabetes results ; when it has become sufficiently severe it may persist in dogs even after cessation of the injections. The animals do not develop excessive loss of weight and may survive several months, unless placed on high carbohydrate diet when loss of weight is rapid. Autopsy of such animals shows degenerative changes in the islets of Langerhans indicating exhaustion and loss of function.

O'Donovan and Collip have prepared extracts from the pituitary of what they termed the " specific metabolic principle," which they considered to be richly present in the pars intermedia and in " pituitary colloid," and which chemically and in distribution

seemed to resemble the melanophore hormone. Their preparation appeared to depress carbohydrate oxidation and increase combustion of fat. They found that it produced ketonaemia in normal and in adrenalectomized rats, decreased total body fat, but increased liver fat in fasting mice ; it increased glycosuria and ketonuria in the Houssay dog, maintained liver and muscle glycogen, and rendered rabbits resistant to insulin. It increased oxygen consumption and depressed the respiratory quotient of rabbits and man. They claimed that while the preparation was also rich in the melanophore hormone it was almost free from other pituitary hormones. It was thermostable, resistant to alkali and pepsin, but destroyed by trypsin. It dialysed through collodion. (Cf. also Billingsley, O'Donovan and Collip, Neufeld and Collip, Rabinowitch *et al.*)

Long (2) has recently summarized the evidence concerning the relationship of the anterior pituitary to protein metabolism. A few hours after injection of anterior pituitary extracts into dogs there is a fall in the blood content of non-protein nitrogen, urea and amino-acids of some 20 to 30 per cent. This fall may persist for some time. Similar results have been observed in rats. Urine nitrogen excretion is also lowered. The liver content of urea and amino-acids is markedly reduced. Prolonged injection of such extracts causes a gain in weight, which is chiefly accounted for by increased content of water and protein.

Such results suggest that there is either an increased synthesis or a decreased catabolism of protein. Most of such experiments have been carried out with extracts rich in growth-promoting activity.

The effect on nitrogen retention, as on growth itself, is not entirely prevented by thyroidectomy (unless at birth), nor by adrenalectomy, nor are the pancreas or gonads essential to the action.

Long (2) concludes that the growth hormone, as part of its action, controls protein metabolism, causing protein retention or formation, and that its influence on growth is in part through this metabolic control. He even is of opinion that in the adult animal in which growth has ceased this hormone is a regulator of the anabolic and catabolic phases of protein metabolism.

The striking effects on carbohydrate and fat metabolism still have to be accounted for. Anterior pituitary hormones functioning in the normal animal might produce metabolic effects by direct action on tissue (*e.g.*, growth hormone), indirect action on tissue (*e.g.*, thyrotrophic and adrenotrophic hormones), or indirectly

through a changed metabolism from such direct or indirect action affecting another endocrine gland not under direct pituitary control (*e.g.*, the islets of Langerhans).

It is doubtful if the thyrotrophic hormone plays an appreciable *rôle* in this connection. The adrenal cortex, through hormones of the corticosterone type, does exert influence on protein and carbohydrate metabolism, leading to formation of liver glycogen and heightened blood glucose at the expense of protein (gluconeogenesis), there being concomitant increase in urinary nitrogen.

The hypoglycaemic action of insulin in tissues (its glycotrophic action resulting in tissue utilization of glucose) can be greatly reduced or abolished by injection of a suitable anterior pituitary extract, and can also be abolished by injection of adrenocortical extracts or of corticosterone, or fairly pure adrenotrophic hormone.

These and other observations suggest that a large part of the diabetogenic activity of the anterior pituitary is brought about by the adrenotrophic hormone acting to produce increased output of adrenocortical hormones (cf. Long (2)).

It also follows from the assumption that the growth hormone lessens protein catabolism that total catabolism is shifted towards increased carbohydrate and fat catabolism, tending, indirectly, to a ketogenesis (cf. Long (2)).

The production of diabetes in experiments such as those of Young can be regarded as due to prolonged stimulation of the islets through continuous hyperglycaemia caused by the pituitary extracts and ensuing exhaustion of the islets. Houssay (2) regards it as not strictly a pituitary diabetes, though it is obviously essentially associated with pituitary hyperfunction and comparable with the diabetes of acromegaly.

Fraenkel-Conrat considers that at present there is little chemical evidence and no certain evidence for existence of a multitude of separate metabolic hormones ; from the preceding paragraphs it may be concluded that there is no necessity to assume the existence of even a single specific metabolic hormone to account for a large part of the metabolic changes associated with pituitary action. Nevertheless Houssay (2) seems strongly of the opinion that a pituitary diabetogenic factor exists, which is not identical with any one of the six accepted hormones, and which regulates carbohydrate metabolism. It is quite evident that until further data are available the problem of the existence or non-existence of a specific metabolic factor cannot be solved. Proof of its existence will rest upon its isolation in fairly pure form. Further

work on O'Donovan and Collip's preparation may yield the necessary results.

Other Hormones

There is no good evidence for existence of other hormones in the anterior pituitary. A parathyrotrophic hormone was formerly postulated, without adequate evidence. A pancreatotrophic hormone has frequently been suggested, but Long (2), after critically examining the evidence, concludes that the production of insulin is not directly under endocrine control of the islets but is governed by the height of blood glucose.

Products of Acidophile and Basophile Cells

Disease states afford some clue to the association of individual hormones with one or other of the two cell types. The acidophile tumours of acromegaly, with its occasional accompanying hyperthyroidism, associate the growth and thyrotrophic hormones with the acidophile cells. The basophile tumours and hyaline changes of basophile cells in Cushing's disease (cf. Chapter XII) suggest that these cells produce the adrenotrophic hormone.

Diseases Associated with the Anterior Pituitary Lobe

These may be associated with hypo- or hyperpituitarism, or mixed syndromes. They will be dealt with in the succeeding

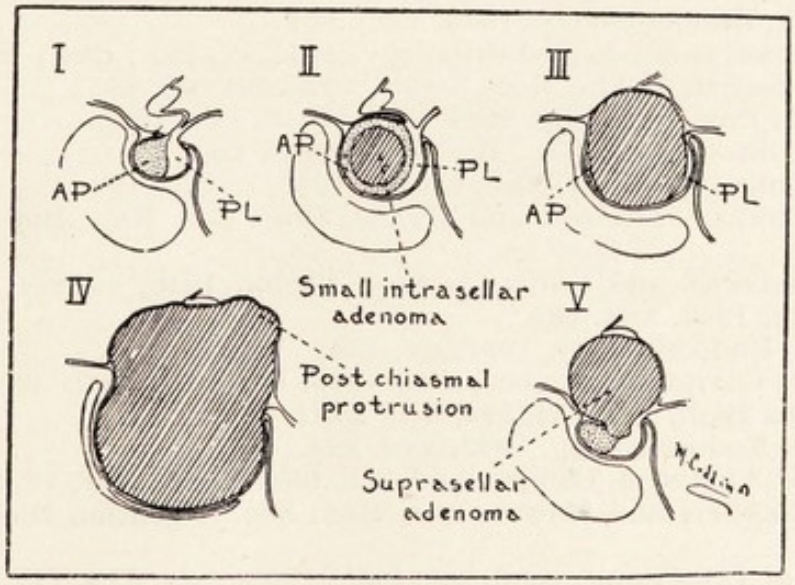


FIG. 52. A series of drawings to illustrate the mechanical effects of an expanding pituitary adenoma. I. The normal pituitary gland and optic chiasm. II. A small intrasellar adenoma with only a slight expansion of the sellar. III. A larger adenoma beginning to stretch the chiasm—a little anterior lobe still remains. IV. A widely expanded sellar and greatly stretched chiasm. V. A suprasellar adenoma which has implicated the chiasm without compressing the anterior lobe. (From Henderson, Endocrinology, 1931, xv, 120.)

chapters. The effects of tumours within and without the pituitary on the pituitary itself and on surrounding structures are shown in Fig. 52 (cf. also Jefferson).

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CHAPTER X

DISEASES CORRECTLY AND INCORRECTLY ASSOCIATED WITH HYPOFUNCTION OF THE ANTERIOR PITUITARY

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INTRODUCTION

In the past certain syndromes, by reason of evidence from autopsies, have been thought to be associated with deficient function of the anterior pituitary, whence it became customary to ascribe to such pituitary deficiency anything at all resembling these syndromes. Many cases, incorrectly so ascribed, were self-corrective, and use of pituitary therapy for them conferred on it unwarranted reputation.

Recently these loosely defined syndromes and their treatment have been considered more critically. Patients with hypofunction of the anterior pituitary are rare, while those benefiting from pituitary therapy are rarer. In critical appraisal it seems to be of some advantage to stress the original description of the syndromes, and that has been done for Simmonds' first case, and Fröhlich's case.

It is not too easy to classify the several syndromes which do involve deficient function of the anterior pituitary. Thus many cases of Lorain-Levi infantilism and all cases of Simmonds' disease are associated with a damaged pituitary, which should link them together. Yet the typical clinical pictures do not so relate them.

It is not presumed that the classification adopted here is entirely logical or entirely accurate, but it fits present knowledge reasonably, and is simple.

SIMMONDS' DISEASE AND ANOREXIA NERVOSA

Simmonds' Disease (Pituitary Cachexia, Panhypopituitarism (Anterior)) results from partial or complete destruction of the anterior lobe of the pituitary, from whatever cause. Simmonds' original description was of a case associated with post-partum necrosis of the pituitary and a considerable proportion of cases are of this type.

Paulesco, in a paper published in 1907, proved that the anterior pituitary is essential to life, and that complete extirpation in adult animals was followed within a few days by a train of symptoms culminating in insensitiveness, diminution in pulse and respiratory rate, fall in temperature, apathy, coma, and death.

Simmonds' first report was published in 1914. A woman, aged forty-six, was admitted to hospital in an unconscious condition which had persisted for two days. The only abnormal findings revealed by examination were subnormal temperature (36° C.), small thready pulse, not accelerated, marked emaciation, and an appearance pallid and much older than her years. She died next day without having regained consciousness.

Autopsy showed a shrunken pituitary which consisted almost entirely of fibrous tissue, practically the whole anterior, intermediate and posterior lobes having been destroyed. The liver, spleen and ovaries were small, but histological examination revealed no pathological changes in them, nor in the pancreas, thyroid, kidneys, adrenals, and parathyroids.

On enquiry it was ascertained that this woman was normal to her thirty-sixth year, and had had five normal children, but that after the birth of the fifth she suffered a severe puerperal sepsis. From that time there was complete amenorrhoea, she remained weak and incapable of work, often became unconscious, lost weight, and aged rapidly. Two years prior to her death she had been examined in another hospital, found to be under-weight and to have a haemoglobin content of 50 per cent., and diagnosed a case of premature senility.

Recalling the asthenia, coma and death following extirpation of the pituitary in animals, Simmonds correctly associated her condition with destruction of the pituitary. He summed up: "A hitherto healthy woman became severely ill with puerperal sepsis and suffered a septic necrosis of the pituitary. The damage to this important organ was followed by menopause, muscle weakness, attacks of vertigo and loss of consciousness, anaemia, and rapid ageing, in short, a premature senility. The remaining intact fragments of the pituitary atrophied gradually in the surrounding fibrous tissue. The organ became absolutely insufficient, and the woman died in coma. Autopsy showed, as the single cause of death, an almost complete disappearance of the pituitary."

If the disease be considered in its widest sense as one in which damage to the pituitary has progressed to the stage in which there is a definite deficiency in the output of its hormones, then, from our knowledge of pituitary function, it is possible to infer a more

involved and variable syndrome than is suggested by the case just described. Through such variable hormonal deficiencies the gonads should gradually cease to function and they and the secondary sex organs should atrophy, the adrenal cortical hormone output should decrease, possibly to the extent of suggesting Addison's disease, while with lessening stimulation from the thyrotrophic hormone thyroid atrophy might follow, even to the extent of a resulting myxoedema, and finally the hormonal balance of control of carbohydrate metabolism might be upset.

These possibilities must be borne in mind in considering the numerous reports of cases of Simmonds' disease which have appeared in the last thirty years. These reports should also be compared with the experimental observations of Smith, which are more accurate and complete than those of Paulesco. He found that extirpation of the anterior pituitary in adult rats produced an invariable syndrome, characterized by progressive loss of weight (cachexia), atrophy of the genital system with loss of libido, immediate cessation of sex cycles in the female, atrophy of the thyroid, parathyroids and adrenal cortex, loss of appetite, weakness and flabbiness, premature senility, and death.

Numerous reviews have appeared in the literature within the past few years, including those of Silver, Calder, Sheehan, and Escamilla and Lisser.

Escamilla and Lisser reviewed 595 cases in the literature which purported to be Simmonds' disease. Many of these, as they themselves conclude, were undoubtedly in reality cases of anorexia nervosa, so that their findings concerning 101 typical clinical cases, all with pathological verification, are most important in determining the chief features of the disease. Unless otherwise stated, the following data are from their findings.

Age and Sex. The disease predominantly occurs in women, the ratio being almost two to one. It is very rarely found before ten years of age or after sixty-five years, there being a fairly even age distribution between twenty and sixty years.

Etiology. Three principal causes of the pituitary damage seem to be post-partum necrosis in women, tumour or cyst formation, and, less frequently, head injury. Of the 70 cases he reviewed Calder considered that only one could be definitely attributed to tuberculosis, and none to syphilis.

Calder also considered the possible mechanisms by which pregnancy could lead to infected emboli (as Simmonds suggested), but drew no definite conclusion, except that probably no single pathological process is responsible. Sheehan concludes that the

necrosis is due to thrombosis of the pituitary vessels during rapid pituitary involution at the time of the puerperium, the thrombosis being consequent upon the collapse of the patient following severe haemorrhage at delivery. He does not believe that puerperal sepsis is of proved etiological importance.

An excellent example of tumour as the cause of pituitary damage is the case reported by Farber and his colleagues.

An unmarried woman, aged twenty-six, exhibited retarded growth and mentality, polydipsia and polyuria, hypotension, impaired vision and ocular disturbances, dry skin, pathological sleep, depressed basal metabolism with hypopyrexia, absence of secondary sex characteristics, including atrophic breasts and genitalia and absence of pubic and axillary hair; cachexia was not present. At autopsy the site of the pituitary was occupied by a calcified suprasellar tumour (craniopharyngioma). The heart, lungs, pancreas, spleen, kidneys, adrenals, ovaries and secondary sex organs were all atrophic. The thyroid weighed 13 grams. Section of the thyroid showed thin flattened lining cells and colloid of varying density.

Cardinal Characteristics. There are four, loss of weight, loss of sexual function, asthenia, and a basal metabolic rate below minus 20 per cent.

Cachexia. The average loss of weight is about 20 kg. (44 lb.). Sometimes it is much greater. Most writers stress it, and it certainly appears to be present in the majority of verified cases, though Sheehan (considering post-partum cases especially) thinks that in these emaciation is relatively unimportant and a late development in the progress of the disease.

Loss of Sexual Function. In women amenorrhoea is an outstanding early phenomenon ; libido is absent. Loss of libido and potence is noteworthy in men. Loss of axillary and pubic hair is frequently reported, although overabundant downy body hair (a characteristic feature of anorexia nervosa) has been recorded in at least one verified case of Simmonds' disease (by Escamilla and Lisser). Genital atrophy or infantilism is common.

Asthenia. This is a noticeable symptom, although it may be a late development.

Low Basal Metabolism. This is to be attributed in part to the malnutrition (Escamilla and Lisser), but in part is frequently due to loss of adequate thyrotrophic stimulation.

Other Findings. Psychic changes are present in the majority of advanced cases. The symptoms most frequently noticed are apathy, dullness, drowsiness, confusion or disorientation, and depression.

Anorexia is occasionally present, intolerance to cold and

subnormal temperature are frequent, pallor is present in about half of the patients, and a fasting blood sugar below normal in almost as many.

In 18 of 42 verified cases in which X-ray examination was made, enlargement, destruction or calcification of the sella turcica was evident, suggesting a tumour, cyst, or chronic infection process (Escamilla and Lisser).

Falling of the teeth, trophic changes in the nails, and thickening and loss of lustre of the skin are noteworthy symptoms (Calder) contributing to the appearance of premature senility which is so often seen in both sexes with Simmonds' disease.

Prognosis and Treatment. Simmonds' disease may run a long course, even up to forty years, or may terminate swiftly; the duration of the disease probably depends on the nature of the factor causing damage to the pituitary and especially on the degree to which adrenal cortical function is affected.

Since the primary condition is in the anterior pituitary, treatment of secondary conditions can only be partial and palliative; this is well illustrated in the case of "pituitary Addison's disease" dealt with subsequently.

Administration of anterior pituitary preparations seems on the whole to be of doubtful value. Claims of benefit are usually open to the criticism that the case treated was in reality one of anorexia nervosa and not of Simmonds' disease at all. Yet Escamilla and Lisser write: "However conservative or sceptical one may be, a careful reading of many of the protocols forces one to believe that in certain cases (of Simmonds' disease) specific pituitary therapy must be given credit for the extraordinary improvement which occurred." It will be seen in the section dealing with "pituitary myxoedema" that in certain types of case the use of pregnant mare's serum (a comparable therapy), along with substitution thyroid and adrenal cortex therapy, seems definitely to be beneficial.

Specific Types of Simmonds' Disease. Since apparently damage to the anterior pituitary lowers the effective output of its hormones to different degrees in different patients, it is desirable to contrast certain different types of the disease. If it be remembered that intermediate grades undoubtedly exist, then from the descriptions of these types a composite picture of the possibilities can be obtained. The following will be considered: (1) the typical post-partum case, (2) "pituitary myxoedema," (3) what may for comparison be labelled "pituitary Addison's disease," and (4) mild Simmonds' disease.

(1) *The Typical Post-partum Case of Simmonds' Disease.* Sheehan's views are presented. He considers that the pituitary insufficiency may be of any degree of severity from general debility to superinvolution of the uterus, or, in extreme form, to Simmonds' disease. He presents the following composite description of a severe case (exceptions to most of the conditions being found in individual cases): "During the puerperium there is complete absence of lactation and sometimes hypoglycaemia. After this, the uterus becomes superinvoluted and the external genitalia atrophic. Menstruation does not return, and libido is absent. There is a gradual loss of the axillary and pubic hair. The patient is apathetic and dull, unable to do her housework, and very sensitive to cold. She may show a myxoedematous or a prematurely senile appearance. The weight is usually little altered unless there is great anorexia. The blood pressure tends to be rather low, and the basal metabolic rate is about — 25 per cent. of the normal. A hypochromic anaemia is present, sometimes associated with a definite eosinophil leucocytosis. The blood-cholesterol may be a little raised, and the blood-sugar rather low, but sugar tolerance tests give a curve with a delayed fall. After ten, twenty, or thirty years the patient may become more typically myxoedematous, or may develop mental changes with anorexia and some loss of weight. At this stage the anaemia may become hyperchromic, the basal metabolism may fall to about — 35 per cent., but the blood pressure is usually normal. Finally, usually as a result of some intercurrent illness or a phase of severe anorexia, the patient goes into coma and dies, usually with hypoglycaemia. *Post-mortem*, the anterior pituitary is represented chiefly by the large scar of the original post-partum necrosis, the suprarenal cortex is atrophic, the thyroid usually shows fibrous atrophy, the ovaries and uterus are shrunken, and the viscera are small."

A typical case is shown in Fig. 53.

Pituitary Myxoedema or Simmonds' Disease Masquerading as Myxoedema. It will be noted that Sheehan seems to stress the development of a myxoedematous *or* a prematurely senile appearance. A number of writers have suggested that the hypothyroidism of certain patients might be secondary to pituitary hypofunction. The description of a definite clinical syndrome, best expressed by Means's phrase used as a heading for this paragraph, is due to Means and his colleagues. The patients in this group exhibit typical myxoedema. Administration of thyroid in usual dosage may precipitate acute adrenocortical failure to such a degree that

death has ensued. Cases that have gone to autopsy have shown the typical pituitary findings of Simmonds' disease. Two cases recently reported by Lerman and Stebbins present the salient facts of this type, and a condensed account of them follows.

Case 1.

A woman, aged sixty-eight, seen because of a fainting spell, presented the clinical appearance of myxoedema, with subnormal temperature, slow feeble pulse, and low voltage and flat T waves in the electrocardiogram. She was given desiccated thyroid in moderate dosage.

FIG. 53. Typical Simmonds' disease. *A.* Patient at the age of fifty-one, eleven years after the last of eight pregnancies. Cachexia obvious. *B.* Aged fifty-three, one week before death. Cachexia extreme, weight 60 lb. Autopsy showed a small, fibrosed pituitary. (From Silver, Arch. Int. Med., 1933, li, 175.)

Four days later she developed alarming symptoms, weakness, nausea, vomiting, and finally coma. It was then learned that at the birth of her only child forty years before, delivery had been difficult and complicated by severe haemorrhage ; myxoedema and amenorrhoea then developed. In the intervening period thyroid had been prescribed from time to time by different physicians, and each time she ceased taking it after a few days because of the nausea, vomiting and weakness it produced.

Examination showed a typical myxoedematous woman, well developed and well nourished, with pale, dry and coarse skin, scanty eyebrows and hair on scalp, no pubic, axillary or body hair, puffy face and large tongue. The heart was not enlarged, the heart sounds regular, rapid,

and feeble. The blood pressure was 90–100/110–130. The temperature was 99·2° F. There was slight anaemia.

She was given intravenous glucose in saline but died several hours later.

Autopsy showed that the immediate cause of death was coronary occlusion. The anterior pituitary was almost completely replaced by dense fibrous tissue ; the posterior lobe appeared normal. The thyroid was completely atrophic, weighing less than 2 grams. Histologically it showed patchy fibrosis, with dense lymphoid tissue, and only a rare thyroid follicle. The adrenals were atrophic, though normal microscopically. The parathyroids and the islets of Langerhans appeared normal. The ovaries were completely atrophied and fibrosed (this being of course consistent with the age).

Case 2.

Another woman had a severe post-partum haemorrhage following the birth of her second child, with inversion of the uterus requiring laparotomy and two transfusions. She subsequently complained of fatigue, headaches, puffiness of eyes and ankles, faintness, aversion to cold and spells of dyspnoea, which symptoms persisted, while she gained 15 lbs. in weight. Amenorrhoea and loss of libido also ensued, without the accompaniment of hot flashes. She was first seen seven years later, when she was admitted to hospital in a state of semi-stupor following onset of an infection of the upper respiratory tract. She complained of vomiting and abdominal cramps. Rapid improvement followed forcing of food and fluids.

She presented a typical myxoedematous appearance at this time, with several atypical features : atrophic breasts, sparse pubic and axillary hair, absence of body hair, atrophic vaginal mucosa, infantile uterus, and low blood pressure (72/94).

Laboratory studies also presented a mixed picture. Hypochromic anaemia, gastric anacidity, low basal metabolic rate (— 40 to — 52 per cent.), low voltage and flat T waves in the electrocardiogram, were all characteristic of myxoedema, but the blood cholesterol was low (112–120 mg./100 c.c.) instead of high, as were also the plasma proteins.

Placed on thyroid, she did not respond normally. Her basal metabolic rate rose to — 18 per cent. in six days, but she developed anorexia, nausea, vomiting, and abdominal pains, became drowsy, with persisting low blood pressure, hypoglycaemia (42 mg. glucose/100 c.c.), and extremely low plasma total base.

It was therefore concluded that this was not a case of myxoedema, but of anterior pituitary hypofunction, and that thyroid therapy had induced adrenocortical insufficiency with hypoglycaemia. Thyroid was stopped and intravenous glucose in saline given immediately, rapid improvement following.

Further laboratory studies confirmed the diagnosis. The insulin tolerance test was of the hypopituitary type (*vide infra*). The urine contained no FSH, indicating pituitary failure, and also practically no 17-ketosteroids, indicating in the female adrenocortical hypofunction ; this conclusion was supported by Wilder's test (cf. p. 215).

Therapy was designed to protect the adrenals. Various pituitary preparations produced no beneficial effect, but injection of pregnant

mare's serum caused marked subjective and objective improvement. There was a definite oestrogenic response, increase of blood sodium and chloride, and definite excretion of 17-ketosteroids. High sodium chloride intake led to still further improvement. On this regimen (with injections of the serum thrice weekly for two weeks, then none for a like interval) she had two normal periods (though subsequently only premenstrual symptoms), a return of normal libido, increase of glandular tissue in breasts, renewed growth of eyebrows, increased hair on scalp, and softer skin. The basal metabolic rate was elevated 10 per cent. A severe infection of the respiratory tract did not lead to coma or abdominal cramps.

Six months later all medication was stopped for six weeks. The blood chemical values returned to abnormal levels. Restoration of the same treatment produced the same improvement. Then, in addition, thyroid was administered in small dosage. The basal metabolic rate rose to — 22 per cent. in two weeks, she lost most of her myxoedematous appearance, and showed no signs of adrenal insufficiency.

Her physical condition remained normal, the basal metabolic rate varied between — 15 and — 20 per cent., she was active and led a normal sex life. There were no further menstrual periods, but abdominal cramps and breast symptoms developed ten to fourteen days after each series of serum injections.

The authors' comment on the results in this case probably applies to all cases that come in this category. "No doubt the ideal treatment . . . is to replace all the trophic hormones of the pituitary or to supply all the hormones produced by the glands which are stimulated by the pituitary. The minimal requirements are thyroid and something to protect against adrenal insufficiency. In this case, extra salt and pregnant mare's serum have proved adequate."

Most cases of this type are female. Means has reported two male cases which showed a corresponding condition and which were markedly improved by high salt intake plus testosterone injections. (Lisser and Curtis report excellent results from use of methyl testosterone in a myxoedematous type of post-traumatic Simmonds' disease in a man aged twenty-eight, who, in the eight years preceding, had failed to respond to a number of pituitary preparations.)

Williams and Whittenberger have reported treatment of five similar cases (four women and one man) which is comparable. Four of these cases had been diagnosed as having had myxoedema for many years and receiving no benefit from thyroid administration. The effective treatment consisted of implantation of desoxycorticosterone pellets, methyl testosterone orally (and testosterone pellets), thyroid orally, and some extra sodium chloride. In each case there was marked increase in strength,

energy and feeling of well-being. The blood pressure, basal metabolic rate, and plasma sodium returned to normal. It was found that, as the dose of thyroid was increased, the dose of desoxycorticosterone had also to be increased.

One of these cases is shown in Fig. 54. She improved remarkably for eight or ten months, then gradually showed signs of recurring myxoedema. Rebalanced some months later with testosterone propionate, she again improved. Six months later, discontinuing the androgen, she relapsed a little; resumption after a month brought

FIG. 54. Simmonds' disease simulating myxoedema. *A*. Patient prior to treatment, and twelve years after birth of sixth and last child. In the interval, with gradual onset of the disease, frequent thyroid treatment had given no proper response. Typical myxoedematous appearance. *B*. One month after treatment commenced (NaCl, methyl testosterone, desoxycorticosterone, thyroid; cf. text). (From Williams and Whittenberger, J. Clin. Endocrinology, 1942, ii, 539.)

improvement again. Finally, three years after the treatment started, she discontinued it completely. A month later she developed bronchitis, then pneumonia, and died. At post-mortem the anterior pituitary was represented chiefly by fibrous material, a small part of the pars nervosa remained, the thyroid was small and mostly fibrosed, the ovaries small and fibrotic, and no adrenals could be found.

Two of the other cases are dead, one after two years' successful treatment, with virus pneumonia, one after six months, apparently from hypoglycaemia. Fairly good results had been obtained with the two remaining cases over periods of two and a half and three years respectively, when the second report was made (Williams *et al.*).

"*Pituitary Addison's Disease.*" While this heading is perhaps not too suitable, I have used it to stress the symptoms of hypo-

corticoadrenalism exhibited by some cases of Simmonds' disease. A case reported by Moss is illustrative.

A sixty-seven-year-old man, living in the southern States, previously in reasonable health, developed extreme fatiguability and lost 45 lb. in a few months. Examination showed low and falling blood pressure (to 82/58 mm. Hg.) and a basal metabolic rate of − 33 per cent. A diagnosis of adrenal insufficiency and hypothyroidism was made, and he was treated with adrenal cortical extract for some time, with considerable improvement. He regained 20 lb., and his blood pressure increased to 138/86 mm. Hg. He was then maintained on thyroid in small dosage, and remained well and able to work for three years. Following recurrence of his former symptoms and further hospital examination, thyroid treatment was stopped, and cortical extract resumed. Subsequently he returned to his former home in Massachusetts and came under Dr. Moss's care. Examination revealed little new, except an enlarged sella turcica (by X-ray) with appearance suggestive of an intrasellar tumour. Wilder's sodium deprivation test was positive for Addison's disease.

High sodium chloride intake plus desoxycorticosterone acetate intramuscularly caused definite improvement for a while, but the patient gradually failed. At this stage thyroid administration caused vomiting, and was discontinued. Adrenal cortical extract (in place of desoxycorticosterone) produced only temporary improvement, and the patient lapsed into coma and died.

Autopsy showed almost complete destruction of the anterior pituitary by a chromophobe adenoma ; there were but few acidophile and still fewer basophile cells remaining. The posterior lobe was compressed but not otherwise markedly affected. There was complete involution of the thyroid, atrophy and focal necrosis of the adrenal cortices, senile atrophy of the testes, and in addition bronchopneumonia, fibrocaseous tuberculosis, and myocardial hypertrophy with moderate coronary sclerosis.

Robertson has reported a case of the myxoedematous type (B.M.R. − 43 per cent.) which developed the crises typical of Addison's disease.

Mild Simmonds' Disease. It is obvious that all grades of damage to the anterior pituitary may be produced, and provided such damage is not invariably progressive, all grades of Simmonds' disease should exist. Mild types have been labelled by v. Bergmann and others with such terms as pituitary emaciation, or pituitary thinness, and according to Spence are less uncommon than typical Simmonds' disease. Escamilla and Lisser believe that most of such cases are really anorexia nervosa ; this seems very probable, and the apparently beneficial results of administration of pituitary preparations are misleading.

Sheehan, dealing solely with post-partum cases, points out that if the delivery can be proved to have been normal, then the patient's symptoms, however severe, cannot be ascribed to a post-partum necrosis. But if there has been severe haemorrhage or

collapse at delivery, then even slight symptoms of the type associated with Simmonds' disease are in all probability due to anterior pituitary necrosis. A certain number of his patients with Simmonds' disease improved without treatment. The degree of improvement varied. In patients who had genital atrophy amenorrhoea persisted, as did the majority of the general symptoms, although two patients regained lost weight. In a number of patients who did not have genital atrophy some recovery of menstruation occurred, though usually it was only at long and irregular intervals. He records almost complete recovery in three cases, two or three years after the significant delivery.

Sheehan states that there is nearly always a pronounced, and often a complete, recovery if the patient becomes pregnant again, and if the delivery of this pregnancy is normal the improvement is permanent. However, conditions which have caused haemorrhage in the earlier delivery are liable to recur and to lead again to serious collapse. He attributes the improvement to physiological hypertrophy of the remaining undamaged anterior pituitary tissue, such as normally occurs during a pregnancy, without subsequent regression to the previous (reduced) volume. A case of Sheehan and Murdoch illustrative of his views is cited in abbreviated form.

A woman had her first delivery at the age of twenty-two. It was complicated by retained placenta, severe haemorrhage, and extreme collapse. There was slight puerperal sepsis ; the breasts did not swell or lactate after delivery. Subsequently she had complete amenorrhoea, lost 20 lb. in weight, all her axillary hair fell out, she became very sensitive to cold, and too weak to work.

Despite the amenorrhoea she became pregnant again after nineteen months. At the second delivery the placenta had to be removed manually, but there was only slight haemorrhage and no collapse. She lactated for ten weeks, regained her weight, abnormal sensitivity to cold disappeared, she became able to do her work again, and menstruated slightly at irregular but decreasing intervals. A third pregnancy began thirteen months after birth of the second child, and delivery was similar to that of the second pregnancy. She lactated three weeks. Menstruation commenced three months post-partum and was thereafter regular and normal ; her general health was excellent. The fourth pregnancy commenced ten months later. At delivery manual removal of the placenta was necessary, and there was severe haemorrhage and collapse. She lactated three weeks, there was almost complete amenorrhoea, and her general health deteriorated. After seven months of ill-health she again became pregnant. In the third month her health began to improve and by the end of six months it was normal. In view of her history a Caesarian section was performed, and two months later she was in perfect health.

Anomalous Conditions. Osgood has reported a case of Simmonds'

disease, chinically characteristic, but which was found at autopsy to have an apparently normal pituitary. Escamilla and Lisser suggest that in such cases the anterior pituitary may be functionally at fault, and that such functional deficiency may not be revealed by present histological procedures. One hesitates to adopt this hypothesis without more stringent clinical criteria for Simmonds' disease.

Escamilla and Lisser also point out that a number of case-reports exist in the literature, in which autopsy revealed destruction of the pituitary, although during life there was no evidence of Simmonds' disease, and consider that this is inexplicable without the hypothesis of some aberrant pituitary tissue.

Diagnosis of Simmonds' Disease. This cannot be properly discussed until an account has been given of anorexia nervosa.

Anorexia Nervosa. Sir William Gull so named the malady in 1868, and pointed out its essential feature, a complete lack of appetite of which the underlying cause was a morbid mental state. In numerous recent papers the disease and its treatment have been dealt with at length, and in several a careful contrast is made with Simmonds' disease.

The disease is one of adolescence and early adult life. It is rare in men and married women. All writers agree that the outstanding feature of a fully developed case is emaciation. In young women, says Ryle, " a psychic trauma or a foolish habit, or some combination of the two, results in a loss of appetite and a suppression of the menses. Starvation follows and with the starvation an aggravation of the anorexia. Faced with these symptoms and increased emaciation, domestic anxiety and sometimes medical indecision still further complicating the situation, a young woman, recently healthy and happy, begins to cause alarm and to look like the victim of a famine privation." Patients have a definite psychoneurotic personality, and frequently a peculiar mental detachment and indifference. The morbid mental state may have a hereditary background ; it is usually associated with the emotional instability of adolescence and young adult life, and with such precipitating stimuli as broken engagements, school attachments, jealousies, unhappy home life, etc. It tends to be perpetuated by morbid pleasure in observing the effect of the illness on the patient's relations and friends, and the resulting sense of power.

The anorexia frequently leads to such a distaste for food as to result in vomiting after any food intake. Sometimes such vomiting is self-induced.

Loss of weight may be marked (to more than 50 lb.). The amenorrhoea is to be attributed to the psychic upset which is responsible for the anorexia, and may precede any appreciable loss

of weight. (However, McCullagh and Tupper think that emaciation is the primary factor in some cases.)

Besides the constant features of emaciation and amenorrhoea (in women) a number of other symptoms and findings are less constant, though frequent.

The basal metabolic rate is usually low, and frequently very low (to — 40 per cent.). Berkman suggests that the low level of metabolic activity, resulting from the starvation, is in itself a factor enabling the patient to survive such starvation for long periods. The mental and bodily activities of these patients are often remarkable, in comparison with the degree of emaciation, and in themselves contraindicate organic disease.

There is frequently a fine downy hairiness on cheeks, forearms, and back. This may be a result of the chronic starvation, as a similar phenomenon has been recorded by Curran as common in children during the severe Irish potato famine of 1845 (cf. Sheldon). On the face the hair is masculine in character, and on the abdomen it often shows male distribution.

The pulse is slow, the blood pressure low, the temperature subnormal. There is an occasional symptomless hypoglycaemia and a tendency to hypoacidity. Anaemia is rare.

Some patients with anorexia nervosa recover without special treatment. For some reason or other, often undetermined, they start to eat properly and get well (cf. Fig. 55). Others, with institutional care (and kept away from relatives) and firm suggestive treatment as to absence of organic disease and need of an adequate food intake, regain a normal appetite and recover. In extremer cases forced feeding may be needed. The rare case dies, through impossibility of controlling the patient and her diet, and complications such as tuberculosis. Such a case is shown in Fig. 56.

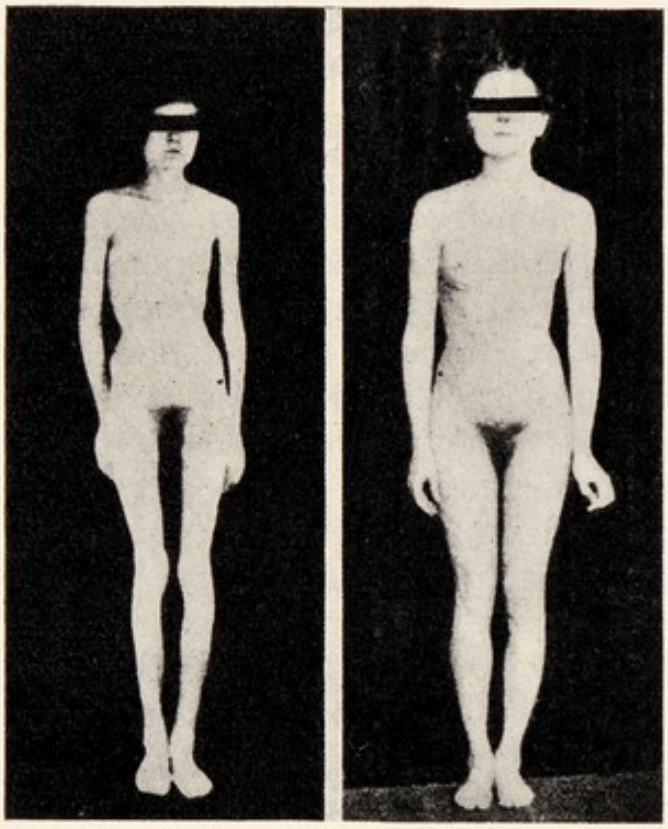
Many have undoubtedly been treated as cases of Simmonds' disease, subjected to various treatments including administration of pituitary hormone preparations, and then their improved condition or recovery has improperly enhanced the therapeutic reputation of such preparations.

Sometimes attempts have been made to stimulate appetite with thyroid or insulin. McCullagh and Tupper quite properly infer that if the hypometabolism in these cases is protective then thyroid therapy is contraindicated. Both they and Berkman believe that the value of insulin treatment is doubtful.

Bartels has presented the case records of sixteen young women, whose treatment consisted of psychotherapy and fattening.

Three did not improve, two only improved slightly, four improved considerably, and seven were cured.

The parallelism which does exist in some degree between anorexia and Simmonds' disease has suggested to some investigators that the pituitary may also be involved in anorexia nervosa. Sheldon considers that one effect of chronic starvation may be



A B

FIG. 55. Anorexia nervosa. *A*. Girl aged twenty, height 62 inches, weight 69 lb., loss of weight in ten months 31 lb. Spontaneous recovery (through becoming interested in music) in the next six months, with lost weight regained. *B*. Nine years later, height 62 inches, weight 95 lb., showing permanence of recovery. (From McCullagh and Tupper, Ann. Int. Med., 1940, xiv, 817.)

FIG. 56. Anorexia nervosa. Extremely advanced emaciation in a sixteen-year-old girl. At subsequent autopsy both pituitary and thyroid were found to be normal. (From Richardson, Arch. Int. Med., 1939, lxiii, 1.)

nervous inhibition of pituitary activity, and this idea receives some support from Breneman's experiments in which limitation of food intake suppressed body growth and testicular growth in male chicks, which he considered was intermediated through the pituitary. Magendantz and Prager have also discussed this question, and conclude that while endocrine factors may be among those which lead to the primary anorexia, the typical features of the disease may all be considered as physiological

responses to weight reduction and semi-starvation, without the pituitary being specifically involved.

Differential Diagnosis of Simmonds' Disease. The following table shows the salient differentiating features between Simmonds' disease and anorexia nervosa, and is based chiefly on the reviews of Escamilla and Lisser, and McCullagh and Tupper.

Comparison of Simmonds' Disease and Anorexia Nervosa

	Simmonds' Disease	*Anorexia Nervosa*	*Remarks*
Sex . . .	Commoner in women.	Much commoner in women.	Hence in men there is greater probability of Simmonds' disease.
Age-limits . .	17–70 and especially 20–60 years.	10–40 and especially 16–25 years.	The younger the woman the greater the probability of anorexia nervosa.
History . .	In women, history of severe haemorrhage in childbirth is frequent.	Association with pregnancy is very rare.	
Symptomatology :			
(*a*) Asthenia .	Pronounced but often late.	Less pronounced.	Unusual activity in an emaciated patient suggests anorexia nervosa.
(*b*) Anorexia .	May be present.	A characteristic of the disease.	Presence of anorexia does not rule out Simmonds' disease.
(*c*) Gastrointestinal symptoms.	Present in most cases.	Present in most cases.	
(*d*) Amenorrhoea in women.	An outstanding early phenomenon.	An outstanding early phenomenon.	
(*e*) Loss of libido and potence in men.	Noteworthy.	Not stressed in case reports.	
(*f*) Weight loss .	Marked.	Marked.	The average weight loss is about the same.
(*g*) Psychic changes	Present in most cases.	Characteristic of the disease.	
(*h*) Intolerance to cold.	Common.	Rare.	

Comparison of Simmonds' Disease and Anorexia Nervosa—contd.

	Simmonds' Disease	*Anorexia Nervosa*	*Remarks*
Physical signs :			
(*a*) Emaciation .	Present in the majority of cases.	Characteristic of the disease.	Sheehan considers that emaciation is not characteristic of mild Simmonds' disease.
(*b*) Premature senility.	Marked (especially in males).	Rare.	
(*c*) Genital atrophy and failure of secondary sex characters.	Common.	Common.	
(*d*) Atrophy of breasts in women.	Present in the majority of cases.	Absent until final stages.	
(*e*) Loss of axillary and pubic hair.	Frequent.	Less frequent.	
(*f*) Hirsutism .	Extremely rare.	Common.	
(*g*) Pallor . .	In about half the cases.	Absent.	
Neuropsychiatric findings.	Dull, poor memory, some intellectual impairment.	Often impulsive and alert mentally. Trend to hysteria.	
Laboratory findings, etc. :			
(*a*) Blood pressure	Tends to be slightly low.	Tends to be slightly low.	
(*b*) Temperature .	Sub-normal in many cases.	Less often sub-normal.	
(*c*) B.M.R. . .	Low.	Low.	
(*d*) Fasting blood sugar.	Frequently low.	Seldom low.	
(*e*) X-ray findings of sella turcica.	Abnormalities in nearly half the cases.	Normal.	Autopsy shows the pituitary in anorexia nervosa to be normal.

Obviously differentiation is most difficult in young women from adolescence to the age of twenty-five. For them Richardson's view holds, that a diagnosis of Simmonds' disease should not be made unless persistent attempts to diagnose and relieve a neurosis, and to increase food intake and ascertain its effect, have failed, in other words, unless anorexia nervosa can be ruled out. For male cases the converse probably holds, since in them anorexia is the rarer disease. On the other hand, one may conclude with Escamilla

and Lisser that "the occurrence of severe weight loss, amenorrhoea, and a low basal metabolic rate in a woman over thirty years of age whose symptoms date from a post-partum haemorrhage and collapse, or whose sella turcica is deformed or contains calcification, or who in the course of the disease loses axillary and pubic hair, warrants a clinical diagnosis of Simmonds' disease."

Differentiation of "pituitary myxoedema" from true myxoedema is assisted by failure of proper response to thyroid therapy. The emaciated case of Addison's disease may sometimes present difficulty, from its resemblance to the type of Simmonds' disease in which symptoms of adrenal insufficiency are prominent. However, the typical bronze pigmentation of Addison's disease is seldom seen in the latter, and the characteristic spotting of the mucous membrane has never been reported. Gastrointestinal complaints are more pronounced in Addison's disease, hypotension usually more severe, while the basal metabolic rate is not so low and hypogonadism less marked.

Fraser and Smith claim that two tests are particularly useful in diagnosing Simmonds' disease, the insulin tolerance test (cf. p. 172) and a urinary 17-ketosteroid assay (cf. p. 414); the curve of the insulin tolerance test shows an initial normal drop but a delayed return. Only the minority of cases of anorexia nervosa show such a curve, though it is given in cases of hyperinsulinism and Addison's disease. Cases of myxoedema show a slow initial fall. The excretion of 17-ketosteroids is generally nil in Simmonds' disease, low in myxoedema, and more nearly normal in anorexia nervosa. It is to be hoped that others will check these findings, which, if confirmed, may prove valuable.

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PITUITARY DWARFISM

The pituitary dwarf has a normally proportioned and symmetrical body. The features often give an appearance older than the true age, and sometimes termed progeric. Hands and feet are small, fingers narrow and tapering, hair soft and silky. Osseous development is usually retarded, the genitalia infantile, the secondary sex characters at most but partially developed. The basal metabolic rate is usually normal, or insignificantly low. In patients that reach adult age sterility and impotence are common, but death frequently occurs at an early age from some intercurrent infection. Since few of these patients come to autopsy the condition of the pituitary has usually to be guessed at. When the child is undersized from birth pituitary hypoplasia may be assumed. When retardation of growth only becomes evident later, perhaps following an acute infectious disease, pituitary damage seems more probable.

When the condition is present from birth it can conveniently be termed congenital pituitary dwarfism. When it arises later from a damaged pituitary the accepted term " Lorain-Levi syndrome " can be given it.

Since dwarfism is a dominant characteristic of such hypopituitarism, it is desirable to consider to what degree dwarfism *per se*, is indicative of pituitary hypofunction.

Dwarfism. Shelton (1942) has recently classified dwarfism and

infantilism on a basis of etiological factors, stressing the difference between growth and development, and stating that in his opinion the thyroid is more concerned with embryonal unfolding (differentiation, development) than with growth, and that for the pituitary the reverse is true, most of the developmental retardation in a primary pituitary condition resulting from secondary thyroid deficiency. His classification is as follows :

(i) The normal, small-statured person, and (an extremer type) the primordial dwarf are the result of inherent or constitutional factors.

(ii) Cases of achondroplasia, mongolism, and micromelic dwarfism (dwarfs with very short limbs) are the result of congenital disturbances of the skeleton.

(iii) Dwarfism may be traceable to anomalies of the circulatory and urinary systems, as in cases with congenital heart and kidney disease, angioplastic infantilism (due to defective development of the vascular system), and renal rickets.

(iv) Dwarfism may result from disturbances of nutrition arising in the following ways :

(*a*) Inadequate food intake (as in slow starvation), or inadequate vitamin or mineral intake (as in rickets and other deficiency diseases).

(*b*) Inadequate absorption of food material through disorders affecting the digestive enzymes, etc. (as in hypochlorhydria, coeliac disease, refractory rickets, and presence of intestinal nematodes).

(*d*) Inadequate utilization of the essential food materials through metabolic or endocrine disorders (as in hypothyroidism, hypopituitarism, and diabetes mellitus).

(v) Dwarfism associated with chronic infectious disorders (as tuberculosis or lues).

This classification severely limits endocrine factors of dwarfism, almost suggesting a minor *rôle*. Sevringhaus comments : " It is still possible that Shelton is too conservative in implying that the pituitary is not the mechanism by which other disturbances lead to reduced growth."

Congenital Pituitary Dwarfism. Probably the most classical case of this type, and certainly one that has been critically and repeatedly studied, was originally reported by Engelbach, and subsequently by Shelton (1934, 1942). The patient, a girl, exhibited from birth marked physical under-development and diminished appetite. During her first two years she was overweight. She could sit alone at six months, but did not walk

FIG. 57. Comparison of a pituitary dwarf girl at the age of 9½ years with a normal boy of the same age. (From Engelbach, Endocrinology, 1932, xvi, 11.)

until four years of age. Growth rate was retarded from the first year, and growth ceased after the sixth year. Her mentality was good, she was physically active, and relatively free from childhood illnesses.

At the age of nine and a half years her height was 35½ inches and her weight 27½ lb., her miniature stature being that of an average child of three and half years. The body measurements, however, were typically those of hypopituitarism (cf. Figs. 57 and 58). The head was large in proportion to the body; the sella turcica was normal for the size of the head.

She was given for eight and a half months injections of a purified preparation of pituitary growth hormone, freed from gonadotrophic hormones. In this period she grew 2·7 inches in height and gained 7½ lb. in weight, with corresponding increases in other measurements. Subsequently, treated for two years with a cruder extract of bovine pituitary, she grew 5·4 inches. Her facial expression altered towards the normal appearance of her years (cf. Fig. 59).

Shelton, writing in 1942, stated that this patient was then about twenty years old, "still very tiny although a full-fledged stenographer," and made the deliberate statement: "This is the only patient that I am convinced grew as a result of the administration of anterior pituitary extracts." Such a statement from an authority in this field carries great weight and must be remembered in considering other claims. Shelton considers that whenever

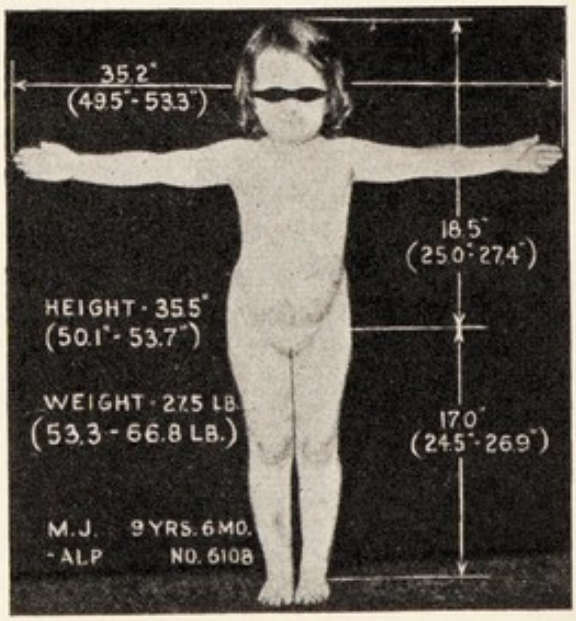

FIG. 58. Comparison of the actual body measurements of the pituitary dwarf of Fig. 57 with the normal maximum and minimum measurements for her age. (From Engelbach, Endocrinology, *loc. cit.*)

similar claims have been made for other cases of pituitary dwarfism, the patient has received other treatment (thyroid or vitamins and minerals, etc.) which may have been responsible for improvement.

Presumably of this congenital type is the "ateleiotic dwarf" reported by Hewer, a woman of seventy-six years, 47 inches high, with a female child aged forty, 5 feet high and mentally defective. At post-mortem the dwarf's pituitary weighed 0·31 gm. and was remarkably deficient in acidophile cells, thus resembling the pituitaries of (sterile) dwarf mice. Speck considers that such pituitary dwarfs are children of normal parents, and the females give birth to normal (not-dwarfed) babies, even if the father is also a pituitary dwarf, while, on the other hand, the female achondroplastic dwarf frequently, although not always, gives birth to an achondroplastic baby.

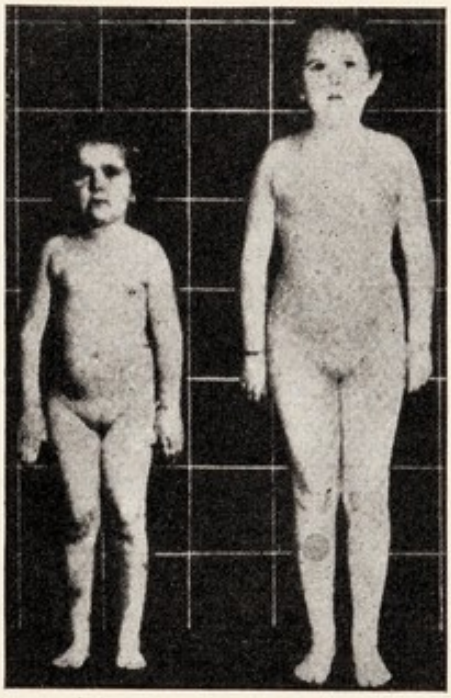

FIG. 59. J. M., pituitary dwarf. Received 3,639 c.c. (approximately 23 c.c. a week) of anterior pituitary extracts during a period of three years. Except for one very brief interlude no other treatment was given. (From Shelton, Endocrinology, 1942, xxx, 1003.)

The Lorain-Levi Syndrome. In 1908 Levi correlated the so-called "Lorain's infantilism," previously ascribed to malnutrition and hereditary influences, with pituitary disease, whence the name of the syndrome. The general features of the syndrome have already been described (p. 370). The degree of dwarfism depends on the time at which the pituitary is damaged. Obesity is usually absent.

Damage to the pituitary from infection can be assumed in some proportion of cases, but has seldom if ever been verified at post-mortem examination. Damage from tumour is a proved cause. Craniopharyngeal duct tumours seem to be the usual agent. Barker, reviewing the literature in 1933, stated that at least four cases had been thoroughly studied both clinically and at autopsy. These four give an idea of the variation in duration of life that can occur in this condition. At autopsy all four exhibited a craniopharyngeal duct tumour.

Altmann's case (reported in 1930) was a girl of seventeen, 129 cm. (51½ inches) in height, with ununited epiphyses. The anterior pituitary had undergone extreme atrophy from the effect of the tumour.

Berblinger's case (1932), a man dying at twenty-two years, was, at age fifteen, 135 cm. (54 inches) in height, and weighed 28½ kg. Between this time and his death he increased only 9 cm. in height and 6½ kg. in weight. He was of good intelligence. Besides the typical signs of pituitary dwarfism he also exhibited signs of intracranial neoplasm (headaches, vomiting, vertiginous attacks, diplopia, left adducens paralysis, and bilateral choked disc). X-ray examination showed a widened sella and above it some shadows due to calcification. Following death from pulmonary and intestinal tuberculosis, the tumour was found to replace the stalk of the pituitary, destroying the pars tuberalis, and flattening the anterior lobe.

Erdmann's case (1916) was a man of thirty-eight, 142 cm. (57 inches) in height, with infantile genitalia, absence of secondary sex characters, and ununited epiphyses. At autopsy a relatively benign tumour, evidently present for a long period, was found to have destroyed most of the anterior pituitary.

Priesel's case (1920) was of a man 132 cm. (51 inches) high, whose growth inhibition was noticeable at the age of fifteen, although he lived to the age of ninety-one. He was a proportional infantile dwarf of good intelligence. The epiphyses had all become united. The anterior lobe of the pituitary was rudimentary, being almost entirely replaced by a cyst, which communicated with a widened portion of a persistent craniopharyngeal duct.

Cushing, dealing with the general effect of craniopharyngiomas, stated that the most striking symptoms are seen in patients in the first and second decades, in whom there is delayed growth or actual dwarfism and retarded maturity or persistence of actual infantilism. Most of these young patients are well-nourished, some may be obese, but others are thin or actually emaciated, suggesting a developing cachexia.

One of the rare cases exhibiting marked cachexia was recently reported by Conley. A six-and-a-half-year-old girl suffered from headache, vomiting, somnolence, and rapid loss of weight, and subsequently developed blindness. Her weight at death was only 21¼ lb., her height just under 40 inches, the dwarfism proportionate. At autopsy a craniopharyngioma (adamantinoma of the craniopharyngeal duct) was found, which had invaded the posterior and compressed the anterior lobe of the pituitary.

Such tumours will obviously produce results varying with the extent of (i) damage to the anterior pituitary, and (ii) damage to neighbouring tissues. The latter is responsible for the occurrence of headache, blindness, and obesity, when any of these are present.

Lurie claims that the pituitary dwarf is mentally alert and tends to be aggressive, while by contrast the child exhibiting Fröhlich's syndrome is gentle, timid, and phlegmatic.

A type of pituitary dwarfism or near-dwarfism is associated with an abnormally small, roofed-in sella turcica. Patients exhibit growth and sexual under-development, and a prematurely old appearance, and have a low basal metabolic rate (Bell).

The mixture of infantilism and senility termed *progeria* is possibly a variation of the Lorain-Levi syndrome, though Talbot *et al.* suggest that a progeric patient studied by them was suffering from a metabolic disturbance characterized by an excessive utilization of calories for energy metabolism (which did not appear to be due to hyperthyroidism), so that nothing was left for growth or accumulation of subcutaneous fat.

Treatment. The (limited) beneficial effect of pituitary growth hormone in Shelton's case has been referred to. Schaefer in 1940 reported that 14 out of 18 pituitary dwarfs responded to treatment with the pituitary growth factor, the criteria being (i) a greater increase in height than the normal increment during treatment, and (ii) a smaller increase in height than the normal increment during periods without treatment. His figures show, however, that the usual increases are very small; the best response was in a patient who grew 4·6 inches in twenty-three months under treatment (normal increment estimated as 1·8 inches), and, without treatment, 0·1 inch in eight months (estimated normal increment 0·4 inch).

It is evident that pituitary growth preparations can, in some cases, produce slight growth, but it seems certain that the growth factor, alone, will never restore a pituitary dwarf to anything resembling normal height. Normally pituitary control involves development as well as growth and the effects of the combines pituitary hormone output on thyroid, gonads, adrenals, and somatic development produce a harmonious result, of which normal growth is but one aspect. Disintegration of these stimuli cannot be expected to conduce to production of a normal person. Yet additional stimulus by gonadotrophic hormones or gonadogens may affect growth by hastening closure of the epiphyses.

Nevertheless Schaefer considers that at the stage when sex maturation is definitely becoming delayed this should be treated primarily, even if a moderate degree of under-development result. In this connection chorionic gonadotrophin probably has a useful place in treatment (Dorff), perhaps allied with gonadogen, or, for male dwarfs, testosterone (McCullagh).

The pituitary dwarf does not respond to thyroid treatment, for

he very seldom shows the presence of a secondary hypothyroidism (cf. Schaefer).

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Pituitary Dwarfism with Atrophic Rhinitis. Mortimer and his colleagues from prolonged roentgenographic studies of crania in hypophysectomized dogs and rats have suggested that in human cases of hyperplasia or hypoplasia of the paranasal sinuses among the causal conditions may be (i) transmitted inherent pituitary disability or (ii) disturbed pituitary function arising during post-natal growth or, possibly, a late manifestation of (i).

Mortimer, Wright and Collip studied a French Canadian family in whom both parents and all nine children (seven female) suffered from atrophic rhinitis. Judged by cranial skiagrams, none of the family showed a normal skull. The elder son showed well marked acromegalic changes, while the two youngest girls showed pituitary dwarfism. The four female members of the family between eleven and twenty years showed in the crania evidence of early hypopituitarism, and two suffered from amenorrhoea. Good results were obtained in two of these cases by treating the rhinitis by local application of oestrogen in corn oil, the other two serving as controls.

Bronstein and Fabricant describe the case of a twelve-year-old girl, 45¼ inches in height and 46 lb. in weight. She exhibited atrophic rhinitis, infantilism, retarded bone development, a sella turcica slightly larger than usual, and with a roughly circular deposit of calcium compounds. They make some rather doubtful claims for beneficial effect of pituitary growth preparations on the growth of this child. The treatment had no effect on the rhinitis.

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Unusual Pituitary Syndrome(s). Turner in 1938 described a syndrome occurring only in girls, and combining infantilism, webbing of the skin of the neck, and deformity of the elbow (cubitus valgus), and reported seven cases varying in age from fifteen to twenty-three years. Retardation of growth and sexual underdevelopment were marked, the webbing of the skin of the neck slight to marked. An apparent shortening of the neck was not real but due to the webbing. The posterior hair margin extended well down on the neck. The increase in carrying angle of the elbow was constantly present. The patients showed no mental retardation. Treatment with pituitary growth hormones was unsatisfactory, though in two cases administration of anterior pituitary gonadotrophins produced definite genital development. According to Moffat six other cases exhibiting the complete triad have since been reported ; he has recently described a seventh.

One case of a similar syndrome was described by Shereshevski in 1925 ; in 1944 he reported five more cases of his own and recorded another described by Slonimski in 1928. These cases, varying in age from eight to twenty-one years, all females, all exhibited uniform retardation of growth, hypogenitalism with absence of mammary glands and of secondary sex characteristics, facial expression older than given age, short neck with skin folds extending from base of skull to shoulders and lending the face immobility (though the photographs of his cases suggest that in some the shortness may be illusory), hirsutism of the entire neck posteriorly, high palate, defective teeth, deformity of helices, and of fingers and toes. Mentality was usually normal ; basal metabolism was normal. Shereshevski suggests that the syndrome is of obscure endocrine origin, with pituitary dwarfism and infantilism secondary to pineal dysfunction.

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FRÖHLICH'S SYNDROME AND OTHER DISEASE CONDITIONS

Fröhlich's Syndrome. Babinski in 1900 reported the case of a girl with obesity, sexual immaturity, and an intracranial expanding lesion in the region of the sella turcica.

Fröhlich's case, type of the syndrome named after him, was reported in 1901, and the report has recently been translated into English by Bruch (1939).

R. D., male, born in 1887, was apparently normal and healthy until twelve years of age, when he commenced to develop severe frontal headaches, usually left-sided, sometimes bilateral, and followed by vomiting. His intelligence was normal, his eyesight good. In the following two years this previously slim boy gained weight rapidly, and, latterly, the

eyesight of the left eye had steadily diminished to complete blindness. Headaches and vomiting had recurred, while the vision of the right eye commenced to fail. The boy tired easily.

Treatment with thyroid led to subjective improvement, some loss of weight, fewer headaches, some improvement of vision of the right eye. The results of a general examination were—except as already noted—negative. The body-weight at this time was 54 kg. considered as 36 per cent. overweight. The height was not recorded and was apparently normal for the age. Fröhlich emphasized the simultaneous development of the adiposity with the other symptoms. The fat distribution was particularly on the abdomen and in the neighbourhood of the genitals ; fingers were plump. Penis and testes were small but normal. Axillary hair was absent, pubic hair very sparse.

Fröhlich diagnosed a neoplasm in the region of the pituitary, and, later, of the pituitary. Subsequently the degree of obesity did not change significantly, and the boy did not develop sexually. Four years later his general condition grew worse. Two years later, the boy then being twenty years of age, an X-ray of the skull showed destruction of the sphenoid and the dorsum sellae, but not of the anterior clinoid processes. His general appearance was still infantile feminine.

von Eiselsberg operated in 1907 by the nasal route and removed a cyst of the size of a hazel nut, which was thought to correspond to the pituitary. Histological examination suggested an adenoma of the pituitary. Following the operation there was general improvement, with fewer headaches and improved eyesight. A year later headaches and dizziness had ceased. Slight sexual development had taken place as shown by hair growth and occurrence of erections.

Biedl reported on this patient in 1913. The general improvement had persisted but had not increased. He continued to be of infantile habitus and obese. None of the several reports on him suggest the presence of diabetes insipidus.

Thus the type case of Fröhlich's syndrome presents a concurrent onset of diminution of vision (leading to blindness of one eye), infantilism, and obesity associated with a tumour either of the pituitary or of the region of the pituitary. There was no dwarfism.

Bruch reviews the subsequent literature, referring particularly to the fact that Erdheim (1904, 1916), Bartels (1906)—who coined the synonym "dystrophia adiposo-genitalis,"—von Eiselsberg and von Frankl-Hochwart (1907, 1908), and Fulton and Bailey (1929), all favoured the view that while pituitary tumours might be associated with obesity, such obesity should not be considered as due to pituitary damage but rather to a lesion of the neighbouring hypothalamus, possibly due to a pituitary tumour, but also possibly due to an extrasellar tumour.

The accurate experimental work of Smith, confirming similar earlier work, completely supports this view. He showed that hypophysectomy in the rat inhibits growth in the young animal and leads to atrophy of the genital system, the thyroid, and the

adrenal cortex, but does not produce obesity, whereas injury to the hypothalamic region of the brain is characterized by resulting marked obesity and genital atrophy, without affecting the thyroid or adrenal cortex, and without invariably producing dwarfism.

The true cases of Fröhlich's syndrome exhibit, if males, unnatural obesity, the deposits of fat resembling those of the female and producing large hips, breasts, and mons veneris. The genitalia remain undeveloped, the testes may remain undescended, the secondary sex characters do not develop. Females exhibit marked obesity. In neither sex is there sex feeling or activity. The skin is soft, pale, fine and hairless except for the scalp ; scalp hair is fine and silky. The epiphyses sometimes remain ununited. The hands are small, fat, and with tapering fingers (Rynearson and Kepler).

It has become common to interpret Fröhlich's syndrome too liberally, and to include in it obese children without a brain tumour, and with somewhat delayed puberty. They have been frequently treated with chorionic gonadotrophin, have improved, and the improvement credited to the treatment. Werner could find no evidence of endocrine disturbance in ten such children, one of whom was not in puberty even at fifteen years of age. He gave them no treatment, except a dietary regimen ; all subsequently went through a normal puberty. He considers that children of this type should not be given endocrine therapy unless they have not matured at sixteen years of age.

Bronstein and his colleagues examined thirty-five obese children of this type and could find no endocrine basis for the obesity. They state : " It may be emphasized that in the absence of any physical defects the adiposity of these children was probably contributed to by their sedentary habits, their abnormal appetite, parental attitudes, and other environmental factors." Bruch's comments are also pertinent. " Fat people, especially the fat parents of fat children, are not inclined to give accurate information about their food intake. . . . A large appetite is so commonly considered an expression of good health that it is not mentioned as a complaint."

Rynearson and Kepler sum up the whole matter forcibly : " Too many patients are being given the diagnosis of Fröhlich's syndrome. . . . It is rather a rare condition, and every fat boy with delayed development does not have a craniopharyngioma which is destroying his pituitary. If let alone, most of these fat boys ' straighten out ' themselves, and many of the ' cures ' reported following the use of endocrine preparations probably would have

occurred if no treatment had been given. We have seen many instances in which treatment was delayed for six months or a year and complete restoration to normalcy occurred. If treatment had been used during this period another report of cure might have been published. Operation on the pituitary should be advised only when *definite evidence of a tumour* exists and usually then only when the *visual* fields are being affected."

Dr. Lennox Bell informs me that the most typically appearing example of Fröhlich's syndrome he has ever seen—at the age of thirteen—with no treatment became at the age of twenty-two a magnificent specimen of manhood, 6 feet 4 inches tall. He states, " If I'd treated him with pituitary extracts, as I planned to do, I would be bursting into print claiming to have produced a giant."

Chromophobe Adenomata of the Anterior Pituitary. Ophthalmologists and gynaecologists first drew attention to a syndrome in which X-ray examination showed an expanded sella in absence of acromegaly. Women with unaccountable amenorrhoea not infrequently complained of disturbance of vision ; examination often gave indication of pressure against the optic chiasm. Men showed, along with the visual disturbance, some degree of gonadal involvement. Cushing has termed the condition " pituitary goitre." Unless it were relieved blindness might ensue. The tumours were found to be of chromophobe tissue of the anterior pituitary. Their symptomatic effects were produced by pressure. Pressure within the sella inhibited the basophile elements and gonadal disturbances resulted. Pressure on the optic chiasm, if the tumour were of sufficient size, affected vision. Successful surgical intervention restored both sight and sexual function (Cushing, Henderson). Careful X-ray therapy sometimes has given good results (Hare and Dyke).

The ocular signs involved through such pressure include perimeter defects and optic disc changes, diplopia and strabismus. The general intercranial pressure signs include deep-seated headache, projectile vomiting, choked disc and photophobia.

Patients with chromophobe adenomata usually exhibit a lowered basal metabolic rate (Cushing and Davidoff).

Cushing considered that chromophobe adenomas are rare in childhood. He reported a case of combined craniopharyngioma and chromophobe adenoma which had been under his observation for eight years. The girl was first operated on at the age of ten, and both tumours removed. Prior to operation the basal metabolic rate was — 36 per cent. ; subsequently it rose to — 24 per cent. Six years later, at second operation in 1930, more adenoma was removed. A year later the basal rate was — 19 per cent. In 1932 replacement therapy was attempted, with

the growth principle. Appetite was improved and there was gain in weight, but at the end of 110 days there had been no gain in height. Treatment was stopped and the patient retrogressed.

It is obvious that Fröhlich's syndrome in the young and the condition associated with chromophobe adenomas of the pituitary in adults have several common features resulting from extrasellar pressure effects.

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The Laurence-Moon-Biedl Syndrome. This was first described by Laurence and Moon in 1866. Bardet added to the description in 1920, but Biedl in 1922 was the first to describe the complete syndrome. Valuable reviews have been published recently by Radner (1940) and McCullagh and Ryan (1941). According to Radner about 200 cases had been reported to 1940, but Schwartz and Boudreau (quoted by McCullagh and Ryan) list only 129 to the middle of that year.

In every case of the syndrome most of the following characteristic conditions are present : (i) mental weakness, (ii) pigmentary degeneration of the retina, leading to blindness usually by the fifteenth year, (iii) adiposo-genital dystrophy (whence the association with Fröhlich's syndrome), (iv) familial occurrence, and (v) polydactylia or syndactylia. Only a minority of cases exhibit all five of these conditions. Thus Reilly and Lisser, reviewing the known cases in 1932, found the complete syndrome present in only 25 of 77 cases. Other anomalies may be present, as nystagmus, atresia ani, deafness, etc.

The pathogenesis is still incompletely understood. In a fairly recent study Hecker and Warren concluded that the mental deficiency is of primary importance and a result of defective germ plasm, other changes being secondary through involvement of the hypothalamus, and, indirectly, the pituitary, though poly-

dactylism or other skeletal defects are considered also to be primary manifestations of defective germ plasm.

McCullagh and Ryan report a family of five children, all boys, one normal, but four exhibiting the syndrome, complete except for the polydactylism. The parents were first cousins, but there was no history of blindness or obesity in them or previous generations.

Radner reported a very interesting family. The eldest child, female, exhibited polydactylism and atresia ani only. The second child, male, was normal. The third, female, showed the complete syndrome, with uterus duplex. The fourth, male, was normal, married, and had a normal daughter. The fifth, female, showed the complete syndrome. X-ray examination of the skull of this patient showed a normal-sized, but bridged-over sella turcica. The sixth, male, exhibited polydactylia, but died at the age of nine months.

Cockayne *et al.*, and Ellis and Law point out that the retinitis pigmentosa in these cases is almost always atypical, and the latter suggest that the eye condition might be more suitably named.

Treatment is unsatisfactory. Endocrine therapy does not improve vision or mentality (Scott and Johnson). McCullagh and Ryan consider that the persistent use of thyroid is of some benefit.

Up till 1941 only six autopsies had been reported, of which two were very incomplete. Anderson, reporting the last autopsy, pointed out that three of the six showed pituitary abnormalities, and in two (the only two apparently so examined) there was a striking predominance of basophile cells in the anterior lobe, his own case showing, by Severinghaus' technique, 42 per cent. basophile, 36 per cent. acidophile, and only 22 per cent. chromophobe. (Yet such predominance of basophile cells does not produce a condition resembling Cushing's disease.)

Jaso and Carbelo describe 3 cases of "monstrous infantile obesity," two girls and a boy of a family of 7 (the others being normal) who were considered to exhibit the syndrome. Evidence was adduced that the obesity was a recessive inherited factor. Polydactilism and syndactilism were absent. It was considered that the pituitary played a *rôle* in the etiology.

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CHAPTER XI

GIGANTISM AND ACROMEGALY

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INTRODUCTION

Both gigantism and acromegaly are associated with hyperfunction of the acidophile cells of the anterior lobe of the pituitary. When such hyperfunction is present from birth, or commences in early life, a giant results. When it only arises after closure of the epiphyses, then the distorted acromegalic results. Its onset during the later stages of normal growth produces the intermediate acromegalic giant.

GIGANTISM

The pituitary giant is, in most respects, the opposite of the pituitary dwarf, and his over-development is symmetrical, giving a proportionate body just as is that of the dwarf (cf. Gunther). In gigantism the hyperactivity of the acidophile cells is generally, perhaps always, due not to tumours of these cells, but to hyperplasia.

One of the most accurately documented cases of gigantism has been reported, first by Behrens and Barr in 1932, and subsequently by Humberd in 1937.

R. W. was the eldest son of a family whose history, as far as known, showed no marked tallness in any of its members, and no endocrine disorders. His father's height is 5 feet 11 inches, his mother is of medium height and weight. Two younger brothers and two younger sisters are all of normal size. When first examined he was just under twelve years of age. Behrens and Barr reported : " At birth he weighed only 9 lb., but began to grow at an abnormal rate. At six months he weighed 30 lb. . . . He started to walk at the age of twelve months. At a year and a half he weighed 62 lb., and by the time he was two years old his extraordinary size attracted general attention. At six he entered school in a suit which was the largest his father could buy for a boy, and which was labelled size 17. When he was nine he measured 6 feet 1 inch, weighed 178 lb., and was able to pick his father up and carry him about." He suffered from a moderate myopia, causing headaches which disappeared when the myopia was corrected by glasses. His water intake was large, but there was no evidence of the polyuria of diabetes insipidus. " His appetite was vigorous. . . . His record in school had been excellent. . . ."

" His expression and appearance are best shown by the photographs. Notable is the wide spacing between the eyes and the complete absence of mandibular prognathism. There is some spreading of the upper teeth. The skin was moist, delicate, and of fine texture, but the hands

FIG. 60. A case of pituitary gigantism. Front view and profile of the patient at the age of 11, showing characteristic facies of preadolescent hyperpituitarism and complete absence of mandibular prognathism. (From Behrens and Barr, Endocrinology, 1932, xvi, 121.)

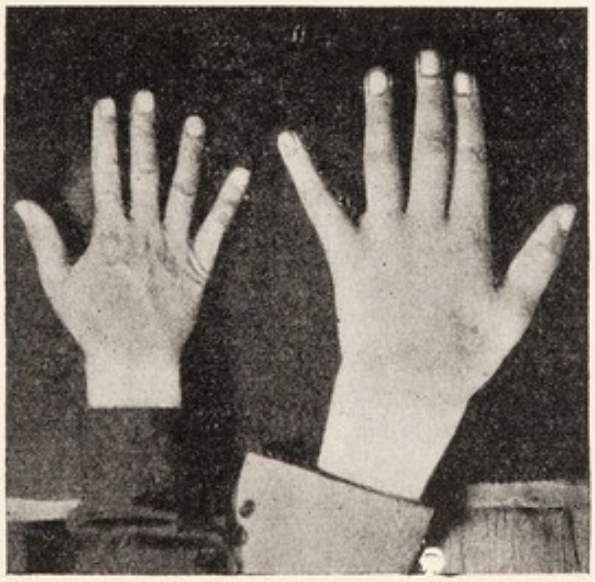

FIG. 61. Hand of patient (Fig. 60) compared with that of a man 6 feet in height. Noteworthy are the long, lightly tapering fingers and the delicate, fine skin. (From Behrens and Barr, *ibid.*, p. 124.)

and feet tended to be cold and slightly cyanotic. He had no hair on his face, and the hair on his body was scanty. His father reported that he had a small amount of pubic hair, and the genitalia might be considered small for an eleven-year-old boy."

" The visual field was practically normal. The heart, lungs, and abdomen were normal. Hands and feet were beautifully shaped in

spite of their size. Many of the essential points of the description are illustrated in Figs. 60 to 63.

"The X-ray examination revealed in the bones of the face and

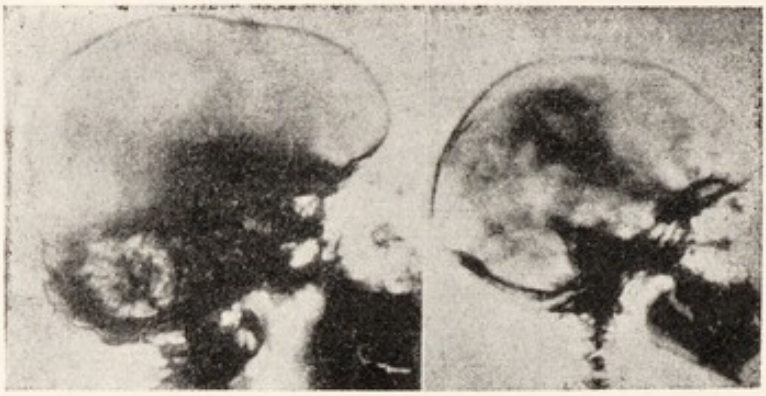

FIG. 62. X-ray photograph of skull of patient (Fig. 60) at age of eleven, compared with that of a normal boy of the same age. There is an extraordinary development of the mastoid air cells. The sella turcica measured 2·5 cm. anterior-posteriorly; it has been outlined with dots to indicate its extent. (From Behrens and Barr, *ibid.*, p. 122.)

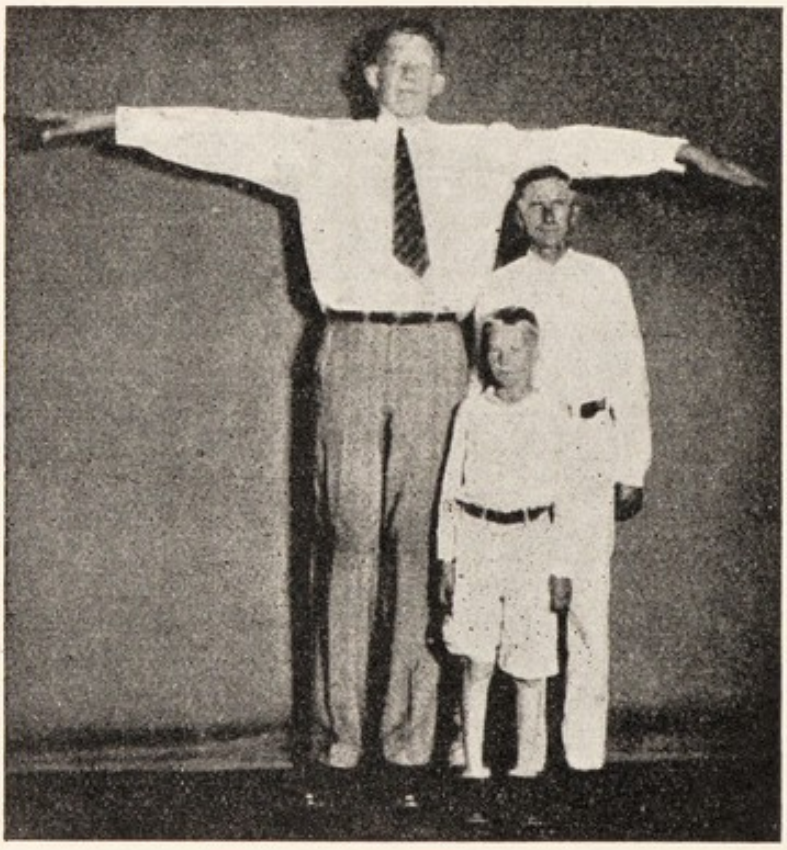

FIG. 63. The patient at the age of 13½, shown standing with his nine-year-old brother, and his father, whose height is 5 feet 11 inches. (From Behrens and Barr, *ibid.*, p. 125.)

maxilla a moderate tendency to prognathic development. The mastoids showed extraordinary development of pneumatic structure. . . . The sella was of extreme size, measuring 2·5 cm. in its anterior-posterior

diameter. The floor of the sella showed a loss of continuity, being broken by a tubular structure which extended downward and forward from the sella and reached almost to the posterior wall of the pharynx, where there was an indefinite soft tissue shadow encroaching upon the lumen of the pharynx itself." It was thought that there was evidence of a persistent Rathke's pouch. X-ray photographs of the hands showed no abnormality in the state of the epiphyses or degree of calcification, as compared with a normal boy of the same age.

He was seen again at the time of his thirteenth birthday. Measurements at the two examinations were :

Age.	11 Yrs. 11 Mos.	13 Yrs.
Weight . . .	112·3 kg.	126·4 kg.
Height (bare feet) .	208·0 cm.	219·0 cm.
Sitting height . .	103·5 ,,	—
Arm spread . .	203·5 ,,	215·0 cm.
Head circumference .	65·5 ,,	—
Chest circumference .	104·5 ,,	107·5 cm.
Length of hand . .	22·0 ,,	23·5 ,,
Length of foot . .	37·0 ,,	38·5 ,,

Fig. 63 pictures the boy at thirteen and a half, with a height of 88½ inches. At this time blood and urine examinations gave normal results, a partial sugar tolerance test was normal, and oxygen consumption was low. " Except for the enormous size of the sella turcica, local signs of pituitary involvement are almost entirely absent. . . . It is extremely difficult to judge whether there is in this patient any retardation of sexual development."

Humberd reported that at the age of eighteen years and three months his height had increased to 99¼ inches. Humberd noted that all sensations (touch, pain, temperature) were void and blank below the ankles, and the loss of pain and temperature senses affected also the middle third of the lower leg. The patient was unaware of a wrinkle in his sock or a foreign body inside his shoe until a blister formed, followed by an ulcer, the general symptoms of a systemic reaction from this arousing him to its presence, and sometimes needing hospital treatment.

He continued to grow steadily till his death at the age of twenty-two, apparently following a foot infection.

Engelbach reported a case in which there was definite hyperfunction of the acidophile cells, and possible hyperfunction of the basophile cells as well. The man, aged twenty-five at examination, weighed 11 lb. at birth. Following a febrile attack at seven months he commenced to grow rapidly, with corresponding strength. At seven years of age his height was that of an adult man. His mentality was normal. Puberty occurred between the ages of nine and ten, at which period he associated with young men of nineteen and twenty and could do a man's work at manual

labour. At thirteen he was known as the strongest man in Holland; his muscular development was supernormal, and he could support a 175-lb. man on each outstretched arm. He continued to grow larger with increasing vigour until the age of nineteen, and an extreme libido began to be manifested. At twenty-three he weighed 312 lb. During the following two-and-a-half years his weight dropped to 243 lb. His height was then 92·2 inches. With the loss of weight he exhibited a progressive loss of strength and diminution in size of the muscles. Occasional frontal headaches occurred and he began to exhibit a slight pigmentation. Libido decreased, without impotency.

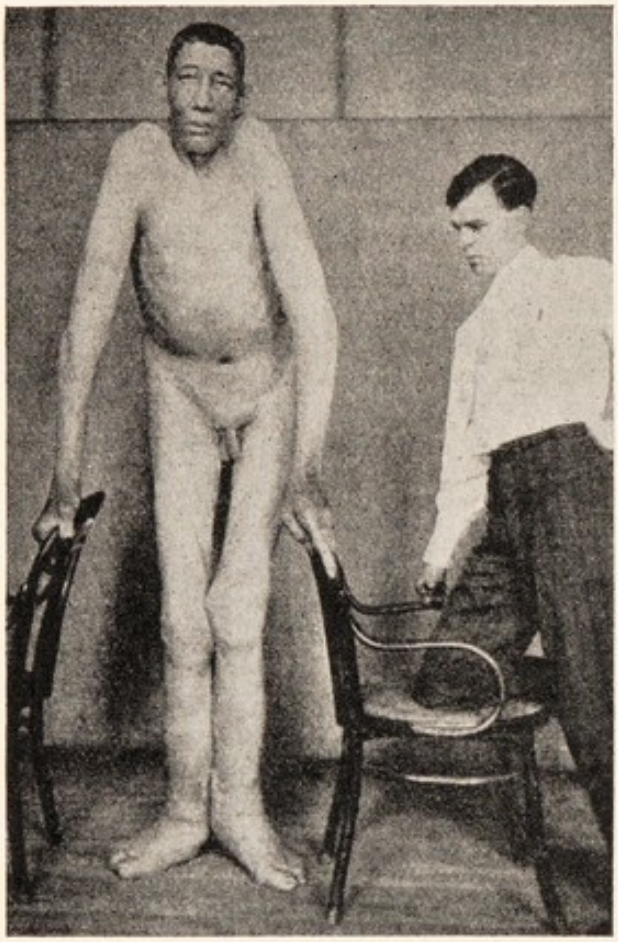

FIG. 64. A case of gigantism. Final stage. Note the narrow chest, large joints, hypotrichosis, and the large size of the hands compared with that of the normal person of height 68 inches. (From Cushing, "The Pituitary Body and its Disorders," Lippincott, 1912, Case XXXII.)

The sella turcica showed no evidence of proliferation or erosion, measuring 13 × 12 mm. The urine showed a faint trace of albumin. The blood cell count and basal metabolic rate was normal, the Wassermann test 4 +. Engelbach considered that the change from hyper- to hypoactivity might be associated with acquired syphilis.

With these two cases may well be contrasted the classical example described by Cushing (1912), a man aged thirty-six, "an extraordinary prototype of the folk-lore giant—overcome by his own size." His appearance is shown in Figs. 64 and 65. His family and personal history reveal little of importance except that his overgrowth dated from childhood, when his size was such an embarrassment to him that he played truant from school and never learned to read or write. His growth became rapid at fifteen years of age, at which time frontal headaches were frequent. His health began to fail when he was twenty-six. His weight at

examination was 275 lb., and his height stated to be 8 feet 3 inches. His complexion at that time was a peculiar greyish-white. There was no definite polyuria, but a slight albuminuria. Temperature and pulse tended to be subnormal. The eyes were normal.

Though without education, he was shrewd, competent, and independent. There were no motor or sensory changes, but extreme muscular enfeeblement. His skin was soft and pliable, with marked hypotrichosis. He had practically no beard, absolutely no axillary hair, and very scant pubic hair. There was considerable pigmentation.

There was no disproportionate hypertrophy of the tongue as in

FIG. 65. The same patient as in Fig. 64. Exhibiting a maxillary, rather than the mandibular prognathism of the acromegalic. (From Cushing, *loc. cit.*)

acromegaly. The genitalia were small, and the testes atrophic. There had never been any temptation to sexual indulgence.

The skeletal framework was enormous. Bony deformation about the joints caused bending at the knees and hips (cf. Fig. 64). The lower extremities gave the appearance of elephantiasis. His gait was feeble and he required the use of two heavy canes.

The overgrowth of the skull was restricted for the most part to the facial bones. The mastoids were huge; the malar bones projected. The facial prognathism involved the maxillary rather than the mandibular jaw (cf. Fig. 65). X-ray of the skull showed a relatively shallow sella turcica, anterior-posterior 2·7 cm., 1·7 cm. in depth. There were huge maxillary and frontal sinuses.

He exhibited a high carbohydrate tolerance.

He died six months later. Autopsy showed diminutive adrenals,

fibrosed testes with almost complete disappearance of spermatogenous cells, and a small and fibrosed pancreas. The pituitary gland was largely represented by a cyst, and Cushing commented : " As regards the hypophysis itself, it is fair to assume that there was originally an extreme functional hyperplasia of the pars anterior with subsequent cystic degeneration."

Humberd (1936) has critically reviewed the heights attributed to various giants in the older literature. While the majority have been probably below 8 feet, some have definitely exceeded this figure. These giants are usually believed to die young and childless. An occasional one reaches middle age. The giant Chang is said to have died at fifty-one, and Palozzi at sixty-six (cf. Cushing, 1912).

A possibility of successful treatment is seen in results quoted by Cushing (1933). In two boys showing giant-like rapidity of growth the growth-curves were arrested by X-ray treatment of the pituitary. Currier *et al.* considered that they had slightly decreased the growth rate of a young giant (eleven years old, 70 inches high) by administering testosterone propionate (5 mg. every fourth day) for 416 out of a 522-day period. During this time he grew $3\frac{1}{4}$ inches. Their results are suggestive but not conclusive.

ACROMEGALY

The condition of acromegaly has been often described, is easily recognized, and never forgotten when once seen. Goldberg and Lisser (1942 *b*) write : " This bizarre malady is not only rare, but it is also impressive in its manifestations, protean in its symptomatology, and kaleidoscopic in its involvement of more tissues and organs than almost any other disease. The onset is likely to be insidious ; the course usually is chronic and of long duration and is marked by successive waves of remission and exacerbation. These characteristics combine to render difficult the clear evaluation of the findings in a single case, and, even more so, of the efficacy of any specific form of treatment. . . . Even the post-mortem observations may be misleading unless a correlation has been established between them and the clinical status at the time of death."

They stated that the total number of cases in the literature to that time was 1,606 (cf. Atkinson). At the Boston City Hospital, in the six-year period 1930–35, there were 14 cases in 210,094 entries (1 in 15,000), while in the University of California hospital in the five-year period 1937–41 there were 12 cases in 35,757

entries (1 in 3,000). The earlier figure is probably close to the true general incidence in a hospital population.

The slow onset of acromegaly is characterized by gradual enlargement of the limbs and head. The face, hands, and feet slowly hypertrophy. The gradual onset of the facial hypertrophy is beautifully shown in the photographs of Cushing's case XXX (1912), reproduced in Fig. 66. The enlargement affects the skeleton generally, as far as that can be enlarged ; the connective tissues become thickened and hypertrophied. The lower jaw becomes prominent, the face lengthens and broadens and the features coarsen ; the tongue enlarges. Some initial degree of hypertrichosis is gradually transformed to a hypotrichosis. As the disease progresses, amenorrhoea in the female and impotence

I. II. III. IV.

FIG. 66. A case of acromegaly. I. Photograph at the age of 24, before onset of the disease. II. Aged 29, at time of onset. III. Aged 37. IV. Aged 42, with pronounced acromegalic changes. (From Cushing, "The Pituitary Body and its Disorders," Lippincott, 1912, Case XXX.)

in the male become distinctive features. Deep-seated headache is a frequent early symptom. The organs usually enlarge, especially the heart. X-ray examination generally indicates an enlargement of the sella turcica, although in the case presented in Fig. 66 such enlargement was not present.

There may be some degree of gigantism, depending on the age of onset. If this is not till after adolescence, when the epiphyseal cartilages are ossified, the long bones cannot grow longer and height is but little affected.

The acromegalic frequently exhibits glycosuria, through a lowered carbohydrate tolerance. The combination of acromegaly and diabetes mellitus is not uncommon, due to increased output of the pituitary hormone with anti-insulin effect. The basal metabolism tends to be raised, suggesting that in some proportion of acromegalics an increased production of thyrotrophic hormone unduly stimulates the thyroid.

Davis has reviewed the findings on the thyroid gland in 166 cases of acromegaly at the Mayo Clinic (87 females, 79 males) and found it enlarged in 86 cases, in 53 of which it contained adenomata. The basal metabolic rate had been determined in 135 cases. In one it was below — 20 per cent., and in 4 between — 11 and — 20. In 27 it was between + 10 and + 19, and in 44 between + 20 and + 79 per cent.

Thyroidectomy had been performed in 27 of these cases, all showing an elevated basal rate. Davis notes that the surgical risk is greater than usual, and while there was generally some fall in the basal rate following operation, it was less consistent than following operation for uncomplicated hyperthyroidism.

At autopsy the acromegalic usually presents an adenoma of the acidophile cells of the anterior pituitary—sometimes even the size of an orange. Such a pathology completely accounts for his condition. This functioning adenoma provides that excess of growth principle necessary to produce such degree of over-development as was possible at the time of commencement of the adenomatous growth. Pressure of this tumour on the basophile cells of the pituitary causes that depression of stimuli to the gonads which results in amenorrhoea, impotence, and depression of secondary sex characters.

Rare instances of acromegaly have been reported in which the condition was associated solely with functional hyperplasia, tumour being absent (Lewis, Krumbhaar).

In the " burnt-out " acromegalic, presumably the tumour causing hyperpituitary effects has degenerated, and a hypopituitary stage supervenes, giving a mixed syndrome. One of its unusual features is an occasional extreme degree of muscular atrophy, almost resembling progressive muscular atrophy, and suggestive of an analogy with the cachexia of Simmonds' disease. The patient has the added disability of dragging round a heavy skeleton with atrophied muscle (Bell).

It is interesting to note that in the adenoma of acromegaly the Golgi bodies of all the cells, whether chromophobe or acidophile, are acidophilic in type, indicating, in accordance with the findings of Severinghaus (cf. p. 318), that the whole adenoma is composed of acidophile cells and cells which can change to acidophile (Cushing, 1933).

The Heart in Acromegaly. It has already been mentioned that the heart usually enlarges in acromegaly. At autopsy, for example, the hearts of four of the cases of Cushing and Davidoff weighed respectively 460, 480, 1,000, and 1,050 gm., while Osborne reported a case in which the heart weighed 1,275 gm. Moehlig mentions similar cases. Levene and Miller report the case of an acromegalic

giant which is of interest as an example of this intermediate syndrome, and also because in this case the heart was relatively small.

This man, when examined, was thirty-four years of age, 90½ inches tall, with a span of 92 inches, and weighed 359 lb. His chest circumference was 46·4 inches. He began to show excessive growth at the age of eight, and attained almost his present height in the ensuing eight years, while during this period he experienced intractable headache, progressive impairment of vision, and weakness. A course of radiation to the pituitary gland resulted in symptomatic relief.

X-ray examination showed the typical acromegalic changes in the skull and the bones of the hands. There was expansion of the diploic table and a marked hyper-pneumatization of the paranasal sinuses and mastoid cells. The sella turcica measured 1·1 × 1·4 cm., its floor being somewhat depressed and irregular. There was a moderate degree of prognathism.

Fluoroscopic examination showed a cardiac rate of 60 with normal rhythm and amplitude of contraction, and no abnormality of contour. X-ray measurements indicated that the heart was only between 56 and 66 per cent. of the normal volume for a man of such a size. He presented no cyanosis, dyspnoea, palpitation, oedema, or ascites, and was carrying on business and leisure activities comparable to those of any normal adult.

Levene and Miller consider that in this man the acromegaly is arrested, and that his better health, in comparison with most acromegalic giants, is at least in part due to the non-enlargement of his heart.

Galactorrhoea in Acromegaly. If, as seems not improbable, prolactin is produced in the acidophile cells, tumours of these cells may lead to its increased production, with the usual sequelae. Atkinson found reference to galactorrhoea as part of the syndrome in five of 607 female cases of acromegaly. Davidoff found persistent lactation in four of fifty-eight female acromegalics and referred to one male case in whom lactation had occurred. Stephens has described the case of a forty-eight-year-old female acromegalic with persistent secretion of milk from both breasts. Oestrogenic treatment (oestradiol monobenzoate, 10,000 R.U. once a week) resulted, within four months, in suppression of the lactation and subjective clinical improvement.

Treatment of Acromegaly. When tumour is definitely recognized as the cause, removal of the tumour (or perhaps X-ray treatment) seems the obvious procedure. Cushing's work illustrates the frequent beneficial effects following surgical removal, including even apparent subsidence in size of extremities.

X-ray treatment usually gives satisfactory results except in those cases where a rapidly growing tumour is endangering vision and where the initial reaction in the tumour after radiation might cause total blindness. Certain hypertrophied tissues, such as the tongue, will shrink following radiation. Over-radiation of the

tumour is undesirable, in that it may hasten the disabling hypopituitary phase (Bell).

Weinstein has reported what appears to be a remarkable result of X-ray treatment.

A woman aged twenty-four developed acromegaly ; menses ceased abruptly, and the characteristic facial changes commenced. Six years later X-ray examination showed marked enlargement of the sella turcica with hypertrophy of the posterior clinoid process. There was evidence (headache and eye-strain) of pressure on the optic chiasm, and also of dysfunction of the left olfactory tract. An adenoma of the pituitary was diagnosed. Deep X-ray therapy was given. Most of the symptoms were rapidly relieved. Four years subsequent to this treatment libido returned and normal menstrual cycles were re-established. The following year she had a miscarriage. A year later she gave birth to a healthy child, and eight years after the treatment there was no evidence that the acromegaly had progressed further. The basal metabolic rate prior to treatment was + 17 per cent., a year after treatment + 23, and five years after − 3 per cent.

Goldberg and Lisser (1942 *a*) report two cases of acromegaly with secondary hypogonadism, in which treatment with the appropriate sex hormones seemed to give satisfactory results.

Hormone Influence on Cranial Form and Structure. The cranial anomalies associated with pituitary disease, and especially with acromegaly, have been several times referred to. Mortimer and his colleagues have contributed much to their study. In a recent review of the subject (1939) he listed five types of cranial dysplasia, which could be correlated in a large proportion of cases with a diagnosis of pituitary dysfunction, indicating that the latter leaves its imprint on the skull.

Type I is found preponderantly in males and is characterized by a large head (or a relatively large head) in children. There is general overgrowth of cancellous bone throughout the cranium ; the frontal bone in women has a brow inclination of the masculine type, and in man is apt to be receding. The paranasal sinuses and mastoid air cells are markedly hyperplastic. The condition is reminiscent of acromegalic change.

Type II shows, superadded to earlier Type I changes, a secondary sclerosis, best seen in the frontal bone. This is considered to indicate that a period of glandular involution has followed a period of overactivity.

Type III is the reverse of I. Growth has failed and differentiation is poor. The head tends to be small, the face infantile. The cancellous bone throughout the cranium and face is hypoplastic ; this is shown most markedly in the hypoplasia of the paranasal sinuses and mastoid air cells. In the calcarial outline the brow angle in adults is infantile, or, in males, feminoid. The frontal sinuses are poorly developed ; the sella turcica is apt to be small. The general picture, as judged by comparison with the hypophysectomized rat, suggests hypopituitarism.

Type IV is similar to Type III, but with a superimposed sclerosis of the brain case and better differentiation of the facial part of the cranium.

Type V crania are normal in size and in proportion of face to brain

case, but have a characteristically local or generalized calvarial hyperostosis.

Mortimer and his colleagues examined 2,950 cranial skiagrams, of which 494 revealed evidence of cranial dysplasia. Of these 74 per cent. were of patients either suffering from pituitary dysfunction, or from conditions suggestive of it. In a more recent study of 43 skiagrams, 17 indicated hyperpituitarism, and 26 hypopituitarism. In every case the clinical evidence was in agreement.

He considered that cranial sclerosis could be regarded as a reliable evidence of hypopituitarism, and was much more frequently found in female than in male patients.

Goldzieher has confirmed Mortimer's findings. He found such cranial dysplasia present in 96 per cent. of 500 consecutive cases of pituitary disease, while in a control group without clinical evidence of such disease only 9 per cent. showed such (less marked) dysplasia, indicating the diagnostic value of such examinations.

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CHAPTER XII

CUSHING'S DISEASE AND THE ADRENOCORTICAL SYNDROMES

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INTRODUCTION

THE description of a very definite syndrome by Cushing in 1932, associated with an adenoma of the basophile cells of the anterior pituitary, has been found to apply closely to many cases without pituitary lesions but with a tumour of the adrenal cortex (and in fact the latter association had been considered probable prior to Cushing's description). In consequence the suggestion made by Kessel in 1936 is gradually being adopted. The syndrome itself, whatever the causative lesion, is becoming referred to as Cushing's syndrome. When it is associated with a pituitary basophile tumour, the entity is termed Cushing's disease or pituitary basophilism (the latter being Cushing's name for it).

That the same syndrome can arise in consequence of either a pituitary basophile or an adrenocortical tumour seems due to the close association of the two endocrine glands through the control of the adrenal cortex by the adrenotrophic hormone of the anterior pituitary, which is probably a product of its basophile cells. Many of the features of the syndrome, as Cushing pointed out, are due to undue secretion of hormones of the adrenal cortex, whether this be a primary defect or a secondary involvement.

Since many patients with tumour of the adrenal cortex do not exhibit Cushing's syndrome, but instead, depending on age and sex, precocious puberty, or virilism, or rarely (in adult males) feminism, while others exhibit all grades between some one of these and the classical type of the syndrome, and since, in addition, disorders of other endocrine glands can result in conditions somewhat simulating certain of these, differential diagnosis is frequently difficult.

CUSHING'S DISEASE OR PITUITARY BASOPHILISM

Cushing's paper of 1932 reviewed a number of cases of his own and of others, all exhibiting a definite syndrome. In several

autopsy had shown the existence of a basophile adenoma of the anterior pituitary ; in others the existence of such a tumour was assumed but not proved. The essential conclusions in this paper may be given in his own words (with his own italics).

" A polyglandular syndrome hitherto supposed to be of cortico-adrenal origin characterized in its full-blown state by acute plethoric adiposity, by genital dystrophy, by vascular hypertension, and so on, has been found at autopsy in six out of eight instances to be associated with a pituitary adenoma which in the three most carefully studied has been definitely shown to be composed of basophilic elements, the lesion in one instance having been clinically predicted before its post-mortal verification." The syndrome is described in detail :

" The following features are characteristic of all cases : (1) A rapidly acquired, peculiarly disposed and usually painful *adiposity* (in one instance representing a 40 per cent. gain in weight) confined to face, neck and trunk, the extremities being spared ; (2) A tendency to become round-shouldered (kyphotic) even to the point of measurable loss of height associated with lumbo-spinal pains ; (3) A sexual dystrophy shown by early *amenorrhoea* in the females and ultimate functional *impotence* in the males ; (4) An alteration in normal hirsuties shown by a tendency to *hypertrichosis* of face and trunk in all the females as well as the pre-adolescent males and possibly the reverse in the adult males ; (5) A dusky or plethoric appearance of the skin with *purplish liniae atrophiae* ; (6) *Vascular hypertension* present in all cases *; (7) A tendency to *erythraemia*, a count exceeding five million having been present in five of the nine cases in which blood counts were recorded ; (8) Variable *backaches, abdominal pains, fatiguability*, and ultimate extreme *weakness.*

To get an indubitable picture of the syndrome of pituitary basophilism it is obviously essential to consider only verified cases, *i.e.*, cases in which a pituitary basophile tumour was found at autopsy, and no adrenal cortical tumour was present. Cases reported by Raab in 1924 (and fully quoted by Cushing), and by Bishop and Close in 1932, seem to comply with these conditions.

Raab's patient is illustrated in Fig. 67. When first seen this man was aged thirty-one. He showed gigantism of moderate degree (6 feet, 5 inches), with very long extremities, externally well-developed genitalia, and distribution of hair of normal masculine type. He complained of suffering from severe headaches for two weeks prior to admission to hospital, and stated that he had gained 10 kg. in weight in that time (Cushing considered that the post-mortem findings indicated that the

* In all the cases in which blood pressure had been recorded.

disease was of longer duration). His libido had always been rather low ; he had been impotent for a fortnight.

The face was markedly obese ; the abdomen was very prominent and showed dark red flame-shaped striae with maximum width of over 2 cm. The hips also showed such striae. His weight was 211 lb. X-ray examination showed a sella which was not excessively large, but suggestive of a process enlarging the intrasellar space.

A few weeks later he developed excessive pains in the lumbar vertebral column. Shortly afterwards he died from acute sepsis resulting from a streptococcal phlegmon of the hand.

At autopsy the pituitary was found to be somewhat enlarged, but not protruding out of the pituitary fossa ; histologically a small basophile tumour was discovered, which had almost entirely replaced the posterior lobe. An osteoporosis of extreme degree involving the vertebral column and the long bones accounted for the vertebral pain. There was a slight degree of kyphosis of the vertebral spine.

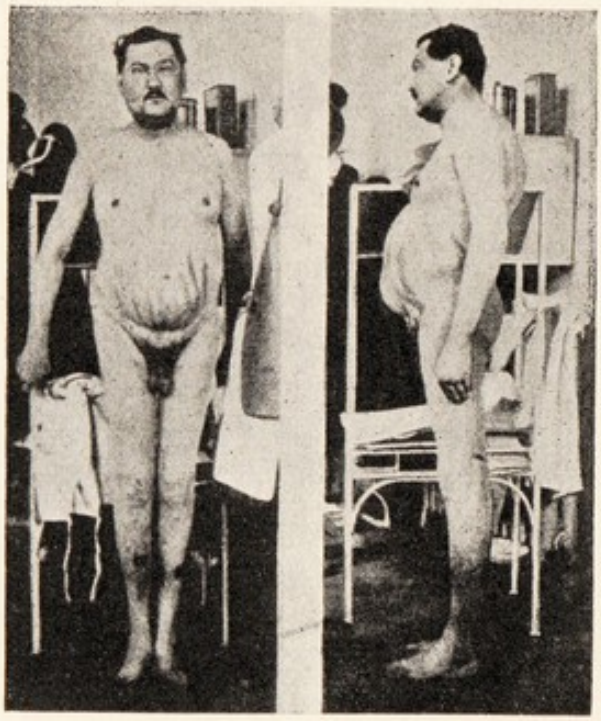


FIG. 67. Dr. Raab's patient with verified basophilic adenoma of the pituitary. (From Cushing, Bull. Johns Hopkins Hosp., 1932, 1, 137.)

The testes were small and atrophied. The thyroid was slightly enlarged and contained much colloid. The remaining endocrine glands were apparently normal.

The essential features of Bishop and Close's case are as follows : The patient, a young woman, was normal till the age of eleven, when she stopped growing and became fat. She developed a ruddy complexion and her hair began to fall out. Menstruation started at fourteen years of age, but ceased a year later, with subsequent complete amenorrhoea except for three consecutive months at the age of eighteen. Fig. 68 shows her appearance at the age of twenty-one. Six months before death the sight of her left eye became affected, and four months before death she began to complain of excessive thirst and polyuria.

Examination in hospital, at the age of twenty-two, showed : A very red complexion, dry scaly skin, hairiness of face, chest and abdomen, stunted growth (height 4 feet 3 inches ; weight 89 lb.), beard sufficiently evident to necessitate use of a razor. There was a patchy red erythrema, localized particularly to her left arm. Headaches were troublesome. The blood pressure averaged 250/180, and sometimes exceeded 300 mm. mercury. There was a marked degree of retinitis with silver wire arteries and a scotoma of the left eye. The blood picture was apparently normal.

The fasting blood glucose was 0·14 per cent., and there was a markedly decreased sugar tolerance. The urine showed presence of albumin and glucose.

Her intelligence was normal. Shortly after admission to hospital she developed signs of acute oedema of the lung and died.

At post-mortem the cadaver showed an obese stunted body, with hair over the entire abdomen and chest. There was considerable oedema of the lungs. Extensive arteriosclerosis was found throughout the blood vessels. The kidneys were small, and their histological appearance consistent with secondary contraction of the arteriosclerotic type.

The thyroid showed large colloid vesicles surrounded by flattened epithelium. The pancreas was greatly reduced in size, but the spleen and adrenals were normal. The uterus was infantile in type, the ovaries small and without visible evidence of Graafian follicles, though these were normal by microscopic examination.

The pituitary contained a small, encapsulated adenoma consisting entirely of basophile cells, and situated near the front of the anterior lobe (cf. Fig. 69).

FIG. 68. Case of Bishop and Close, aged 21. (From Bishop and Close, Guy's Hospital Reports, 1932, lxxxii, 143.)

The size of the tumour varies considerably in different cases, but it is always relatively small in comparison with acidophile and chromophobe tumours. The

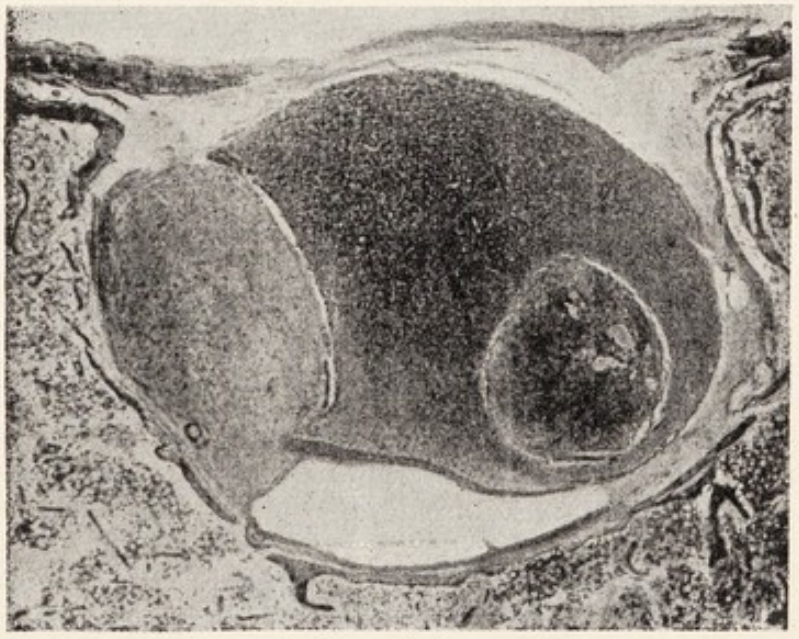


FIG. 69. Cross section of the pituitary from a case of pituitary basophilism. (From Bishop and Close, Guy's Hospital Reports, 1932, lxxxii, 143.)

typical picture in Fig. 69 illustrates why in these cases no definite enlargement of the sella is produced, and also suggests that the polyuria in the case just quoted could not be attributed to pressure damage to the posterior lobe.

Since the publication of Cushing's paper numerous cases have been reported. These have undoubtedly all been cases of Cushing's syndrome, but unless the presence of a pituitary basophile adenoma has been verified at autopsy, they cannot definitely be termed cases of Cushing's disease.

Rasmussen and Nelson have described two cases of basophile adenoma originating from the pars intermedia ; the first showed no symptoms definitely attributable to the tumour, but the second exhibited adiposity, striae, hirsuties, high blood pressure, and a florid face.

Furtado and Morato have reported an unusual case in a boy aged seventeen. The syndrome was associated with an enlarged sella turcica, marked optic atrophy, and hemianopsia. At operation a large tumour the size of a walnut was found between the two optic nerves, and most of it was removed. Twelve hours after operation an epileptic seizure occurred, and death followed. The tumour apparently contained acidophile, basophile and chromophobe cells.

CUSHING'S SYNDROME WITH ADRENAL CORTICAL TUMOUR

The following cases illustrate the practical identity of the syndrome associated with adrenocortical tumour with that associated with a pituitary basophile tumour.

A Case of Kepler et al. (1934). The patient, a girl, was first examined at the Mayo Clinic at the age of nine years. Birth and early development had been normal. When she was four years old her mother noticed unusual development of the breasts, generalized growth of hair over the body, and deepening and coarsening of the voice. A year later pubic hair was abundant and the external genitalia had developed abnormally. At eight years the child menstruated for four days, and subsequently there had been menstrual spotting at intervals of about two months. Her mentality and personality were apparently normal though she tended to shun the company of other children.

Her appearance suggested a considerably older age than nine years (cf. Fig. 70, A). Her height was 4 feet 5 inches, within normal range, but her weight was 103 lb., estimated to be about 36 lb. overweight. The outstanding abnormalities were (i) obesity affecting principally the face, neck and trunk ; (ii) hypertrichosis of face and body ; (iii) purplish atrophic striation over abdomen, thigh and buttocks ; (iv) precocious development of breasts and external genitalia ; and (v) acne of face and trunk.

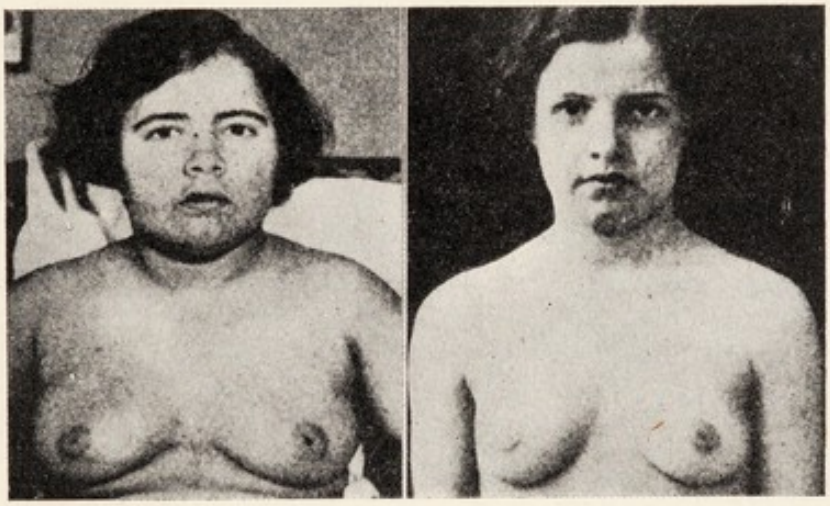
Her blood pressure was 132/97 mm. mercury. The blood picture was fairly normal. X-ray examinations showed an apparently normal sella turcica, and no thymic shadow. The outline of the kidneys in the intravenous urogram was normal. A glucose tolerance test was normal. The basal metabolic rate was — 20 per cent.

At surgical operation the right adrenal was about half the usual size (a section was removed and proved normal histologically). The site of the left adrenal was occupied by a large encapsulated tumour, 6 × 4 × 2 cm., which proved to be a cortical adenoma.

A potent cortical extract was administered during the first six post-operative days.

Within three weeks her weight commenced to fall, and her excessive hair to disappear. Later on the hair became smooth, the voice of higher pitch, and the breasts and genitalia smaller. There was no further menstrual flow. She associated more with other children.

Four months after operation (cf. Fig. 70, B) her weight was 72 lb., her blood pressure 98/62, basal metabolic rate − 9 per cent. The skin of the face was clear and healthy, almost all the body hair had dis-



A B

FIG. 70. Tumour of the adrenal cortex in a girl of nine years of age. A. Photograph taken fourteen days after removal of the tumour, before any external changes had occurred. B. Taken four months later. For details, see text. (From Kepler, Kennedy, Davis, Walters and Wilder, Proc. Staff Meetings Mayo Clinic, 1934, ix, 169 ; and Annals of Surgery, 1934.)

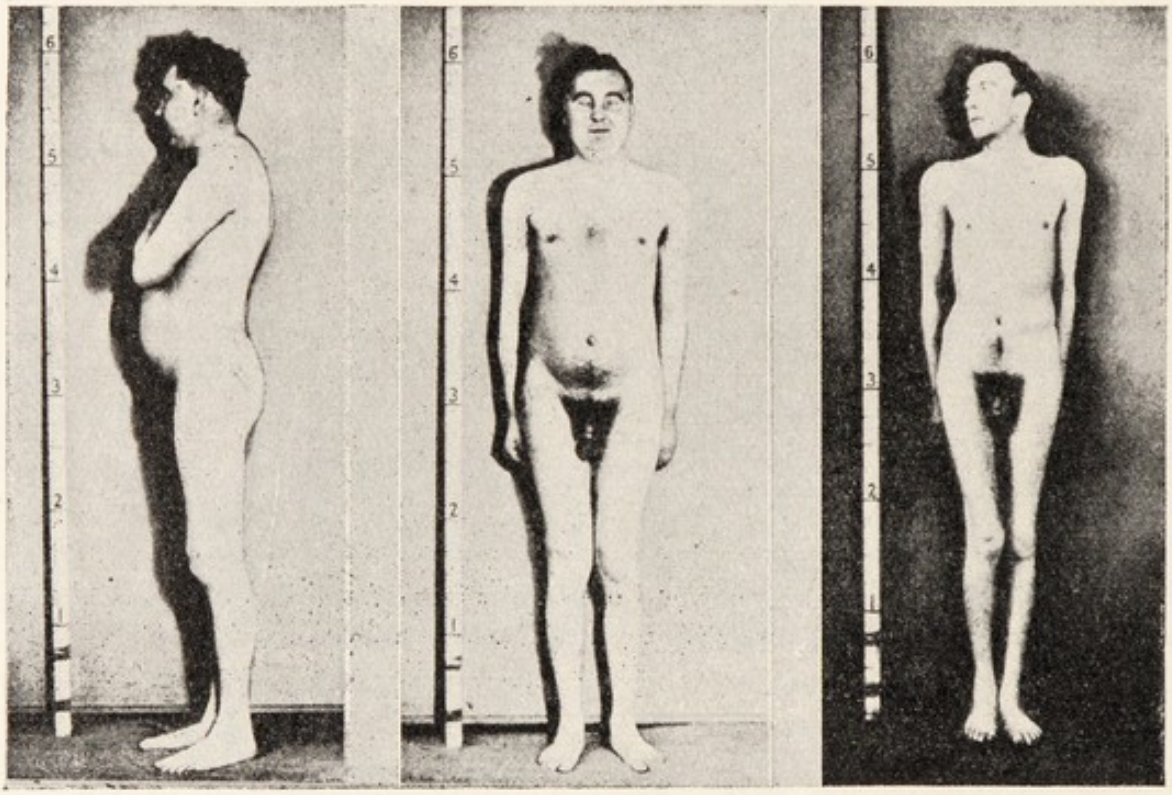
appeared, and the bodily proportions were normal except for the breasts.

A Case Reported by Crooke and Callow (1939). A single man, aged twenty-five years, was admitted to hospital in January, 1938. Four years earlier he had begun to have dull frontal and occipital headaches, while eighteen months before admission he began to gain weight, increasing from 147 to 193 lb. in the interval. The obesity affected face and trunk but spared the limbs. His face became excessively red. Purplish striae began to appear in his groins and later in the folds of the axillae. He gained 2 inches in height (to 6 feet). He became easily fatigued. There was no alteration in hair growth. Some months before admission a diagnosis of pituitary basophilism had been made elsewhere, and he had been given deep X-ray therapy directed to the pituitary fossa.

His appearance on admission is shown in A and B, Fig. 71. There

was marked obesity of the face and neck, with a pad of fat over the lower cervical vertebrae. The obesity of the trunk was less marked, and the limbs were normal. Long purple striae were present on the upper anterior and lateral aspects of both thighs, and in the lumbar region, in the anterior and posterior axillary folds, and a few on the medial aspects of both knees.

The face was red, the distribution of hair on face and trunk normal. There was marked acne on the back, less on the chest, and none on the face. There was a moderate kyphosis on the upper dorsal and cervical



A B C

FIG. 71. Case of Crooke and Callow. A and B. Appearance of patient with Cushing's syndrome before operation ; C. Appearance six months after operation. (From Crooke and Callow, Quart. J. Med., 1939, viii, 233.)

regions. There was pitting oedema of the feet, extending halfway up the shins.

At admission the blood pressure was 140–160/100–115, but subsequently never above 125/95 mm. mercury. The pulse rate varied between 74 and 84. Heart, lungs and kidney were normal. The abdomen showed no tenderness, and nothing abnormal was palpable. Sugar tolerance tests were normal. The blood showed 5·8 million red cells and 14,600 white cells per c.mm., and a haemoglobin of 120 per cent. Blood chemical findings were normal. The cerebrospinal fluid was normal. The basal metabolic rate was – 20 per cent.

X-ray examination showed a rather small but otherwise normal sella turcica. Other X-ray findings were normal.

The urinary excretion of 17-ketosteroids was two to three times that

of a normal adult man (40 to 64 mg. per twenty-four hours, with a general tendency to increase). This result suggested an adrenal cortical tumour. Following perirenal insufflation of 250 c.c. of air X-ray films showed a large tumour mass lying above the left kidney.

This was removed at operation by Mr. V. W. Dix. It was a partially encapsulated friable mass, about 16 × 9 × 6 cm., histologically a carcinoma of the adrenal cortex, along with a trace of atrophied cortex.

The patient had a stormy post-operative course, during which he was treated with adrenal cortical extract and intravenous and oral sodium chloride.

He re-entered hospital five and a half months later for re-examination.

A B

FIG. 72. Case of Calder and Porro. A. Photograph taken two years before onset of disease ; B. Photograph taken at time of admission to hospital. (From Calder and Porro, Johns Hopkins Hospital Bull., 1935, lvii, 98.)

His weight was now only 138 lb., his height 6 feet 1 inch. His appearance is shown in C, Fig. 71. The characteristic obesity, the bright red coloration of the face, and the acne of the chest had disappeared. Striae were still present, but of a pale greyish-mauve colour, much less conspicuous. The blood pressure was 118/85, the haemoglobin 72 per cent. Blood chemical findings and basal metabolic rate were normal. Four weeks later, at discharge, he felt and looked well, and was able to walk without assistance.

Case of Calder and Porro (1935). A housewife aged thirty-three was admitted to hospital in January, 1932, and died twenty-two months later. Four years before admission she was tall, thin and fair, and able

to work hard and efficiently. Somewhat later a pustular eruption gradually covered face, neck, thorax, back and arms. During 1930 there was amenorrhoea ; periods again ceased two months before admission. A year before admission she suffered a severe infection beneath the fascia lata of the right thigh, was confined to bed with a high fever, the lesion excised, and a litre of pus withdrawn. Following this infection she underwent a gradual steady change in appearance and disposition. The skin became coarse and thick, her complexion changed to a red, plethoric hue, and a heavy growth of hair appeared on face and axillae, in the pubic region and over the body gradually. Her eyes became swollen and puffy, her face round, her neck and trunk larger. There was definite decrease in stature. She became nervous, irritable and weak, and at the time of admission was unable to perform any physical labour. Shortly before admission her blood pressure had increased within a period of five or six weeks from a systolic level of 100 to 160/100, the higher level persisting.

Her appearance earlier, when normal, and at the time of admission, is shown in Fig. 72, A and B respectively.

At examination the pertinent characteristics were : Pulse 106, blood pressure 190/130, plethoric and florid face with prominent vein markings on a background of dusky red skin, profuse growth of beard with deep black hairs of maximum length 7 to 8 mm., eyelids rather puffy, obesity confined mainly to face and trunk, apparently advanced acne on back and front of trunk, a few striae on outer sides of thighs, heavy growth of lanugo all over the body, typical masculine distribution of pubic hair, hypertrophied clitoris, marked thoracic kyphosis.

The red blood cells were 5·08 million, haemoglobin 16·1 per cent. Sugar and albumin were occasionally present in the urine. Sugar tolerance was decreased. The basal metabolic rate was − 8 per cent.

The sella turcica was indistinct by X-ray examination, and the posterior clinoids eroded. There was marked narrowing of several of the vertebrae, with almost complete collapse of the eleventh dorsal vertebra.

The diagnosis was pituitary basophilism.

At autopsy the pituitary was normal in appearance ; serial section of the entire gland showed no adenoma present and no increase in basophile cells. The pineal, thyroid and parathyroids were normal. Both ovaries contained primordial but no well developed Graafian follicles. The pancreas showed somewhat irregular and shrunken islet cells.

The right adrenal was distinctly atrophied, the left adrenal replaced by a large, well-defined tumour, 15 × 20 × 5 cm., consisting of rather friable, mottled, yellow tissue, containing several collections of pus, Histologically the tissue resembled normal cortex. The necrotic areas were infected.

It is obvious that these cases present all the chief characteristics of Cushing's disease, along with the adrenal cortical tumour. It is to be noted that in the first two—as in many others in the literature—there is only presumptive evidence that the pituitary is normal—based on their recovery following operation and subsequent good health.

OTHER SYNDROMES WITH CORTICAL TUMOUR

The results with adrenal cortical tumour tend to vary with the age and sex of the patient. Such varying results are illustrated by the cases described in the previous section, and those now described, which illustrate precocious growth and puberty, virilism, and feminism.

Fraser has reported a case of precocious puberty in a boy aged twelve months. There was no pertinent family history. He was normal for the first six months, then his penis began to enlarge rapidly, so that at twelve months it was equal in size to that of a youth of eighteen years, and the prostate was the size of a walnut. The testes, however, were of normal size for the age. Erections were almost constant and masturbation frequent. There was sparse pubic hair and acne of puberty on face. The face was old for the age, the voice deep pitched, the muscular development excessive, and the appearance of the epiphyses in advance of the age. The body-weight was excessive. Fraser summed up the changes : Calendar and mental age twelve months, bone age five years, dentition three years, penis and prostate (but not testes) eighteen years.

The urinary excretion of 17-ketosteroids was, per litre, greater than that of a normal adult man.

The boy was operated on at the age of eighteen months and a right adrenal tumour of the size of a golf ball removed. He collapsed and died twenty hours later.

At post-mortem the pituitary was found normal, the seminal vesicles and prostate were enlarged, the left adrenal was normal. The tumour mass, with a fringe of adrenal tissue, weighed 38 gm., and sections gave a strongly positive reaction with the ponceau fuchsin stain (Vines).

Gross recently reported the case of a three-year-old boy, apparently normal till four months previously. Then the genitalia rapidly increased in size, the body-weight increased rapidly, pubic and mammary hair appeared, the voice became deep and husky. The arm and leg musculature showed progressive weakness and the child fatigued easily. He had had intermittent attacks of abdominal pain for a month.

When examined, he had the stature of a six- or seven-year-old boy, with greatly hypertrophied genitalia, both penis and testes being of the size of adolescent youth. There was abundant pubic hair. X-ray showed the bone age to be six or seven years. A mass of the size of a grape fruit filled the left upper quadrant of the abdomen.

At operation a very vascular left adrenal tumour was found, which ruptured. The boy died in shock two hours later.

Reilly has reported very fully the case of a boy who had shown, since two years of age, precocious sex characteristics, including acne and rapid skeletal growth. (One maternal cousin was precociously developed and died at the age of thirteen from meningitis.)

When five and half years old this boy suffered a twelve-hour attack of pain in the right upper abdomen and passed some red urine. A year later he had a similar attack, with the sequence : fever, abdominal

distension, pain and rigidity. A mass appeared in the right upper quadrant, and within twelve hours the boy was stuporous and delirious.

At this time, six and half years old, he had the sexual development and characteristics of a sixteen-year-old boy. His height corresponded to the average of twelve and half years and he was very muscular. Acne was marked on face and chest, the voice was deep, there was heavy axillary and pubic hirsutism, a downy growth on lip and chin, and profuse growth on arms and legs. The size of penis, scrotum and testes was like those at sixteen years, but the prostate seemed relatively smaller. (There was subsequently found no sperm, but a normal prostatic secretion.) The denture was that of twelve years, the skeleton the thick lateral type.

The abdomen was distended, rigid, and quite tender, especially in the right upper quadrant, where a large mass could be vaguely felt under an enlarged liver. The boy was semicomatose, his colour ashen grey, his skin cold and moist, the pulse 80, blood pressure 120/70, respiration 20, temperature subnormal.

The urine was red and contained albumin and blood cells. The blood sugar was 0·16 per cent. ; a two-hour tolerance test showed poor tolerance but no glycosuria. The basal metabolic rate was normal.

X-ray examinations showed an enlarged liver, deformation of the upper portion and displacement of the right kidney, calcification in the periphery of the right adrenal, and an epiphyseal age between fifteen and sixteen years.

Assay of the urine showed no free or combined oestrogens, but 29 I.U. of androgens per day (a normal figure for an adult man).

His intelligence was normal.

His condition of shock was thought to be due to acute adrenal cortical insufficiency, and he was treated as for an Addisonian crisis with saline, glucose, and whole adrenal cortical extract.

He slowly improved and was operated on thirty-six days later. Pre-operatively he was given adrenal cortical extract, and post-operatively this, and desoxycorticosterone and transfusions. A mass weighing over 500 gm., and attached by a pedicle to an apparently normal right adrenal, was removed (and proved to be a degenerated adrenal adenoma, with no evidence of malignancy). The blood pressure was 100/80 before operation, and rose to 150/80, dropping to 110/80 on removal of the tumour, and subsequently to 90/50. The post-operative therapy was maintained for twenty-seven hours, during which period the patient received in all 30 mg. desoxycorticosterone, 64 c.c. of " eschatin," and 4,500 c.c. of fluid (blood, glucose, saline) without symptoms of over-dosage.

Nine months later he had grown only a further 0·2 inch ; union of the epiphyses had progressed. The acne was better, the voice higher. There had been no loss of sexual hair. The blood pressure was 110/60. Emissions were less frequent, the penis smaller. The excretion of 17-ketosteroids in urine, per twenty-four hours, was still very high (5·6 mg.). Pregnanediol was absent.

Gross has described the case of a girl of three years, three months, whose chief complaint was enlargement of the clitoris to such degree that

encroachment on the external urethral meatus caused difficulty in urination. This enlargement and the growth of pubic hair had been progressive from birth. The child started to talk at thirteen months and had an unusually deep voice. Her size and strength were abnormal so that at three years she was larger and stronger than her five-year-old sister. Her appetite was voracious. She had had acne since the age of three months. She was of masculine contour, height 42 inches, span 41 inches, weight 45 lb. The breasts were not enlarged. Bone age (judged by hands and feet) was eight or nine years. The sella turcica was normal. X-ray examination showed a mass above the right kidney.

The blood cholesterol was very low (three determinations showed 38, 47 and 58 mg. per 100 c.c.). The urine was extremely rich in both androgens and oestrogens.

At operation an orange coloured tumour, 5·5 cm. in diameter, replacing the right adrenal, was removed. It was well-encapsulated and weighed 110 gm.

After recovery the urinary androgens were normal, and the oestrogens not far from normal. Within two months the acne, excessive strength and excessive appetite had disappeared, and the clitoris had shrunk. Eight months after the operation the pubic hair was unchanged, the voice still somewhat husky, but the child was more feminine in appearance and activity.

An excellent example of virilism with none of the striking characteristics of Cushing's syndrome has been reported by Lukens and Palmer. The female patient was normal till the age of six, when she had scarlet fever. A few months later it was noticed that her voice was becoming deep and hoarse, then hair appeared on her upper lip, and by the time she was nine years old she had a full beard, and her entire body was covered with hair. She had a masculine figure, great muscular strength, and was considered tall for her age. Psychologically she always remained distinctly feminine.

At the age of eleven an exploratory laparotomy revealed normal female pelvic organs, while no gross pathology could be detected by palpation of the adrenal regions through the abdominal incision. Her visual fields, and the X-ray findings of the pituitary fossa were normal. The basal metabolic was − 15 per cent.

Subsequently she only grew 1 inch.

At the age of sixteen she had never menstruated and there was no breast development. Examination at this time showed extreme hirsutism of face and body and acne on face and back. She was short, not obese, with relatively wide shoulders, narrow hips, a deep voice, and masculine or prepuberal breasts. The scalp hair was coarse, wiry, and thin. The clitoris was enlarged. Her blood pressure was 110/80. There was complete union of the epiphyses of the pelvic bones, upper ends of the femora, and vertebral spines, and she was considered to have a bone age of twenty-four to twenty-six years. Glucose tolerance tests showed a decreased tolerance, but no glycosuria.

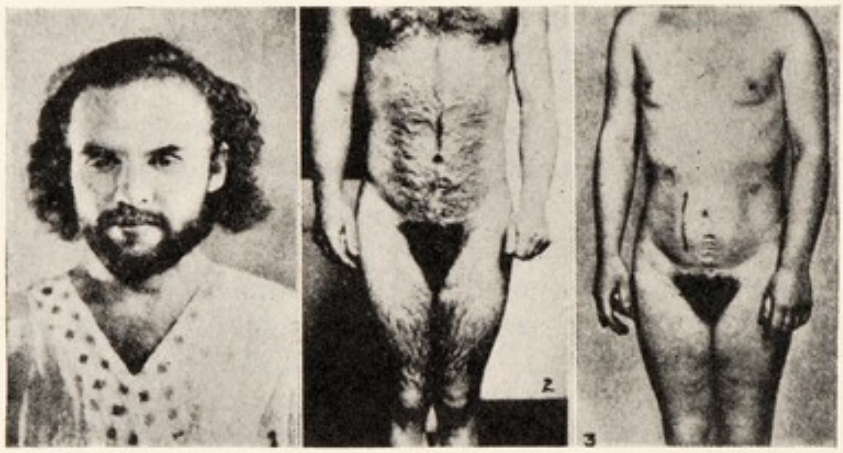
A roentgenogram after perirenal insufflation showed a large tumour in the region of the right adrenal. She was operated on eleven months later, and a well-encapsulated tumour, 6 cm. in diameter, was removed.

The tumour cells were of adrenal cortical type. The post-operative course was somewhat stormy, but she made a complete recovery.

Her appearance before operation is shown in A and B, Fig. 73, and that thirty-four months later in C.

Following operation she improved steadily. Three years later the voice was softer, but still a deep feminine voice. Acne disappeared within three weeks. She menstruated three months after operation and subsequently regularly. Her excessive muscular strength disappeared. The hair of the head became softer and finer. The rate of growth of the beard decreased, but the beard still persisted. The body hair had largely disappeared within a year and was practically normal in three years. By the end of two years normal adult breasts had developed. The bodily contour became feminine in type.

Prior to operation there was excessive excretion of androgens. Subsequent to operation this excretion became normal.



A B C

FIG. 73. Case of Lukens and Palmer. A and B. Preoperative appearance, arms shaved ; C. Two years and ten months after removal of tumour. (From Lukens and Palmer, Endocrinology, 1940, xxvi, 941.)

Those cases of sexual precocity and virilism in children who survive operation seem to remain normal. Reilly records that a boy reported on by Lisser in 1933 is well ten years after operation, and a girl reported on by Reilly, Lisser and Hinman in 1938, is well seven years after operation.

In the extremely rare cases of adrenal cortical tumour in adult man which do not show the characteristics of Cushing's syndrome, feminism seems to be the usual result. A recent case in the literature is that reported by Simpson and Joll.

The patient was a physician with one child. At the age of thirty-two the breasts began to enlarge ; within a year there was loss of libido, partial impotence, and some atrophy of the genital organs. During this year there was gain in weight from 154 to 182 lb., and during the

following year a more rapid fall to 126 lb. Hair on the trunk had always been profuse ; the patient believed it to have increased.

He entered hospital about this time. At examination blood pressure was 116/70, pulse 70, haemoglobin 80 per cent., red blood cells 4·6 million per c.mm. A diagnosis of gallstones and an ill-defined tumour in the left hypochondrium was made.

At operation a large malignant tumour of the left adrenal gland was removed, 14·5 × 11 × 8 cm., and weighing 656 gm. No normal adrenal tissue could be found in it. Histologically there was marked resemblance to adrenal cortical structure, with all three zones represented. No fuchsinophil cells were found (Vines).

Convalescence was protracted, but after two months the patient began to gain weight and strength, the breasts became smaller, and the genitals larger. There was incomplete return of sexual urge and potency.

Courses in deep X-ray therapy were started three months after operation, and were continued intermittently. Within eight months of the operation the original condition began to return. The patient looked plethoric, the breasts were full, the genitals rather small. Sexual desire and potency decreased gradually to complete impotency. Beard growth may have decreased somewhat during this time. There was a steady fall in body-weight.

Twenty-one months after the first operation a laparotomy showed metastatic growths in the liver, and the patient died two months later.

No estimations of androgen and oestrogen excretion were made prior to the first operation, but subsequently both seemed to be less than normal for some months, and then excessive excretion of oestrogens occurred, coincidently with the decline in the clinical condition, being, indeed, the first evidence of metastases.

ADRENAL CORTICAL HYPERPLASIA

Since in cases of pseudohermaphroditism adrenal cortical hyperplasia is frequently found at autopsy, it has been suggested that such hyperplasia is causally related to the condition. Kepler and Keating do not consider that this inference is justified by present evidence.

A curious syndrome has recently been described by Di Ruggiero and Jolly (1938) and Dijkhuizen and Behr (1940), who reported on five infants dying in the fourth to sixth week after some weeks' persistent vomiting simulating pyloric stenosis. Autopsy in three cases showed tremendous hypertrophy of the adrenals, and especially the cortex, of which the surface was thrown into folds. Two of the five cases were siblings, the male of the pair being a pseudohermaphrodite (cf. Kepler and Keating).

Numerous cases exhibiting the characteristics of Cushing's syndrome, in the absence of pituitary and adrenal cortical tumours and apparent presence of some degree of cortical hyperplasia, have been assumed to be due to such hyperplasia.

Theoretically, if it can be assumed that such excess of cortical cells can produce excess of the same hormones as are produced by a cortical tumour, then there is good basis for this argument. A parallelism exists in cases of hyperinsulinism with no islet tumour but apparent hyperplasia of the islets (cf. p. 168).

The theory is strengthened by the findings that at autopsy of a number of cases of Cushing's disease the adrenal cortex has been found enlarged and presumably hyperplastic, while at autopsies of certain cases of Cushing's syndrome neither pituitary tumour nor adrenal cortical tumour was found, hyperplasia of the adrenal cortex being the only observable anomaly (cf. Kepler and Keating).

The proportion of such cases in which virilism is the outstanding feature, rather than the typical Cushing's syndrome, is perhaps greater. Broster (1939) has reviewed this type of case rather fully, and advocates removal of one (the larger) adrenal.

Adrenal cortical hyperplasia in itself, however, does not necessarily lead to virilism or Cushing's syndrome. As Kepler and Keating point out, at autopsy the adrenal cortex has been found to be enlarged and presumably hyperplastic in a number of diverse conditions in which endocrine symptoms were known to be absent during life.

There are, in the literature, at least three cases recorded showing a degree of resemblance to Cushing's syndrome, associated with a thymic carcinoma and adrenal cortical hypertrophy, with absence of pituitary or adrenal tumour; two were reported by Leyton, Turnbull and Bratton, and one by Kepler (1933).

Leyton's first case was a boy of eleven, showing facial and abdominal obesity, thin arms and legs, hair on upper lip and chin, sparse hair on pubes, slight hair on shins and back, and diabetes mellitus. His blood pressure was 125/85.

Leyton's second case, a man of thirty-one, had a florid complexion, obese neck and abdomen (developed in less than two months), thin arms and legs, purplish striae, blood pressure 170/100, polyuria, but no glycosuria or diminished sugar tolerance, and two months later glycosuria, hyperglycaemia, and albuminuria.

Kepler's case a woman of forty-five, presented somewhat similar findings, including the diabetes.

Cases of Cushing's syndrome have been reported, which were associated with "adrenal-rest" tumours of the ovary (cf., *e.g.*, Kepler *et al.*, Green and Lapp; McLetchie and Scott). Such tumours in young girls can, however, lead merely to sexual precocity (cf. Karnaky).

DIFFERENTIATION AND TREATMENT

Introduction. From the earlier sections of this chapter it should be obvious that adrenal cortical tumours can give rise to Cushing's syndrome—so that differentiation is necessary between a pituitary basophile adenoma and an adrenal cortical tumour (or hyperplasia) —or to sexual precocity and virilism, or to some intermediate syndrome. In addition, cases of adrenal cortical tumour occur without any endocrine symptoms.

It is necessary to consider these syndromes carefully from the point of view of differentiation, and also to consider what conclusions may be drawn from certain histological tests, and the diagnostic value of urinary estimations of androgens and oestrogens, of perirenal insufflation methods, and so on.

There have been several important recent reviews, dealing more particularly with adrenal cortical tumours and differential diagnosis. Among them may be mentioned those of Dorfman, Wilson and Peters (1940), Albright, Parson and Bloomberg (1941), Kepler and Keating (1941), Wintersteiner (1941), Cahill, Melicow and Darby (1942), and Lukens (1942).

Vines' Staining Reaction. According to Vines, when sections of adrenal cortex are stained with the " Ponceau fuchsin " stain and counterstained with aniline blue, normal cells stain blue, but the cytoplasm of the cells, chiefly of the inner layer of the cortex, from adrenals removed at operation on cases of virilism, stains a vivid red colour. Almost all cases of virilism with hyperplastic adrenals give this reaction. The intensity of the reaction seems to bear a definite relation to the degree of virilism. Vines and Broster conclude that this indicates an altered functional activity of the adrenal cortical cells in this condition of virilism.

Also, according to Vines, this red stain is taken up by the acidophile cells of the pituitary, the interstitial cells of the testis, and the cells of the young corpus luteum, while the staining reaction is given by the cells of the adrenal cortex during a short period of early foetal life (more strongly and for a longer period in the male).

In carcinoma of the cortex patchy areas may stain.

Vines and Broster consider that the staining reaction is associated with clinical masculinization of the female (cf. Broster, 1939).

It has already been mentioned that Simpson and Joll's case of feminism did not give this reaction (cf. p. 408), while Fraser's case of precocious puberty in a one-year-old boy gave it strongly (cf. p. 405).

Cahill, Melicow and Darby state that this reaction is given by all

adrenal cortical tumours, in some diffusely, in some in granules, whether or not endocrine symptoms are present, although it is apparently more pronounced in the presence of such symptoms.

Crooke has reported that a case of pituitary basophilism gave a negative fuchsinophile reaction with the adrenal cortex.

Perhaps related to Vines' work is Goormaghtigh's observation that virilizing adrenal cortical tumours contain endocrine islets in whose cells lipoid material undergoes changes leading to the formation of siderophile or fuchsinophile granules, while in the feminizing tumour of Simpson and Joll (cf. p. 408) these granules were absent, but yellow pigment granules were present.

Crooke's Staining Reaction. In 1935 Crooke described a hyaline change in the pituitary basophile cells, which suggested altered physiological activity rather than cell degeneration. In cases of Cushing's syndrome the normal cytoplasm charged with ripe basophile granules is replaced by a dense homogeneous hyaline cytoplasm, which stains a uniform greyish-blue by a modified Mallory's acid-fuchsin aniline-blue method. The extent of this change shows great variations, from a small hyaline area to entire hyaline cytoplasm. The change was slightly present in a few basophile cells in nine out of 250 pituitary glands from patients in whom Cushing's syndrome was absent (the other 241 glands showing no change at all). It was present in marked degree in six cases of pituitary basophilism, three cases of Cushing's syndrome with cortico-adrenal neoplasm or hyperplasia, and the three cases of thymic neoplasm already referred to (cf. p. 410).

The cases showing no hyaline change included one with a pituitary basophile adenoma but no definite evidence of the syndrome (a woman with *generalized* obesity, slight hirsutism, striae atrophiae, normal menstruation), six other cases with basophile adenoma but no sign of the syndrome, and a case of virilism and excessive skeletal development in a girl of six years with carcinoma of the adrenal cortex.

Crooke concluded that the hyaline change is the alteration of fundamental significance in the causation of the syndrome.

Several cases of the syndrome have been reported in which there was no tumour present in the pituitary, adrenals or thymus, and adrenal hyperplasia was absent, but Crooke's staining reaction was definitely positive (cf. *e.g.*, McLetchie ; Cluxton *et al.*). McLetchie considers that the hyalinization is a cytoplasmic change resulting from hyperactivity of the basophile cells, such hyperactivity being the essential abnormality of the syndrome. (Cf. also Mellgren.)

On the other hand, Kepler (2) points out that, in presence of a basophile adenoma, the cells of the adenoma are unaffected, the hyaliniza-

tion occurring in the extra-adenomatous basophile cells, that such hyalinization in conspicuous degree is only found in presence of the syndrome and then not invariably, and that hyalinization is usually regarded as indicative of degeneration and never of functional over-activity. He gives other pertinent arguments supporting the view that Crooke's changes are a result and not a cause, and suggests that they may be the result of depressive action on the basophile cells by excessive output of adrenocortical hormones. (Cf. also Heinbecker.)

Netto has reported a case of basophile adenoma of the pituitary with Crooke's hyalinization but without Cushing's syndrome.

Excretion of Androgens and Oestrogens. While such staining reactions as those just described can only be applied to post-mortem material, and that obtained at operation, and thus can only give possible assistance in determining the mechanism of the disease syndrome, study of androgenic and oestrogenic excretion may actually prove a useful diagnostic aid.

Many steroid compounds have been isolated from the adrenal cortex, the majority of which are physiologically inactive. The active compounds fall into two groups (cf. p. 203), one concerned with mineral and carbohydrate metabolism, the other related to the sex hormones. Certain related compounds have been isolated from urine, which are undoubtedly of adrenal cortical origin (though they may have been chemically altered before excretion).

It is convenient, though with present knowledge it cannot be regarded as proved, to regard the various compounds of the second group as bye-products, or intermediate compounds produced during formation of those of the first group, normally without specific influence on sex organs and characteristics (except perhaps during the development of the young child), but, when produced unduly in the hyperplastic gland and especially in cortical tumours, capable of producing marked gonadal effects. In the majority of cases the effect is androgenic in type, in a few the reverse.

The list of these excretory compounds that have been isolated and identified is steadily increasing. They include : dehydroisoandrosterone, androsterone, aetiocholane-3(α)-ol-17-one, androstane-3(α)-11(β)-diol-17-one, oestrone, pregnanediol, pregnane-3, 17, 20-triol, Δ^5-androstene-3(β)-17(α)-diol, etc., androgens, oestrogens, and neutral compounds (cf. Wintersteiner ; Mason and Kepler ; Miller, Dorfman and Sevringhaus).

Mason and Kepler have made a careful comparison of the relative excretion of these compounds in cases with respectively adrenal tumours and adrenal hyperplasia. Relatively large amounts of dehydroisoandrosterone were excreted in five or six

cases of tumour, and little or none in four cases of hyperplasia, thus confirming the view of Crooke and Callow that excessive excretion of this compound is characteristic of the presence of a tumour.

The usual biological tests are available for measuring androgenic and oestrogenic activities in such urines, but in addition, an important chemical test has been devised by Callow, Callow and Emmens which estimates the total amount of the steroids with a keto group in position 17, the so-called 17-ketosteroids, including both the inactive compounds and those with androgenic activity (preliminary treatment removes oestrone, which is also a 17-ketosteroid). The estimation depends on a reaction with meta-dinitrobenzene in strongly alkaline solution, producing an intense red colour.

It is to be expected that these androgenic compounds will be more likely to increase in output in cases of adrenal cortical tumour or hyperplasia, than in cases of pituitary basophilism, though in the latter, with increased adrenal stimulation, an increase in lesser degree seems possible.

Crooke and Callow (1939) compared two verified cases of Cushing's disease with two verified cases of Cushing's syndrome due to adrenal cortical carcinoma. The urines for the two latter showed high values for the 17-ketosteroids by chemical test, and for androgens by biological test. The urines from the cases of Cushing's disease showed low values by comparison. (One of the adrenal cortical cases has already been referred to ; cf. p. 401).

Patterson, McPhee and Greenwood state that in adult normal women the daily excretion of 17-ketosteroids is between 3·5 and 14·6 mg. (in terms of crystalline androsterone), and in man, 9·4 and 20·9 mg., the amount varying with size. The excretion is not appreciably changed through the menstrual cycle. In young children with sexual precocity due to adrenal tumour, and in adults with Cushing's syndrome associated with such tumour, the excretion is very high (from four to ten or even twenty times the normal amount), but in cases of mild post-pubertal virilism (an ill-defined group) about half the cases are within normal limits.

Hamblen *et al.* found in thirty-four women of ages seventeen to forty, with adrenal activity varying from moderate hirsutism to marked virilism, excretion of 17-ketosteroids varying from normal to 400 per cent. above normal.

While present records are insufficient to draw final conclusions, it does appear that marked excess excretion of 17-ketosteroids probably excludes a pituitary adenoma as cause of a case of

Cushing's syndrome. The results of further examinations, with verification of the type of case, seem very necessary.

Perirenal Insufflation. Cahill considers this procedure is especially useful to diagnose the presence of small adrenal tumours, both of the cortex, and phaeochromocytomas. The amount of air necessary varies, and with the obesity of Cushing's syndrome larger amounts are required than in thinner patients. He thinks the risk is slight, but that with larger adrenal tumours, with tortuous, thin-walled blood-vessels, there is some risk of air embolus.

Kepler and Keating write : " There seems to be little doubt that in the hands of careful and experienced surgeons the method is reasonably safe, and that it is capable of disclosing the presence not only of a gross lesion but of hyperplasia and small adrenal cortex adenomas. Negative results obtained by (this) method cannot necessarily be regarded as conclusive. In some centres—at the Mayo Clinic, for example—surgical exploration remains the method of choice for determining the status of the adrenal glands. If the procedure is carried out by a competent surgeon the risk is slight, provided that both adrenal glands are not partially resected or damaged by rough handling."

Differentiation. Pituitary basophile tumours can occur in absence of the syndrome (cf. p. 412). Adrenal cortical tumours can also occur without endocrine symptoms. Some of them are highly malignant, with a tendency to metastasize to the liver and lungs. Others are encapsulated and relatively benign. (Cf. Kepler and Keating, Wu.) Cahill, Melicow and Darby point out that these tumours are relatively infrequent, and occur usually in adults over thirty, of both sexes. They are usually large and of long standing before being diagnosed because of local and generalized phenomena arising from an expanding malignant and metastasizing intra-abdominal mass. Loeb has reported a case in which recovery followed removal of a 2¼-lb. tumour from a woman of forty-eight years.

In the course of routine autopsies adrenal cortical adenomata are not infrequently found, though there was no evidence of endocrine disease during life (Kepler and Keating).

Several of those who have reviewed this subject seem to consider that virilism and Cushing's syndrome are separate entities, with, perhaps, intermediate complexes. Thus Haymaker, Webb and Anderson differentiate between the adrenogenital syndrome and Cushing's syndrome. They consider that in the latter there is over-production of the cortical hormones which control electrolyte

and carbohydrate metabolism, while in the former there is over-production of sex hormones. Wintersteiner makes a somewhat similar distinction. Kepler and Keating, on the other hand, write : " Although it may be freely admitted that individual cases have been reported which serve as typical examples of the afore-mentioned extremes, the majority of cases fail to conform to such a precise definition and as a group embrace virtually every conceivable combination of symptoms."

Such conclusions as are at present possible from the use of Vines' and Crooke's staining procedures support the differentiation.

If the views of Haymaker *et al.* were correct, then in Cushing's syndrome there should be not only a tendency to diabetes (which there is), but also an electrolyte metabolism changed oppositely to the changes in Addison's disease. Such changes have rarely been found, but in a few instances high blood sodium and carbonate with low potassium and chloride have been recorded, along with a persistent tendency to alkalosis, and the majority of such cases are of Cushing's syndrome (both pituitary basophilism and adrenal cortical tumour) (cf. Kepler and Keating).

Whichever be the syndrome associated with an adrenal cortical tumour, since surgery is the desirable treatment, undue stress need not be laid on the differentiation, although at least one surgeon has pointed out that post-operative treatment may properly differ in the two types of case (cf. below).

The specific characters of Cushing's disease and the typical adrenogenital syndrome will now be briefly contrasted, the means of differentiating between pituitary and adrenal in Cushing's syndrome summarized, and mention made of certain other lesions that can lead to similar syndromes.

The Adrenogenital Syndrome (*Virilism*). (Cf. Wintersteiner ; Cahill, Malicow and Darby.) This is rare in children, commoner in girls than in boys, and is still more common in young women.

Boys show homologous precocious puberty, with sometimes increased muscular strength. Up to 1941 there were only 14 recorded cases (Keating and Kepler).

Girls show sexual precocity, with or without some degree of masculinization, including enlargement of the clitoris, pubic hair and hirsutism. There is sometimes growth of breasts. Sometimes the voice becomes deep and coarse. There had been 40 recorded cases to 1939 (Reilly, Lisser, and Hinman).

In both sexes excretion of 17-ketosteroids is above normal.

These children show a rapid transient growth, followed by closure of the epiphyses, and later, in consequence, relative

shortness. These changes are not specific, but accompany various endocrine disorders (Gross).

When the syndrome arises at the normal time of puberty in girls, the appearance tends to be masculine, and menstruation usually does not commence (though there are four recorded cases of menstruation). When the onset is subsequent to puberty the chief characteristics are hirsutism and amenorrhoea.

In the absence of *several* of the definite stigmata of Cushing's syndrome (such as peculiar fat distribution, purple striase atrophiae, hypertension, osteoporosis, frank or latent diabetes) the conclusion can be drawn that the pituitary is not primarily involved, and that the condition is due to either adrenal cortical tumour or hyperplasia.

It must, however, be remembered that in boys sexual precocity can also arise from pineal tumours (Weinburger and Grant), testicular tumours (Parkes Weber and Rowland), and even in absence of tumour (Rush). Differentiation is usually not difficult. Thus in pinealoma (and fourth ventricle tumour) there are usually neurological signs, papilloedema, increased intracranial pressure, and disturbance of the visual fields. There is also possible increased calcification and displacement of the pineal, revealable by a ventriculogram. The excretion of 17-ketosteroids is normal (Lukens).

The Adrenogenital Syndrome (*Feminism*). This is limited to adult man. There are only six cases in the literature. There is excessive excretion of oestrogens. The main features are given in the case report on p. 408.

Cushing's Syndrome. (Cf. Albright, Parson and Bloomberg; Cahill, Melicow, and Darby; Kepler and Keating.) The outstanding features are unrelated to age or sex, or to the primary involvement of adrenals or pituitary (cf. Cushing's original description, p. 397).

Obesity is usual, but of specific type (" buffalo type "), confined to face, trunk and abdomen, with thin extremities. " The full, moon-like face, the pad of fat high in the dorsal region, and the other changes which occur in the distribution of fat, produce a characteristic habitus " (Kepler and Keating).

Hirsutism is common in women, without other evidence of virilism.

Certain skin changes are almost invariable The face is plethoric, dusky red in colour Often the skin of the entire body is mottled, with dusky purplish red areas, most noticeable in the extremities. There are *purplish striations*, chiefly on abdomen, buttocks, thighs and arms, often 1+ by 10+ cm. in size.

Hypertension is frequently present, affecting both systolic and diastolic pressure.

Osteoporosis is fairly common (the serum phosphatase is normal). The skull and spine are frequently involved; compression fractures may occur in the vertebral bodies (cf. Sussman and Copleman).

Frank *diabetes mellitus* is rare, but when present is insulin-resistant (Albright *et al.*) and probably represents the so-called Achard-Thiers complex of the bearded woman with diabetes. A *decreased sugar tolerance* is common.

Amenorrhoea in woman and *impotence* in man are almost always present.

Muscular weakness, fatigue and pain are met with (especially backache and nerve-root pain from osteoporosis. Basal metabolism may be low.

Acne is common, polycythaemia occasional and slight. The visual fields and the pituitary fossa are normal.

Albright, Parson and Bloomberg consider that the disturbance in carbohydrate metabolism is due to a hypergluconeogenesis, which leads to a protein shortage, from which result weak muscles, thin skin (hence the striae), easy bruisability, and osteoporosis (through lack of bone matrix), there being in these cases a negative nitrogen balance. Kepler and Keating do not accept this view.

Differentiation between the Pituitary and the Adrenal as cause of Cushing's Syndrome. The syndrome itself shows no distinguishing features. Any evidence that incriminates the adrenals is useful in excluding the pituitary.

Pituitary basophilism is extremely rare below the age of twelve years (Gross). In adult man the adrenals are but seldom involved.

Presence of a palpable tumour mass at the site of one or other of the adrenals, or X-ray evidence following perirenal insufflation fairly certainly incriminates the adrenals.

Marked excess excretion of 17-ketosteroids probably indicates the adrenals, but further controlled data are necessary.

Women with some degree of hirsutism, sometimes associated with menstrual disturbances, sometimes with some degree of obesity, or a slightly masculine habitus, may or may not belong here, as pre-syndrome cases. Therapy in this group is almost always without benefit (Kepler and Keating; Bissell and Williams).

Some patients in this ill-defined group who have amenorrhoea give a vaginal smear test indicative of low oestrogenic activity.

In an interesting recent editorial in the Journal of Clinical Endocrinology, Lisser points out that an embarrassing moustache and beard with excessive hair growth elsewhere on torso and extremities occur far more frequently in adult girls and women than is generally sup-

posed, and that unfortunately the overwhelming majority of these hirsute women have no other complaints and display no other abnormalities than the heterosexual hypertrichosis, which is, at least in many of them, an intensified racial characteristic. Endocrine treatment, including oestrogenic treatment, has not proved beneficial. Lisser quotes the paradox that it would be better for these women were they worse, in so far as if there were definite accompanying evidence of an adrenal cortical tumour, removal of this would remove the hirsutism, as well as the more severe effects of the hypercortico-adrenalism.

The rare cases of thymic tumour with adrenal cortical hyperplasia seem to come within the scope of Cushing's syndrome. X-ray differentiation should be possible.

Cases of *arrhenoblastoma*, while exhibiting several of the features of Cushing's syndrome, can usually be distinguished by absence of the characteristic obesity, usually absence of striae atrophiae (if present, they are scarcely ever purplish), usually absence of hypertension, absence of osteoporosis and diminished sugar tolerance (cf. Dorfman, Wilson and Peters).

Treatment. When an adrenal cortical tumour or hyperplasia can be diagnosed, surgery is the treatment, whether the patient exhibits the adrenogenital syndrome or Cushing's syndrome.

Reports, especially the earlier reports, indicate a high operative mortality, which Keating and Kepler attribute to the frequently induced inactivity of the unaffected adrenal, so that after removal of a tumour there ensues a state of acute adrenal insufficiency. It is becoming customary to prepare the patient for one or two days before operation, and to continue the treatment for seven to ten days after operation, as with a crisis in Addison's disease.

The treatment at the Mayo Clinic is as follows : A litre of physiological solution of sodium chloride to which has been added 5 gm. sodium citrate and 10 c.c. of a potent adrenal cortical extract, is injected intravenously during the day before operation, and again both pre-operatively and post-operatively on the day of operation, and daily thereafter for three or four days ; then the amount of cortical extract is reduced to 5 c.c. per day, intramuscularly, intravenous sodium chloride is discontinued, but equivalent amounts of sodium chloride and citrate are given orally. The treatment is maintained till the need seems no longer apparent, then is discontinued gradually.

Concerning the after results of operative removal of a tumour, the following authoritative statement may be quoted from Kepler and Keating : " Except in instances of tumour among children, in which precocious epiphyseal union may occasionally have produced irreversible dwarfism, and in certain instances in which facial hair has persisted, the disappearance of symptoms is usually complete after total removal of the tumour. If the tumour has penetrated its capsule, eventual recurrence, either locally or in the form of widespread metastasis, is to be anticipated."

Cahill, Melicow and Darby found in two cases (girls of sixteen and eighteen years) in which there was only masculinization, and no evidence of the true Cushing's syndrome, removal of tumours was not accompanied by acute adrenal deficiency " because with only excess androgens excreted there was not reasonable expectation of functional atrophy of the opposite adrenal." Recovery in both cases was uneventful, without Addisonian treatment. Excess androgens disappeared from the urine.

When there is only adrenal hyperplasia, either unilateral adrenalectomy, or partial bilateral adrenalectomy is performed, according to the preference of the surgeon. Improvement appears not quite so certain as after satisfactory removal of a tumour.

In cases of Cushing's disease, irradiation of the pituitary has been carried out and " at times has led to remarkable improvement, but on the whole the results of treatment of Cushing's disease have been most unhappy " (Kepler and Keating). Luft, reporting on the results of eight cases treated by irradiation, states that good results were obtained in five, and moderate results in the others. In one the apparent cure had lasted ten years. Crooke (2) advocates implantation of radon seeds.

Albright, Parson and Bloomberg have reported that the use of testosterone propionate in three cases of Cushing's syndrome in which adrenal cortical carcinoma was not present (and which were presumed to be pituitary basophilism) resulted in the establishment of a positive nitrogen balance (cf. p. 390), retention of phosphorus, increase of strength of the patients, decrease in skin redness, and loss of easy bruisability. In one patient, when the therapy was stopped, the changes were reversed. Oestradiol benzoate did not produce such improvement, and progesterone was much less effective.

On the other hand Rakoff, Cantarow, and Paschkis treated two cases of apparent pituitary basophilism with stilboestrol, and claimed to obtain clinical improvement, return of normal carbohydrate metabolism, reduction of blood pressure, and (in one) return of normal menstrual function.

The brief case reports reproduced in the earlier part of this chapter illustrate a number of the above points.

Addendum. Roholm and Teilum (Acta med. Scand., 1942, cxi, 190) have published a detailed account of a case of feminizing tumour of the adrenal cortex with an excellent summary of the six cases earlier reported in the literature. These cases exhibit gynæcomasty, genital atrophy, and loss of sexual function, and, where examination has been made, marked increased excretion of œstrogen and slighter increased excretion of androgen.

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CHAPTER XIII

SOME OTHER HORMONES AND SOME RELATED PROBLEMS

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ACTUAL AND PRESUMPTIVE HORMONES OF THE GASTROINTESTINAL TRACT

Secretin. In 1902 Bayliss and Starling demonstrated the existence of secretin and its action in stimulating the outflow of pancreatic juice and bile. The first considerable concentration of the hormone was accomplished in 1928 by Mellanby. Ågren and Wilander in 1933 isolated a crystalline polypeptide with a molecular weight of about 5,000 and one atom of sulphur to the molecule (cf. Hammarsten *et al.*).

In 1938, Greengard and Ivy isolated a crystalline secretin picrolonate which they considered to be a still simpler compound. It gave negative ninhydrin, Hopkins-Cole, and Millon's tests, and a doubtful biuret reaction. The discrepancy between these results is obvious.

Scott and Still have found some evidence for the existence of a pro-secretin.

According to Florey and Harding the secretion of Brunner's glands is under the control of secretin. Fogelson and Bachrach agree that intravenous injection of secretin is followed by the secretion of a viscid juice from the Brunner gland area of the duodenum, but consider that proof is still lacking that such secretion is entirely independent of the increased duodenal motility accompanying the secretion.

Injection of secretin leads to gastric secretion, probably by direct action on the glands of the stomach mucosa. Pratt found that the smallest dose which would activate the pancreas also produced secretion of pepsin.

Intravenous injection of secretin has proved of use in diagnosis of pancreatic diseases; a clear uncontaminated specimen of pancreatic juice can be obtained for analysis by means of a double lumen gastroduodenal tube (cf. Diamond and Siegel).

Nothing is known of any condition associated with hyper- or hypofunction of secretin.

Pancreozymin. Harper and Raper have demonstrated that extracts of duodenal mucosa contain two hormones affecting the external secretory activity of the cat's pancreas. One is secretin, and the other they term *pancreozymin*. Secretin stimulates the production of fluid and bicarbonate by the pancreatic acini, while pancreozymin does not possess this property but causes a marked increase in the production of pancreatic amylase.

Greengard, Grossman, Wooley and Ivy have confirmed these results. They separated pancreozymin from secretin by precipitation with aniline. It stimulates equally the formation of pancreatic amylase, lipase and trypsin. Incubation with blood serum inactivates it, suggesting that normally it is slowly inactivated in blood by some enzymic action.

Gastrin. Edkins in 1906 claimed that gastrin (corresponding to secretin) existed in the gastric mucosa. Later work did not support this view. Ivy isolated histamine from acid extracts of the pyloric mucosa and adduced some evidence that gastrin might be histamine, but the work of Babkin's pupils, McIntosh and Komarov suggests that they are not identical. The existence of gastrin is still uncertain.

Babkin has shown that histamine stimulates the parietal cells of the gastric glands (and can inhibit the activity of the peptic cells in appropriate concentration). Its diagnostic clinical use is limited to determining the ability of the stomach to produce hydrochloric acid. Babkin has shown further that subcutaneous or intravenous injection of insulin provokes a copious secretion of gastric juice in animals and man, only a little less acid than that produced by histamine, but rich in pepsin and mucus. Insulin administration therefore stimulates both parietal and peptic cells, and does this presumably through production of a hypoglycaemia which stimulates appropriate brain centres to cause the needed vagal stimuli.

Cholecystokinin. Ivy *et al.* found by cross-circulation experiments that when acid is injected into the duodenum, something passes into the blood which causes the gall-bladder to contract. They claim to have prepared an extract from the upper intestinal mucosa free from secretin, which when injected into dogs, cats, or man (but not rabbits), causes contraction and evacuation of the gall-bladder. They consider that an endocrine principle is involved, and term it *cholecystokinin*. Still has obtained similar results. (Cf. also Walsh ; Houssay and Rubio.) Ågren has prepared a highly active extract, free from secretin.

Enterogastrone. An extract has been prepared from the upper intestinal mucosa, which inhibits gastric motility and secretion, and is believed by Ivy and Gray to contain a specific hormone which they term enterogastrone. It is considered to be liberated from the intestinal mucosa when neutral fat and glucose come into contact with the mucosa. Urine also appears to contain this substance. As prepared from urine, it is termed *urogastrone*. It seems to be a complex organic base. Injected into dogs, it inhibits the gastric response to histamine, and also pancreatic and biliary secretion, but not salivary secretion. It is not " kallikrein " (cf. Gray *et al.*).

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THE THYMUS AND PINEAL GLANDS

The Thymus Gland. Numerous diseases affect the thymus, but scarcely any can be considered as directly associated with it. It appears to be enlarged in Graves' and in Addison's diseases, and is persistent after early castration, while it diminishes in size in wasting diseases, and in starvation and inanition.

Enlargement is especially associated with " thymic stridor " and " thymic asthma " occurring at or shortly after birth, and the so-called " status thymico-lymphaticus," though the existence of these as entities is by no means certain, let alone their association with the thymus.

The earlier literature was reviewed by Rowntree *et al.* (2) in 1935 ; they gave an extensive bibliography. For long it has been believed that the thymus was associated with growth. Asher and his colleagues prepared a concentrate from thymus which appeared to accelerate growth in rats. They considered that it contained a hormone, which they named *thymocrescin*. Rowntree *et al.* (1, 2) tested a preparation made by Hanson from calves' thymus glands, and found that continuous injections into rats over several generations appeared to accelerate growth and precocious development markedly (cf. Fig. 74). Later work suggested that this might be due to glutathione (Rowntree *et al.* (3) ; Lee and Ayres), which is present in the thymus (Shaffer and

Ziegler). Rowntree also claimed that thymectomy in successive generations produced retardation in growth, but only a mild retardation in sex development. Chiodi repeated Rowntree's work and could not confirm it.

Segaloff and Nelson (1) repeated Asher's work with a "thymocrescin" preparation and were unable to confirm his results. Later (2) they have listed results of a number of investigators, several of whom used Hanson's preparations, and neither these, nor Segaloff and Nelson themselves, could confirm Rowntree's results, either as regards precocious growth or precocious development. Segaloff and Nelson suggest that a partial explanation of the phenomena observed by Rowntree and his collaborators might be that his *control animals*

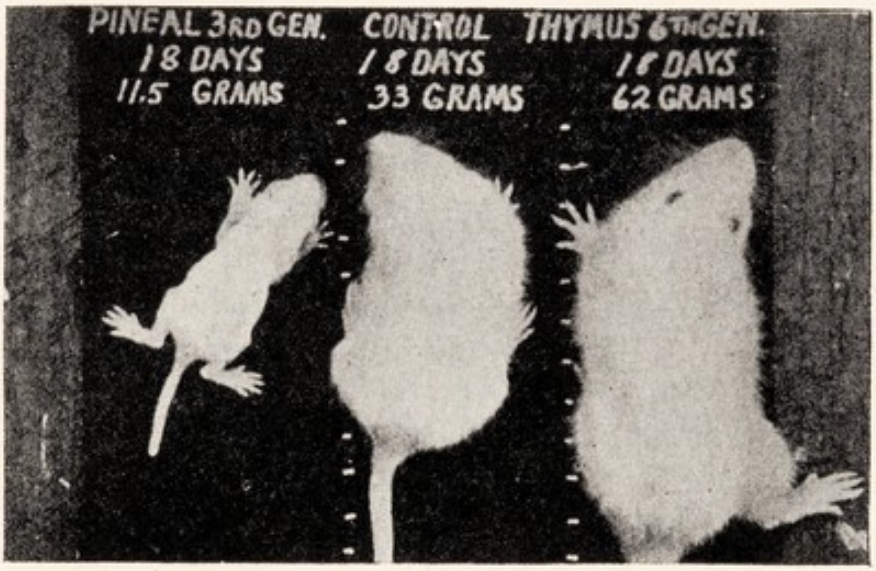

FIG. 74. Comparison of a thymus-treated rat of the sixth generation, a pineal-treated rat of the third generation, and a control, all eighteen days old. (From Rowntree *et al.*, Ann. Int. Med., 1935, ix, 359.)

showed inferior growth and delayed maturation due to dietary deficiencies.

It would appear that at present there is no satisfactory evidence associating the thymus with growth.

A high percentage of autopsies on patients with myasthenia gravis has shown thymic hypertrophy or tumour (Eaton). Thymectomy has been stated to have produced good results in this disease (cf., *e.g.*, Blalock *et al.*; Harvey, Lilienthal and Talbot), especially when thymic tumours are present (Campbell *et al.*), or there is a persisting and possibly hypertrophic thymus. X-ray irradiation of the region of the thymus also produces marked improvement, so that Eaton considers there is strong evidence relating the disease to abnormalities of the gland. Symptoms resembling those of myasthenis gravis have been produced in the experimental animal by thymus implants or injections. Thymectomy has become an important adjunct to the available drug treatment of the disease (by prostigmine, ephedrine, potassium salts in relatively high dosage, and guanidine hydrochloride (cf. also Clagett and Root).

Thymic tumours are rare. Homburger found 14 cases of thymic enlargement in adults in 6,000 autopsies. Of these 3 were cases of carcinoma, 3 of persistence associated with thyrotoxicosis, and 2 of non-cancerous thymic tumour coincident with myasthenia gravis. In these two epithelial metaplasia was an outstanding feature, and was accompanied by extreme scarcity of the corpuscles of Hassall.

Wilson and Stoner find that the blood of patients with myasthenia gravis contains a substance which interferes with neuromuscular transmission, and which may be associated with the thymus. It probably inhibits the normal action of acetyl choline on voluntary muscle.

The association of thymic carcinoma with Cushing's syndrome has been dealt with (p. 410).

There is still no definite evidence that the thymus produces a hormone.

The Pineal Gland. The two outstanding pieces of information about the pineal in the earlier literature are : (1) Boys with a teratoma of the pineal exhibit abnormal growth, associated with some degree of premature genital development, and die young following symptoms of brain tumour (cf. Vincent) ; and (2) the feeding of ox-pineal to tadpoles along with plant food, from the beginning of larval life, causes a translucency lasting about three hours, and sufficient to permit the beating heart to be visible, the phenomenon persisting to the stage of metamorphosis (McCord and Allen ; Huxley and Hogben ; Addair and Chidester). Neither phenomenon has been explained.

The results of Rowntree *et al.* (4) with injections of pineal gland preparations into rats were in part the antithesis of those they obtained with thymus preparations (cf. Fig. 74). They have not been confirmed. Einhorn and Rowntree found that pinealectomy in successive generations had no effect on the offspring (cf. also Sullens and Overholser).

Fischer claims to have prepared an extract of the pineal which delays the opening of the intact vaginal membrane in mice.

There is still no definite evidence that the pineal gland has endocrine functions.

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OTHER SUGGESTED HORMONES

A Blood-Pressure Depressant. Various groups of workers have prepared extracts from the pancreas, which are stated to be free from insulin and to have a definite effect on the circulation, lowering the blood pressure. Beneficial results have been claimed from the use of such extracts in cases of hypertension.

It would seem probable that the same substance is responsible for these effects, although neither its specificity nor its endocrine nature can be regarded as established. Gley and Kisthinios made an acidified-alcoholic extract and termed it *angioxyl* (cf. Giroux and Kisthinios). Kraut and Frey's extract is termed by them *kallikrein*, while Santenoise has termed his preparation *vagotonine*; the term *padutin* is also used for this substance. *Carotidin*, from the carotid gland, may be similar (Christie). According to Bischoff and Elliott kallikrein is of colloidal protein nature and somewhat unstable. They consider that its physiological significance is questionable.

Renin. Vasopressor extracts of the cortex of the kidney were first prepared by Tigerstedt and Bergmann in 1898, and the active constituent termed by them *renin*. Within recent years much work has been done on this compound by numerous investigators, and especially by Houssay and his co-workers in Buenos Aires, and Page and his colleagues in Indianapolis. The independently obtained results of these two groups, in close agreement with each other, stress the accuracy of their conclusions. The work on renin has recently been reviewed by Houssay and Braun-Menendez, and by Fraenkel-Conrat. Schales has critically discussed methods of preparation.

Renin is an enzyme, and a globulin. It is secreted by the kidney into the blood stream, and there acts upon a globulin *hyperten-*

sinogen (the " renin-activator " of Page) to produce *hypertensin* (Page's " angiotonin "). Hypertensinogen originates in the liver. The fate of renin in the blood is not certainly known, although blood and tissues contain an enzyme *hypertensinase*, which destroys it. It only appears in the urine when injected in large amounts.

Page and Helmer have prepared crystalline salts of hypertensin, which is thermostable, dialysable, and fluorescent, and appears to be a polypeptide with phenolic groups (since tyrosinase and amino-peptidases inactivate it). Plentl and Page (2) state that tyrosine, phenylalanine, and dihydroxyphenylalanine radicals are absent.

Pepsin will also convert hypertensinogen into hypertensin, Pepsin will also convert hypertensinogen to hypertensin (though Plentl and Page (1) state that the pepsin and renin products are not identical) and, in addition, it produces compounds with some pressor activity by its action on casein, egg-albumin, and other proteins. Only gelatine yields no pressor derivatives, which suggests that tyrosine radicals are necessary in the active polypeptides (cf. Croxatto and Croxatto). While pepsin is non-specific in this action, renin is highly specific (cf. Bean). The renin of man will only act on the hypertensinogen of man.

Renin, when injected intravenously into dogs, produces a gradual rise in blood-pressure which lasts ten to thirty minutes, depending on the amount injected. Consecutive injections of large doses at short intervals produce each time a smaller response, a phenomenon described by Tigerstedt and Bergmann and termed " tachyphylaxis." Renin itself, however, is neither vasoconstrictor nor vasopressor ; the effects are due to the hypertensin produced by its action.

After partial constriction of the renal arteries there is evidence that renin is present in the venous blood leaving the kidneys. Re-establishment of the renal circulation of the kidney *in situ* after total ischaemia lasting two to six hours causes a rise in arterial blood pressure similar to that produced by injection of renin, and presumably due to it. Similarly, if the ischaemic kidney of a hypertensive dog is grafted into the neck of a normal dog, a rise in blood pressure follows.

Hypotension due to haemorrhage or shock causes liberation of renin by the intact kidney of the normal anaesthetized dog (Huidobro and Braun-Menendez).

All these results lead to the inference that the kidney participates in the regulation of arterial blood pressure, and that renin

is used by the body to maintain haemostasis ; it seems probable that further work will lead to valuable clinical applications.

The secretion of renin, an enzyme, into the blood by the kidney for functional purposes, conforms to the old definition of an internal secretion, making renin a hormone and the kidney an endocrine gland. This seems, however, a slight extension of our usual conception of endocrine glands.

Splenin (?). Ungar states that certain trauma, haemorrhage, starvation, and certain noxious stimuli elicit an endocrine response involving the pituitary, the adrenal cortex and the spleen, which he considers to be the same phenomenon as is seen in Selye's " alarm reaction " (cf. p. 208). The response is inhibited by splenectomy. The spleen contains an active substance which will when injected reproduce the reaction to the original stimulus. This " splenin " has been isolated in pure crystalline form, has a low molecular weight, and is soluble in water, ether and chloroform. In extremely low concentration it shortens the bleeding time of guinea-pigs. It is thought to be part of an anti-enzyme system which protects proteins against proteolytic enzymes, and may possibly be a hormone.

Goormaghtigh postulates on histological grounds a hormone elaborated by the afibrillar smooth muscle cells of the kidney, itself non-protein in character, but activating globulins in the arteriolar wall to form vaso-active substance.

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ANTIHORMONES

Antihormones are antibodies formed in an organism in response to injection of protein-hormones whose precise nature is foreign to that organism. All protein-hormones do not produce anti-hormones.

A Presumptive Anti-thyroid Compound. Early therapeutic treatment of hyperthyroid conditions included use of the serum of thyroidectomized animals. Such preparations as "anti-thyreoidin Möbius" had a long vogue, but ultimately more critical appraisal led to disuse (cf. Falta-Meyers). More recently Blum prepared a concentrate "Katechin" from dried blood, believed to contain an anti-thyroid compound, and sold under the name of "Tyronorman." Good results have been claimed for it in treatment of Graves' disease (Herzfeld and Frieder) though its value is doubtful (Zondek).

An Anti-thyrotrophic Compound. Soon after the discovery that certain pituitary extracts possess thyrotrophic activity, it was observed by a number of investigators that chronic treatment with such extracts rapidly ceases to affect the thyroid suggesting that some protective action gradually sets up an immunity. Detailed studies of the phenomenon were made by Collip and Anderson, who showed that chronic treatment of normal or hypophysectomized rats or guinea-pigs with a purified thyrotrophic preparation produced an initial rise in basal metabolism, which after two or three weeks fell to normal, and then to levels much below normal; further treatment, even with larger doses, then produced no apparent effect, though the thyroids of such animals were still hyperplastic, while the animals themselves still responded to thyroxine.

Chronic injection of a mare with an active thyrotrophic preparation yielded a serum with anti-thyrotrophic potency, which definitely inhibited the action of the thyrotrophic preparation on normal or hypophysectomized rats.

Anti-gonadotrophic Compounds. Collip and his co-workers showed that chronic overdosage with the follicle-stimulating hormone of the pituitary, or with A-P-L of pregnancy-urine similarly led to production of anti-compounds (cf. Collip).

Present Views on the Nature of the Antihormones. Numerous investigators suggested that the anti-reactions set up were really of immunological type. This view is now generally held (cf. Chase). Injection of glandular tracts from one species of animal into animals of the same species do not seem to produce an anti-hormone effect, provided fresh glands are used for the extracts (cf. Wintersteiner and Smith; Cutting).

It must not be forgotten, in considering this problem, that it is quite likely that the majority of pituitary preparations used in all experimental work at present are artefacts, containing proteins which are potent as hormones, but altered from those actually

formed by the pituitary, and therefore through this alteration potentially foreign proteins capable of eliciting antibody formation. It must also be remembered, even if antihormones are merely antibodies whose formation is due to foreign proteins, that their effects must still be considered in interpretation of all experimental work in which their formation is possible.

There is some evidence that therapeutic injections (especially if over some period) of pituitary preparations and of equine gonadotrophin lead to antibody formation in patients (Leathem ; Rakoff).

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INTERRELATIONSHIPS

The marvellous integration of functions of the animal organism involves numerous examples of close interrelationships in the functions of various endocrine glands. A number of these have already been considered. Full discussion would need much space, and much reiteration of material already presented. Only the briefest recapitulation is possible, supplemented with additional data briefly recorded.

The pituitary functions in large part through its control of the thyroid, the adrenal cortex, and the gonads. The relationships are not entirely one-sided. Thus thyroid extirpation in rabbits is followed by a definite enlargement of the pituitary, and some histological changes have been noted, including increase in colloid. Some degree of pituitary hypertrophy has been observed in thyroidectomized lambs. Man and other animals with endemic goitre or cretinism have enlarged pituitaries. When goitre is produced in rabbits by a cabbage diet (p. 33) the pituitaries of the animals are affected in a fashion similar to that following thyroidectomy. There is increase in size of all glandular cells, and partial or

complete disappearance of stainable granules in the acidophile cells. Administration of thyroid or iodine to the goitrous rabbit, and of thyroid but not iodine to the thyroidectomized rabbit, prevents these changes, which must therefore be due to lack of the thyroid hormone (cf. Marine *et al.*).

When thyroid is fed to normal rats the pituitaries become subnormal in weight, with perhaps a slight increase in the percentage of basophile cells, and a definite increase in their size and granular content, accompanied by a change in staining properties. These changes are most marked in animals in which suppression of the oestrous cycle is most evident, suggesting a triangular interrelationship (cf. Campbell, Wolfe and Phelps).

Chu and You conclude from experiments on rabbits that the thyroid hormone inhibits the output of FSH from the pituitary and increases that of ICSH.

The reciprocal relationship between thyroid and anterior pituitary is becoming stressed, the two glands being regarded as setting up in the normal animal some kind of equilibrium. Salter speaks of the pituitary-thyroid axis (cf. Means). Severinghaus has reviewed the interrelationship from the point of view of histological changes.

The reciprocal relationships between the pituitary and the gonads have been fully discussed already (cf. Chapters VIII, IX).

In addition to these direct relationships evidence has also been adduced of certain indirect relationships, in some of which the pituitary plays a part. Thus the islets of Langerhans respond to a hyperglycaemia by increasing their output of insulin, and such hyperglycaemia can result from increased pituitary activity (cf. p. 321). A similar indirect relationship may be considered to exist between the islets and the thyroid, in that they also respond to the hyperglycaemia that may accompany a severe hyperthyroidism ; this indirect relationship is indeed the probable cause of a small percentage of cases of diabetes (cf. Regan and Wilder).

Houssay has shown that prolonged administration of thyroid does not produce diabetes in normal dogs, but does so in dogs (7 to 12 kg.) which have had five-sixths or seven-eighths of the pancreas removed, though they still have normal blood sugar. Such diabetes may persist only during the period of thyroid feeding (thyroid diabetes) or may become permanent (*metathyroid diabetes*). In the latter case the beta-cells of the pancreatic islets have become permanently damaged, and the diabetes has the same characteristics as clinical diabetes.

Houssay states that co-existing diabetes and hyperthyroidism mutually aggravate each other.

There is also evidence relating the thyroid and gonads. In

woman, at puberty, during the menstrual periods, and during pregnancy, the thyroid enlarges. Thyroidectomy in young animals results in some degree of sexual infantilism. Myxoedema is accompanied by depression of sexual function in both sexes. Thyroid disorders are frequently accompanied by menstrual disturbances ; an uncontrolled rhythm is often recorded and seems especially characteristic (Rowe). Administration of thyroid is frequently beneficial to women with amenorrhoea, somewhat low basal metabolic rate, but no specific hypothyroid symptoms (cf. Haines and Mussey).

Injections of oestrone into rats, rabbits and dogs lead to changes in the thyroid in the nature of colloid goitre, or suggesting hypofunction (Bialet-Laprida ; Kapp and Kostriewicz).

Such an interrelationship need not necessarily involve direct control of either gland by the hormone of the other.

Pancreatectomy augments blood inorganic phosphate and lowers blood calcium, producing definite lesions of the parathyroids (Gershman and Marenzi ; Houssay and Sammartino).

Numerous similar examples of interrelationships might be cited, many of them indirect, and perhaps mediated through non-endocrine organs.

Pluriglandular Disorders. In many endocrine disorders more than one endocrine gland is involved, through such interrelationships as have just been discussed. These are not examples of pluriglandular disorders.

Only when two unrelated endocrine disorders co-exist in a patient can a pluriglandular disorder truly be said to exist. Examples are the co-existence of hyperthyroidism and diabetes mellitus, present in scarcely if any more patients than the laws of chance suggest is probable (cf. Wilder ; Regan and Wilder ; Joslin and Lahey, Foster and Lowrie), and, much rarer combination, hypothyroidism and diabetes (Wilder ; Rowe).

Rowe, writing in 1932, stated, " In a series of over 5,000 cases the writer has seen but two or three in which there has been apparently a co-existent primary disturbance in more than one endocrine gland."

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