A REVIEW OF SEX CHARACTERS

WITH SPECIAL REFERENCE TO THE
ADRENAL CORTEX

BY

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Science, so far, has been unable to explain what determines sex in animals. Among mammals, with rare exceptions, the sex once acquired is definite and unchangeable, but this stability of the sexes steadily declines as we descend the evolutionary scale. In man we have come to regard the differentiation of the sexes so much an accepted and universal feature of nature that any deviation from this rule at once excites our curiosity. There are cases, however, in which characters common to both sexes have, from time to time, been observed, and it has fallen to my lot as a surgeon to study several cases of women in whom male secondary sexual characters have appeared. This has led me to consider the biological factors concerned, which are presented in this review. By the study of the abnormal we may hope to obtain a better understanding of the normal; and it is for this reason that these cases can make their contribution to our knowledge of sex physiology.

HISTORICAL

In Greek and Roman mythology we read of transformations, both fantastic and picturesque. Sir John Bland-Sutton, in his *Story of a Surgeon*, quotes the following:

"We learn from Ovid, the master of romance and vivid fancy, that Tiresias in his youth interfered with two engendering snakes, and was in consequence turned into a girl. Seven years later, he saw the same pair of snakes again copulating, and separated them with a stick. He was again turned into a man, and became the most celebrated philosopher in Thebes."

In Greek mythology we learn the story of Hermaphroditus, son of Hermes and Aphrodite, who was worshipped as a divinity. He had inherited the beauty of both his parents, and thus excited the love of the nymph of the fountain of Salmacis. She tried in vain to win his affections, and as he was one day bathing in the fountain, embraced him, praying to the gods that she should ever be united to him. The gods granted her request, and the bodies of the youth and nymph became joined together, retaining, however, the characteristics of each sex. The figures of Hermaphroditus, half man and half woman, are common in ancient art. This double sex is also attributed to Dionysus and Priapus, embodying in one being the two principles of generation and conception. Dionysus, the young, beautiful, but effeminate god of wine, is described as having a manly form, but approaches the female in softness and roundness.

Sex abnormalities have not failed to attract attention in the sphere of art. M. Achard and M. Thiers record a picture by Ribera of Madeline Ventura, who, bearded at the age of 52, is suckling an infant. In the National Museum at Munich there is a statue in wood of the bearded St. Madeline.

The primitive instinct is one of antipathy towards the abnormal. Among animals their presence in a herd is not tolerated; it is not unusual to see them feeding at a distance, and they are often attacked and killed. This same antipathy has been shown by man. Crew quotes the case of a cock which, in 1474, was sentenced and burned at the stake in Basel for the heinous and unnatural crime of laying an egg. The executioner, a man with an inquiring type of mind, after fulfilling his office, discovered three more eggs inside. Apparently the same fate befell the sexually abnormal up to 1730. Our attitude has changed since then.

SEXUAL EVOLUTION

In the vertebrate kingdom there are present in each sex, rudiments of the accessory sexual parts of the opposite sex. There are, however, exceptions to this rule. Some individuals combine not only the bodily characters, but also the generative cells of both sexes, and are spoken of as true hermaphrodites. Others, again, with the generative cells of one sex combine the bodily characters of both. No hard-and-fast line can be drawn between the two groups. True hermaphroditism is rare in man, but more common in animals. In pigs, for example, the numbers have been estimated at 1 in every 80,000. Pseudo-hermaphroditism is common in man, and in Warsaw the ratio was 30 to every 800,000 of the population.

In the case of animals and plants with separate sexes, it is obvious that the two elements must always unite for each birth. In true hermaphrodites it is not obvious why they should unite; nevertheless, they either occasionally or habitually do so, for the reproduction of their kind. All vertebrate animals, all insects, and some other large groups of animals pair for each birth. Many hermaphrodite animals do not habitually pair. The vast majority of plants are hermaphrodite. In plants and aquatic hermaphrodites cross-fertilization can be explained by such agencies as winds and insects on the one hand, and of currents on the other. Apparently no land animal is capable of self-fertilization. It is a curious anomaly that in plants some species of the same family are hermaphrodite and others unisexual, yet the difference between them is very small. Hence it appears that, with plants and animals, intercrossing between distinct individuals is almost a universal law of nature. Hermaphroditism may occur in varying degrees in one organism. It may be demonstrable in early life (tadpole) and disappear in adult life as maleness or femaleness predominates, or it may be normal in the adult. Other animals are bisexual; they produce ova at one time and spermatozoa at another. Certain facts suggest that hermaphroditism is a primitive condition, and that the unisexual condition is a secondary differentiation. Yet other facts, where cross-fertilization may be difficult, suggest that the bisexual condition may have arisen as a secondary adaptation.

Another less understood variant in the modes of reproduction is that of parthenogenesis, in which ova produced by the female develop without being fertilized by the male element. This obtains among rotifers and small crustaceans, where the males in some cases have never been found, or are absent for a season. In bees the males may be absent for the summer, or be artificially segregated for years, without affecting the rapid succession of sterile female generations, and the production of drones in the beehive from eggs which have never been fertilized.

Reproduction in the elementary forms of life is by simple cell division. Thus the amoeba splits to form two complete individuals. For all its simplicity, we see its analogy in the highest forms of reproduction, the same division of the fertilized ovum into two cells, each of which may ultimately develop into separate individuals—the so-called uni-ovular twins. In the metazoa the same primitive form of asexual reproduction obtains. In sponges, groups or clumps of cells sequester off to form new individuals, and if a sponge is cut into pieces these may regenerate the whole. In the higher forms of life this attribute of regeneration remains the sole legacy of the reproductive cells. Volvox, on the borderline between the protozoa and metazoa, presents several peculiar biological phenomena. The adults are balls of cells. In such a ball reproductive units are sent adrift and divide to form new individuals. At other times some of

the cells develop into ova and others into spermatozoa. The large cells are fertilized by the small. We may find volvox balls in which only ova are being made, and others with only spermatozoa. Here we have an organism illustrating the differentiation between somatic and reproductive cells, and occurring in asexual, hermaphrodite, and unisexual phases. The analogy between the higher and lower forms of life can be pushed even further. For, in the protozoa, processes corresponding to fertilization are of general occurrence. Periodically, conjugation takes place in which two individuals unite temporarily or permanently. This is an incipient sexual process—the fertilization of an ovum by a spermatozoon.

SEXUAL CHARACTERS

Only when one set of sexual glands (ovary or testis) predominates is it possible to determine the sex of the individual. These are called the primary sexual characters. Associated with this predominance is the development of the correlated sexual organs; and sexual maturity is declared by the acquisition of secondary sexual characters, which are liable to much variation. When the sex glands are completely absent or experimentally removed, as in castrates, the secondary sexual characters shift towards the neuter or intersexual type, and not to the opposite sex. The alternation of maleness and femaleness in the same individual occurs both naturally and experimentally. Sir John Bland-Sutton gives a most vivid description of this sex reversal in the Mexican sword tail:

"It is a pretty fish, almost transparent and about three inches long. In sword tails the sexes are distinct. In the male the anal fin is represented as a pair of claspers, and the lower part of the tail is elongated, and in shape like a sword. The female has a tail of the usual shape among carp—she produces viviparously. It happens not infrequently that after producing fry two or three times, she changes her sex completely. The anal fin becomes claspers, and the lower part of the tail elongates into a sword, as in the male. Indeed the female becomes male, not only in the assumption of male livery, but sheds milt. The change is correlated with the acquisition of functional testes."

Similar changes of sex have been described in fowls.

Another curious biological phenomenon is presented by the so-called freemartin, the female twins of cattle, who not uncommonly exhibit sexual abnormalities. They are sterile, resemble castrates, and have their internal genitalia undeveloped. In twins of different sexes the female is usually abnormal. It has been found that there exist connecting blood vessels between the foetuses and a fusion of the chorions. It has been suggested that the female undergoes masculinization under the influence of the male sexual hormone entering the blood of the female. Where no such fusion of blood vessels obtains, the females are normal.

Secondary Sexual Characters

The variety and intensity of secondary sexual characters has been one of the most conspicuous features in evolution. The male differs primarily in his increased power of locomotion, his special prehensile organs, his greater size, strength, endurance, and pugnacity, and in his special weapons of offence and defence; in birds, by his gorgeous plumage, decorative ornaments, his engaging antics, and his enchanting song. The females are naturally endowed with organs of nourishment and protection for the young. Darwin attributed the greater decorativeness of the males to the sexual selection exerted by the females. The handsomest and most vigorous males succeed in their courtship better than their rivals, and are more successful in begetting a large number of offspring.

The theory of sexual selection is dependent upon the laws of inheritance, the transmission and development of

characters. The equal transmission of characters to both sexes is the commonest form of inheritance. But characters are commonly transferred to that sex in which they first appear. Now, secondary sexual characters are transmitted by both sexes, though developed in one. Occasionally characters proper to the male appear in the female, when she grows old or becomes diseased—for example, in the common hen. The first development of characters in the female and transference to the male is less commonly observed. Reversion of characters, which may have been transmitted through two or three generations or many generations, may appear under certain unknown favourable circumstances.

We do not know why certain characters should be inherited by both sexes, and other characters by one alone—namely, by that sex in which the character first appeared; but it seems in a general way that variations which originate late in life tend to be developed in the same sex alone, while variations which first appear early in life in either sex tend to develop in both sexes. In a few cases it must be assumed that there is an embryonic difference in the sexes to account for some characters which are seen only in one sex. For instance, haemophilia is transmitted from the parent male through the daughters, who remain unaffected, to their sons. The same obtains in some forms of colour-blindness. It is probable that the parent transmits characters of the asexual type which are capable of reacting to the male and female influence of a given species.

Hair, which may be considered a secondary sexual character, holds an anomalous position. It seems probable that man is descended from some hairy progenitor, yet its loss must have been an inconvenience to primitive man. The commencement of denudation is seen on the under surface of the female anthropoid ape. As women are less hairy than men, females apparently first had their bodies denuded of hair, possibly as a sexual attraction, and transmitted this character equally to both sexes. On the other hand, our male ape-like progenitors acquired beards as a sexual ornament, and transmitted them to their male offspring.

DEVELOPMENT OF SUPRARENAL GLAND

Suprarenal tissue, comparatively speaking, is of recent acquisition to the animal kingdom, and the history of its development is marked by definite and gradual progress. Appearing first in fish, it is present in all higher animals, increasing in importance so as to become essential to life. Bilateral adrenalectomy in man is followed by death. Associated with this increase in functional importance, we find a corresponding and interesting change in the development process. In its primitive form its origin is single and very intimately connected with the reproductive glands; later, this portion commences an association with the cells of the sympathetic system, of quite a different origin. The completed organ therefore is of dual origin. The suprarenal glands were first described by Eustache during the Renaissance. The term "suprarenal capsule" is really a misnomer, for it was originally thought that the glands were hollow, until Meckel in 1806 pointed out that they were solid, and named them adrenals. Pettit's researches first showed that in mammals and other vertebrates these glands lie not only along the upper poles of the kidneys, which is their common position, but also along the inferior vena cava, the renal veins, and along the large trunks of the abdomen; and that their structure and location varies in different animals.

In man the suprarenal glands lie across the upper poles of the kidneys, and consist of a central portion, or medulla, surrounded by the cortex. The medulla is composed of the chromaffin cells, which have a special affinity for, and stain yellow with, chromate salts. The

cells of the cortex are more compact in texture, being differentiated into three zones. They have an abundance of fatty granules, and readily stain with osmic acid. To differentiate these cell types, Balfour in 1878 chose the name of interrenal organ for the lipid-containing cortex, as opposed to the suprarenal, comprising those cell groups which simulate the adrenal medulla.

Development of the Interrenal or Cortex

The interrenal or cortex is derived from the mesothelium of the Wolffian ridge from which the gonads arise, and extends from the pronephros to the cloaca. About the fourth week a series of buds, resembling a chain or rosary, can be distinguished from these coelomic cells at the root of the mesentery. These buds sequester off, and coalesce, forming a ridge, which projects into the colon between the mesonephros and root of mesentery. In the 6 mm. embryo it appears as cell groups just caudal to the pronephros, and in the 9 mm. embryo it is a dense cluster of cells medial to the Wolffian body; in the 12.5 to 14 mm. embryo there are signs of capsule formation, and the cells are well vascularized, becoming arranged in layers.

Development of Medulla

The cells of the medulla have the same origin as the nervous cells of the abdominal sympathetic ganglia. They proliferate and separate off to form an association with the cells of the cortex.

Fusion of Elements

The changes associated with the formation of the adrenal gland in man are peculiar in that the same process has not been observed even in the higher apes. In the third month the sympathetic formative cells (sympathogonia) commence to grow into the cortex to form the medulla. This invagination proceeds along the central fold which contains the main vein in such a way that the greatest surface of contact obtains between cortex and medulla, until the medulla is entirely closed by the cortex. Just before birth the maximum stage of development is reached, in which the adrenal is about one-third the size of the kidney, whereas in the adult the ratio is only 1:28. No other organ shows such marked changes in its subsequent history. In the newborn (till the end of the second month) the cortex gradually becomes reduced by a process of absorption. Fatty infiltration in the form of coarse fat drops appears in the hyperaemic cortical cells, for the most part in the middle and inner zones, and these cells are gradually destroyed. The external layer, whose cells contain only fine granules of fat, survives to regenerate the cortex, which is completed, with adult form, about the second year; and the organ then grows *pari passu* with the rest of the body. The onset of puberty heralds a new and active growth of the cortex. At this stage it is twice as heavy as the testis, whereas later it is one-half or one-third this weight. The three zones become more sharply defined. The outer, germinal or glomerular, zone forms the two inner zones, and the cells contain fine fat droplets, but are poor in lipoids. The fascicular zone is rich in lipoids, and the cells contain large fat droplets. The reticular zone cells contain small fat droplets, but are laden with pigment, which increases with age. In woman the glomerular layer is increased in comparison with man; it enlarges at each period and with pregnancy, and these differences are akin to those found in the pituitary. Between the fourth and fifth decades, the cortex is at the zenith of its development. From this time on there is a gradual senile involution, more marked in the glomerular layer; while the fascicular layer increases in volume. These changes are greater in males than in females.

During the course of this development two facts may be stressed. In the adrenal of the newborn, during the stage of fatty disintegration of the hyperaemic cells, haemorrhage may readily occur—a point which should be borne in mind in applying violent methods of resuscitation. In cases of foetal anencephaly it has been noticed that the adrenals are unusually small. Microscopically it has been found, not that the glands have failed to develop, but that the post-partum changes described have occurred during foetal life, and that the adult gland has already been established. Since the brain is so largely composed of those complex lipid cells upon whose production the adrenal may have some influence, it is possible that the failure of cerebral development in these cases is due to a disturbance of lipid metabolism induced by the premature maturity of the adrenal glands.

COMPARATIVE ANATOMY

The story of the adrenals would not be complete without some reference to their comparative anatomy. In fishes—the elasmobranchs, the teleosts, and selachians, groups comprising the sharks and rays—the two cell systems are separate and distinct. Medullary tissue is found scattered along the parietal vessels and sympathetic chain, whereas the cortex exists as a separate structure, the so-called interrenal body. Coexisting with this interrenal body we find a marked development of the sexual system. The pelvic fins have their hinder ends modified in the male to form special copulatory organs, the myxipterygia or claspers. In the teleosts specialized corpuscles are found on the dorsal and ventral surfaces, and even in the substance of the kidneys. These were first described by Stannius, who considered that they corresponded to the interrenals of the selachians. In amphibians the adrenals are placed loosely along the ventral surface of the kidneys, and stand out as yellow flecks against the dark brown kidney. In some classes of amphibians they appear as a large number of yellow nodules placed in series along the kidney. In this group the first advance of the two cell systems towards each other is observed, and islands of medulla cells are scattered about in the substance of the cortex. In reptiles the morphological characters of the adrenals present more intimate association with the genital glands than with the kidneys, with a large preponderance of cortical tissue. In some species we find an even closer association between the two cell systems, the medulla lying dorsally and the cortex ventrally. In other species there is a tendency for the medulla to be situated peripherally around the cortex. Chromaffin substance is also found in the sympathetic ganglia, and along the inferior vena cava and renal veins. In birds the adrenals, two yellow-coloured masses on either side of the vena cava, lie in the neighbourhood of the upper poles of the kidneys, the left just posterior to the ovary. Microscopically the two cell systems are mixed together in groups, with a preponderance of cortical tissue.

ACCESSORY ADRENALS

From the nature of the developmental process it is to be expected that accessory or misplaced adrenal tissue should be of common occurrence. Chromaffin cells are usually found in relation to the sympathetic ganglia, and may exist as accessory structures. These have been described from time to time in the region of the root of the superior mesenteric artery, and along the abdominal veins. Similarly, any failure on the part of the interrenal buds to coalesce would give rise to accessory interrenal bodies. Such bodies are usually referred to as accessory adrenals, but from their nature it would be wiser to differentiate them as accessory interrenal bodies. True accessory adrenals composed of cortex and medulla are rare, whereas accessory interrenals are very common, and are most often

found near the adrenals, about the gonads, in the broad ligament, along the spermatic veins and inguinal canal, and in the epididymis.

PATHOLOGY

In comparison with tumours of the medulla, those of the cortex are more homogeneous in type, yet their differentiation has been the source of fierce debate among pathologists. Nor has the matter yet reached finality. The contest has raged round the subject of the so-called hypernephroma. True adrenal hypernephromata arise from the cortex of the adrenal or accessory interadrenals. Their entity was challenged by the discovery, nearly forty years ago, by Grawitz, of tumours closely resembling the cortex in structure, but arising outside the sphere of the adrenals. These hypernephromata, or what should be termed renal hypernephromata, have been most commonly found in the kidneys, and have been recorded in places where accessory adrenals occur—namely, the retroperitoneal tissues, pancreas, broad ligament, and even in the ovary and testes. This led Grawitz to attribute their origin to adrenal rests. The position of the Grawitzian hypernephroma has been strongly attacked by Stoerk, Glynn, and others, and many have relegated them, more especially the papillary forms, to the category of renal adenocarcinomata. The classification of these tumours has been complicated by the fact that it has been found that many tumours of the ovary which have been described as ovarian hypernephromata are really not hypernephromata at all, but lutein tumours. Glynn, in an admirable paper, has done much to clear up the subject, and considers the acceptance of Grawitz tumours has been too complete.

In view of the difficulty and unsettled pathology, it appears reasonable to adopt for the present an arbitrary clinical classification of hypernephromata into those which are associated with virilism and those which are not:

A. Tumours of the Adrenal Cortex

1. Hyperplasia. Nodular and diffuse, or bilateral.
2. Hyperplasia. Unilateral.
3. Adenoma.
4. Hypernephroma of the adrenal cortex.
5. Carcinoma.

These are invariably associated with virilism.

B. Tumours Resembling the Adrenal Cortex

1. Renal hypernephroma.
2. Ovarian hypernephroma.
3. Large lutein tumours.

These are not associated with virilism.

The hyperplasias are rare, and we find gradations between these and the adenomata. They are commonly found in infancy and old age, and when bilateral they give rise to pseudo-hermaphroditism (feminine). Unilateral hyperplasia is found after puberty in the second and third decades, and is associated with marked virilism. This type receives scant reference in the literature, is probably the commonest and most important of all the groups, and will be more fully described later. The adenomata may be single or multiple. They are circumscribed, rarely encapsulated, may be large, with a tendency to haemorrhage and softening, and often become malignant. Carcinoma occurs frequently. The atypical cases are difficult to dissociate from sarcoma, and the ratio of carcinoma to sarcoma is 10:3. They form soft yellow tumours, which grow rapidly, and are prone to necrosis and cystic change. Bony metastases are infrequent, and their progress is rapid and fatal.

Hypernephroma

In view of the variability displayed by this tumour, it may be well to emphasize some of the characters observed in the different groups.

True Adrenal Hypernephroma.—Macroscopically, this tumour resembles the more common renal hypernephroma, with a tendency to haemorrhage and necrosis, but it is less yellow and has not the same tendency to form cysts. Microscopically, the resemblance to the normal adrenal cortex is slight; the cells and their nuclei are distinguished by the greater variation in their size and shape, by the absence of the characteristic clear and very vacuolated cytoplasm, and apparently by the complete absence of well-formed gland lumina. The histological appearances are a small index to malignancy, and there is no real difference whether the tumours are from the young or old, male or female, with or without sex changes. Virilism with amenorrhoea is invariably present.

Renal Hypernephroma or Grawitz Tumour.—Macroscopically, there are large, yellow, fatty, vascular, circumscribed tumours, prone to haemorrhage and cyst formation. There is usually a central fibrous area surrounded by a more cellular portion. They arise within the kidney capsule, displacing the renal substance, and may extend along the renal vein. Microscopically, there is a striking resemblance to one of the zones of the adrenal cortex. The cells are arranged either in small circular groups separated by strands of connective tissue (zona glomerulosa), or the elongated cords of zona fasciculata may predominate. The cytoplasm is slightly granular, numerous lipid and glycogen granules yielding a foamy texture. Lumina are present. Virilism is absent. These tumours become highly malignant, are rapidly fatal, and very commonly disseminate in bone.

Ovarian Hypernephroma.—Macroscopically, these are solid yellow tumours with haemorrhagic and necrotic areas; sometimes there are a few degenerate cysts of yellow colour, containing fat. Microscopically, there is a general resemblance of groups of clear or very vacuolated cells lying in a capillary stroma very much like the zona fasciculata. The cytoplasm is clear and extensively vacuolated, and the presence of glycogen and lumina is well marked. There is a close resemblance to the structure of the adrenal cortex and to the renal hypernephroma, and consequently these tumours have been thought to be of adrenal origin.

Lutein Tumours

Macroscopically, these tumours apparently arise in the ovary. They are large, generally about the size of a foetal head, usually malignant, yellow, haemorrhagic, and with necrotic areas and cysts. Microscopically, there is a resemblance of clear or very vacuolated cells in a capillary stroma to the zona fasciculata. The cytoplasm is clear and vacuolated, glycogen and lumina are present, but to a lesser degree than in ovarian hypernephroma. The cellular hyperplasia of the lutein layer has been mistaken for ovarian hypernephroma, and, both macroscopically and microscopically, there is no essential difference between these tumours. Glynn, in an exhaustive examination of these tumours, comes to the conclusion that only in one case (Bovin's) of a hypernephroma in the broad ligament associated with virilism was there evidence to show that the tumour was a true adrenal hypernephroma of an accessory suprarenal. Considering that accessory suprarenals are common in the broad ligament, few hypernephromas have been recorded there; and there is no proved case of cortical rests either in the ovary or in the testis. This case is probably the only true adrenal hypernephroma which has been described as occurring in the female pelvis.

Virilism, either complete or partial, has been described in association with cystic or dermoid tumours or semi-solid tumours of the ovary, but there is no evidence that the adrenals in the cases were examined.

CLINICAL SYNDROME

It has long been known that the ductless glands exert a powerful influence on our health and physical development. The facts at our disposal show that they function as a whole in a concerted and orderly manner. We have been able to assign certain clinical syndromes to pathological processes in the majority of them, and we ascribe their influence to an internal secretion, which acts in virtue of its over-secretion, under-secretion, or disordered secretion, via the blood stream. Any dysfunction of one is apt to unsettle the balance between the others, and it is the interpretation and correlation of this intricate system of interaction to which so much study is now being devoted.

There is abundant evidence to show that certain of these glands are intimately concerned with general bodily growth, and of such organs as the sexual in particular; that the continued secretion of these glands is necessary for the maintenance of this growth at a normal level; and that growth will be inhibited when the flow ceases or diminishes. The most striking change associated with the adrenal group is the accentuation of the male secondary sexual characters, and these may be most aptly described under the heading of "Virilism," rather than the more cumbersome appellations in literature, such as the "Adreno-genital syndrome." As long ago as 1756 W. Cook established the association of hypertrichosis and adiposity with adrenal tumour. The association of secondary sexual changes with adrenal tumour was known to John Hunter, and, though cases were sporadically recorded, it was not till 1905 that the true correlation was confidently emphasized in a publication by Bulloch and Sequeira. Unfortunately, many of the earlier case reports are unsatisfactory in that the clinical manifestations were ascribed to various pathological processes, and the real causative factor was either overlooked or not examined.

The clinical changes which constitute virilism may be grouped as follows:

Changes Involving the Sexual Organs.—In women, atrophy of the uterus, changes in the ovary, under-development of the labia, and overgrowth of the clitoris. In males, precocious sexual and somatic development—for example, a boy aged 6 may possess the sexual and somatic development of a full-grown man.

Changes Affecting Bodily Contour.—In women, narrowing of the hips, broadening of the shoulders, atrophy of the mammae. Either marked muscular development or the deposition of fat.

Disturbances in the Sexual Function.—Irregular menstruation, amenorrhoea, miscarriages, and failure to bear children.

Alteration in the Secondary Sexual Characters.—Hirsutism of the male type; either a beard and moustache or mutton-chop whiskers. The hair on the body is of the male type, curly and crisp, and well marked on the limbs. On the body the pubic hair extends up to the umbilicus, and may be well developed on the chest, shoulders, and small of the back. Development of the larynx in women is accompanied by cracking of the voice with a concomitant bass voice. Linea distensae are sometimes found on the flanks and thighs, and are probably a result of increased adiposity.

Psycho-sexual Change.—This is difficult to ascertain, but Holmes quotes a case in which there was lack of modesty and loss of erotic feelings.

The type of virilism depends on the time of onset and the duration of the symptoms, and may be conveniently classified as follows:

1. *Congenital Type.*—Probably all cases of feminine pseudo-hermaphroditism belong to this group, in which the sexual glands are female and the secondary sexual characters are male. Serious misapprehension as to the sex of the individual may arise in later years. These cases are associated with bilateral hyperplasia or occasionally an enlarged accessory adrenal.

2. *Puberty Type.*—This is a common variety, and changes commence at puberty or soon after. It is entirely confined to young women, who develop either the obese or muscular type of virilism, in which hirsutism and menstrual disturbances predominate. Whether this type is a direct result of the increased activity of the adrenals which takes place at puberty, or at birth, we do not know; but we do know that it is associated with adenoma and unilateral hyperplasia; and it may even occur with adrenal tumour.

3. *Adult Type.*—In adult women, including multipara, the reversion to the male type is less marked; hirsutism followed by amenorrhoea, involution of the breasts, atrophy of the uterus and ovaries, obesity; miscarriages may supervene. The pathology is identical with Group 2.

4. *Obstetrical Type.*—After the menopause, hypertrichosis followed by obesity, psychical disturbances, and asthenia supervene. The loss of hair follows the masculine rule, and it is not uncommon to see the recession of the hair, and even temporal baldness in elderly women. This group, like the congenital, is accompanied by bilateral adrenal hyperplasia. There is now evidence to show that, after surgical removal of adrenal tumours in suitable cases, women have shown a most striking reversion to their own type, in regard both to psychical and to secondary sexual characters.

PATHOGENY

On the analogy of the behaviour of other endocrine glands it is probable that the adrenal cortex elaborates an internal secretion, which passes into the blood stream and, when present in excess, is capable of producing the changes already referred to. How this hormone acts is subject to much speculation. Swale and Vincent maintain that it acts directly on the reproductive system. It is also suggested that it is an adjuvant to the testicular hormone in the amplification of the secondary male sexual characters, and is not antagonized by the ovary; or that it acts reflexly on the sex characters via the pituitary, pineal, ovary, and testes. Blanchard contends that it is the interstitial cells of the gonads which are directly responsible for virilism. Krabbe offers an ingenious explanation by asserting that the ovary is originally bisexual, the cortex being male and the medulla female, and that cortical hypernephromata are tumours caused by riotous growth of misplaced sex elements in the adrenal. This view has been criticized by Gordon Holmes, Kemp, and others, who doubt such chance inclusions, and point out that these tumours, associated with sex changes, approach in microscopical appearance the normal structure of the adrenal cortex. Keith believes that it is through the adrenal cortex that the gonads produce the changes associated with puberty. Lipschutz maintains that the adrenals exercise a masculinizing effect on the sex glands. In support of this is our knowledge that pineal and pituitary tumours may be associated with the same changes. Crosbie and Smith assert that the sex characters are regulated by the interstitial cells of the gonads, and that this function may be assumed by the adrenal cortex.

So far there is no evidence that hyperplasia of the cortex can be produced experimentally.

It is difficult to come to any definite conclusion as to what type of hormone is elaborated, but it is probably a hypersecretion, upsetting the endocrine balance in which the gonads are concerned. It is essentially a masculinizing effect, heightened in the presence of the male sex gland, but apparently not much modified or altered in the presence of the ovary. Nor are we able to say precisely which cell type is concerned with the elaboration of this hormone. The available evidence points to the cells of the adrenal cortex and sustentacular cells of the testis. The latter are the more potent in producing the finer points of male characterization. In the adrenal cortex it is probable that the cells of the outer zone are most directly responsible. This is not surprising in view of their common ancestry.

PHYSIOLOGY

Since the discovery of the blood-pressure-raising effect of extracts of the adrenal medulla in 1894 by Sir E. Sharpey-Schafer, a great deal of attention has been devoted to its physiology, but no such far-reaching effects have been accorded to the cortex. Apart from the production of virilism, the cortex is credited with a close association with lipid metabolism, being the storage organ for cholesterol fats.

It has been suggested that the cortex forms a precursor to epinephrin, but there is no valid reason to indicate that any mutual co-operation exists between cortex and medulla. There is, however, evidence that the cortex acts as a detoxifying agent. During the acute infections—streptococcal, diphtheria, and scarlet fever—the protoplasm of the cortical cells shows marked vacuolation and loss of lipoids, and it is thought that in this process the cholesterolin or cholesterolin esters saturate or inactivate poisons or toxins. Yet in starvation the lipid content of the cells remains unchanged.

Modern Conception of Gonadal Internal Secretions

A vast amount of experimental work has been devoted to the influence of the sexual glands, in an endeavour to explain the problem of the sexes. The bulk of this work emanates from the Continent, and the inquiry has been pursued from two aspects: (1) the grafting of sex glands; (2) the injection of extracts from the sex glands.

It is now accepted that every organism in its earliest development passes through an asexual stage, and that the soma reacts to maleness or femaleness by the specific action of the sexual hormones. This theory is supported by castration experiments in which the animal more or less loses its sex characters and tends to assume an asexual or neuter form. If a gonad is transplanted into a castrated animal of the other sex, the animal reacts to the former—that is, the hormones act as a sex specific. The most successful grafting experiments have been of this nature, for it has been found that there exists a certain antagonism between ovarian and testicular grafts on uncastrated animals, although simultaneous ovarian and testicular graft can produce experimental hermaphroditism, with variations in psycho-sexual behaviour. In these experiments it has not been possible to discount the interaction of the other endocrine glands. Thus, it has been possible to establish certain facts: (1) Formation and persistence of sex characters depend on sexual glands. (2) The formative and causative influence of the sexual glands do not relate to all sex characters. (3) The formative and causative influence of the sexual glands concern not only the sex characters involved in sex function—that is, genitals, heat, psycho-sexual behaviour—but characters in special relation to sex function—plumage, etc.

Internal Secretion of the Testis and Ovary

The clinical evidence available with regard to the testis shows that the interstitial cells are a necessary part of the testicular hormone, and there is no proof of an independent hormone elaborated by the cells of Sertoli or the tubules. With regard to the ovary, the position is less clear, and the endocrine function is intimately connected with processes taking place in the follicle. Consequently, all experimental results based on the injection of gonadal extracts have been conflicting and disappointing. This is not surprising considering the compound structure of the sexual glands, and the fact that we cannot control the rhythm of their normal function. Moreover, it has been found that the sexual hormones are not specific for each species. It is not until we can establish the quanti-

tative rate and rhythm of the secretory action of the gland that we can hope for more success from the injection of extracts.

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UNDULANT FEVER IN INFANCY

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During recent years sporadic cases of undulant fever have been recorded in these isles from time to time, and it would appear that they constitute only a small percentage of the cases which actually occur. There seems to be no question that the infection is spreading, and that what was formerly known as Mediterranean or Malta fever has been found in practically every country in Europe; it is also widespread throughout the United States. The causal organism, the *Brucella melitensis*, has been found in goats, cattle, horses, pigs, cats, and dogs, and the prevalence of animal infection in this country was shown by routine agglutination tests carried out at the Royal Veterinary College, London, in 1927-28, which returned positive results in 31.8 per cent. of 928 cows and heifers.

Sir W. Dalrymple-Champneys, in his report to the Ministry of Health on undulant fever, makes the statement that children under 5 years are almost exempt, and it is chiefly on this account, and because of our inability to find any previous record of a case in infancy in Britain, that we have made the following communication. As in the majority of cases described in this country, the causal organism was not isolated, but serologically and clinically there is no doubt that the following case was one of undulant fever.