Organs of Special Sensation

It has been generally assumed that the epidermis is the seat of pain and the dermis the seat of touch. This view, which has hitherto prevailed, has been challenged recently by Waterson. Waterson has emphasized that it is possible to shave off the epidermis, at any rate as far as the deeper layers of the stratum mucosum, without causing pain, while the exposed surface remains sensitive to touch. It has already been remarked that, whether one supposes the epidermis to be the seat of touch or of pain, these sensations are so closely packed at the surface that an abundant innervation must be present to act as their receptors. Such an abundant innervation is not to be found. Here and there, with great difficulty, nerves in the epidermis can be found. Most usually they are branches of medullated nerves continued to the stratum Malpighii, where they end often in the form of Merkel's corpuscles, or they are a continuation of Meissner corpuscles into the epidermis, where, again, they end as Merkel's corpuscles, or, especially in regions like the hand, where tactile acuity is high, large uniform fibres can be traced in the epidermis as far as the stratum granulosum. Thus what can be easily demonstrated in the epidermis is the continuation of endings like Meissner and other medullated nerve endings often regarded as incomplete Meissner endings, these with good reason always having been associated with touch. These are most easily demonstrated in regions where acuity is high and the epidermis well developed. The same observations apply to hairs and special structures, such as Eimer's organ in the snout of certain animals. These special tactile organs are also ones in which it is easy to demonstrate epidermal endings, as in the outer root sheath of the hairs.

That the nerves of the epidermis form an accessory organ of touch is made still more likely by the fact that it is possible to demonstrate the existence of a close mesh-work of naked varicose fine nerve fibres in the sub-epidermal tissue, immediately below the stratum Malpighii. This mesh anastomoses, and also forms endings which terminate sometimes by entering the epidermis—though mainly it is a plexus below the epidermis. This plexus, apparently continuous, has been traced for a distance of six centimetres. It has all the characters that we might expect from the history, the physiology, and the quality of the pain sensation. By the analysis of the areas upon which this sensation has previously been indicated, cold has been found to assume the form of compact terminal subdivisions each of which ends in a blunt expansion. These are borne on the ends of medullated fibres, the diameter of which is about 7 μ . They lie quite superficially and near the stratum Malpighii in the subepidermal tissue.

In regard to heat we have not been so fortunate. The long latent period has made it certain that the heat receptor lies further from the surface. The large gaps between adjacent receptors make it more difficult to discover groups of endings, and the deep situation has rendered it impossible for us to use an *intra-vitam* stain. We have had to resort to sections stained with silver. In thin sections it is very hard to recognize actual endings. To map the heat spots we have used a metal junction and passed a constant current through this for a constant period, so that we have always applied to the skin the same amount of heat. Spots so found have been excised, and after staining with silver have been cut into sections. In such cases we have always found that our prick which marked the heat spot has perforated exactly the hair follicle complex passing into the vicinity of the sebaceous and sweat glands. We have found many nerve bundles and fibres and endings in the course of these pricks, but we are unable to say what type of endings, if any, are

especially associated with heat. Further investigations are in progress.

It is a common enough observation, mentioned by many others, to find a thin fibre entering into a nerve ending, a fibre quite distinct from the medullated nerve that carries the nerve ending. This additional accessory ending has on the ground of its thin non-medullated character been reckoned as sympathetic. It may, however, and in our judgement even more probably, be regarded as an accessory nerve of pain, and may form the anatomical basis of the oft-repeated statement that excessive stimulation of any receptor may end in pain. It is not suggested that a receptor changes its sensation, but that these accessory fibres furnish the protective pain sensation. In the eye this function is supplied by the fifth nerve, which furnishes pain receptors and pain only to the eye itself. In the case of the internal ear the same function is undertaken by the seventh nerve. The accessory fibre exercises the same function for the hairs, Meissner corpuscles, Pacinian corpuscles, and other deep endings.

THE PROBLEMS OF EMBRYOLOGY*

BY

C. H. WADDINGTON, M.A.

FELLOW OF CHRIST'S COLLEGE, CAMBRIDGE

Embryology may be, and often has been, regarded as a branch of comparative anatomy. According to this way of thinking, the fundamental subject of biology is the study of adult organisms; this study can be divided into two main groups of sciences, which we may call the anatomical, which relates to the forms of animals, and the physiological, which relates to the physical and chemical mechanisms by which organisms perform the business of keeping alive. If we confine our attention to adult animals, it is clear that the phenomena dealt with by the anatomical sciences must be studied before those with which the physiological sciences are concerned, since the physiological functioning of any highly evolved organism is founded on the principle of specialization, by which particular organs are set apart to perform particular functions.

Even when we investigate the progress of a relatively simple chain of chemical processes occurring in a restricted region of the body, perhaps in a single cell, more and more evidence is accumulating to show that the progress of the reactions is dependent to a large extent on the morphological arrangement of the particles of the living protoplasm. I need only remind you of the numerous and important researches on the properties of biological membranes and the orientation of protein molecules in muscle cells, and of the recent demonstration of the position effect, by which the effect of a Mendelian factor, or gene, is shown to depend on its position on the chromosome relative to the other genes. In some cases we are already in a position to try to discover the forces which hold the molecules in these microscopic patterns, and we are here approaching one of the fields in which the debt is the other way round, and it is anatomy which must follow in the footsteps of physiological advances.

Among the anatomical sciences embryology is often relegated to a subordinate position. If we attempt to give an account of the facts of comparative anatomy in terms of the theory of evolution, the embryological data come in as interesting additional evidence. In the heyday of comparative anatomy, embryonic development was explained by reference to adult forms; in Haeckel's theory of recapitulation the sequence of embryonic stages was compared with the evolutionary series of ancestors. But

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it must always have been clear, and was soon specifically stated, that in its development an animal recapitulated not an adult ancestor but an embryonic ancestor. Thus the gill slit of a human embryo does not resemble any sort of functional adult gill, but only the embryonic gill arches out of which gills are developed in the less highly evolved types.

The acceptance of this point of view involves giving up any attempt to explain embryological development in terms of adult structures, and accords to comparative embryology a position exactly equivalent to that of comparative anatomy. It is an explicit admission that animal form cannot be considered as a static thing, but that the changes which occur during development are essential to our understanding of it; the time element cannot be neglected.

In recent embryological writings this point of view has been carried even further. It has been urged, for instance by Dalcq and Gerard in their recent textbook of embryology, that it is no longer profitable to attempt to reduce the various embryonic stages of different species to common fundamental types, but that we should try to homologize processes instead of forms. Thus the recent work on gastrulation, in which the movements of vitally stained patches of tissue have been watched, forces one to the conclusion that no comprehensive definition of gastrulation in vertebrates can be given in terms of structures such as the archenteron or blastopore, but that such a definition must be framed in dynamic terms—that is, in terms of the processes by which the three germ layers are arranged on top of each other.

The importance of this change of viewpoint is that it brings descriptive embryology much nearer to experimental embryology. Experimental analysis must necessarily deal with processes and not with static unchanging structures. So long as descriptive embryology considered the blastopore of a frog as an organ to be homologized with the blastopore of other forms, while experimental embryology considered it as a focus of a set of movements, there was a cleavage between the fundamental ideas of the two subjects which is now being repaired by the adoption of a more dynamic point of view in the descriptive branch.

The experimental analysis of development discovered its first causal principle as lately as 1918, when Spemann showed that in the newt the dorsal lip of the blastopore acted as an organization centre which stimulated the neighbouring ectoderm to undergo differentiation into a neural plate. It looked from the very first as though Spemann's discovery had revealed one of the general types of causation which are effective in embryonic development, and this supposition has been amply confirmed by later work. Organization centres have been discovered in most groups of vertebrates, in the birds and fish, and less certainly in mammals. In each case the organization centre is related to the process of gastrulation, not indeed in any simple way to definite blastopores or archenterons, but to the foci of the gastrulation movements, so that the comparative study of gastrulation may now be said also to involve a comparative study of organization centres.

Spemann pointed out in 1931 that the organization centre does more than merely stimulate the ectoderm to nervous differentiation; it also determines to some extent what part of the neural plate shall be formed at a given place. These two functions of stimulation and of regional determination seem to be comparatively independent of one another. I could show, in 1933, that in the chick the organizer would induce the formation of a neural plate even when it was already accompanied by one neural plate of its own, so that the stimulation of neural development, which was later called "evocation," is not

bound up with any tendency of the organizer to modify its surroundings so as to form a complete system. On the other hand, the regional determination does seem to involve just such an attempt to build a single complete unit, for which reason it has been called "individuation." Thus an isolated part of an organizer, if it is not too old, tends to become rearranged so as to induce a whole neural plate, the two combined then forming a whole embryo; similarly two organizers placed near together tend to fuse into a single complete embryo.

Action of the Evocator

For a complete analysis of the process of induction we must consider, as well as these two aspects of the process, the condition of the ectoderm on which the organizer acts. The embryonic ectoderm will not react if it is too young nor if it is too old; during the period when it is capable of reacting to the organizer it is said to be "competent," and we must assume that it is in some unstable state; there must be two series of processes which may occur in it, one leading to neural differentiation and one to epidermal differentiation, and between these two the organizer decides.

Before we can consider how the competent tissue is acted on by the evocator and individuator components of the organizer, it is necessary to have some picture of the subsequent development of the neural plate and of the organizing tissues. The organizing tissues become the notochord and somites, and the neural plate develops into the neural tube with the various brain vesicles and so on. In both cases each particular part develops in a particular way; development must consist of an integrated system of physical and chemical processes, and we could theoretically give a value to the processes at any given point. Such a system of developmental processes I call an individuation field; and I also include among the processes which are referred to in the phrase "the individuation field of the organizer" the regionally specific properties of the organizer, which must underlie its determination of the regions of the neural plate which it induces.

Now the evocator part of the organizer has no regionally specific properties; in fact evocation can be performed by chemical extracts of the organizer, in which the active substance is in perfectly homogeneous solution, so that no possibility arises for there being particular properties for particular parts within the inducing mass. If we could get the evocator to act on ectoderm which was isolated from any other organization centre, we should be able to find out exactly how far the neural plate individuation field is inherent in the competent ectoderm. This experiment has not yet been performed, at least in a satisfactory manner, but the evidence, such as it is, suggests that the competent tissue can probably produce a complete organ, with all its regionally different parts, even when acted on by a simple evocator.

This is perhaps rather a disheartening conclusion. What we are really interested in is the set of processes which cause the development of an organ of a particular shape, the processes in fact which we have summed up as the individuation field. Now the best we can do in the way of analysis of the organizer is to isolate the evocator component, which is just the component with which these processes have least to do; they remain hidden either in the competent tissue or in the unanalysed residue which we have called the individuation field of the organizer.

There are two lines along which we may hope to advance towards their discovery. In the first place, the individuation field is not unalterable, but is to be recognized as the cause of the regulation of parts of the embryo to make whole units. We can hope in the future to

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

S. ZUCKERMAN, M.A., D.Sc., M.R.C.S.

BEIT MEMORIAL RESEARCH FELLOW

(From the Department of Human Anatomy, Oxford)

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.