THE INTERSTITIAL GLAND.*

BY
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It has long been known that the reproductive glands both in man and woman preside over the determination of what are called the secondary sexual characteristics. The primary sexual characteristics are, of course, penis and scrotum in the male, and vagina and uterus in the female. Among the secondary sex characteristics are the beard and the bass voice in the male, and in the female the smooth skin, the treble voice, and the development of the mammary glands. There are other physical differences between the two, such as stature and breadth of pelvis, and these are accompanied by certain mental and temperamental differences upon which I need not insist. Ever since castration was first performed—and castration is probably the oldest of all surgical operations—it has been evident even to superficial observers that castrates differed in several very important particulars from those who had not been subjected to this mutilation. It has thus become a matter of common knowledge that the testes in the male and the ovaries in the female supplied some element to the economy which not only determined, but served to maintain, what we call maleness in the one and femaleness in the other. In the case of man it was believed until comparatively recently that this element or essence was derived from the tubuli seminiferi, and to some extent perhaps from the prostate gland. This, though a very natural inference, has proved to be erroneous. It has now been shown beyond any manner of doubt that this essence or hormone is secreted by what is known as the interstitial gland.

The interstitial gland was first described by Leydig of Frankfort in 1850, who wrote as follows:

"Comparative histology has shown that in addition to the seminal tubules, blood vessels, and nerves, the mammalian testicle contains another constant structure, which appears as a group of cells which, when small in number, seem to follow the course of the blood vessels, but when plentiful seem completely to surround the seminal vesicles as though to embed the latter."

This observation of Leydig's, if at the time of its publication it was noticed at all, was regarded merely as an histological curiosity entirely devoid of physiological significance, and no reference appears to have been made to it until 1903, when Ancel and Bouin published the first of their series of papers which have since become classical. It is interesting to note that about the time of Leydig's observation, Claude Bernard was delivering at the College of France a series of lectures on experimental physiology in which he coined the term "internal secretion." It was many years later that his co-worker Brown-Séquard, after experiments on himself, scandalized London and even Paris by proclaiming that he could cure sexual senility by injections of fresh testicular extract. As we shall see presently, he was much nearer the truth than his contemporaries imagined.

Such, then, is the now famous interstitial gland—a mass of minute structures not unlike fatty globules situated in the connective tissue of the testicle, separate from and unconnected with the vesiculæ seminales and vas deferens, and endowed with the function of supplying an internal secretion to the economy which determines and maintains not only the secondary sexual characteristics, but also the copulative capacity of the individual. So far, I have dealt only with the testicle. The ovary also contains an interstitial gland, but as the presence in the adolescent and adult ovary of the corpus luteum produces a complication which renders the train of events rather difficult of clear comprehension, I shall not attempt to deal with it here. In elucidation, however, of some points of considerable importance I must briefly consider the question of the development of the interstitial glands in the two sexes. At the moment of conception two elements, a male and a female, combine to form an entity. These elements are warring elements, each of them potentially charged with their characteristic interstitial glands, which develop very early in embryonic life. For several weeks this embryo is neuter, and we are to suppose that the male element and the female contained therein are striving for mastery the one over the other. Then comes the time when one, say the male, has definitely gained the victory, so that penis and scrotum instead of vagina and uterus result. But the victory is never complete. The embryonic inter-

stitial glands on both sides have been mobilized, the armies have been engaged, and albeit the one may win, the other, though defeated, is by no means annihilated. Thus it comes about that in every child born there remain a certain number of these antagonistic interstitial gland cells which, entrenched opposite their victors, continue to glower at them, spoiling for the next encounter. The two armies now cease firing and go into winter quarters. Then at the age of puberty there ensues a second battle royal. The fact that the external evidences of maleness are firmly entrenched does not prevent the female interstitial cells from making one last desperate attempt to gain the mastery; so that side by side with the secondary male characteristics which should accompany the penis and scrotum there may appear some secondary female characteristics, such as a broad pelvis, high-pitched voice, together with female mentality and feminine tastes. There is no man but has some taint of the woman in him, and no woman without some smatch of the male. When the victory in favour of maleness is complete the result is a Caesar, a Napoleon, a Bismarck—active, resolute, and ruthless. When less complete you have the ordinary man, respectable, hard-working, but with engaging weaknesses. With yet another dose of the female interstitial gland in his composition you come upon the effeminate artistic male, who, whatever his practices, is usually homosexual at heart. Reverse the medal, and you are in the presence of such an eternal femininity as Josephine or Mary Queen of Scots. With added male elements, in different degrees, you see Queen Elizabeth, Catherine of Russia, Madame de Staël, or the latter-day suffragette. It is more than probable that among the ranks of the last were a large proportion of women in whom the male and female elements were so nicely balanced as to render them frankly homosexual, and that their activities were directed, subconsciously perhaps, to obtain, not so much a vote, as the right to dispute on equal terms with their male adversaries in the gate of the forum and the market place. "Infirm of purpose," you can hear them shout with Lady Macbeth, "infirm of purpose, give me the daggers." The lineal representatives of these portents of a generation ago are now engaged, some of them, in the exercise of what they are pleased to call "self-expression" in journals and novelettes. And someone recently compared their methods to those of the little boy, newly awakened to the stirring of sex within him, who writes obscene words on the vicar's garden gate.

From these considerations two points of social importance emerge. One is the question of the determination of sex in a young embryo; the other is the attitude which a civilized community should adopt towards homosexuality. Taking the latter point first and briefly, I am entirely of the opinion, suggested rather than expressed in a recent lecture by my friend Julian Huxley—namely, that the present law on the subject requires revision. Regarded in the light of pure physiology, it is no more reasonable to punish a man for being homosexual than it would be to punish him for having red hair. Both of these things are burdens cast upon him by forces over which he has no sort of control, nor can he alter or even modify them by any effort of the will. It is high time that the members of our profession expressed strong and clear views on this question. Let us remember that it is not so very long ago that people were tortured for being insane, and that it was a great-hearted French physician, Philippe Pinel, who died in 1826, who, at the risk of his own life and liberty, insisted upon the humane reforms which were afterwards generally adopted.

On the second point, the question of the artificial determination of sex soon after conception, though the present state of our knowledge does not permit of dogmatism, I should like to say that if the train of events which I have sketched above is even approximately correct it is reasonable to suppose that by reinforcing the male element in the embryo by male interstitial gland, administered to the mother, we ought to be able to determine the victory in favour of definite maleness in the full-time child, and that by exhibiting the same extract when puberty threatens we could ensure against anything in the nature of homosexuality in the adult.

But things are not always what they seem, and this is even more abundantly true in the domain of the ductless glands than elsewhere. These glands constitute a hierarchy of interdependent entities. I am fond of comparing them to the eight rowers in an outrigger boat. All are pulling in the same direction, and yet some of them antagonize certain others. If you reinforce one his antagonist will immediately be stimulated to retort, so that unless you have experience to guide you, especially in the dose of the original reinforcement,

* A paper read before the annual meeting of the Westminster Division of the British Medical Association.

you may bring about a result which is the exact reverse of what you desire. I am nevertheless of opinion that in a proper dosage of the appropriate interstitial gland we hold the key to the solution of the vexed and much-debated question of the artificial determination of sex.

Let us now return for a moment to the mammalian testicle. We have seen that it has two sets of glands—the tubuli seminiferi and the interstitial glands. The former of these supplies an external secretion which is conducted by the vas deferens to the vesiculæ seminales, where it is stored for emergencies. The second, the interstitial gland, is a ductless gland which pours its secretion directly into the blood vessels to act as a hormone—that is, as a specific stimulant to certain parts of the economy. Now, the interesting point about these two activities is that they are in some senses antagonistic. Let me say, parenthetically, that the more you study the endocrine glands, the more deeply do you become impressed by this element of strife within the body. There is war between the male elements and the female in the product of conception; there is war between the thyroid and the pancreas; there is an armed neutrality between the thyroid and suprarenal; it is pull devil, pull baker, between the pituitary and the gonads; and here in a single structure, the testicle, we find, where we should least expect it, a never-ending combat between its internal secretion on the one hand, and its external on the other. The bone of contention seems to be the lion's share of the blood supply. Both the external and the internal appear to demand more than the other, for it has been shown that when one is down and out the other multiplies abundantly.

In 1903 Ancel and Bouin described some of the effects of ligaturing the vas deferens on one side in dogs. This experiment has been frequently repeated, and the result has always been a gradual atrophy of the seminal vesicles on the side of the ligature. Recently, however, another result has been observed—namely, that *pari passu* with the atrophy of the seminal vesicles there has appeared a definite hypertrophy of the interstitial element. The knowledge thus obtained has been applied clinically to prevent or counteract the degenerative effects of senility. In America very largely, to some extent both in France and Austria, though, so far as I know, not yet in this country, the operation of ligaturing the vas deferens on one side has been performed in elderly men, and has been followed by a remarkable access of mental and physical vigour. As to how long the rejuvenescence thus produced may be expected to last there do not seem at present to be any data upon which to form an opinion. Brown Séquard's successful experiments on himself were similar to, though by no means identical with, those which are now being performed; but if his case is to be accepted as any guide we must not place too much reliance upon these methods of defying time, for he was no more than 77 when he died.

Soon after the x rays were introduced it was found that many very serious penalties attached to the pioneers in this fascinating means of diagnosis and treatment. Among the less serious drawbacks to constant exposure to these rays it was found that the operators became sterile. They did not lose their sexual capacity or their sexual appetite, but they became incapable of begetting children. In 1905 Bergonié and Tribondeau showed that the effect of the rays was to cause atrophy of the seminal vesicles and concomitant hypertrophy of the interstitial glands—the same result, in fact, as is now known to be produced by ligature of the vas deferens. It therefore comes to this: an elderly man who wishes to renew his youth need not subject himself to the operation of ligature of one vas deferens so long as he can find a radiologist who can expose one testicle, and one only, to the activities of the x rays for a period sufficiently long and in a dose sufficiently powerful to ensure the atrophy of the seminal vesicles on that side. The interstitial glands will then hypertrophy and fructify, with results which may or may not be altogether desirable even to the individual. On that point there is only Faust to interrogate, and he is silent.

There are some other influences of what may be called a more normal kind than the foregoing, which seem to give rise to results somewhat analogous. Chief among these are the poisons of alcohol and tuberculosis. It is a common observation that alcoholic drinks produce an aphrodisiac effect upon some people. The porter in *Macbeth* informs us that "drink is a prevaricator with lechery; it creates the desire and takes away the performance"; the physiological

meaning of which is that while stimulating the interstitial gland, it paralyses the sphincters of the veins in the corpora cavernosa. That chronic alcoholism leads to an hypertrophy of the interstitial element in the human testicle is now a recognized fact; that it leads to a concomitant inactivity of the seminal vesicles is a reasonable deduction from many of the confidences, some of them embarrassing, which we receive in the consulting room. In the matter of tubercle, it has long been recognized in France that a very early manifestation of the disease is a heightening of the sexual appetite. In this country the matter is, of course, regarded from the opposite point of view, the pulmonary plithisis, when it appears, being confidently ascribed to the direct intervention of the Almighty for the punishment of the premonitory sexual excess. Wherever the truth may lie, all the authorities who have written on the subject agree that after death from pulmonary tuberculosis the interstitial glands are found to be much hypertrophied.

I have already said that the interstitial gland is a member of the hierarchy of glands of internal secretion known as the endocrine system. To endeavour to think in terms of this system is to understand the fascination of the will-o'-the-wisp and its elusiveness. I try, as I have said, to think of it as a trim and true outrigger boat, manned by trained men and wisely guided by a cox, but ever and anon in sheer desperation I cry aloud that it is naught but a cage full of wild and ineffectual monkeys. To try and establish any constant rule or relationship between the component glands is deeply to sympathize with Sisyphus, or rather Balbus, for just when you think to have built your wall the whole bag of tricks comes tumbling about your toes. It is therefore in a chastened mood that I venture to suggest—I would not dare to dogmatize—some of the relationships which the interstitial gland appears to have with some other members of the hierarchy. First, then, there is the suprarenal, which appears to be a predominantly male gland. Its cortex seems to supply a combative element to the character, and when the whole gland is well developed and active, the stature is medium or short, the trunk is hirsute, and the individual is normally or even abnormally sexually inclined. There is here some very obvious association between the interstitial gland and the adrenal, but the exact nature of that association remains to be explained. Then there is the thyroid, a predominantly female gland, which is nevertheless not only the great stimulator of metabolism in general, but seems to exercise a particular effect upon the sex glands in the male, inasmuch as when orally administered, the extract will cause the descent of a hidden testicle in young adults. And again there is the pituitary, which presides over the type of the bony skeleton, and is therefore presumably under the direction of the appropriate interstitial gland, male or female, as the case may be. And yet it seems to have a peculiarly intimate connexion with the ovary, for ordinary amenorrhœa is more surely and more swiftly cured by oral exhibition of its extract than by all the curative and curative ministrations of the operating gynaecologist. Nor need I remind you that Fröhlich's syndrome as it is called, dystrophia adiposæ genitalis—or, as Jonathan Hutchinson, who was the first to describe it, originally christened it, lipomatosis universalis asexualis—proclaims a direct and intimate relation between the pituitary and the interstitial glands in the male, for the dystrophy is simply, surely, and swiftly cured by administration of extract of the whole gland by the mouth. Then there are the glands, notably the thymus and the pineal, which seem in some measure to act as a drag or check upon the activities of the gonads, while there are facts concerning them which point in a direction precisely opposite.

It would be easy to continue thus to pose problems concerning the interdependence of individual glands to which neither I nor anyone else can at present supply satisfactory answers, but to do so would probably serve only to spread my own bewilderment; so I will ask you, for the present at any rate, to join with me in an endeavour to regard these glands, not so much in their individual capacities as in their collective, to look at the boat as a whole, and not at the individual oarsmen.

In the existing state of our knowledge we must be content to treat the endocrine system as a system, and not as an agglomeration of individual glands, so that where there seems to be deficient or superabundant activity in any one gland we must make our therapeutic appeal for regularization to the system at large. That such is the proper course is obvious when we consider that our main enemies are toxins, and that our defences are the ductless glands. If a time should ever

be when we shall be able to allocate to each gland its responsibility for a particular toxin that time is not yet; so that our only rational course is so to husband the resources of the endocrines by protecting them from unnecessary poisons as to keep them fresh and alert to deal with such as are inevitable in our present artificial communal life. If we fail thus to protect them they become prematurely worn out by the ceaseless conflict with poisons which come from without. That is why a gradual decline in vitality so often begins at about 50 years of age, why cancer comes, and arteriosclerosis and other degenerative conditions. The endocrines thus gradually retreating before the advancing toxins are at last driven to capitulate, and the end comes. Now, looking at the matter from the point of view of comparative biology, there is no reason why man should be senile and effete at 70. If we argue from analogy we must admit that in relation to the time which it takes him to arrive at maturity man ought to live to the age of 100 or 120 years. That he does not do so indicates quite clearly that the kind of life he is now leading is not in accordance with physiological laws; that the poisons which he introduces into his system are either too concentrated or too persistently applied for the endocrines to withstand for more than a relatively short period.

It is an interesting fact that the glands in both sexes which show the first signs of fatigue are those which seem to have the closest connexion with the gonads—namely, the suprarenal in man and the thyroid in woman. In woman the reproductive capacity is definitely brought to a close at the menopause, and it does not surprise us that the necessity for redressing the endocrine balance consequent upon the withdrawal of the ovary from practical politics should give rise to considerable constitutional disturbance. It is nevertheless, to me at any rate, rather surprising to find that the gland to which we appeal most effectually in such cases is the thyroid. And here let me say, with all the emphasis at my command, that the appeal to thyroid extract should always be made cautiously at first—that is, with very small doses, never more than 1 grain per diem. I have been preaching this gospel for many years, and, although I am pleased to say I have made many converts, even now scarcely a week passes without my being profoundly shocked by the seemingly light-hearted manner in which members of the profession throw 5-grain tablets at their patients as though they were dealing with confetti at a carnival. That the combative gland, the suprarenal, shows declining vigour as the years advance is a matter of common observation. Bacon tells us that "men of age object too much, consult too long, adventure too little, repent too soon, and seldom drive business home to the full period, but content themselves with a mediocrity of success," which is only another way of saying that the gland of fright and fight has lost its recoil.

It is often said that a train of phenomena takes place in men between 60 and 70 in many ways comparable with the menopause in women. I have never been able to support this view. It is undoubtedly true that in most men the copulative and reproductive capacity begins in that decade sensibly to decline and ultimately to peter out. But by no means in all men. We could all of us cite outstanding instances of men who have retained a large measure of sexual power well into the following decade, but no one except the biographer of Sarah has ever recorded a case of a woman who has reproduced her kind at such an advanced age. There is obviously no reason why a man should lose his copulative and reproductive power so long as his gonads retain their efficiency, and this efficiency usually becomes impaired about the sixties because of the accumulation of poisons in the system. We have already seen that certain poisons (and I have instanced two only among many) cause an atrophy of the seminal tubules and an hypertrophy of the interstitial glands. Now it is more than likely that the interstitial hypertrophy represents an endeavour on the part of these glands to repel a chronic toxæmia. The hypertrophy succeeds for a time in supplying the extra quantity of necessary antidote, but at last, overwhelmed by the strength of the invader, the gland succumbs. We see this train of events so often in the case of the thyroid—the goitrous cretin, for example—that it seems reasonable to offer the same explanation in the case of the interstitial gland. Then there is the senile hypertrophy of the closely associated prostate to account for. Is it possible to doubt that this too is an anti-toxic gland, or that its gradual enlargement with advancing years is due to the constant endeavour to prevail in the unequal combat against lethal poisons introduced from without? The removal of the gland—which is, after all,

a simple surgical procedure—has been shown to be followed at no very long intervals by symptoms which go far to support this view.

And so we come to the question as to what are these toxins which the endocrine system is at such pains to neutralize and nullify. The answer is altogether outside the terms of my present reference, but to indicate the sanction for the views which I hold very strongly let me remind you that man is the only animal who has lost the instinct of physiologically selecting his food; that man is the only animal who cooks his food; and that the Almighty no more invented the kitchen than He ordained the gin palace or the opium den. Cooking destroys vitamins, and vitamins are to endocrines what endocrines are to the economy. The kindly fruits of the earth to which we do lip service in the Litany are ruthlessly relegated to a back seat in our everyday lives, and until we see reason in this respect while it is yet day we shall continue to poison our endocrines and to pass ignobly into nothingness with our allotted tasks but partially accomplished.

NOTE ON THE PEPTONE TREATMENT.

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IN the use of peptone for certain cases of asthma and other conditions of sensitization we have, as a rule, to rely on commercial products. These differ widely in composition, and consequently in their pharmacological actions. The latter are at present undergoing investigation, and some very divergent preliminary results have been obtained by Professor A. J. Clark with some samples submitted to him. What is really needed are preparations physiologically standardized. The proteoses are by far the most important constituents. A peptone solution fit for clinical use may be roughly tested by adding to a few cubic centimetres in a test tube two or three drops of strong nitric acid. A copious white precipitate is immediately produced, consisting of primary proteoses. On heating, the precipitate entirely dissolves, and reappears on cooling.

In a former paper¹ it was stated that Witte's peptone, even in the small doses of the 2 per cent. solution, may produce an immediate sharp reaction in certain subjects. Flushing, salivation, headache, palpitation, cyanosis, and dyspnoea are the usual symptoms. The dyspnoea is asthmatical in character, and may last a considerable time. Faintness, sickness or vomiting, purgation, and localized oedema or urticaria may supervene in very sensitive subjects. In the mildest cases flushing, alone or with a sense of constriction in the chest, occurs. Any combination, however, may be encountered. There seems to be no doubt that this almost instantaneous and sometimes alarming syndrome is caused by histamine in the peptone. The above symptoms can be faithfully reproduced when histamine is administered intravenously, and are due to a sudden injurious dilatation of the capillaries and venules, peripherally induced, together with stimulation of smooth muscle. Hanke and Koessler,² by an ingenious and exhaustive process, though finding no histamine in blood, fresh tissues, casein, etc., as originally affirmed by Abel and Kubota, nevertheless recovered it from Witte's peptone in the proportion of 0.00335 gram to 100 grams peptone. It might be urged that this represents too small a quantity in the intravenous injections to be effective, and that the symptoms must be referable to the peptone itself. Now these figures give 1/1,500 mg. histamine (the equivalent of 0.3 c.cm. of a 1 in 500,000 aqueous dilution) in about 1 c.cm. of a 2 per cent. solution of Witte's peptone (an average dose). This dilution, I found, gave a positive dermal reaction (0.5 cm. and over) in many subjects, but the intravenous injection of 0.3 c.cm. in the subjects tested was either very slight in effect or negative. However, when this amount was mixed with the usual doses of a histamine-free peptone, the injections, previously negative, gave the histamine effect in numerous instances. Apparently, therefore, the peptone reinforces in some manner the action of the histamine. The intensity of the effect depends on the amount of histamine-peptone present in the blood per unit of time—in other words, on the rapidity of the injection. The reaction to the peptone (protease) itself, should it occur, requires some time and is pyrexial in character.