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Suprarenocortical syndrome and pituitary basophilism

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SUPRARENOCORTICAL SYNDROME AND
PITUITARY BASOPHILISM

LEONARD HOBBS BARBER

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INTRODUCTION

From various sources in recent years new facts have been unearthed both in clinic and laboratory which have thrown light on many heretofore obscure activities of the pituitary gland and adrenal gland.

The existence of what we now speak of as an internal secretion was perhaps first experimentally demonstrated by Berthold's studies in 1849 on transplantation of the cock's testis. (1) The idea was given further impulse by Bernard's classical investigations on hepatic function showing the existence of a secretion interne (glycogen) in addition to the known secretion externe (bile). In the same year, 1885, appeared Addison's immortal monograph attributing a definite clinical syndrome to a destructive process of diseases of the suprarenal capsules. The way was thus prepared for the concerted action of experimentalists, pathologists and clinicians, whose brilliant series of studies in the later years of the century resulted in placing our knowledge of the disorders of the thyroid gland and their effective treatment almost on its present plane. (1)

The other glands have notably lagged behind with the pituitary body at the tail of the procession. For though this structure was added to the group of so-called ductless glands by Liegeois some seventy years ago, its inaccessibility has been sufficient to discourage investigation even were there no other difficulties to be confronted. One important principle, however, underlying the whole subject of ductless gland disorders, namely that lesions of one gland affect the structure and function of others,
was the outcome of studies made by Rogowitsch on alterations in the hypophysis due to thyroid extirpation. (1)

That a primary derangement of the pituitary gland, whether occurring spontaneously or experimentally induced, was particularly prone to cause widespread changes in other endocrine organs was appreciated even at that early day and it was strongly suspected that this centrally placed and well protected structure in all probability represented the master-gland of the endocrine series.

The multiglandular hyperplasias of acromegaly so evident in the thyroid gland and adrenal cortex, were already known and the no less striking atrophic alterations in these same glands brought about by the conter state of pituitary insufficiency were coming to be equally well recognized by 1912. (1) Out of this obscurity, those seriously interested in the subject have, step by step, been feeling their way in spite of pitfalls and stumbling blocks innumerable. (2) The usual method of progression has been somewhat as follows: A peculiar syndrome has first been described by someone with a clarity sufficient to make it easily recognizable by others. This syndrome in course of time has been found to be associated with a destructive lesion or with a tumefaction primarily involving one or another of the organs in question. These tumefactions have proved in most cases to be of adenomatous character and it was finally recognized (first in the case of the thyroid) that adenomas of this kind were functionally active structures that produced hypersecretory effects. It then gradually came to be realized that the tumor need not necessarily be
bulky but, quite to the contrary, striking clinical effects might be produced by minute symptomatically predictable adenomas. So it is the degree of secretory activity of an adenoma, which may be out of all proportion to its dimensions, that evokes the recognizable symptom-complex in all hypersecretory states.

**Primitive Views of the Pituita.**—Nature saw fit to enclose the central nervous system in a bony case lined by a tough, protecting membrane, and within this case she concealed a tiny organ which lies enveloped by an additional bony capsule and membrane. No other single structure in the body is so doubly protected, so centrally placed, so well hidden.

When anatomists first undertook roughly to describe the brain, they were so baffled by the complexities of the region overlying the sella turcica that the best Galen, the greatest of them all, could do was to call it "the seine-like net," and as he thought it an astounding structure those who came long afterward to put him into Latin, used the term rete mirabile. It however was not until well into the seventeenth century that Willis began to untangle the net by describing the vascular "circle," both arterial and venous, which surrounds it. The function of the pituita was thought to be a filter or trap whence the slime or pituita—the waste product of the transformation in the cerebral ventricles of vital into animal spirits—found its way into the nose and pharynx. The ascidian larvae have permanent communication between the ventricle and primitive mouth, and a demonstrable duct actually exists in the embryonic stage of all vertebrates. In 1778 the gland was newly named the hypophysis cerebri and brushed...
aside and assigned the limbo of vestigial relics. (3)

It was not until 1894 when Schafer discovered extracts in the posterior lobe were pressor substances that the structure was not vestigial after all. (3)

But this disclosure, important though it was, was not what first drew renewed attention to the neglected organ. Our knowledge of the processes of disease almost invariable starts with the description by someone of a clinical syndrome which others quickly recognize, and only then does the labor of running it down to its seat and cause really begin. So from clinicians such as Addison and Gull, Graves and Basedow, and Marie, to mention but a few of them, came our first recognition of the group of maladies we have learned to associate with disorders of the ductless glands.

The suprarenal glands were first described by Eustachius in 1563. (4) Despite much speculation and considerable investigation no true inkling of their function in the body was apparent until the memorable studies of Thomas Addison, culminating in 1855 in his classic description of the disease which now bears his name, morbus addisonii. In the following year Brown-Sequard showed that these glands were essential to life, and Vulpian, the discoverer of the chromaffin system, demonstrated in them the substance, probably adrenalin. The cortical hormone, which concerns the syndrome concerned in this thesis, the substance essential to life, has eluded the chemist until quite recently when a mildly active aqueous extract was prepared by Rogoff and Stewart in 1929. (5)
Due to the curious interdependence between endocrines, there are innumerable case reports of mixed syndromes apparently greatly benefited by various forms of endocrine therapy. Doubtless pure endocrine dysfunction does exist, but it is the belief of many authorities that the great bulk of syndromes with pituitary insufficiency or hyperactivity have an organic basis. The pathologic lesions underlying certain pituitary and suprarenal cortical hyperplasias are being established, and these will be described in some detail with the clinical syndrome produced.
ANATOMY OF THE HYPOPHYSIS AND ADRENAL

The development, structure, and relations of the hypophysis have assumed, in recent years, a position of major importance. Modern physiologic and pathologic research have demonstrated that in spite of its small size, it occupies a most important position among the endocrine glands and its surgical removal or its destruction by disease is incompatible with life. As it is located among important nerve structures at the base of the brain, its lesions are evidenced by disturbances in function sufficiently localized to permit early clinical recognition. (6)

The hypophysis occupies the hypophyseal fossa (sella tursica), being attached to the base of the brain behind the optic chiasm by the infundibulum, weighs about one half gram, and has a transverse diameter of 12 to 15 mm, and a vertical and antero-postero diameter of from 5 to 8 mm. It consists of an anterior lobe (pars anterior), a posterior lobe (pars nervosa), and a middle lobe (pars intermedia).

The anterior lobe forms two-thirds of the pituitary, and partially envelops the posterior lobe. It is derived from Rathke's pouch, an outgrowth from the buccal cavity, and is composed of columns of epithelial cells and with numerous blood sinuses and vessels. It is apparently not essential to life (Camus and Roussy). (7)

The secretion influences: (a) the growth of the skeleton, skin, and soft tissues; (b) the sexual organs; (c) calcium and magnesium metabolism; (d) carbohydrate metabolism; (e) basal metabolic rate.

The pars nervosa and infundibulum develops from a down growth
of the cerebral vesicle, the thalamencephalon. The posterior lobe - rather avascular and made up chiefly of neuroglia without true nerve cells or fibers - has an internal secretion, pituitrin.

The suprarenal glands are composed of a cortex and medulla: (a) the cortex (of mesoblastic origin) consists of a (1) zona glomerulosa with columns of rounded cells; (2) zona fasiculata, with lipoid granules; (3) zona reticularis, with pigmented cells.

The cortex influences strength, mental development, and secondary sexual characteristics, including growth of hair.

(b) medulla (of neuro-ectodermic origin) consists of strands of ectodermal chromaffin cells, blood spaces, nerve cells, non medullated nerve-fibers. The active principle of the medulla is the internal secretion, epinephrin. (7)
NORMAL PHYSIOLOGY OF THE PITUITARY

The Effects of Extirpation.—Experimental surgeons are agreed that ablation of the neurohypophyseis is not fatal and accompanied at most by polyuria and sometimes glycosuria. As regards the importance of the anterior lobe for life, the data brought forward by equally competent surgeons has been contradictory. Those who regarded the gland indispensable for life (Cushing, Bell, Dort, Homans and Crone) (8) suspected the retention of accessory hypophyseal tissue. Others who believe it unessential (Victor Horsely, Hendelmann, et al) were inclined to attribute the symptoms following its removal—low metabolism, somnolence, lethargy, fall in temperature, rapid emaciation, ataxia and finally death—to injury of the hypothalamus. The brilliant experiments of Bailey and Bremer, (9) together with less spectacular evidence that the hypothalamus heads the sympathetic system, threatened seriously to challenge the postulate that the pituitary gland subserves an endocrine function at all.

There is considerable evidence however that surgical or other forms of trauma in the region of the pituitary body may coincidentally affect the internal secretions of the pituitary and the vegetative centers of the hypothalamus and there is the further possibility that the pituitary body and hypothalamus constitute a functional control unit for many vegetative functions of the body.

Injury to the anterior pituitary and neighboring structures leads in young mammals to arrested development and growth, a decreased metabolic rate and deposition of fat in the omentum and
subcutaneous tissues. In dogs and rabbits there is a frequent tendency to hypoglycemia and convulsions and their sensitiveness to insulin and epinephrine is increased. (10) The genitals also fail to develop and secondary sex characteristics do not appear. The animals remain small, the epiphyseal unions are delayed and the teeth undergo faulty development. The entire complex resembles a condition recognized clinically under the term Frohlich's syndrome. Some of these disturbances apparently follow slight and circumscribed lesions of the hypothalamus alone and particularly when the tuber cinereum is involved. Thus, the weight of evidence seems to favor the view that the adiposity is not due to a pituitary derangement but to disturbances of the hypothalamic centers. (10) On the other hand such neurological lesions may affect the pituitary secretion in a number of ways, e. g., (a) by interference with its vascular supply, (b) by interrupting its nerve control, or (c) by preventing the absorption of hormones into the third ventricle. Finally extensive destructive in the hypothalamic region occurs clinically with never a symptom resembling that of pituitary involvement. (8)

Experimental and clinical observations together strongly suggest that the anterior lobe is necessary for (a) proper growth to adult stature, (b) for a normal development and function of the reproductive system and (c) for controlling the activities of other endocrine glands.

The effects on other endocrine glands and further modification of bodily functions and structures through changes so induced are far reaching and justify designating the anterior pituitary portion
the master or moderator of the whole endocrine system. Ablation of the pituitary gland causes involution of the thymus and atrophy of the thyroid with manifestations of cretinism or myxedema depending on the age of removal. Hypophysectomized tadpoles neither grow nor metamorphose and even when fed thyroid substance the processes of growth and metamorphosis are not completed. Injection of suitable anterior pituitary preparations produces hypertrophy of the thyroid and symptoms indicative of its hyperfunction.

The control of the sex glands by the anterior pituitary has been amply demonstrated. Following hypophysectomy in young females, ovarian follicles fail to develop, the genital tract atrophies and cyclic oestral changes cease. An interrelation with adrenal function is indicated by the observation that ablation of the pituitary body causes atrophy of the adrenals, particularly in the cortex; but the cachectic symptoms leading to progressive decline are not ameliorated by use of adrenal cortex preparations alone. (8)

Active Principles or Hormones of the Anterior Lobe.—It is doubtful whether the anterior lobe yields substances that have an effect on body functions when administered orally. A large number of preparations have been made by simple saline extraction, by treatment with weak acids and alkalies or other solvents that exert effects on diverse body functions following injection. These effects may be listed somewhat as follows: (1) stimulation of growth during active growth period, (2) stimulation of sexual development and ripening of ovarian follicles resulting in ovula-
tion, (3) stimulation of lutein cells, causing cessation of ovulation and imprisonment of ova, (4) enhancement of sexual maturity (5) Stimulation of metabolism by increasing specific dynamic action of foods, (6) stimulation of the thyroid gland, (7) lowering of basal metabolism, (8) increasing water intake and excretion, (9) exciting lactation, (10) lowering non-protein blood nitrogen and (11) initiating the bleeding of menstruation. (8)

Despite the fact that different extracts have been made which appear to induce one or the other of these effects predominantly and despite the demonstration also that one and the same preparation may exert quite different actions, depending upon modes of administration and the biological state of animals, we are far from able to conclude that these many actions are due to as many separate hormones. However, available evidence indicates that five or six substances or groups of substances can be separated from the anterior lobe that may tentatively be regarded as specific hormones. These are (a) the growth hormone, (b) the gonadotropic hormone, (c) the thyrotropic hormone, (d) the adrenotropic hormone, (e) the lactogenic hormone and (f) a diabetogenic factor.

The Growth Hormone.— The existence of a growth hormone was foreshadowed by many clinical and experimental observations. Removal of the anterior lobe in immature animals results in failure to grow, together with retention of juvenile characteristics such as retention of milk teeth, fine hair coats and open epiphysal cartilages. The state of dwarfism which results is later attended by pathological changes such as shrinking of epiphysal
cartilages and obliteration of pulp cavities of incisors by dentine. (11) On the clinical side, the association of gigantism and acromegaly with acidophilic adenomas is well established. Concrete experimental proof for the existence of a growth hormone was first supplied when Evans and Long (11) demonstrated that giant rats could be produced experimentally by injection of saline extracts of the anterior lobe.

A considerable amount of confusion in interpreting the effects of the growth principle and even regarding the efficacy of extracts arose in the earlier experimental work owing to the fact that most of the preparations used consisted of a relatively crude mixture of several endocrine factors. The presence of these hormones naturally modified considerably the specific changes in growth and particularly those involving the skeleton. According to Evans, the growth factor can now be purified so that it yields a white powder, containing about 15 per cent protein nitrogen which produces maximal growth in adult female rats in daily doses of 0.5 mg. (11)

The Sex Hormones. — That the anterior hypophysis contains a sex factor is demonstrated by the fact that its ablation in youthful animals prevents development of the sexual apparatus and in adults causes a retrogression. In males, the testes, prostate, seminal vesicles, etc., become atrophic and differentiation of male sex characteristics fails to occur. In females, a similar recession of the ovaries, uterus and tubes takes place. In short growth and maturation of the germ cells, as well as the endocrine activities of the gonads, are inhibited in both sexes. An interpretation of the actions is however more reliably made in
relation to the ovaries and for this reason more extensive use has been made of female animals. (12) Mixed anterior pituitary extracts containing predominantly sex factors cause follicular growth and ovulation and stimulate formation of the follicular hormone. In addition they lead to exuberant growth of the lutein cells and cause luteinization of the follicles and imprisonment of the ova. The first factor is associated with increased sexual activity, the second with repression of sexual activity and hypoplasia of the genital organs. (13)

Practical methods for separation of the two gonadotropin factors have apparently been devised. (14) One fraction seems to stimulate growth of follicles in immature rats and rabbits, but causes no luteinization. The other has little action on the ovaries of immature rats but causes formation of corpora lutea in rabbits with small follicles. Graafian follicles to a cystic stage without production of luteinization or alternatively have produced extensive luteinization of immature ovaries. Such experiments, if substantiated, will serve to remove one of the most critical objections to the dual nature of the gonadotropic hormone. Other suggestions that still other specific sex principles exist have occasionally arisen. Thus it was found that injection of anterior pituitary extracts may bring on menstruation in monkeys. (15)

The Lactogenic Hormone.—It has been demonstrated that the anterior pituitary contains a factor which stimulates milk secretion in the developed mammary gland. This has been confirmed by many workers. (16)
The Thyrotronic Hormone. — It would appear that the secretion of the thyroid is controlled at least to some extent by the pituitary body. Low metabolic rates occur in patients with anterior pituitary involvement and the thyroid fails to develop in hypophysectomized tadpoles with failure in metamorphosis. Further thyroid atrophy occurs in young rats after hypophysectomy.

Evidence that that hormone concerned is not identical with the growth and sex factors seems to have been adduced first by the chemical separation of the potent thyrotrropic principle from aqueous extracts and secondly by the demonstration that its administration leads to rapid changes in the thyroid vesicles and produces eye symptoms characteristic of exophthalmic goiter. (17)

The Adrenotropic Hormone. — The sex glands and suprarenal cortex develop together with the excretory system in the dorsal mesothelium of the premordial cavities of the body. (18)

The suprarenal capsule is composed of two glands distinct in origin and separate in function. The cortex, with which we are chiefly concerned, is derived from the mesoderm adjacent to that giving rise to the urogenital fold. At six weeks of embryonal age strands of cells from the celiac plexus grow ventrally, penetrate the cortical tissue and thus form the medulla. The intimate relation of the cortex to the genital glands is attested by the occasional migration of cortical tissue with the gonads and the occurrence of accessory suprarenal tissue in the ovary and broad ligaments. The extirpation of the suprarenal cortex is incompatible with life and consequently we have no knowledge of what would happen to sex characteristics in the complete absence
of cortical hormone. (18) The injection of active preparations of cortical tissue has not produced very striking effects on sexuality. (19)

The pronounced changes in the adrenal glands which follow hypophysectomy naturally suggested that the anterior pituitary gland may regulate their functions. It could not be accepted that this is due to a specific hormone until a fraction had been isolated which upon injection has no effect on growth, gonads or the thyroid gland, but repairs the damages done to the adrenal cortex by hypophysectomy. This appear to have been accomplished by Collip and his associates. (20) The suggestion has naturally been made that the effects of the anterior pituitary gland on carbohydrate metabolism may be mediated through its effects on the adrenal cortex, but such conclusions must be held in reserve until the role of the adrenal cortex in carbohydrate metabolism is more generally agreed upon. (20)
THE PITUITARY ADENOMAS

The anterior-pituitary body, as distinct from the neuro-hypophysis, is a compact of cellular elements of three recognizable sorts, divided by histologist, on the basis of their staining reactions, into two principal types: (1) those having a non-granular cytoplasm, and (2) those with a cytoplasm which is distinctly granular. Cells of the former type are known as neutrophil (chromophobe) elements and of the latter - the granular type - as chromophil elements of which there are two sorts: (a) those whose granules show an affinity for acid dyes (acidophile cells); and (b) those with an affinity for basic dyes (basophil or cyanophil cells). Each of these three cellular types - chromophobe, acidophil and basophil - is capable of producing its own peculiar adenomatous formations.

Whether these three types of cells are fixed in character or represent different stages in activity of the same original cell is a matter of dispute. The most recent advocate of the unitarian view is Collin of Nancy who, purely on anatomical grounds, presents a convincing argument to show that the non granular cell represents the primitive stage of activity of an element which in the process of ripening acquires a granular cytoplasm that is primarily acidophil but which may in turn become basophil. (22)

When the ripened granular cytoplasm comes to be discharged, little is left but the nucleus and membrane of the cell which may then either degenerate or, in a renewed cycle, once more pass through these same stages to be again discharged under proper stimulus.
But if this is actually what takes place, the fact that each of these varieties of cells is capable of forming adenomas whose elements appear to be of fixed rather than of a changing type is highly peculiar. (21) What is more, one would naturally expect that adenomas composed of the non-granular mother cells would be more likely to show evidences of cell division than would adenomas composed of elements in the more advanced stages of secretory activity. But just the opposite occurs: the elements composing the common chromophobe adenomas rarely if ever show cell division, whereas those of a chromophil adenoma, whether acidophil or basophil, are frequently multinuclear and show numerous mitotic figures. (21)

Meanwhile experimental pathology has provided us with some fairly definite facts concerning the function not only of the anterior pituitary considered as a whole, but, in turn, of its different cellular constituents. When its frequent association with a pituitary tumor came to be recognized, it was at first supposed that acromegaly was an expression of glandular deficiency and theoretically should be reproducible by experimental extirpation of the gland. This, however, in the majority of cases led to early death, at least of adult animals, whereas younger animals when hypophysectomized, though they might recover for long periods, ceased to grow and remained sexually infantile.

It had already been observed that tumors, grossly indistinguishable in situation and type from those associated with acromegaly, were of far greater frequency and provoked a syndrome, so far as its constitutional manifestations were concerned, of a
wholly different character. Individuals affected by these tumors when of adult age, instead of a tendency to overgrowth, showed on the contrary a tendency to become adipose, to lose their secondary sex-characters, and to become impotent, in company with recognizable atrophic changes in the sexual organs. When altogether comparable changes were seen occasionally to occur in animals after incomplete experimental hypophysectomy, it became evident that the syndrome represented a deficiency state which was termed hypopituitarism; and this furnished an added reason to assume—what had already been conjectured—that acromegaly almost certainly represented the counter state of hyperpituitarism.

The final experimental proof of the correctness of this assumption was delayed until Evans and Long (11), succeeded in producing experimental overgrowth in the rat, an animal whose epiphyses do not close throughout life; and subsequently in the dog, whose epiphyses like those of man normally do unite.

But this is only half the story. There was evidently a complicating element in these experiments. If only a single pituitary principle had been involved in experimental hyperpituitarism of this kind, one might well enough have expected increased growth to go hand in hand with increased activation of the reproductive functions. Quite to the contrary, while the injections unmistakably served to promote growth they at the same time checked the normal ovulatory cycle of the animals. In consequence of this observation, Dr. Evans (11) was led to suspect the presence of dual glandular hormones and he came to believe, indeed, that they were in some peculiar way opposed in their action.
The common tumors of the anterior pituitary - first looked upon merely as a local expression of acromegalic overgrowth, and subsequently as sarcomas or "strumas" of the gland - were first clearly differentiated in 1900 as varieties of adenoma; and we have slowly come to understand with some degree of definiteness the clinical pictures produced by those whose cells possess a granular and acidophil cytoplasm and those with a non-granular or chromophobe cytoplasm. The former, even when so small that they may easily escape post-mortem detection, are productive of unmistakable acromegaly or gigantism or a combination of the two. The more common chromophobe adenomas, on the other hand, usually attain a size sufficient to distort the chiasm before they give appreciable clinical symptoms, and it is quite probable that the cells which comprise them possess no secretory activity - that is, produce no hormone. They nevertheless cause their own peculiar constitutional disorder, this being a deprivation syndrome brought about through compression of the residual acidophil and basophil elements which no longer are able to produce their peculiar secretory product. (23)

This in general terms at least approximates the truth. It must, however, be admitted that there are certain borderline syndromes in which a primary wave of pathological overgrowth appears to have been succeeded by a hypopituitary state - a condition which for lack of a better term has been called "fugitive acromegaly," the adenoma in these states proving to be of a mixed cellular type. Though the cells of these mixed adenomas are predominantly chromophobe, a few of them show a
peripheral disposition of acidophil granules suggesting the functional retrogression of previously mature acidophil elements; and since these cells resemble the hypo-acidophil stage of development as described by Collin, the observation might be construed as an argument favouring his views. In other words, the supposed functional immutability of the cells of an anterior-pituitary adenoma may prove to be a misconception; but this need not particularly concern us here.

Two examples of a third type of anterior-pituitary adenoma, composed of basophil elements, were first described twenty years ago by Erdheim,(24) the tiny lesions having been looked upon as curiosities of morbid anatomy rather than as findings of any conceivable clinical significance. In one instance a small basophil adenoma, 1.5 mm. in diameter, was found in a woman forty years of age supposedly the victim of Basedow's disease. The other example was found in a forty-three year old acromegalic whose relatively small pituitary body was chiefly occupied by a fair-sized eosinophil adenoma, the minute basophil adenoma measuring only 1 mm. in diameter having been regarded as an accessory finding.
BASOPHILIC SYNDROME OF THE PITUITARY

Having considered something of the anatomy and physiology of the pituitary gland, we come now to a more limited discussion of that obscure, polyglandular syndrome known as pituitary basophilism. Whether this is due primarily to dysfunction of the pituitary is not known for certain. It is maintained by some authorities that the primary cause is to be found in the suprarenal cortex. Other of the endocrine glands may also be involved. Pardee (25) has given a very good description of the clinical syndrome met with in these cases. According to him the symptoms and signs fall into the following groups:
(1) adiposity of the face and trunk, usually sparing the extremities; (2) amenorrhea, or sexual impotence in the male; (3) hypertrichosis of the face and trunk (masculine in type) in females and adolescent males, and possible the reverse in adult male; (4) dusky or plethoric skin with purplish lineae atrophicae, acrocyanosis, cutis marmorata and purpura-like ecchymoses; (5) vascular hypertension; (6) a tendency to polycythemia and polynucleosis; (7) osteoporosis, with softening of the bones of the skeleton and kyphosis; (8) headache, pain in the back, asthenia and fatigability; (9) hyperglycemica and albuminuria; (10) intracranial signs, with exophthalmos, diplopia, papilledema, dimness of vision, polyphagia, polydipsia and polyuria.

All the cases reported showed a striking uniformity of symptomatology. The syndrome was most frequent in young persons of short stature and of an average age of 18 years. In the fatal cases the average duration of the illness to death was about five
years. The three patients who recovered, one of them spontaneously, are still under observation.

Since the description of the basophilic syndrome, shortly over a year ago, it has been brought more and more to my attention that numerous causes of virilism are not altogether typical of the aforementioned group. However, whether they present pure suprarenal or combined suprarenal and pituitary syndromes, these cases are of special interest in an attempt at evaluating the factors that contribute toward an excessive growth of hair. Some of the patients, in whom hypertrichosis is a readily recognizable sign, have on further study been found to present a sufficient number of the signs of the basophilic syndrome to allow them to be placed unequivocally in this broader group, leaving it to the future to settle the question of the presence or absence of a basophilic adenoma. (25)

A better understanding of this polyglandular syndrome can be obtained by the study of some of the few cases of this condition which have been reported to date.
CASE HISTORIES

The original example of the syndrome around which the present discussion hinges was described in Cushing's monograph (24) as having shown a syndrome of painful obesity, hypertrichosis and amenorrhoea with overdevelopment of secondary sexual characteristics. Whether these symptoms were chiefly attributable to disordered pituitary, adrenal, pineal or ovarian influences was uncertain. I will report this case in its entirety.

Case I.—Minnie G., an unmarried Russian Jewess, aged 23, referred by Dr. Stetten of New York, was admitted to the Johns Hopkins Hospital on December 29, 1910.

Clinical History.—One of a numerous and healthy family, though slight and undersized, she was well until sixteen years of age, having escaped the customary children's ailments. Her menses which started at the age of fourteen were regular for two years and then suddenly ceased. She began to grow stout and in the two years prior to admission her weight had increased from 112 to 137 pounds. She suffered greatly from headaches, nausea and vomiting sometimes accompanying the more severe attacks. She complained also of aching pains in the eyes which latterly had become prominent, and there had been occasional periods of seeing double.

Other noteworthy symptoms were insomnia, tinnitus, extreme dryness of the skin, frequent sore throats, shortness of breath, palpitation, purpuric outbreaks, recurring nose-bleeds, and marked constipation accompanied by bleeding piles. A definite growth of hair had appeared on the face with thinning of hair.
on the scalp. She had become increasingly round-shouldered having lost at least 4 inches in height. Muscular weakness had become extreme and there was constant complaint of backache and epigastric pains.

Physical Examination. - This showed an undersized, kyphotic young woman 4 feet 9 inches in height, of most extraordinary appearance. Her round face was dusky and cyanosed and there was an abnormal growth of hair, particularly noticeable on the sides of the forehead, upper lip and chin. The mucous membranes were of bright colour despite her history of frequent bleedings. Her abdominal body had the appearance of a full-term pregnancy. The breasts were hypertrophic and pendulous and there were pads of fat over the supra-clavicular and posterior cervical regions. The cyanotic appearance of the skin was particularly apparent over the body and lower extremities which were "marbled" and spotted by subcutaneous ecchymoses. Numerous purplish striae were present over the stretched skin of the lower abdomen and also over shoulders, breasts and hips; and a fine hirsuties was present over the back, hips and around the umbilicus. The skin which everywhere was rough and dry showed considerable pigmentation, particularly around the eyelids, groins, pubes and areolae of the breasts. The peculiar tense and painful adiposity affecting face, neck and trunk was in marked contrast to her comparatively spare extremities.

From a neurological aspect nothing was notable other than what at the time were taken to be signs of intracranial pressure: namely, headaches, slight exophthalmos, diplopia, puffiness of the eyelids and congestion of the optic discs. The cranial X-ray
showed what for the day was regarded as a normal sella turcica. The epiphyseal lines were still roentgenologically visible. Not only did the skin bruise easily but spontaneous ecchymoses frequently appeared. Lumbar puncture, pricking of ear, etc., caused subcutaneous extravasations. Blood examination showed 5,300,000 erythrocytes and 12,000 leucocytes with a haemoglobin of 85 per cent. The systolic blood pressure was consistently high, averaging 185 mm. Hg.

There were no clear therapeutic indications and she was discharged. She reentered the hospital in July 1911, at which time, owing to the assumption that her continued cephalalgia might be due to intracranial pressure, an oldtime subtemporal decompression was performed, a wet brain being disclosed without subsequent protrusion at the site of the bone defect. She also at this time complained so greatly of backache and pain in the left side that an exploration of the kidney and adrenal gland was under contemplation.

Because of her continued complaints with an increase of weight up to 151 pounds, on Dr. Stetten's recommendation she again came under observation for a period of two months from May to July 1913, at the Brigham Hospital in Boston.

Her symptoms and general condition at this time were found to be essentially unaltered. Though there was no protrusion at the site of the old decompression, the optic discs were still hyperaemic and congested with hazy margins, while the fields of vision were contracted and the acuity considerably reduced. Her blood pressure fluctuated around 180/110, on one occasion reaching
210/140. She was still somewhat polycythaemic, the erythrocytes slightly exceeding five million, the highest count having been 5,248,000 with a haemoglobin estimation of 105 per cent. Several differential blood counts were essentially within normal limits.

She was for a time studied by my medical colleague, Dr. Christian. On the basis of a defective excretion of phenolsulphonephthalein and the presence in the urine of a slight trace of albumin with occasional hyaline casts, he felt that a vascular type of nephritis was the probable cause of her hypertension. She was again discharged with no therapeutic recommendations.

On November 15, 1922, after an interval of nine years, she was for the second time admitted to the Brigham Hospital. It was then learned that her menses, after complete cessation for ten years, had late in 1913 again become irregularly reestablished; also that in 1917 she had had an exploratory operation for a stone in the left kidney, but she was uncertain whether a calculus had actually been found.

The blood-pressure at this time averaged in the neighbourhood of 160/95; the blood-count showed 5,240,000 erythrocytes; the basal metabolism was minus nine. Her general appearance was much as before, though she had lost some weight. The cranial roentgenograms taken at this time show an unmistakable diffuse decalcification of the bones of the vault. Renal pyelograms were made, no trace of stone or other renal abnormality being disclosed. There was no evidence of advancing nephritis and on the whole she seemed at least no worse than in 1913. She accordingly was dis-
charged once more without further light having been thrown on the nature of her disorder.

The patient came under observation again on February 8, 1932. She was in reasonably good health and had lost many of the former stigmata of her malady. The former acuteness of her malady was unquestionably in abeyance. Her weight was only 52.4 kg. The metabolism was plus 4 and showed a pronounced rise on a specific dynamic test. Her red cells were counted at 5,190,000 and her haemoglobin was 111 per cent. The non-protein nitrogen and cholesterol and blood were in normal limits. Differential white count showed only 61 per cent polymorphonuclears. Her former plethora was gone and the striae in the skin were now pale instead of purplish. She no longer had any tendency to bruise. Her blood-pressure was normal. The urine showed the slightest trace of albumen but the uthalein test indicated normal elimination.

Her kyphosis had distinctly increased but the X-ray films of the spine showed no collapse of the bodies such as had been expected. The bones of the cranial vault showed a peculiar mottled porosity suggesting osteomalacia. The aorta was markedly tortuous and multiple calcified plaques were present in the arch. There were irregularities in the ribs of the left side suggesting old fractures of which there was no clinical history.

In the intervening years six other examples of the same or a highly similar disorder have been carefully studied at the Brigham Hospital. The patients were all comparatively young women who, in association with a more or less abrupt amenorrhoea,
had become rapidly obese with a peculiar tense and more or less painful adiposity chiefly affecting head, neck and trunk. They were all plethoric in appearance, all had become abnormally hirsute, all but one showed purplish cutaneous striae. Vascular hypertension with a high erythrocyte count and haemoglobin percentage was usually present; and all complained of aches and pains and general enfeeblement. In some of the patients the acuteness of the condition appeared to subside, and only one, so far as known succumbed to her malady. (24)


Miss A. O., a previously healthy and normal young woman, in 1907 when 20 years of age, suddenly ceased menstruating and began to grow obese. Three years later, she observed a tendency for her extremities to bruise easily. She gradually became increasingly round-shouldered thereby losing two and a half inches in height. Her chief complaints were of pain in the back.

The face was extremely fat and florid and the texture firm. The hair of the head was dry and somewhat scanty, as was the pubic and axillary hair, but there was a growth of fine short hair over the back and upper legs. Notable were the large pendulous mammae and the great obesity of the abdomen, which had the contour of a full term pregnancy.

The obesity of the trunk was in marked contrast to the somewhat thin extremities which below the knee were of a dark brownish colour, interspersed with recent ecchymoses. The skin had a
parchment-like texture. Numerous broad, red, atrophic striae were present over the abdomen and thorax. An apparent partial absorption of the posterior clinoid processes was shown by cranial roentgenograms. A glistening subretinal exudate was present in the right eye, probably from an absorbed haemorrhage. The systolic blood-pressure was high, varying between 200 and 185 mm. Hg. There had been a tendency to polycythaemia, the erythrocytes on one occasion having been counted at eight million and on another at six million. The urine contained no albumin. Carbohydrate tolerance was normal.

Subsequent history.—This was briefly given in a later article by Dr. Parkes Weber. Several spontaneous fractures occurred from time to time, involving sternum, clavicle, and ribs. Multiple ulcers and subcutaneous abscesses developed, and in May 1914, seven years from the symptomatic onset of the disorder, death ended the story.

Autopsy.—The body was that of an hirsute woman with "abundant hair on the chin" and multiple subcutaneous abscesses and ulcers. There was found a chronic nephritis, an hypertrophic ventricle of the left heart, a fatty infiltrated liver, and an enlarged left suprarenal gland of "bulky cortex." The ovaries were small. The bones showed calcareous deficiency and were so soft they could be easily cut with scissors. "Nothing abnormal was found in the pituitary and thyroid glands." (26)

An exceedingly obese and abundantly hirsute young woman, 20 years of age, admitted to hospital in a comatose condition due to a meningococcal meningitis, was under clinical observation for only three days before she died.

Owing to her physical condition, a personal history was not obtainable, but it was learned that at the age of nine she had a continuous menstrual flow lasting four months. Subsequently, at the age of 14, she was said to have attained a normal adolescence, but her periods were subsequently most irregular. From the age of 15 she had grown exceedingly stout, the maximum weight of 206 pounds having been recorded seven months before her hospital admission. Because of excessive fatiguability she had consulted a physician at about that time, and when he found she had a basal metabolic rate of plus 33, her enlarged thyroid was roentgenologically radiated. This was said to have caused little or no symptomatic improvement.

At autopsy, a suppurative meningococcic leptomenigitis was found to be the obvious cause of death. The pituitary body appeared to be of normal size, but suspecting from the patient's general appearance what might be found, Dr. Teel had the gland serially sectioned and a small but unmistakable basophil adenoma measuring 2.5 mm. in diameter was disclosed. There was a persistent thymus, a slight enlargement of the thyroid, questionable enlargement of the pancreatic islets, and a definite enlargement of the suprarenals with no histological change of structure, no definite secondary adenomas being present in any of these organs. The ovaries were enlarged apparently from increase in stroma;
there was a single large corpus luteum with a small central haemorrhagic area and several smaller ones in various stages of organization. The only true neoplastic growth was the small anterior-pituitary adenoma to which the other endocrine changes were regarded as purely secondary. (27)


A woman, at the age of 23, in association with a menstrual irregularity which in two years was followed by total amenorrhoea, became increasingly obese, the adiposity sparing the limbs. The adipose areas were tender on palpation. She suffered much from headaches, pains in the chest and eyeballs, the eyes having become somewhat exophthalmic. She acquired a reddish complexion with facial hirsuties. She developed a tendency to petechial haemorrhages and purpuric outbreaks on her arms and legs, the slightest contusion provoking ecchymoses. The systolic blood-pressure was 185 mm.; the red blood count approximated five million. Muscular weakness became extreme, and she finally died from increasing asthenia. The whole course of the malady was something over five years.

At the post-mortem examination, arteriosclerosis with "chronic interstitial nephritis" was found. The ribs were brittle and easily fractured. The ovaries and uterus were senile in character; the thyroid was slightly enlarged; the parathyroids were normal;
the thymus atrophic. In the medulla of one of the suprarenal glands which were "slightly enlarged" was a small pea-sized tumor, microscopically resembling the structure of the zona fasciculata. The anterior pituitary contained a small adenoma the size of a millet seed close to the pars intermedia. In the rest of the anterior lobe "the basophil cells were apparently increased at the expense of the eosinophil cells." (22)


Autopsy.- Marked osteoporosis of the skeleton was found, it being possible to cut the vertebral bodies with a knife. Follicular atresia of the ovaries, lipomatosis of the pancreas, an increase of colloid in the abnormally small thyroid, hypoplasia of the thymus, and capillary dilatation of the parathyroid glandules were additional findings. The pituitary body showed a decrease in size of the anterior lobe with an increase in size of the pars nervosa. In the vicinity of the anterior lobe a dense fibrous tissue was found into which the glandular elements of the anterior lobe gradually passed over. There were nests of adenomatous-like structure enclosed in the masses of fibrous tissue. The identity of these cells with the anterior-pituitary cells could not with certainty be determined although it was thought that they probably arose from the hypophyseal duct.

pigmentation and abscesses. Duration 5 years. Death without autopsy.

S. G. an undersized child, 12 years of age, was admitted to the Montefiore Hospital complaining of weakness and adiposity. In her sixth year she began to put on flesh and became disproportionately adipose, gaining about 75 pounds. She was seen by many physicians and treated symptomatically with various glandular preparations. Polyuria and nycturia developed a little later.

Upon physical examination, an undersized obese child was found with red, plethoric facies. There was a well marked growth of hair on the chin and cheeks. The skin was dry and the abdomen had pigmented striae. There were abscesses on the back and neck and ulcers on the legs. There was no edema.

The heart was enlarged to the left. The blood pressure was 160/130. The urine contained sugar but no acetone. There was a heavy cloud of albumin but no casts nor cellular elements.

The patient was placed on an anti-diabetic diet and digitalized. The urine rapidly became normal; the sugar and albumin disappeared completely. The abscesses of the neck and back finally healed. At this juncture she was removed from the hospital and died three weeks later. Although no post-mortem examination was obtained, the clinical picture was so characteristic of suprarenal hyperplasia that there was little doubt of the diagnosis. (38)

Autopsy. — There was no tumor in either adrenal gland, but the medullary substance was apparently rather in excess. The left ventricle of the heart was hypertrophied. There was slight chronic interstitial nephritis. In the anterior lobe of the pituitary gland was a minute adenoma consisting of basophil cells. There was no evidence of disease in the thyroid gland or in the ovaries; the latter were said to have been rather small but histologically normal.


E. G., a student, 19 years of age, complained of obesity, hypertension and recurrent pains in the region of the spine for six months.

He was undersized and had grown rapidly stout during the last few months. His abdomen had become penduous and his face ruddy. He was thought to have kidney trouble. There was shortness of breath and palpitation. Libido was absent.

Patient was short with pendulous abdomen. The mammae were well developed, the genitals small, and the fat distribution was of the feminine type. There was overgrowth of hair at the bridge of the nose and the body was covered with a fine lanugo. The heart was enlarged to the left. The skin was dry. The bones were thin and under developed according to X-ray examination. The patient died a year later of pneumonia. No autopsy was obtained.

Case IX. — Acute painful obesity sparing extremities.
Cutaneous pigmentation. Spinal deformity from osteoporosis. Duration three years. Autopsy: osteomalacia with multiple fractures; cardiac hypertrophy; atheromatous vessels; contracted kidneys; acute pancreatic necrosis; testicular atrophy; pituitary body large but said to be normal. (22)

The gross pathological diagnosis was lipomatosis, osteomalacia, multiple fractures of the ribs, vertebral collapse, hypertrophy of the cardiac ventricles, atheromatosis of aorta and of the cerebral vessels, encephalomalacia of the right occipital lobe, fibrino-purulent peritonitis, necrosis of the pancreas, hypoplasia of the thymus, granular atrophy of the kidneys.

The principle histological findings of note were those relating to the peculiar structure of the softened bones. The kidneys showed slight glomerular fibrosis and the cerebral vessels an endarteritis proliferans. No abnormalities was found in the adrenals, pineal or pituitary glands. (22)


The autopsy revealed an oscculum sellae which was, as usual, concave; the pituitary body was scarcely enlarged; the posterior lobe was softened supposedly by postmortal changes. There was no growth. Histologically, however, a small basophil adenoma was discovered which had almost entirely replaced the posterior lobe and showed central softening—a verification of the clinical diagnosis.

This patient, a dentist 30 years of age, first noticed five years before admission that he began slowly to grow round shouldered and stout. In the course of the next three years he gained 25 pounds and during the fourth year there was a more rapid gain of 35 pounds, his weight reaching 220 pounds. He then began limiting his diet and finally succeeded in losing a few pounds, but under this regime he soon found himself without energy easily fatigued, unable to concentrate his mind on his work; and fits of unnatural irritability alternated with period of depression.

Upon again changing his diet he began to gain weight rapidly again and his abdomen became prominent with localized masses of fat on his face.

A little later he began to have an excessive thirst associated with a polyuria which was more marked at night when he would be obliged to void from four to six times. He experienced also susceptibility to fatigue, forgetfulness, restlessness, palpitation on slight exertion, swelling of the feet and ankles, generalized weakness, and impotence. A distinct loss of body hair was observed.

pituitary adenoma; adrenal hyperplasia.

Male, 24, entered the hospital May 6, 1930, and died there three months later. He had always been well but his puberty was delayed until the age of 20 when he began to grow abdominous and the colour of his face and hands became bluish red. He had polyphagia, polydipsia, and polyuria. He perspired freely when at work. He needed to shave only twice weekly. There was no headache or dizziness. His vision had become impaired in later years and he had lost some weight under treatment during the nine months prior to admission.

The appearance was that of a man older than his age. He was slight stature. Height 161.5 cm. weight 61.3 kg. There was quite marked adiposity, localized around abdomen, thorax and face, the extremities not being affected. No dyspnoea while resting. The teeth were carious. The thyroid gland was covered by a cushion of fat, but not enlarged. No peripheral adenitis. No cardiac enlargement was detected. There were numerous pigmented naevi on the chest.

On both sides of the abdomen were reddish striae distensae, 1 cm. in width and 5 to 6 cm. in length; otherwise nothing abnormal. The external genitalia were not hypoplastic. The face and hands showed a deep red-blue colour. There was cyanosis of the lower legs with spots of light brownish pigmentation which contrasted with the varices which were present. At the time of the examination there was a four days growth of beard which amounted to 2 mm. at the most. The hair on the head, eyebrows, axillae and pubis was normal.
Autopsy.—The extremities were lean compared with the trunk. There were striae distensae on the abdomen, running longitudinally to thorax and even axillae. The skin was without edema, apart from that on the left forearm and back of hand. The growth of hair was natural, except the beard, which was scanty. Broncho-pneumonia was found, also marked hypertrophy of the left ventricle and atheroma of the aorta and common iliacs. The mesentery was exceedingly fat. The kidneys were slightly granular. The thyroid gland was small and firm. The right adrenal was normal, but the left was hyperplastic, weighing 27 grams; the tissue on fresh section appeared normal, but the medullary portion was oedematous and of a brownish-green colour. The pituitary gland, on removal of the brain, was found to be replaced by a soft tumor like growth of reddish colour, which measured 3 by 2 by 2.5 cm. The brain itself was oedematous, the ventricles moderately dilated.

Discussion of the Above Cases.—The twelve patients whose case histories have been more or less fully presented, were all young adults. Their average age at the onset of the malady, so far as can be estimated has been 18 years, the youngest 6 and the oldest 25. The female patients were all undersized. The average duration of the disease has been about five years. (From onset to death) The following features are characteristic of all the cases: (1) A rapidly acquired, peculiarly disposed and usually painful adiposity confined to face, neck and trunk, the extremities being spared. (2) A tendency to become round-shouldered even to such a degree that there was appreciable loss in height. (3) A sexual dystrophy shown by an early amenorrhoea in the females.
and ultimate functional impotence in the male. (4) An alteration in normal hirsuties shown by a tendency to hypertrichosis of face and trunk in all the females as well as the preadolescent males. (5) A dusky or plethoric appearance of the skin with purplish lineae atrophicae particularly marked on the abdomen. (6) Vascular hypertension, present in all cases except 4, 7, and 9 where no mention was made of blood pressure. It varied from the highest recorded in 6 of 230/170 to the lowest in 11 of 178/100. (7) A tendency to erythraemia, a count exceeding five million having been present in five of the nine cases in which the blood counts were recorded. Other findings are present in the individual cases but none common to all.

Post Mortem Findings.—The malady appears to leave the patients with a definite susceptibility to infections. Death in the nine fatal cases eight of which came to post-mortem examination, was ascribable to, or associated with, multiple cutaneous abscess and ulcers, intercurrent erysipelas, acute pulmonary complications, intercurrent meningitis, a streptococcal phlegmon, pancreatic necrosis. Chronic nephritis of a mild degree was found, in the absence of any definite clinical signs in some of the cases. An osteoporosis of the skeleton most marked in the spine was a common finding in most of the cases. A basophil adenoma of the pituitary was found in 4 of the cases, an undifferentiated adenoma in two and fibrosis of the gland in two. Only two of the normal cases had what was called a normal pituitary gland. The supra-renal glands showed hyperplasia in two cases and a small adenoma was found in one with 4 of them showing no abnormality.
In 1933 four cases of polyglandular dyscrasias were presented by members of the Mayo Clinic (18). The patients were women aged twenty-seven, thirty, thirty-four and forty-eight years, respectively, with the following abnormalities in common: rapidly acquired obesity confined to the face, neck and trunk; atrophic purplish striations of the skin; hypertrichosis; amenorrhea; vascular hypertension; dusky and florid complexion, and weakness. Two of the patients had frank diabetes and diabetic reaction to glucose tolerance tests was obtained when the other two were examined. There was definite roentgenologic evidence of osteoporosis in two cases; in two, ecchymosis occurred.

The evidence at the time was insufficient to warrant a positive opinion as to the relative part in the production of the syndrome played by each of the glands of internal secretion. The suprarenal glands had been examined in each instance, but necropsy had been obtained in only two and in one of these the hypophysis was not removed. The patient in the case in which postmortem study was satisfactory had markedly hyperplastic suprarenal glands and a thymoma, while serial sections of the hypophysis revealed nothing that could be called an adenoma. (18) The patient in the case in which necropsy was incomplete also had very marked hyperplasia of both suprarenal glands and a roentgenogram of the skull revealed a normal appearing sella turcica. The suprarenal glands in the remaining two cases appeared normal at surgical exploration. In one of these the sella turcica was slightly but definitely enlarged, and the posterior clinoid processes were slightly eroded. In the other case the roentgenogram of the sella turcica seemed
without abnormality. This last patient has died since our previous report. The hypophysis was removed and was sent to us for examination. It contained an adenoma composed of basophil cells. (18)

There have been three further cases reported in 1934, in all of which were morbid characteristics essentially like those described before. In one of these surgical exploration revealed the third instance of gross bilateral hyperplasia of the suprarenal glands and necropsy later disclosed nothing abnormal in the hypophysis; in the other two, unilateral suprarenal tumors were encountered at operation, and their removal was followed by remarkably complete recovery, as is to be described. (29)

Case I.- An unmarried woman, thirty-two years of age, a stenographer, came to the Clinic January 15, 1934, with complaints of nervousness and irritability of several years' duration. Slight abrasions of the shins would fail to heal for months. The menses had never been regular, but for the past six months they had ceased altogether. During the past year the patient had had a ravenous appetite and gained 25 pounds. A beard had grown on her face, so that she had resorted to shaving.

Examination revealed that the excess of fat was confined to the trunk and face and spared the extremities. The abdomen was protuberant and there was a conspicuous prominence over the upper thoracic and cervical portions of the spinal column, due apparently to a pad of fat. The face was definitely broadened. Coarse dark hair was distributed over the chest, abdomen and thighs.
The face had been shaved. The skin was dry and rather dusky, and atrophic striations were present over the thighs and lower part of the abdomen. These were bluish. The thyroid gland was slightly enlarged, soft and symmetrical. The blood pressure in millimeters of mercury was 168 systolic and 118 diastolic. The basal metabolic rate, in one determination was -15 per cent. The value for hemoglobin of the blood was 15.4 gm. per cent and erythrocytes numbered 4,460,000 per cubic millimeter of blood. The urine was free of sugar by the qualitative Benedict test. The concentration of blood sugar was not determined. Osteoporosis of the thoracic portion of the spinal column was noted at roentgenologic examination. The value for serum calcium was 10.0 mg., and for phosphorus 2.7 mg. per cent.

Bilateral surgical exploration of the suprarenal glands disclosed that both were definitely enlarged. Portions removed for microscopic examination seemed normal histologically. Convalescence from this operation was uneventful until the tenth day, when it became complicated by mild parotitis. Tonsillitis followed and then extensive cervical cellulitis with pneumonia, death following.

At necropsy, the hypophysis was removed and was examined by serial sections. It did not contain adenomas. The combined weight of the two suprarenal glands was 35 gm., estimated to be more than twice normal. There were two small cortical adenomas in the left suprarenal gland, measuring 3 and 4 mm. in diameter. These are of questionable significance. The thymus was atrophic and was replaced by fat. The heart weighed 345 gm. The ovaries
were small and sclerotic. They contained small cysts.

Case II.—A married woman, twenty-five years of age, always had been well until the onset of her present illness. She was referred to the Clinic August 28, 1933, by Dr. W. P. Freligh of Albert Lea and Dr. J. J. McGroarty of Easton, Minnesota, with the diagnosis of an affection of the suprarenal glands. She had been examined for life insurance in December, 1932, and had been accepted. The blood pressure was then normal, but the menstrual flow had diminished in amount and duration; two months before we saw the patient the menses had ceased. The weight had increased in the past year from 145 to 165 pounds. The extra fat affected the face, neck and trunk, whereas the legs and arms remained unchanged in contour. In this period also hair began to grow on the lips, cheeks, arms and legs, whereas previously the patient had had very little hair. The general appearance

Fig. 1. (Case II). a, Appearance of patient September 1, 1933. An adenoma of the right suprarenal gland was removed September 11, 1933; b, appearance of same patient March 14, 1934.
changed to such an extent that friends failed to recognize the patient. She complained in addition of great loss of strength, of an acneform eruption of the face and of bruising easily. Increased thirst, with polyuria had been present for two or three months.

The face was full and round, and the body fat was distributed as described. The shoulders were rounded, largely because of fat in the upper thoracic region. The blood pressure was 180 mm. of mercury systolic and 120 diastolic. Long, fine hair grew over the face, arms and legs. The skin was dry; that of the face was highly colored and mottled. Acne was present on the face and thorax, and atrophic purplish striations affected the thighs and lower part of the abdomen. One specimen of urine contained 1.08 per cent of sugar; the value for blood sugar, fasting was 82 mg. per cent. The basal metabolic rate was plus 1 per cent. The sella turcica was normal roentgenologically, and the perimetric fields were normal. The hemoglobin content of the blood was slightly elevated, 17.5 gm. per cent, but the erythrocyte count was normal. There was slight osteoporosis of the spine. An intravenous urogram revealed the pelvis of the right kidney to be rotated outward and displaced downward, suggesting an overlying tumor.

In accordance with our present policy it was decided that the suprarenal glands should be explored. This was done September 12, and a yellowish, soft, friable, encapsulated mass, 10 to 12 cm. in diameter, was found in the place of the right suprarenal gland, extending as high as and attached to the diaphragm. The
tumor was so friable that it had to be removed piecemeal. It was removed, except for a very minute portion attached to the vena-
cava. This was crushed with clamps. Examination of the tissue showed it to be an adenoma containing tissue of cortical origin.

A few hours after operation symptoms developed suggesting cortical insufficiency. Accordingly, the patient was treated with cortical hormone, injections of solutions of sodium chloride and transfusion of blood. Convalescence was further complicated by a secondary hemorrhage. The patient was taken back to the operating room, the incision opened, and the generalized oozing controlled by gauze packs and transfusion of blood.

The patient is now apparently well. She weighs 147 pounds and her appearance, her friends tell her, is as it was before her illness. The excessive hair is gone, and the blood pressure is normal. Menstruation has returned and occurs regularly. Her former strength has not been regained entirely, and some acne persists.

Comment.– Van der Bogert recently has pointed out that the manifestations in infancy of tumors of the suprarenal cortex are: "obesity, precocious development, hirsuties, voice changes, virilism, and marked hypertrophy of the clitoris and external genitalia, together with hypertension and cardiac enlargement." (30) He reported the case of a girl, aged two years, who presented the characteristic syndrome and had a carcinoma of the cortex of the suprarenal gland. The onset of symptoms had been at nine months of age, and a mass was palpable in the right side of the abdomen. Still younger patients are on record.
Case III.—A girl, aged nine years, was referred to us in September, 1933, by Dr. O. S. Ely of St. Paul. There was nothing significant in the family history. Birth and development had been normal, and the patient had been a healthy child until the onset of the present difficulty. She had had measles and whooping cough. When the child was four years of age, the mother had observed unusual development of the breasts, generalized growth of hair over the body, and deepening and coarsening of the voice. A year later the pubic hair had become abundant and the external genitalia had developed abnormally.

At eight years of age the child menstruated for four days, and afterward there had been some menstrual spotting at intervals of about two months. The mentality and personality had undergone no great changes, but the child seemed to spend most of her time at home and to shun the company of other children. In her selection of companions she showed no preference for either sex. She
was in the fifth grade at school and was doing well with her lessons. At examination the child apparently was placid in disposition, with features suggesting an age considerably greater than her actual age. Her height was 53 inches which was well within the normal range for girls nine years of age, but her weight was 103 pounds about 36 pounds more than the normal for her sex, age and height. The most striking abnormalities were: (1) obesity affecting principally the trunk, neck and face, (2) hypertrichosis of the face and body, especially prominent in the axillae an on the mons veneris, (3) purplish, atrophic striations over abdomen, thighs, and buttocks, (4) additional development of the breasts and external genitalia, and (5) acne of the face and trunk.

Fig. 5. Cells of the suprarenal tumor in case 2. The tumor is more cellular than that in case 3. The cells vary greatly in size, are more oval in shape, and contain many mitotic figures.

The blood pressure in millimeters of mercury was 132 systolic and 97 diastolic. Urinalysis gave negative results. The basal metabolic rate was -20 per cent. The concentration of hemoglobin in the blood was 17.3 gm. per cent. Erythrocytes numbered 4,620,000 and the leukocytes 8,400 per cubic millimeter of blood. The sella turcica appeared normal, and no thymic shadow was observed on roentgenographic examination. Development of the bones was
commensurate with that of a child aged twelve years. The response to the test for glucose tolerance was normal, but one specimen of urine obtained before the test was slightly reducing. The concentration of serum phosphorus was 4.1 mg. per cent; the value for phosphatase was normal. The concentration of serum calcium was 10.9 mg. and 11.7 mg. per cent. The outlines of the kidney in the intravenous urogram were normal.

Surgical exploration was performed in October, 1933. The right suprarenal gland was about half the usual size. A section removed for microscopic examination was normal histologically. The position of the left suprarenal gland was occupied by a large encapsulated tumor a portion of which projected into an enlarged suprarenal vein. The tumor was completely removed and was found to be a cortical adenoma.

Cortical hormone was administered during the first six days after operation. There was some fever for twelve days, but otherwise the postoperative period was uneventful.

Within three weeks the weight had fallen, and the excessive hair was beginning to disappear. Later, the skin became smooth, the voice pitched higher, the breasts and external genitalia smaller. Also, the child began to be more playful, and instead of wanting to be at home with her mother as before, she now preferred to associate with other children. The appetite was reduced and indeed, the patient became rather finicky in the choice of her food. There has been no menstrual flow of any kind since the operation and that part of the hair of the head which has grown since operation is lighter in color and finer than the old hair.
Examination now shows that the weight is 72 pounds which represents a loss of 31 pounds in the last four and a half months. The blood pressure is 98 mm. of mercury systolic and 62 diastolic. The basal metabolic rate is -9 per cent. The value for serum phosphorus is 4.0 and that for calcium 11.5 mg. per cent. The value for phosphatase is normal. The skin of the face is somewhat redundant, as a result of the loss of weight, but is otherwise clear and healthy in appearance. The proportions of the body are normal except that the breasts, although smaller, are still of the adult type, and breast tissue is palpable. The face, back and extremities are hairless and only a few hairs are left on the thorax. The genitalia are still of almost adult size, but the clitoris is definitely smaller than it was. (30)

Comment.—The patients in four of these cases have died, and the hypophysis has been examined in three of them. Basophil adenoma of the hypophysis was present in one; in the other two the appearance of the hypophysis was normal. Serial sections were obtained. The fifth patient is alive, but roentgenograms of the sella turcica give evidence of some enlargement, with slight erosion of the floor and of the posterior clinoid processes. Thus two of our seven cases appear to belong in the category of pituitary basophilism, as described by Cushing (2), while the others seem to be instances of primary disease of the suprarenal cortex.

Another point that should be held in mind is the not infrequent presence of adenomas of the hypophysis, suprarenal cortex and other glands of internal secretion in the absence of any physio-
logic disturbances. Recently 1,000 hypophyses obtained at random in postmortem examinations in cases with no history of endocrine abnormality. Each hypophysis was sectioned serially at intervals of 1 mm. Approximately 20 per cent of them contained adenomas but only about a fifth of these were basophilic. With the random incidence of basophil adenoma less than 4 per cent, as this seems to indicate, it must be more than a coincidence that we should have one and possible two instances of basophil adenoma in these seven cases, and that Cushing (2) should have been able to report six instances in the ten cases he described. The possibility is entertained that a basophil tumor of the hypophysis incites the hyperplasia and the growth of adenomas in the suprarenal glands. However, the only tumors of the hypophysis that are known to cause hyperplasia of suprarenal glands are those which provoke the increased growth of the body as a whole, with all its organs; namely, the acidophil adenomas of acromegaly. There is no proof that basophil tumors have any such effects, and it is equally logical to suppose that suprarenal overfunction provokes the growth of basophil elements in the hypophysis. In other words, from the evidence at hand in this disease, one might speculate that the dominant part was taken by the suprarenal gland, even in cases in which basophil tumors of the hypophysis were present.

Cortical adenoma and hyperplasia of the suprarenal cortex are encountered in a large percentage of patients who present the peculiar syndrome described herein. Removal of the adenomas is highly beneficial, and reduction of the mass of cortical tissue in cases in which there is bilateral suprarenal hyperplasia may
be helpful, as is the analogous reduction of diffuse hyperplastic thyroid tissue in exophthalmic goiter. The suprarenal glands can be explored by operation with very little surgical hazard; therefore, this ought to be done in all cases in which the syndrome in question is encountered. If a cortical tumor is found, it ought to be removed. If the suprarenal tissue is hyperplastic, its mass may be reduced by resection, with later treatment of the hypophysis by roentgen rays. This, we believe to be a better plan than to reverse this procedure and to depend primarily on treatment directed at the hypophysis. Treatment of the hypophysis by roentgen rays has been significantly ineffective in cases in which this syndrome has been presented, and cannot be expected to help at all in cases in which suprarenocortical adenoma is present.
SUMMARY AND CONCLUSIONS

It would appear from the foregoing, then, that the syndromes of pituitary basophilism are numerous and at the present time can only be tentatively outlined.

(1) The Cushing syndrome, with a rapidly developing basophil adenoma, terminating, in most reported cases, in death within five years. The clinical picture of this syndrome is a characteristic one with well marked physical signs.

(2) A syndrome in which the disturbances appear to point to involvement of the suprarenal cortex, but in which with more complete understanding of the basophilic syndrome one may consider a possible involvement of both the suprarenal and the pituitary glands.

(3) A mixed syndrome of intrasellar pituitary disease, with evidence of a neoplasm. These patients present features of basophilism, though less marked and less numerous than those in group 1. They may also present signs of acromegaly and an evidence of acidophil cellular overactivity; this comgination has also been reported by Cushing.

(4) A prepubertal or pubertal basophilic syndrome. This is a disturbance of developmental growth in which there is precocious sexual development, associated with evidences of pituitary basophilism. Rarely do these cases pass into group 1; more commonly compensation takes place and they reach a static phase compatible with health.

(5) Postmenopausal basophilic syndrome. This includes the group of women whose ovarian activity has ceased, with the devel-
opment in pituitary gland of so-called castration cells. These cells, largely basophilic, may be the cause of the production of such signs, which one so frequently sees, as pituitary headache, hypertrichosis with a beard, hypertension, obesity, hyperglycemia and often associated thyroid and suprarenal signs. No doubt this group is the precursor of the "bearded old woman" type.

It has been my desire to confirm the characteristic syndrome of pituitary basophilism described by Cushing and to demonstrate that all basophilic syndromes are not necessarily progressive and fatal; likewise that pituitary adenomas presenting many features of this syndrome exist, and are either pure pituitary basophilism or combined with acidophilism and disease of the suprarenal glands; also, that "transitory or mild degrees of pituitary basophilism" do exist, not only in adolescents but in premenopausal and post menopausal states.

One need not inquire what produces an adenoma of the basophil cells, for the solution of the problem of tumors is still far removed. But what does produce a predominant activity of these cells? The close relationship of the pituitary gland to the gonads is, no doubt, an important factor, because this syndrome occurs more frequently in women. It has been affirmed that the basophil cells produce the gonad-stimulating hormone of the pituitary gland. This is an assumption which is not yet well founded and which will probably be altered on both experimental and practical grounds. These patients present every evidence of underactivity of the sex function rather than a stimulatory effect probably upon a basis of a polyglandular disorder.
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