The Arris and Gale Lectures

ON

THE GENITAL FUNCTIONS OF THE DUCTLESS GLANDS IN THE FEMALE.

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BY

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[Abstract.]

LECTURE I.

INTRODUCTION.

ANY attempt to describe the special correlated functions of the ductless glands, or, to be more exact, of the internal secretions, appears to be avoided by those who have worked most at the subject. Correlations are admitted; points in support of them are produced, and the matter is then dropped. In many ways this is much to be deplored, for, to some extent, it is accountable for the present disordered condition of our knowledge.

I do not wish it to be inferred from these remarks that I am in any way prepared to give in these lectures a complete explanation of the interactions of the ductless glands in regard to the genital functions. It would be impossible in the time at my disposal, even had I the knowledge, which I certainly have not. I do, however, wish to call attention to the fact that the genital functions in the female must be considered from a very wide standpoint in view of our accumulated knowledge concerning them. I shall deal most fully with those parts of the subject on which I have myself worked, and I shall bring forward experimental results to clear up some of the points at issue.

My endeavour will be to emphasize, if I can, the importance of all the internal secretions in the special economy of the female. So that those who are interested in gynaecology may come, if they have not already done so, to look upon all the ductless glands as genital glands—not, of course, exclusively so, nor all in the same way in a metabolic sense, but rather that each is absolutely indispensable to the harmony of the genital functions, which are, therefore, not solely dependent on the functional activity of the special genital gland.

Until recent years attention centred round the ovary, as if it were the only controlling factor in the genital processes. I shall, therefore, first consider the functions of this organ.

THE FUNCTIONS OF THE OVARY.

These are: To provide ova, and to produce an internal secretion or secretions. We need not consider further the liberation of the ova.

The internal secretion of the ovary has never been isolated. Indeed, it is still a matter of considerable dispute as to how and where it is produced. The only evidence that there is an internal secretion rests upon the results of extirpation and destruction experiments, and, to a lesser degree, on clinical observations. The resulting atrophy of the uterus is taken to indicate the loss of some secretion which normally activates this organ.

Some believe that there is more than one secretion, and various authorities have considered that different secretions are produced by the lutein cells of the corpus luteum, by the interstitial cells of the stroma of the ovary and by the membrana granulosa cells; but that they differ in the degree of importance to be ascribed to each.

Prénant, and later Born and Fränkel, were probably the first to call attention to the importance of the lutein cells; and the last named showed that destruction of these cells led to abortion in pregnant rabbits. Hick and I, and many others, invariably produced abortion by the removal of both ovaries in these animals.

It has been supposed that the corpus luteum provides a secretion which assists in maintaining the position of the embedded ovum intact. Experiments on animals seem to support this view; but cases in the human subject are on record in which both ovaries have been removed during the first few weeks of pregnancy for such discrete tumours as fibromata, without interrupting the course of gestation. And herein lies one of the great difficulties in the study of our subject; different orders of mammals have organs of internal secretion which are structurally and even functionally different, although perhaps in degree only. Individuals in the same species may vary, both in animals and in man. Consequently, some of the contradictory statements made by different experimenters may be explained on the ground of these variations.

The interstitial cells of the ovary also are believed to possess a special internal secretion. Limon first compared the ovaries of many species of mammals, and found an enormous difference in the preponderance of interstitial cells in the different ovaries.

Every one is familiar with the structure of the human ovary and the obvious scarcity of secretory cells—apart from those connected with the follicles. But if we examine the ovary of an adult rabbit, or any other rodent, we see a most remarkable structure. The whole organ is composed of a mass of cells which are epithelioid in character. And still more remarkable is the appearance of the corpora lutea, the cells of which can only be distinguished, if at all, from the cells of the stroma by their larger size. The Graafian follicles are crowded round the periphery of the ovary as though pushed outwards.

From very close observation of the corpora lutea in all the stages of development I have come to the conclusion that they do not undergo involution in rodents as in the higher mammals, but that they ultimately form the so-called interstitial stroma cells. Often one can see the cells of the corpus luteum merging into the similar cells in the stroma of the ovary.

If we examine the ovaries of rabbits a few weeks old, we find them composed entirely of primordial ova and a few follicles, separated by bundles of connective tissue. There is an entire absence of interstitial cells. This also indicates the probability of the origin of these cells from corpora lutea, although it is possible that in the human ovary, and in the ovaries of animals which contain very few interstitial cells, these arise from the capsular epithelium, or possibly from special stroma cells. Thirdly, there are the Graafian follicles with their linings of membrana granulosa cells to which some attribute an internal secretion. In favour of this view I shall adduce some evidence later.

The question now arises whether we are justified in assuming that there is only one type of secretory cell in the ovary. If we were to put aside the liquor folliculi as an internal secretion, I do not think we should be wrong in assuming that the interstitial cells and the corpus luteum have the same function, especially if we believe that they are derived from the same source. In experimental investigations of the ovarian functions we have no means of separating the various parts of the ovary, and can, therefore, only estimate the total function.

My own experiments have been carried out on dogs, cats, and rabbits. As already stated, the ovaries of the carnivora resemble in structure the human ovary more closely than is the case with the ovaries of rodents. The methods of investigation have consisted in noting the effects of oöphorectomy on the pregnant and non-pregnant uterus, on the other ductless glands, and on the general metabolism of the body.

Effects of Oöphorectomy on the Genital Functions.

Hick and I pointed out some years ago that the effect of oöphorectomy on the non-pregnant uterus was to produce, first of all, atrophy of the muscular coats.

We concluded that the normal muscular contractions were abolished and atrophy supervened in the manner usual to muscles that are not utilized. This has been confirmed and accepted by Marshall and others. The total ovarian secretion exercises a somewhat remarkable experimental effect on the uterus. Hick and I found that when injected intravenously it caused contractions in the oestrous uterus of the rabbit, but inhibited the

contractions of the pregnant uterus. We were, however, not always been able to produce the latter result.

Recently I have investigated the important question whether the metabolic conditions of the body are materially altered by oöphorectomy, or not.

Effects of Oöphorectomy on the General Metabolism.

In the early part of last year I removed the ovaries of six cats which were kept for periods ranging from 139 to 251 days. The urine was collected and fully examined at frequent intervals both before and after operation.

It was found that the specific gravity was higher after operation than before in half the cases. This, of course, would lead us to expect a larger proportion of solids in the latter period of observation, and this was more or less borne out except in the case of one cat. Since there was some irregularity in the individual results, and we had a sufficient number of animals, an average estimation of all six cases was worked out. From this we drew our conclusions.

The calcium excretion was diminished by one half. The chlorides were slightly diminished. The phosphorus excretion was much increased, as was the total nitrogen and urea percentages. The ammonia was slightly increased. There was no real change in the ammonia coefficient.

Knowing as we do the marked changes in the nitrogen metabolism which normal animals undergo, we cannot look upon the changes recorded in regard to the nitrogen as of much importance.

The increased phosphorus excretion was somewhat curious in view of the definite decrease in the excretion of calcium.

I may, perhaps, be allowed to recapitulate a few other facts which afford evidence contributory to the view that the ovaries are concerned in promoting calcium excretion. During pregnancy and lactation the function of the ovaries is in abeyance in regard to menstruation, and at these times first the fetus and then the breasts utilize all the available calcium—indeed, the mother's tissues are sometimes drawn upon to her detriment.

With regard to the mammary secretion, although it is so intimately connected with the genital functions, I look upon it as of subsidiary importance. That is to say, the secretion of milk is produced by a special arrangement of the general metabolism in response to various hormones connected with the necessities of the occasion. In women there is sometimes no response.

I do not propose to discuss lactation in these lectures, since it is one of the side issues, and the metabolic processes connected with the production of milk are comparable with those which provide for the building up of the fetus in the uterus. It is a process with which all the ductless glands are directly or indirectly concerned.

Osteomalacia, about which I shall have more to say in the next lecture, has often been cured by the removal of the ovaries, and this result indicates a condition of calcium retention in the tissues. My experiments are therefore supported by clinical observations.

We know quite well, of course, that from a casual inspection of animals which have undergone oöphorectomy we can detect no outward change, except some degree of adiposity, yet apparently there is a constant metabolic disturbance in regard to the calcium retention and increased phosphorus excretion as shown by the urinary analyses.

On the other hand, we know well from our clinical experience that outward changes of a marked character may occur in women in whom an artificial menopause has been induced by oöphorectomy. At the same time it has been a matter of very lively speculation why one woman should suffer all manner of evils when her ovaries are removed, and another suffer very little.

And this is another reason why experimentation on animals has to be very carefully considered. The metabolism of women is much more easily disturbed than is that of the lower animals; and psychoses and neuroses which are not observed after oöphorectomy in the latter are often the source of the greatest distress in women.

But we shall see that, in addition to certain constant and positive results which are always reliable in regard to the metabolism, experimentation provides us with other

most useful information, and this information is just that which we cannot obtain in our clinical work, although it may be at the bottom of many obscure phenomena. I refer to the effects produced on the other ductless glands by removal of the ovaries. No doubt the differences in the effects of oöphorectomy in women, just alluded to, are largely dependent upon the individual variations that we know exist with regard to the adjustments of the internal secretions, and are evidenced by the outward characteristics of adiposity and thinness, lethargy and brightness, and many other physical and psychical attributes. So that it is clear that if one woman be better adjusted than another against the removal of the ovarian secretion, she will show less signs of the menopause. Animals do not vary in the same way. They all seem to have a remarkable power of readjustment. But with the higher psychical evolution of woman it is not surprising that removal of the ovaries often causes a severe alteration of temperament.

It has been supposed that the changes that occur in other members of the ductless gland system after removal of one of their number are in some cases compensatory, and consequently that disturbances in the body metabolism may thus be made good or prevented.

Effects of Oöphorectomy on the Thyroid.

If one were to select any other order of mammal than the rodent one would come to the conclusion that any alteration in the functional activity of the thyroid after oöphorectomy was of little or no importance in so far as histological evidence was concerned. For instance, in the cat I have been unable to detect any material difference after oöphorectomy in the thyroid itself or in the parathyroid.

But if one compares the thyroid of a normal female rabbit with the thyroid of the same animal after removal of the ovaries, one sees a very different picture. The thyroid of the normal non-oestrous and non-pregnant female rabbit is not a very active organ in so far as the production of colloid is concerned. But after removal of the ovaries there is great distension of the vesicles, which are filled with colloid. Further, the colloid is seen to be basophile in character, staining blue with haematoxylin instead of pink with eosin, whereas the normal thyroid colloid is, of course, acidophile and stains with eosin.

Before attempting any explanation of the changes in the thyroid after oöphorectomy we must not forget that this organ in the pregnant rabbit shows a relatively great increase in the amount of colloid, but that it is then eosinophile in character.

It may safely be asserted that there is a considerable increase in functional activity of the thyroid of rodents after oöphorectomy.

Why the colloid should be basophile instead of eosinophile we can only conjecture. I have carefully considered the question of an artefact, but I think this must be rejected for many reasons, into which I need not enter here. We are, however, assisted in our attempt to arrive at a conclusion by observations made on the pituitary body, some of which will be referred to more fully later.

The normal colloidal secretion of the anterior lobe and pars intermedia of the pituitary is basophile, but under conditions of increased activity it is eosinophile. Further, like the thyroid, in a condition of greater hypophysial activity no colloid is formed, but the secretion is abstracted directly from eosinophile cells. In conditions of the greatest activity of all, as I shall show later, the secretion is directly abstracted by the blood or lymph from faintly staining basophile cells, that is, from the so-called chromophobe cells. There is, in fact, a cycle of events to be demonstrated in the hypophysis according to the needs of the moment.

It is probable, then, that the basophile colloid found in the rabbit's thyroid after oöphorectomy represents a storage secretion, which is formed to meet the altered conditions of metabolism, but which is not of a great degree of activity in this order of mammals.

As I have previously suggested, the inactive thyroid which is found in rodents is probably related to the very marked development of the interstitial cells in the ovaries of these animals; and, as a consequence, a marked reaction is produced in the thyroid of rodents by

oöphorectomy, and not to the same degree in other mammals, such as the carnivora.

Effects of Oöphorectomy on the Thymus.

Calzolari first showed that castration produced hypertrophy of the thymus. His experiments were carried out on rabbits.

No work has been done in regard to women, but eunuchs have been found to possess thymuses which have not undergone involution. It has also been noted by Marrasini and by Gellin that castration, after genital activity has been established, gives rise to enlargement of the thymus.

In my experiments on cats we found the thymus much larger after oöphorectomy than in the normal adult animal, and on section it appeared to resemble the normal gland in the active stage before puberty.

Effects of Oöphorectomy on the Pineal Gland.

I have personally made no observations of the pineal gland after oöphorectomy; indeed, very little physiological work has been done in this connexion.

Biach and Hülles published a paper last year, in which they gave the results of castration of male and female kittens a few weeks old. The animals were kept from seven to eight months. These investigators arrived at the conclusion that atrophy of the pineal gland occurred in all cases. Other observers have been able to find no changes in this organ.

Later on I shall consider the effect of pathological changes in the pineal on the genital functions.

Effects of Oöphorectomy on the Suprarenals.

I have examined many suprarenals after oöphorectomy in rabbits and cats, and have found that there appears to be a definite increase in the reticulated portion of the cortex, at the expense of the zona fasciculata. What the interpretation of this is I cannot say.

Clinical Observations of the Effects produced on the Thyroid by Ovarian Insufficiency in Women.

No experimental finding in regard to the interrelationship of the internal secretions can be considered of real or practical value unless it be supported by clinical evidence.

Indeed, it may be considered that experimental evidence concerning the functions of the ductless glands, which, as I have already pointed out, are subject to individual variations, is most useful in giving us a lead in the interpretation of those difficult cases with which we may be confronted, but are now beginning to understand more fully. This understanding has been brought about by dovetailing our experimental results into our clinical experiences. A brilliant example of what may be accomplished along these lines is afforded by Harvey Cushing's recent work on the pituitary body.

What evidence have we, then, of a clinical nature concerning the correlation of the thyroid and ovary, in the circumstances under discussion—that is, with ovarian insufficiency?

I have many times alluded, as have other writers, to the well-known enlargement of the thyroid in pregnancy. It is probable that normally this enlargement corresponds with that found after oöphorectomy, for in certain respects the ovary is quiescent during pregnancy. We know that this enlargement normally does not produce the signs associated with exophthalmic goitre, but is, as I have already shown, due to excess of colloid material. At the same time I have known more than one case of Graves's disease commence during pregnancy.

It is probable, also, that the enlargement of the thyroid seen in girls during menstruation about puberty is due to the incomplete state of development of the ovaries, and histologically is the same in character as that occurring during pregnancy. I am not aware, however, that such a thyroid has ever been examined microscopically, for obvious reasons.

In addition to this we have other evidence of a pathological nature. No doubt many gynaecologists have had experiences similar to mine.

In one case, Mrs. J., aged 46, I removed both ovaries for cystic adenomata; on histological examination adenocarcinoma was found in a portion of one of the cysts, as is frequently the case when the patient is over 40 years of age. All went well for two months; then the patient developed slight enlargement

of the thyroid. The condition passed rapidly into one of acute exophthalmic goitre, from which the patient actually died within a year of the operation.

I have recently seen a most remarkable case which I believe to be unique.

G. R., aged 25, was referred to me by one of my medical colleagues at the Liverpool Royal Infirmary. She had been married for three years, and had had one child eleven months before she came under observation. The delivery was difficult and was effected with forceps. She was able to nurse the baby for a few weeks only, owing to deficient secretion of milk.

The patient presented herself with typical symptoms of early exophthalmic goitre, and her pulse-rate was 150 per minute. She had never menstruated since her confinement, but had always been regular before she became pregnant—three to four days per mensem.

I found she had the somewhat rare condition of superinvolution of the uterus. The length of the uterine cavity measured under 2 in. The left ovary was palpable and apparently not atrophied.

Now, the pathology of superinvolution is not completely understood, but I think that there must sometimes be an insufficiency of ovarian secretion, even if it be not possible to recognize histological changes in the ovary by our present methods of investigation. At the same time, as we shall see later, insufficiency of other ductless glands may lead to the same condition.

In view of the facts recorded, I think it is amply proved that ovarian insufficiency leads to changes in the thyroid, which may either be of the type seen after experimental oöphorectomy—namely, colloid accumulation—or, more rarely, that represented by exophthalmic goitre.

Until we know a little more of the relation of colloid secretion to the excessive secretion without colloid formation that occurs in exophthalmic goitre, we cannot go into details concerning the exact pathological reactions that occur in the general metabolism. My own view is that it is the regulation of the calcium metabolism that is concerned in these changes. We have seen that oöphorectomy diminishes the output; and we know that the excretion is much increased in Graves's disease, so that this condition may represent a counter-effect to ovarian insufficiency. This at least seems obvious, although I am fully aware that the changes in the thyroid may be merely the gross representation of a number of most intricate changes connected with growth, reproduction, and the life of the individual in which all the ductless glands are concerned.

Effects of Oöphorectomy on the Pituitary Body.

The close relationship between the pituitary body and the genital system has long been recognized, and I have made a number of observations of the effect of oöphorectomy on this intracranial organ.

The interpretation of these observations necessitates the formulation of definite ideas as to what the changes observed may mean. We read of "hyperplasia" or of "increased activity" of the anterior lobe, which can convey little meaning to any one until we have decided what are the appearances associated with increased activity and the reverse in the pituitary body. So far as I know, tentative views only have been put forward, and no very decided statements have been given concerning this complex and interesting organ.

As every one knows, the pituitary consists of three parts: the pars anterior, the pars intermedia, and the pars nervosa.

To each of these various portions, or perhaps more especially to the pars anterior and to the pars posterior—which consists of the pars intermedia and pars nervosa—have been assigned different functions. Authorities are still very much in disagreement concerning them.

Thus we find that Harvey Cushing arrived at the definite conclusion, as the result of his experiments, that the anterior portion was largely concerned in the well-being of the genital organs and in the metabolism of the carbohydrates and of the bony skeleton. As the result of some, if I may say so, rather insufficient clinical observations, he completely changed his opinion, and now asserts that it is the posterior lobe which is responsible for the integrity of the genitalia, and for carbohydrate metabolism. Bernhard Fischer had previously propounded this view.

After careful consideration and observation I have come to the conclusion that we must look upon the pituitary body as *one organ*, and not two. In this way only can we

reconcile all the facts of experimentation and clinical observation.

The secretion of the active chromophobe cells of the anterior lobe, such as are seen in pregnancy, is probably not different from that of the pars intermedia. And I believe that the secretion of the cells of the pars intermedia, which are developmentally the same as those of the pars anterior, may be regarded as pro-infundibulin, and that when it passes into the pars nervosa it becomes modified and acquires pressor qualities. In connexion with this passage of secretion into the pars nervosa there are many very important and interesting facts which are not actually concerned with our subject, so I refrain from discussing them here.

Next we must come to some definite conclusion concerning the interpretation to be placed upon the remarkable differences in staining properties possessed by the cells of the anterior lobe.

Although these variations in staining affinities are well known, I must recapitulate them in order to explain my views concerning their meaning. The cells, then, of the anterior portion are chromophobe or chromophile—they stain indifferently or well. The chromophile cells are either eosinophile (acidophile) or haematoxylinophile (basophile). With eosin they stain red, and with haematoxylin blue. The chromophobe cells stain lightly with haematoxylin.

There are two opinions held concerning this extraordinary grouping. The one, first put forward by Saint Rémy and Benda, finds expression in the belief that these appearances represent different phases of secretory activity. While the other opinion, propounded by Gemelli, represents the idea that each type of cell has a special secretion. My own view coincides with the first suggestion, and after careful investigation I have come to the following conclusions regarding the cycle of events.

First, the eosinophile cells represent the actively secreting cells, which ordinarily discharge their secretion into the blood vessels or lymphatics. If there be no great demand for the secretion the cells may become basophile and enlarge. They gradually become darker until finally they discharge basophile colloid among the neighbouring cells, which may form a vesicle-like wall around it.

After the discharge of colloid we see the small shrunken chromophobe cells all with large nuclei in which a network of chromatin fibres can be seen.

In certain circumstances, as in pregnancy or after removal of the thyroid, there is a great and immediate demand for secretion. Under these conditions the small chromophobe cells regenerate into large chromophobe cells, and eosinophilia—a more leisurely process—does not occur to the usual extent. These chromophobe cells have been called “pregnancy cells,” owing to their constant appearance in the pars anterior during pregnancy.

Finally, it must be mentioned that the pars intermedia secretes colloid—normally basophile in reaction, but in some circumstances, to be mentioned directly, eosinophile. The colloid, which is formed in the pars anterior and pars intermedia, is probably a storage secretion, like the colloid seen in the thyroid.

The more active method of secretion in both parts of the pituitary is intracellular. In the pars intermedia the cells swell up and become fused, and the secretion is, I believe, taken up straight away by the blood or lymph. Some of the secretion of the pars intermedia, and even the actual cells, pass directly into the pars nervosa, whence absorption occurs; and it is in the pars nervosa, in my opinion, that the pressor qualities of infundibulin are acquired.

To return from this digression. Removal of the ovaries appears to exert a certain influence over the secretory functions of the pituitary body on the lines indicated. But in my experience the change is moderate and not quite constant. Thus, in one experiment—Cat No. 6 of my ovarian removal series—after an interval of 210 days, there was no divergence from the normal to be recognized histologically.

I believe the effect is more or less temporary, and in no way comparable to the genital lesions seen after partial extirpation of the pituitary. In most of my cats, however, definite changes were found as long as 245 days after oöphorectomy. There was a large preponderance of

eosinophile cells in the anterior portion. This shows activity, but not the great activity seen after thyroidectomy. In the pars intermedia the cells are fused, and there are colloid vesicles, and sometimes colloid cysts. This colloid stains with eosin, in contradistinction to the normal condition of basophilia.

It is interesting to note that the changes which occur in the pituitary with ovarian insufficiency are not comparable with those found in pregnancy; so that the relation of the pituitary body to the genital glands differs in this respect at least from the ovarian-thyroid relationship in similar circumstances.

Fichera, however, believes that the “hyperplasia and hypertrophy” that follows oöphorectomy resembles that seen in pregnancy. Accordingly he believes that the change in the anterior lobe in pregnancy is due to ovarian insufficiency. As already stated, I have seen nothing to lead me to adopt this view.

Clinical Observations of the Effects produced on the Pituitary by Ovarian Insufficiency in Women.

There is extremely little evidence of any absolute value in regard to this, partly owing to the inaccessible position of the pituitary body and partly owing to the few attempts that have been made to investigate any possible changes present.

As we have seen, there is a peculiar and active state produced in the pars anterior and pars intermedia in pregnancy, but our evidence does not lead us to suppose that this is due to ovarian insufficiency. It is probably concerned with the fetal metabolism, for, unlike thyroid enlargement, it appears to become more pronounced late in pregnancy.

The hemianopia that is sometimes seen during gestation has been attributed to the pressure produced by the enlargement of the pars anterior. And, in the increased secretion of this portion of the pituitary some have sought to find an explanation of the enlargement of the hands and lower part of the face, also sometimes noticed during the period of pregnancy. But there is no evidence I know of that goes to show that the enlargement is skeletal. Indeed it is usually merely a temporary thickening of the soft tissues, such as may be seen after oöphorectomy.

Again, because atrophy of the genital organs is associated with lesions of the pituitary, especially in the condition known as dystrophia adiposo-genitalis (Fröhlich), some authorities (Tandler, Gross, and others) have endeavoured to attribute the primary cause of the pituitary affection to the atrophy of the genital glands. But this is hardly to be believed on the present evidence at our disposal, and it is much more likely that the genital atrophy is subsequent to the pituitary lesion.

The facts I have brought forward in this lecture illustrate the influence of the ovaries on the uterus, on the general metabolism, and on the rest of the principal organs of internal secretion.

With regard to the influence of the ovary on the uterus, we have seen that to some extent the implantation of the fertilized ovum is assisted, possibly by the secretion of the corpus luteum. Further, the activity of the uterus is maintained and regular contractions promoted, probably by the secretion of the interstitial cells.

In the general metabolism the total ovarian secretion appears to promote the excretion of calcium and the retention of phosphorus. And lastly, total ovarian insufficiency arouses increased activity in all the remaining ductless glands.

THE third biennial congress of the Far Eastern Association of Tropical Medicine will be held in Saigon from November 8th to 15th next, under the presidency of Dr. Clarac, inspector of the sanitary and medical services of Indo-China. Papers offered will be classified for reading by a scientific committee, and it is hoped to receive contributions on protozoology and helminthology, on cholera, plague, leprosy and tuberculosis, on malarial and other tropical fevers, on beri-beri and dysentery, on obstetrical surgery and infantile diseases, and on climate and sanitation. Dr. M. L. R. Montel, medical officer to the Saigon municipality, is acting as secretary to the congress; the official language will be English, but papers may be read also in French or German. The subscription is 10s. 6d. (6 dollars, Saigon currency).