the expert nursing which is more important in this than in almost any other infectious disease.

Secondly, every outbreak should be fully studied by an expert bacteriologist. It seems that sometimes no more is done than the minimum necessary for diagnosis. This is not enough. The bacteriological history of each patient should be recorded as fully as the clinical. Investigation of the channels of spread should be checked by repeated examinations of sewage, water, milk, etc., and this may now be attempted with a reasonable hope of success. If it were done regularly our knowledge of and control over enteric fever would be materially increased.

THE SEX GLANDS THEIR ANATOMY, PHYSIOLOGY, AND BIOCHEMISTRY*

BY

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Since subsequent speakers will discuss in detail the administration of various sex hormone products, I shall perhaps be able to fulfil my function as the opener by giving a brief summary of the present position with regard to therapeutic substances. The object of those who organize discussions such as this is to provide a practical survey of the subject, and I therefore propose to deal only with those substances which are of practical value and which can be obtained in an active stabilized form in the ordinary commercial market.

In the physiology of the sex glands it is necessary to consider two separate stages: first, the activation of the secondary sex glands by hormones of the anterior lobe of the pituitary; and, secondly, the hormones secreted by the sex glands after activation. The relation between the anterior lobe of the pituitary, the ovaries and testes, and the mammary glands can be seen in the following diagram, which is self-explanatory.

Hormones of the Anterior Lobe of the Pituitary

It is a well-known fact that the injection of extracts from the anterior lobe of the pituitary into immature animals will produce the precocious appearance of puberty

associated with ovulation and the formation of corpora lutea in the case of the female; and in the case of the male descent of the testis and spermatogenesis will occur. Conversely, in the hypophysectomized adult animal all sexual activity ceases; and this again can be restored by the injection of a suitable extract. Up to the present, however, there is no such extract of the anterior lobe available for clinical trial.

It was discovered that in certain species the urine of pregnancy contains a substance capable of stimulating the ovaries of the immature animal. The test for the presence of this gonadotropic substance forms the basis for the well-known Aschheim-Zondek reaction; the substance was given the name of prolactin by the original German investigators. The problem then arose as to whether this was a single substance or whether, according to the German view, it was composed of two parts—prolactin A stimulating the ripening of the follicle, and prolactin B being responsible for the luteinization of the follicle. The material which is at present on the market is agreed by nearly all workers to be almost entirely the luteinizing fraction. Therefore when we speak in subsequent discussions of the urinary gonadotropic hormone it must be borne in mind that we are dealing almost entirely with the luteinizing fraction.

It has recently been shown that the serum of the pregnant mare during certain stages of gestation contains a very active ovary-stimulating factor. This has been separated, and is available for clinical trial under the name of "antex." Most workers have agreed that antex is mainly follicle-stimulating, as opposed to the luteinizing fraction.

With these two substances—namely, urinary prolactin and antex—it would appear that the clinician is provided with all the factors necessary for the control of ovarian secretion; but the clinical applications of these will be discussed by subsequent speakers. With regard to the chemical constitution of these substances little is known, but they are available in a stable and standardized form.

Hormones of the Ovary

Reference to the accompanying diagram will show that there are three substances—namely, oestrone, oestradiol, and progesterone. There are other oestrogenic compounds in addition to these, but since they are not available for clinical trial they will not be discussed here. Both oestrone and oestradiol, when injected into ovariectomized animals, will produce all the changes associated with the sexual cycle in the rodent. They will also cause the onset of premature puberty, and they only differ one from the other in their relative potency; oestradiol is by far the more potent of the two substances. Both oestrone and oestradiol are available clinically in the form of benzoates. These esters are used because their absorption is slower, and therefore with a single injection it is possible to get an effect very nearly approaching that of the normal function.

If either of these substances be administered to the monkey it is found that the menstrual cycle cannot be reproduced. Experiments on the ovariectomized rabbit have shown that a second factor is necessary for the complete reproduction of the cycle, and that this may be obtained from the corpus luteum. This material, called progesterone, has been isolated from alcoholic extracts of the corpus luteum, and has been characterized chemically. It is produced commercially in two ways—from the corpora lutea and also by the complex degradation of stigmasterol. If oestrone or oestradiol be in-

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jected into an ovariectomized woman for a certain length of time, and this be followed by injections of progesterone, a complete menstrual cycle can be instituted. It can thus be stated that the clinician is supplied with the necessary agents for the production of the menstrual cycle.

One of the great difficulties in the past has been the question of dosage. When these substances were first isolated their effects were studied exclusively on rats and mice and other small animals. This led workers to think and speak in terms of rat units and mouse units. Consequently when raw material first became available for clinical trial patients were injected with relatively small numbers of units. No progress at all was made until it was realized that sex hormones all follow the rules of body-weight ratio. It was thus shown that the use of the same material with identical methods of injection and smearing gave a rat unit which was roughly ten times the mouse unit—that is, in proportion to the body weight. It follows, therefore, that hundreds of thousands of mouse units will have to be given to the human subject to obtain similar results. This question of high dosage is apparent rather than real, and it is to be hoped that in the near future these substances will be prescribed like other therapeutic chemical agents, in terms of weight of the pure chemical substance.

Hormones of the Testis

The isolation of these substances has been the result of intensive studies of the effect of extracts of the testis on the comb growth in the capon. The fundamental observation was a demonstration that an alcoholic extract of bull's testis was capable of restoring the capon's comb to that of a normal cock. The most potent substance of known chemical constitution at the present time is called testosterone; the formula can be seen in the diagram. This hormone is produced by the complex method of sterol degradation, and it is standardized by its comb-growth-promoting properties.

Apart from promoting growth of the capon's comb, this hormone is able to restore the atrophied seminal vesicles of the castrated animal to their former size. The clinical applications of this substance have not yet been fully explored, since it is only comparatively recently that large amounts of material have been available for investigation. Its use has been suggested for the treatment of enlargement of the prostate and for replacement therapy in all conditions where the secondary male sexual characteristics have diminished. Its use in the treatment of enlarged prostate is based on the observation that prostatic enlargement caused by oestrone in animals may be successfully treated by the administration of testosterone.

Form of Administration

When the pure crystalline hormones were first isolated one of the difficulties at once appreciated was the question of absorption from subcutaneous injection. Earlier experiments had shown the fundamental difference of behaviour between the injection of hormones dissolved in oil and those administered in the form of an alcohol-aqueous solution. In general it may be stated that the ideal medium for injection is one which will allow a slow and steady absorption, thus imitating as nearly as possible the natural conditions. In the case of the sex hormones this is accomplished by their administration in the form of oily solutions. In order to slow up the absorption still more various esters have been prepared. Thus oestrone and oestradiol are available in the form of

oily solutions of their benzoates. The benzoate is slowly hydrolysed in the body, thus giving a steady supply of the oestrogenic agent to the subject.

In the case of testosterone a very interesting observation was made when it was shown that the presence of certain fatty substances very much enhanced the activity. Out of this has developed the ester testosterone propionate, in which form the hormone is available to-day. This ester is many times more potent than the free testosterone, and the whole question of potency of this group of substances is very largely bound up with the type of ester which is administered.

Evaluation of Results of Therapy

This presents little difficulty in the treatment of amenorrhoea, since success or failure is apparent. On the other hand, in the treatment of menopausal disturbances it is difficult to exclude the psychological element. Recently, however, the introduction of the vaginal-smear method has provided us with an entirely new technique for the evaluation of therapeutic measures in the menopause. It has been shown that the vaginal smear of post-menopausal women presents an entirely different cell picture from that of pre-menopausal women, and that suitable therapy will transform the post-menopausal smear into the pre-menopausal one. Subsequent speakers will describe their experience with this new method.

Conclusion

In conclusion, it can now be stated with certainty that the labours of the biologist and the organic chemist have placed in the hands of the clinician a series of very powerful therapeutic substances. No longer is it possible for the practitioner to doubt the activity of endocrine products. If he will but take the trouble it is possible for him to obtain highly potent, stable, and standardized preparations of hormones; and let us hope that the discussion which is to follow will give him some indication of the possible uses to which he can put these substances.

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H. G. Huber (*Kinderartzl. Prax.*, **8**, 152) states that while encephalitis is not a rare event in certain infectious diseases, such as influenza, measles, whooping-cough, varicella, mumps, small-pox, scarlet fever, and vaccinia, only a few cases have been recorded of its occurrence in typhoid fever. In the cases described by Elias, Schäcter, and Lemlakis typhoid encephalitis was manifested by bulbar, mesencephalic, spastic, cerebellar, or cortical symptoms. The bulbar type with tachycardia and polypnoea is usually fatal; paralysis of deglutition is rare. In the mesencephalic type the symptoms are hyperkinesia, pseudo-lethargy, oculomotor palsies, and in rare instances facial paralysis; while in the cortical type hemiplegia, epilepsy, and aphasia appear. Huber records the case of a girl, aged 11, who in the second week of typhoid fever developed stupor, facial paresis, spasms of the extremities, slight nuchal rigidity, Kernig's and Brudzinski's signs, and well-marked aphasia. The tuberculin reaction and x-ray examination of the chest were negative. Complete recovery took place after ten weeks' illness.