I started treatment on October 25th, and continued it every other day until November 4th, but discontinued it on November 6th, as she had started to menstruate. I restarted treatment on November 8th, and continued it every third day till November 23rd, when the ulcer on the leg had healed. By November 9th the ulceration on the face had cleared, although there was still some thickness, as well as dilated venules to be seen.

Her general health improved greatly, and she looked better and felt in better spirits than she had done for a long time.

The readiness with which the edges of the ulcer took on a healthy appearance was extraordinary, especially as she had ceased to respond to the ordinary methods of syphilitic treatment.

After each injection there was a marked reaction, the face becoming very flushed, and the temperature rising in a short time afterwards as indicated by the two-hourly chart. The four-hourly chart shows it still better.

Her general improvement was a matter of comment by all the others in the ward, and both Dr. Edwards and Dr. Dunbar were surprised.

CASE II.

T. A., aged 35, had been in the navy, but after leaving was employed at some works in the neighbourhood, where he received a blow on the arm, as the result of which there was a thickness which persisted longer than the usual bruise. With a history of syphilis, I naturally concluded that this was a syphilitic thickening of the periosteum, and gave him the injections of distilled water every other day. At the end of the fortnight the swelling and pain had disappeared, and he returned to work.

CASE III.

T. J., aged 46, was admitted to the infirmary on March 6th suffering from multiple ulcers of the left leg and foot. There was the brownish scar on the right shin, which confirmed the diagnosis of syphilis. The ulcers on the left leg and foot would nearly heal and then again break down, but never assumed a healthy appearance. I started injecting distilled water on October 31st, and continued the treatment every other day until November 16th, when I did it every third day. By the end of the first week the edges of the ulcers had taken on a very healthy appearance, and the pain from which the man suffered had practically disappeared.

There were ten ulcers altogether, and by November 23rd seven of them had healed over, and the two largest were two-thirds covered with new tissue. The man appeared healthier, and some colour had returned to his face. He said he felt much better, and looked forward to the time for each injection.

A reference to his temperature chart shows that there was a reaction after each injection, but the temperature did not rise nearly so high as in Case I.

CASE IV.

B. T., aged 24, had a hard chancre $\frac{1}{2}$ in. in diameter on the dorsum penis, which appeared a fortnight before I saw him.

I started injecting him with distilled water on November 2nd, and injected him every third day, and by the 14th it had practically disappeared, as well as the enlargement of the glands in the groin. His general health improved rapidly, and he looked much better after a fortnight's treatment.

CASE V.

M. S., aged 20, single, was admitted in November, 1911, as she was pregnant and infected with syphilis. After confinement and some treatment she was discharged, to be readmitted on November 11th, 1912, suffering from tertiary ulcers in different parts of the body. There was a small sore on the right ear and one on the right eye, whilst one seemed to be forming on the forehead.

Treatment was started on November 12th, and by November 19th there was considerable improvement, the ear and eye being practically well, and the swelling on the forehead had subsided.

All the other ulcers had taken on a healthy appearance, so that by November 25th they were all covered over.

Her general health improved greatly, she seemed brighter, looked healthier, and had colour in her cheeks, whilst the appetite improved. She much appreciated the treatment, although she cried on the first occasion.

The temperature reactions in this case were very marked, as in Case I, rising a few hours after each injection to 100° F.

CASE VI.

W. E., aged 26, admitted October 10th for sores on the right leg. Was infected with syphilis in the army.

Treatment was started on November 10th, and, after injections every third day, the gummata on thigh and leg were all covered over by healthy tissue on November 25th. A sore inside the right cheek also subsided, whilst his general appearance became more healthy.

THE fourth International Congress of School Hygiene will be held at Buffalo, New York, in August next (25th to 30th), under the honorary presidency of Dr. Woodrow Wilson, President of the United States. The actual president is Dr. Charles W. Eliot, formerly president of Harvard University. The general secretary is Dr. Thomas A. Storey, Professor of Hygiene, College of the City of New York.

The Arris and Gale Lectures

ON

THE GENITAL FUNCTIONS OF THE DUCTLESS GLANDS IN THE FEMALE.

DELIVERED AT THE ROYAL COLLEGE OF SURGEONS ON
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BY

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[Abstract.]

LECTURE II.

IN the last lecture I endeavoured to estimate the direct and indirect influences of the ovaries in regard to the genital functions. In considering the indirect influences I discussed the effects of ovarian insufficiency, both in physiological and pathological circumstances, on what I may, perhaps, describe as the rest of the genital system of ductless glands; and I also demonstrated the effects produced on the general metabolism by this condition.

In this lecture I shall reverse the process and endeavour to trace as far as possible in the time at my disposal the influence of the rest of the ductless glands upon the ovaries and the reproductive functions generally.

THE RELATION OF THE THYROID TO THE GENITAL SYSTEM.

We shall, perhaps, be in a better position to consider the changes that occur in the rest of the genital system if we first discuss the effect on the general metabolism of removal of this organ.

Effects of Thyroidectomy on the General Metabolism.

Different mammals vary very much in their power of withstanding the disastrous results which may follow complete removal. I have never observed any grave effects supervene on the removal of the thyroid in rabbits. This has been explained on the ground that the parathyroids are relatively large, and lie well away from the thyroid itself, and consequently cannot be removed without a careful search—in other words, they escape removal during the operation of thyroidectomy.

Swale Vincent and Jolly have shown that after thyroidectomy the parathyroids actually secrete colloid, and, in fact, perform the functions of the thyroid, just as they resemble it in structure after this operation. But I do not believe that this question of the remaining parathyroids is the whole truth.

I think rodents have less need of the thyroid than other mammals, such as the carnivora. It may be because the diet is different, but also I feel sure it is due in some measure to the variations in the structure and function (or degrees of function) seen in the other ductless glands. I have already alluded to the differences in structure between the ovaries of rodents and the higher mammals. If we take cats and remove their thyroids many die in a few days, usually with convulsions. In these cases it is probable that the immediate result is due to the removal of the whole thyroid apparatus (thyro-parathyroid). Some, however, survive the operation for a long period of time. In all these cases one can demonstrate the removal of the whole thyroid together with the internal parathyroids, which are embedded in the two lobes of the thyroid. So that one gets in these animals the true effects of thyroid insufficiency. The number in which the metabolism was investigated fully was small, for, as already stated, many died too soon for the metabolism, as represented by the urinary excretion, to be estimated. The record of one non-pregnant cat, which was destroyed two and a half months after operation, has been selected as typical. Other cases were complicated by the cats having had kittens shortly before operation, and in consequence did not appear to be suitable for averaging.

In this animal acetone was present three times in twenty estimations after operation. The calcium excreted

after operation was the same in quantity as before operation. There was a drop in the phosphorus excretion, in spite of the increase in the post-operation specific gravity; and the total nitrogen and urea were increased out of proportion to this rise in the specific gravity. The ammonia coefficient also was slightly increased.

Before considering the effect of thyroidectomy on the rest of the ductless glands I will bring forward a rather important series of experiments in which thyroidectomy was performed on three pregnant cats, which survived the operation for some time. They were carried out in order to observe the influence of the thyroid on the metabolism during pregnancy, especially with reference to the possible production of the symptoms of eclampsia with marked alterations in the ammonia coefficient.

Acetone, albumen, and sugar were found a good many times after operation in one cat, and more frequently after parturition than before, without any real disturbance of the ammonia coefficient.

We found that so long as the cats remained pregnant the calcium excretion remained constant, but that after parturition it was increased to three times the quantity. The phosphates after the birth of kittens showed a remarkable increase, and there was a drop in the urea excreted. There was no real disturbance of the ammonia coefficient.

It does not appear probable, therefore, that the thyroid is in any way specifically connected with the production of eclampsia, as was originally suggested by Nicholson. It is true that two of our cats, which were in the first half of pregnancy, died with convulsions in a few days, but the manner of death was similar in every respect to that seen in non-pregnant animals in similar circumstances.

Effect of Thyroidectomy on the Ovaries and Uterus.

The normal ovary of the cat, with which we are concerned in these experiments, shows certain affinities for eosin in some of its elements. The zona pellucida, the liquor folliculi, the interstitial cells, and the cells of the corpora lutea, all stain faintly with eosin. After thyroidectomy all these elements show an increased avidity for this stain. This is especially true of zona pellucida and the liquor folliculi, and appears to be a matter of some importance.

It seems that removal of the thyroid calls for a response from the ovary, just as oophorectomy did from the thyroid. And the nature of the response, if my observations be correct, is one of considerable interest, for it brings forward evidence that the granulosa cells of the Graafian follicle form an organ of internal secretion. But this secretion is not connected with the integrity of the uterus, for the effect of thyroidectomy on this organ is remarkable. The uterus of the thyroidectomized cat shows very considerable muscular atrophy, quite as much as occurs after oophorectomy. But the same effect is obtained in the non-pregnant animal. The importance of this intense atrophy will be considered directly; for before drawing our final conclusions of these results it will be advisable to consider the clinical observations that have been made in regard to insufficiency of the thyroid.

Clinical Observations of the Effect of Thyroid Insufficiency on the Genital Functions in Women.

These are quite well known. We frequently see young girls with adiposity suffering from amenorrhoea, or we see the more marked insufficiency which produces myxoedema, and is also invariably associated with suppression of the menstrual function.

Now, both the minor and the major state of thyroid insufficiency are readily amenable to thyroid treatment, with one reservation: if the girl has suffered from thyroid insufficiency for some years past the period of puberty, and has never menstruated, then it may be impossible to relieve her genital condition, and the uterus may remain under-developed. If, on the other hand, the insufficiency has arisen later, after the subject has possessed full genital activity, then the uterus may, even after a long period of inactivity, resume its normal functions.

Further, the full and increased activity—if my interpretation of the staining properties be correct—of the secretion of the membrana granulosa cells, with inactivity of the uterus, puts out of court the hypothesis that the cyclic changes in the uterus are due to this secretion. On

the other hand, it is possible that the secretion of the interstitial cells is rendered insufficient in the absence of thyroid secretion.

Effect of Thyroidectomy on the Suprarenals.

The normal suprarenal structure is well known, but I shall briefly refer to it in order better to illustrate the changes that occur—physiologically and pathologically—in the cat.

The suprarenal is divided into two parts, the cortex and the medulla. These have different physiological properties when examined experimentally. The medulla produces the well-known pressor effect of adrenin, while the cortex is inactive.

Now the changes that seem to indicate excessive activity of the suprarenals occur in the cortex. They may be seen normally in pregnancy and, so far as we know, in ordinary circumstances. The normal appearances differ, however, from those associated with the activity which follows thyroidectomy.

In three of my animals an actual calcareous deposit was found in the zona fasciculata subsequent to thyroidectomy. I have not seen this condition in a normal suprarenal gland.

Effect of Thyroidectomy on the Pituitary.

The changes that occur seem to be an increase in active eosinophile cells of the pars anterior at the expense of the large basophiles. And both in the pregnant and non-pregnant animal there is an increase of large active chromophobe cells, such as occurs normally in pregnancy. The latter are, of course, most pronounced in an animal in which thyroidectomy has been performed during pregnancy.

The condition was well seen in Cat X of my series. Forty-eight hours after operation two premature kittens were born. After a further interval of 120 days the animal was destroyed with chloroform. In this length of time all the chromophobe "pregnancy" cells would have disappeared in the ordinary course of events. But as the result of thyroidectomy they not only persisted but showed an increase in secretory activity. The secretion appeared to form vacuoles among the cells. In this case the pars nervosa showed no abnormal invasion of pars intermedia cells.

In the case of a non-pregnant cat (No. 9) killed 79 days after thyroidectomy again many active chromophobe cells were to be seen in the pars anterior, and an increase in active eosinophile cells at the expense of the basophiles.

We learn, then, from these observations that thyroidectomy causes an increase in the secretory activity of all parts of the pituitary body.

THE RELATION OF THE PINEAL TO THE GENITAL SYSTEM.

The pineal gland has never been successfully removed from mammals; and, owing to its inaccessible position in the brain, there seems to be little likelihood of experimental extirpation ever giving satisfactory results.

The effects of castration on the pineal have already been mentioned.

Clinical Effects of Pineal Disease on the Genital System.

Comparatively few observations have been made, but in most cases where a tumour has been observed it has been a teratoma, and somewhat remarkable symptoms have been seen. When the patient was a child, as was usually the case, there was a precocious development of the skeletal structures and also of the genital organs. According to L. Kidd, who has recently reviewed the literature of the pineal body, all the cases recorded occurred in boys. In a few instances obesity has been seen, but apparently unaccompanied by genital atrophy.

THE RELATION OF THE PITUITARY TO THE GENITAL SYSTEM.

Some of the normal physiological changes in the pituitary which occur are well known. But there is much need for a systematic investigation into the age changes in this organ. So far as I know, only a few isolated observations have been recorded.

There is reason to believe that the secretions of the pituitary determine many of the metabolic functions necessary for the establishment of puberty, or sexual maturity.

We fully recognize the remarkable enlargement and the histological changes that occur in this gland as the result of pregnancy. The eosinophilia disappears and a large majority of the cells of the pars anterior become chromophobe, and, as already mentioned, have been called "pregnancy" cells.

A few years ago Dale and also Hick and I showed that an extract of the posterior lobe produces powerful uterine contractions. This effect may be produced physiologically in labour by the infundibular extract.

Ott and Scott first showed that the same extract is a galactagogue. It is probable that there is an expressor effect. It would be interesting if it were a fact—of which we have no proof—that the pituitary normally promotes the secretion of milk. It is, however, certain, in my opinion, that after the birth of the child the stream of metabolic products directed to its maintenance and growth in the womb are diverted to the mammary secretion which is to supply its post-natal necessities.

Effects of Removal of the Pituitary (Partial or Complete).

Most of the early work on the extirpation of the pituitary was absolutely unreliable, and it was not until Paulesco improved the technique, which Harvey Cushing and Biedl subsequently adopted, that results worthy of consideration were obtained.

Cushing's conclusions may be summed up as follows: Complete extirpation caused death in a short time. The same effect was obtained by complete extirpation of the pars anterior. Partial removal of the anterior lobe led to the condition known as dystrophia adiposo-genitalis; that is to say, there was great obesity, with atrophy of the genital organs and undergrowth in young animals.

Biedl confirmed these findings, and also stated that the posterior lobe (pars intermedia and pars nervosa) might be removed without producing symptoms.

It is difficult to believe in the results of experiments in which the anterior or posterior lobe are said to have been removed separately. But there can be no doubt that partial removal of the anterior lobe is not difficult to accomplish; and the results following this procedure should be reliable.

Effects of Removal of the Pars Anterior.

On the Ovaries and Uterus.—There is no good description of the histological appearances found, but Cushing states that the Graafian follicles disappear while the interstitial cells persist. The uterus also undergoes atrophy. I have had no opportunity of examining ovaries after this operation, but, in view of the genital atrophy, would have expected the same changes as those which follow thyroidectomy—that is to say, the reverse of what has been found by Cushing.

On the Thyroid.—It has been noted by Cushing and others that there is a remarkable degree of hyperplasia in the thyroid after partial removal of the anterior lobe. This condition eventually subsides, and is superseded, it is said, by a considerable colloid formation, with apparent disappearance of epithelial activity.

On the Thymus.—This leads to hypertrophy of the thymus, just as the condition of hypopituitarism is often associated with thymus enlargement.

On the Suprarenals.—The operation, according to Cushing, is followed by hyperplasia and lipid vacuolation of the cells of the zona fasciculata.

Clinical Observations of the Effect of Pituitary Insufficiency on the Genital Functions in Women.

These have been made chiefly in regard to acromegaly and the condition already described as dystrophia adiposo-genitalis. The former disease is supposed to be due to excess of secretion, and the latter to deficiency.

The relationship of these two conditions, however, is not quite so simple as the above statement would seem to imply. It is usual to find amenorrhoea both with acromegaly and with the condition which is supposed to represent the opposite in regard to secretory activity.

With acromegaly the excessive thickening of bones indicates calcium retention—a condition which appears associated with masculinity, as we shall see when dealing with the suprarenals.

In cases of dystrophia adiposo-genitalis genital atrophy is invariable, yet there is no doubt that, if the individual

has had functional activity before the onset of the disease, this activity may return on relief of the condition by decompression or by administration of pituitary extract. I have observed this result follow injections of anterior lobe extract in dystrophia adiposo-genitalis. Similarly I have seen good results after the administration of this preparation in cases in which the patient was very obese and suffered from amenorrhoea, without showing the signs of intracranial pressure which are usual when the condition has reached the stage of dystrophia adiposo-genitalis.

Success is more likely when the patient has had some functional activity previously; but it is possible that delayed menstruation with obesity might be successfully treated if the patient has not long passed the usual age of puberty.

THE RELATION OF THE THYMUS GLAND TO THE GENITAL SYSTEM.

The thymus has been shown to have a very important relation to the development of the individual and of her reproductive functions. It is probable that once the genital functions are established the thymus rapidly undergoes atrophy, and plays no further part in the metabolism of reproduction. We have already seen that the thymus undergoes hyperplasia after removal of the ovaries.

Effects of Thymectomy on the Ovaries and on the Calcium Metabolism.

Paton found that if the operation be performed before puberty there is a rapid development of the genital glands. It appears, therefore, as if the thymus either inhibits the development of the ovaries (Biedl), or that their development follows the withdrawal of the thymus secretion.

It is highly probable that the thymus is intimately connected with the calcium metabolism; but it can hardly be, as Biedl suggests, that the effect of its secretion is to cause calcium retention in the bones—although several investigators (Basch, Cozzolino, Tarnelli, and Lo Monaco) have found that rickets follows thymectomy in young animals, an effect not confirmed by Paton—for the skeletal structures become much more heavily laden with calcium phosphate after puberty when the gland atrophies.

Effects of Thymectomy on the Other Ductless Glands.

No reliable work appears to have been done on these lines. It is urgently needed, in order to clear up many of the difficulties concerning the relation of the thymus to the general metabolism.

THE RELATION OF THE SUPRARENALS TO THE GENITAL SYSTEM.

These glands may be studied in the same way that we have already adopted—that is, from a physiological and pathological standpoint.

In pregnancy certain changes occur normally in the suprarenals. So far as my own observations go these are confined to the cortex. The cells of the zona fasciculata appear swollen and cloudy.

Some observers (Guicysse and Gottschau) have found that in pregnancy the zona fasciculata increases in thickness at the expense of the zona reticularis and medulla. My own observations are in accord with this.

Effects of Removal of the Suprarenals.

In most mammals complete removal of the suprarenals causes death in from a few hours to a few days.

Many rats, owing to the fact that a large percentage of them have accessory interrenals, consisting of cortical substance, are said to be able to survive extirpation of the main organs. I have had no experience of extirpation experiments on these animals. My investigations have been carried out on rabbits and cats. Those from which both suprarenals were removed, either at one or at two sittings, died within forty-eight hours. I tried, therefore, the effect of the removal of one suprarenal in the hope of being able to produce insufficiency, since we know the other suprarenal hypertrophies in these circumstances, and shows a condition somewhat comparable with the hyperplasia of pregnancy. Two cats gave negative results in

regard to the metabolism; but with regard to two rabbits I obtained definite results. One of the animals was destroyed at the end of thirty days, as it was obviously dying. It was much emaciated, its weight having dropped from 2,000 to 1,400 grams.

The other rabbit died at the end of 127 days. It also was greatly emaciated, its weight having decreased from 1,710 to 1,020 grams. At first it gained weight after the operation, and then it steadily lost ground.

No cause for death was found in either case.

These results are apparently of some value, for, according to most recent authorities, unilateral extirpation in rabbits produces no symptoms.

With regard to the metabolism, we obtained very interesting results. In each case a considerable increase in the excretion of calcium was observed.

In one case the average quantity excreted after operation was seven times as much as that excreted before operation. In the other case it was sixteen times as much. The average for the two cases was, of course, between these figures. The excretion of phosphorus was not increased in proportion, as one might have expected.

The urea excretion was increased out of proportion to the differences between the specific gravities before and after operation.

Now this increase of the calcium excretion is of very considerable interest. It is well known that the view has been advanced that osteomalacia is due to insufficiency of suprarenal secretion, and Bossi first called attention to the beneficial results to be obtained by the injection of adrenin in these cases. Unfortunately I have not met with a case of osteomalacia in recent years. So I have had no experience of this treatment. But these experiments give very strong support to this view of Bossi, not only in the metabolism results, but in a most striking way in regard to the bones of one of these animals.

The bones of the forelegs—on which I presume a good deal of weight would fall—were found to be markedly bent. The bones of the backlegs, which are thicker, were only slightly curved. But owing to the manner in which a rabbit sits very little weight would fall on these bones.

Effects of Suprarenal Removal upon the Pituitary Body.

The changes that occur seem to be much the same whether the insufficiency be acute or chronic; thus in cat No. 1 of my series of suprarenal removals, the glands from both sides were removed at the same time. There was an interval of thirty-six hours between operation and death.

The cells of the pars anterior show a marked degree of chromophobia with a moderate degree of faint eosinophilia. In many places the nuclei are very deeply stained with haematoxylin.

In the pars intermedia the cells are discrete—that is to say, they are not fused, and show no special activity; the nuclei stand out prominently.

The pars nervosa is freely invaded by the cells of the pars intermedia, but the nuclei only are prominent, as though they were left stranded after the disappearance of the cell cytoplasm.

We cannot, therefore, come to any conclusion other than that the anterior lobe shows increased activity. The pars intermedia is certainly not in an actively secreting condition, but the extensive invasion of the pars nervosa by pars intermedia cells, and the rapid disappearance of the cell cytoplasm, appear to indicate that an attempt is being made to counterbalance the loss of adrenin by the rapid production of infundibulin.

Effect of Removal of the Suprarenals upon the Thyroid.

I have been unable to trace any histological change either in acute or chronic suprarenal insufficiency.

Effects of Removal of Suprarenals on the Ovaries and Uterus.

There appears to be no histological change of importance in the ovary; but it is worthy of note that the normal eosinophilia of the zona pellucida is not decreased—rather, if anything, is it increased. After removal of one suprarenal, if insufficiency be produced, the uterus appears to undergo changes comparable with those that are seen

after thyroidectomy, but the muscular atrophy appears to be less in extent; probably this is due to the state of incomplete insufficiency.

Clinical Observations of the Effect of Pathological Lesions of the Suprarenals on the Genital System.

We meet with conditions in the human subject which represent both an under-secretion and an over-secretion of the suprarenals. This is decided on clinical and histological evidence. At the same time, we are still in the dark as to the exact relationship of the cortex to the medulla.

In Addison's disease we have what are apparently the symptoms of insufficiency of medullary secretion, as is shown by the low blood pressure and general muscular weakness. But in this disease the cortex also is destroyed.

It is doubtful if sufficient pathological observations have been made with a view of observing changes in the ovary and uterus to enable us to give any definite statements regarding them.

Amenorrhoea is, I believe, usually associated with Addison's disease, but this may be due solely to the effects of a condition which produces general progressive enfeeblement. On the other hand, our experimental evidence indicates that atrophy of the uterus, and presumably insufficiency of the function of the interstitial cells, occurs in these circumstances.

The other pathological lesions which have been subjected to a good deal of attention lately are hyperplasia and tumour formation in the suprarenal cortex. For some years these lesions have been known to be associated with extraordinary changes in the primary and secondary sex characteristics. Attention was first called to these interesting phenomena by Woolley, Bulloch and Sequiera, and Neugebauer.

Last year my colleague, Professor Ernest Glynn, reviewed exhaustively the whole subject and added 5 fresh cases in children to those already collected by Bulloch. Out of 17 cases in children 14 were females. In these there was usually skeletal overgrowth, hair on the face and pubes, and sometimes hypertrophy of the clitoris. Further, Glynn collected 6 cases occurring in young adult females, in all of whom there was growth of hair on the face, shrinkage of the breasts, amenorrhoea, and sometimes a masculine voice.

Pathologically the suprarenal enlargement in the children and young adult females was unilateral and neoplastic in character, and directly or indirectly caused death. Metastases were sometimes found.

In a second group of cases there were 13 pseudo-hermaphrodites—12 being females—and in these the suprarenal enlargement was bilateral, hyperplastic in character, and there were no metastases.

Glynn suggested that in these cases hyperplasia of the suprarenal cortex occurred in fetal life before the differentiation of the genital ducts, and led to the persistence of the Wolffian derivatives, thus causing female pseudo-hermaphroditism.

No sex changes are associated with tumours of the suprarenal cortex when they occur in adult males or in women after the menopause.

THE CORRELATION OF THE INTERNAL SECRETIONS IN REGARD TO THEIR GENITAL FUNCTIONS.

I have endeavoured to trace, for the most part from my own observations, the disjointed facts concerning the influences exerted by the different members of the ductless gland system upon one another and on the metabolism generally, in so far as the genital system is concerned. And in so doing I have sometimes shown clearly the nature of the associations between the different organs. But it is absolutely impossible at the present time to correlate fully all their functions, so that perhaps the less said now the less there will be to withdraw at some future date.

In view, however, of what I said at the commencement as to the necessity for a lead in this intricate matter, I cannot refrain from enunciating what I believe to be the general principles. I shall not have time further to analyze the details.

It appears, from the evidence at our disposal, that, in spite of great variations in the structure of the ductless

glands in different mammals, the *total functional result* is the same so far as the genital processes are concerned. The variations in function that depend on the differences of structure are probably related to differences in the food and habits of life.

In adapting our knowledge to the requirements of human physiology and pathology we must take into account *both* the essential functions I have already referred to—the individual metabolism of the mother and the metabolism of her reproductive functions—for they are completely interdependent.

We have seen as the result of our studies that the ovaries, on the one hand, have as their share of these dual functions the onus of ensuring the reproduction of the species, by furnishing the ova and by keeping active the rest of the genital structures and functions. And, further, the secretions of the ovary are concerned in keeping the other members of the ductless gland system in touch with the necessities of the reproductive situation. The latter function is of the deepest importance, and is one which explains much that would otherwise be obscure.

When the reproductive functions cease and the ovaries atrophy at the menopause the harmony that previously existed between the general and the genital metabolism is temporarily deranged, and various disturbances may ensue. And it is only by the careful investigation of each menopausal case that one can arrive at a determination of the manner in which the balance has been upset. It is impossible always to alleviate the symptoms, but the basis of treatment rests on the regulation of the existing disarrangement by the administration of the necessary secretions. Some patients react to thyroid extract, some to pituitary, others again to combinations, so great are the individual variations. In most cases a natural readjustment takes place in the course of time. So that, strictly speaking, the ovary is only concerned in the temporary function of reproducing the species, and, by its hormones or internal secretions, of bending the metabolism of the body to its purpose. As accessory to these functions the ovary has been supposed to be responsible for the beauty of the vessel by means of which its ends are to be attained. But to-day we are beginning to wonder how far the ovary does influence secondary sex characteristics, and whether full individual secondary characteristics can be obtained by the influence of the ovary alone.

We have evidence that hyperplasia of the suprarenal cortex can upset any influence the female genital gland may be supposed to possess, and can produce in a female some of the secondary characteristics of the male, and even partially change the genitalia to complete the picture.

I well remember seeing a case under the care of Dr. Russell Andrews. The subject possessed every female characteristic except for the absence of uterus, Fallopian tubes, and ovaries; instead there were testes within the abdominal cavity. This individual was a male pseudo-hermaphrodite with the pure secondary characteristics of a female, and a prepossessing one at that. Such a condition could not have existed with hyperplasia of the suprarenal cortex.

Any influence the ovary has over the general metabolism is, then, related to and dependent on its primary reproductive function. I do not believe that it influences the metabolism except in so far as this special function is concerned. Of course, removal of the ovaries may produce a temporary disturbance, but this has already been explained, and does not invalidate the view just mentioned.

On the other hand, the rest of the ductless gland system is related to the genital function in various ways.

First, some of the members—the thyroid, pituitary, and suprarenals—influence the development and subsequently preserve the integrity and activity of the genitalia, as I have already demonstrated. Others—the thymus and possibly the pineal—appear to prevent sexual precocity.

Secondly, all the ductless glands control the metabolism in response to the necessities of the genital functions; but, in addition, they adapt the whole organism to the possibility of the situation and regulate the secondary characteristics, both physical and psychical, to suit the needs of the individual. Once, however, the reproductive organs

are removed or undergo atrophy, the primary genital functions of the rest of the ductless glands cease, and the rearrangement of the metabolism that follows produces what are known as the symptoms of the menopause. Contrariwise insufficiency of the thyroid, pituitary, or suprarenals causes the cessation of the genital functions with atrophy of the uterus.

As to the more particular parts played in the metabolism by each member of the ductless gland system, these have already been specified.

In spite, therefore, of the reluctance to correlate our knowledge shown by most investigators, the matter is not one of very great complexity if my views be correct in a general way, although there remains much detail to fill in.

As soon as possible we must come to a conclusion as to what are the facts. So much work that has been done is contradictory. There is therefore so much more the need for further efforts.

In concluding, I would again insist that in order to solve completely the problems surrounding the genital functions we must focus at one and the same time the two essential processes of life—the individual metabolism and the reproductive metabolism. They are absolutely interdependent. Indeed, the individual metabolism is the reproductive metabolism. It is the neglect of this point of view that has brought about much of the confusion that exists.

Weismann and Ray Lankester describe the relation between the reproductive cells and those of the soma in still more striking terms. The latter says: "Among the multicellular animals, certain cells are separated from the rest of the constituent units of the body, as egg cells and sperm cells; these conjugate and continue to live, whilst the remaining cells, the mere carriers as it were of the immortal reproductive cells, die and disintegrate. The bodies of the higher animals which die may from this point of view be regarded as something temporary and non-essential, destined merely to carry for a time, to nurse and to nourish the more important and deathless fission products of the unicellular egg."

Whatever views we may hold as to details, I question whether this philosophical statement is open to contradiction.

The function of reproduction in all its preparations and performances commences in the early stages of segmentation, and may be said to continue in man until the care of the offspring is completed.

In many insects, male and female, the act of reproduction is also the cause of death. Evolution and the pressing necessities of individual life have led men to look upon the function of reproduction as of vastly inferior importance to their own individual metabolism. No doubt women will soon come to think so too, for they seem to be changing. Whether this change be due to an increasing hyperplasia of the female suprarenal cortex I do not know. But just as we are beginning to think that our knowledge of their special functions is becoming well defined they invite us to follow their further evolution, which apparently they think will not involve them in the joys of motherhood.

Alchmont said "*Propter solum uterum mulier est quod est*"; Chéreau changed this to "*Propter ovarium solum mulier est quod est*."

Virchow reiterated this statement and, according to Biedl, added that "All the peculiarities of her body and mind . . . everything, in fact, which in the true woman we admire and revere as womanly, is dependent on the ovary."

In the light of our present knowledge I venture to think that the following aphorism more nearly describes the cause and effect:

Propter secretiones internas totus mulier est quod est.

The original work detailed in these lectures, which were illustrated with many photomicrographs and colour photomicrographs, was carried out in the Biochemical and Pathological Laboratories in the University of Liverpool; and I am much indebted to Professor Benjamin Moore and Professor Ernest Glynn for help in various directions, and especially for the facilities accorded to my assistants, and for the superintendence of their work.

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