discover something about how this regulation occurs; it is significant that the regulation is towards a complete unit pattern, which seems to represent an equilibrium position for the processes involved. The equilibrium may perhaps be between the concentrations of diffusing substances, but perhaps more probably we shall find that what is involved is molecular orientation of the kind found in liquid crystals. Secondly, the possible chains of reactions which are open to the competent tissues seem to be very directly related to the genes which are contained in their nuclei, and it is possible that we shall shortly be able to discover some of the connexions which must exist between genetic factors and the forces which control development.

Conclusion

As a result of this discussion we reach the conclusion that embryonic development must be considered in terms of processes which are integrated together to form systems (individuation fields) which are characterized by positions of equilibrium to which they tend to return. The equilibria are, of course, four-dimensional ones; after disturbance the embryonic tissue does not return to a definite shape and then remain in that shape, but it returns to a normal sequence of shapes which it follows in its subsequent development. As to the nature of these processes, we have definite evidence that embryonic development involves the stimulation of competent tissues by evocator substances, and it is possible that an individuation field is constituted by diffusions of evocators from localized regions; but the main evocator which has been studied seems, as we have seen, to be rather little concerned with individuation.

MORPHOLOGICAL AND FUNCTIONAL HOMOLOGIES OF THE MALE AND FEMALE REPRODUCTIVE SYSTEMS*

BY

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The sexually undifferentiated embryo possesses both Wolffian and Müllerian systems, whose further development is dependent on gonadal differentiation and endocrine environment. In the male the Wolffian, and in the female the Müllerian duct form the groundwork of the definitive reproductive organs, the suppressed Müllerian duct being represented in the male by the sessile hydatid of Morgagni and the uterus masculinus, and the suppressed Wolffian duct in the female by the less constant epoöphoron, paroöphoron, and duct of Gärtner. The alternating dominance of these embryonic systems suggests a morphological sexual antagonism, and it is usually held that differentiation of the reproductive organs occurs under the influence of either "male" or "female" hormone, elaborated by gonads, the specific sexual differentiation of which is predetermined by the genic constitution of the zygote formed at fertilization.

The Gonads

The mechanism whereby the sexual bias genetically given the undifferentiated gonad is realized in either a definitive ovary or definitive testis has been shown by Witschi¹ to be one of induction determined by tissue environment. Germ cells differentiate into oögonia in the

cortex and into spermatogonia in the medulla of the developing gonad under the influence of "inductors of female and male differentiation," which are elaborated in these regions. The inductors are mutually antagonistic, respectively promoting and inhibiting the spermatogenetic and oögenetic functions. The male inductor is the more powerful of the two. In amphibia it can bring about complete sex reversal of the germ cells. In birds, however, transformation of the vestigial right gonadal rudiment, following left ovariectomy, into a testicular structure is rarely accompanied by spermatogenesis—a fact indicating that the presence of germ cells is unnecessary for testicular differentiation. In mammals transformation never proceeds as far as spermatogenesis, and the "freemartin" gonad may, in spite of its general testicular structure, still contain oöcytes. Witschi suggests that the failure of the mammalian germ cell to respond to male induction is due to a too distinctly gonochorist-female zygotic constitution. If the gonads are regarded as their source, the occurrence of "male" hormone in the female organism, and of "female" hormone in the male, is anatomically understandable on the basis of gonadal homologies.

The Accessory Organs

The Wolffian and Müllerian systems develop specifically in accordance with the sexual differentiation of their associated gonads. Although their constituent cells are presumably biased in one or other sexual directions by the genic constitution of the zygote from which they are descended, their essential non-specificity is indicated by the fact that their differentiation in both genetic males and genetic females can be influenced by alterations of their sex hormone environments. Experimental parabiosis and grafting in amphibia show that in most instances it is the female system that is dominated by the male, sex reversal of the male reproductive organs being extremely rare. Reversals of the latter kind never occur in cattle and pig twins, freemartins always being zygotic females. It is possible to explain this fact on the basis of the view that sexual differentiation of both male and female accessory systems is under control of the secretions of the corresponding gonads.

Wiesner² has suggested an alternative explanation. According to him the differentiation of the female system is entirely controlled by the genic constitution of the zygote, whereas that of the male requires the participation of a "male" hormone. While "female" hormone is without effect on differentiating reproductive organs, male hormone can thus influence a developing female. Such effects as the provocation of mammary growth in male mammals by ovarian implants and extracts, which exponents of the more orthodox hypothesis adduce in support of the view that "female" hormone does in fact cause differentiation of undifferentiated organs, Wiesner explains as effects on tissue already differentiated.

The Sex Hormones

The reciprocal domination and repression of the Wolffian and Müllerian ducts implies, on the basis of the usual di-hormonic view of sexual differentiation, a mutual antagonism of the "male" and "female" sex hormones. It is known, however, that the gonadotropic hormones of the pituitary are not sex-specific. Those gonadotropic hormones which in the female respectively stimulate follicular and luteal development operate in the male on the germinal epithelium and interstitial tissue.³

It has also been demonstrated that the ill effects produced in the gonads and accessory organs of one sex by the administration of the contrary sex hormones are not direct expressions of endocrine antagonisms, but indirect effects produced through the pituitary. Moore and Price⁴

* Paper read in the Section of Anatomy at the Annual Meeting of the British Medical Association, Oxford, 1936.

state definitely that "gonad hormones have no direct effect on the gonads of either the same or the opposite sex," and, furthermore, that "gonad hormones stimulate homologous accessories, but are without effect upon heterologous accessories." Whereas there appears to be little evidence which conflicts with the view that sex hormones do not directly influence the gonads, recent work has conclusively shown, in opposition to some earlier findings, that the "male" and "female" hormones may act not only on their corresponding, but also on the opposite reproductive tract.

The little known at present about the action of "male" hormone on the female reproductive system⁵ cannot safely be built into an effective theory. Investigation of rats, mice, monkeys, ground squirrels, and dogs⁶ shows, however, that the "female" hormone oestrin may cause profound changes in the male reproductive system. These newer findings do not necessarily conflict with Moore's second thesis as defined by him; they do, however, demand a revision of current ideas on the specificity and sphere of action of oestrogens, and they also suggest some modifications of our views on the embryology and phylogeny of the reproductive organs.

Although oestrone is not sex-specific, some workers have found that it has no effect when injected into normal mature male rats. There is experimental justification for the view that this is due to a neutralizing action of the male hormone elaborated in the testes of the experimental animals.⁷ Progesterin has been found to act similarly in relation to oestrin, and the explanation has been offered that it increases renal permeability to oestrin.⁸ These hormone antagonisms, which have not been well investigated as yet, are of importance, not only because they uncover a previously unconsidered physiological mechanism, but because they have important bearings on the problem of the aetiology and treatment of benign enlargement of the prostate.⁷

Oestrin causes fibro-muscular growth throughout the male and female reproductive tracts. This response may be regarded as an undifferentiated effect of the hormone on tissues derived from the mesoderm of both the urogenital ridge and genital cord.

The epithelial changes induced in the male by oestrogens have been well studied in small rodents. The prolonged administration of the hormone induces hyperplastic and metaplastic changes (leading to stratification and desquamation) in the epithelium of all the reproductive organs, including the urethra and urethral glands, different regions varying in their sensitivity. Corresponding epithelial changes can be produced in the vagina, uterus, and urethra of the female. The internal epithelial sensitivity to oestrin thus appears to be confined to tissues derived from the Müllerian and Wolffian systems, and the urogenital sinus. Since urethral stratification occurs in response to oestrogens, and since there is embryological support for the view that the vaginal epithelium is often partly or wholly derived from the sinus, stratification in response to oestrogenic stimulation could be regarded in general as a primary response of tissue, in whose development sinus epithelium has played a part.

This view is well supported by the analysis of the changes induced by oestrogens in the reproductive tract of male monkeys,⁹ and it assists in the understanding of the different types of epithelial response shown by different mammals. For it implies, what has been suspected by some embryologists, that sinus epithelium may invade tubular structures which open into the sinus, and that the different gradients of stratification in the reproductive organs in response to oestrogens may be regarded as indicating in part varying degrees of replacement. For example, the fact that little epithelial stratification occurs in the vagina of the rabbit in response to oestrin would

imply, on endocrinological grounds, that it is derived mainly from Müllerian, and not sinus, epithelium.

A further embryological issue is raised by the oestrogenic sensitivity of sinus epithelium. Apart from the internal changes they produce, oestrogens act on ectodermal tissues (for example, mammary gland, feathers, sexual skin), which appear to be specifically sensitive to these compounds. The sexual skin reaction in monkeys appears to grade into that of the sinus epithelium, and the endocrinological evidence can thus be taken to support the view, put forward by some comparative anatomists, that the urogenital sinus is an ectodermal structure. Moreover, it is of interest also, from the point of view of the sensitivity of epithelium belonging to some parts of the Wolffian system, that certain authorities maintain that the primordial Wolffian duct is partly formed from, and phylogenetically related to, the ectoderm.

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Clinical Memoranda

A Fatal Case of Agranulocytic Angina

Although agranulocytic angina is now a well-recognized condition and many cases have been described in England, America, and on the Continent, it is still sufficiently rare to warrant interest, and the following account of a fatal case treated with "pentnucleotide" (Smith, Kline, and French, Philadelphia) may prove worthy of record.

CASE RECORD

On July 13th, 1936, whilst calling about 6 p.m. to see the husband (who suffers from angina pectoris) in a boarding-house, I noticed that the wife (aged 60) looked ill. On inquiry it appeared that she had been suffering from severe pains in the limbs and joints for the past six days, but had continued her work of managing the establishment. She had no appetite, and "felt limp," but had no other symptoms. On examination she showed a temperature of 102.6° F., pulse 112, respirations 30. All her muscles were tender, but otherwise there were no physical signs.

About 10.30 p.m. I was rung up and told that she was very much worse. Her temperature by this time was 103.6°, pulse 120, respirations 32. There was increasing tenderness everywhere, particularly in the right hip and abdomen. I called in Mr. Molesworth, because of the abdominal tenderness, but he decided that the condition was not surgical, and queried typhoid fever. The patient was removed to a nursing home forthwith and put under typhoid precautions. The next morning she complained of a dry, sore throat, but had no physical signs except a soft apical systolic murmur, which had not been present on the previous evening.

Dr. L. P. de Costobadie kindly did a blood count, and returned the following result: red blood cells, 4,500,000; haemoglobin, 85 per cent.; colour index 0.9; leucocytes, 4,000 at 11 a.m., 2,100 at 5.30 p.m. Differential count: polymorphs, nil; lymphocytes, 89 per cent.; large hyalines, 11 per cent. A blood culture was taken at the same time (returned July 21st), which showed a pure culture of *Staphylococcus aureus*.