"HORMONES AND GENETICS"*

BEING A CONSIDERATION OF SOME OF THE FACTORS
CONCERNED IN THE RESPONSE MADE BY CERTAIN
TISSUE CELLS TO HORMONIC INFLUENCES

BY

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One of Mendel's most important contributions to genetic knowledge was his establishment of the particulate nature of the heredity process. He showed that in plants—and the same is true of animals—the factors or gene complexes on which hereditary characters depend are transmitted in a particulate manner. They do not lose their identity during the passage from one generation to the next, and under appropriate conditions of mating may reappear in their original form.

It is not necessary to stress the importance of this knowledge to physiology or to preventive medicine. Let us take, for example, diabetes, which, as we know, depends on some defect in the quantity or quality of the secretion poured out by the cells which line the acini of the pancreatic islets into the blood stream, which thus controls carbohydrate metabolism. It is true that the continued administration of insulin will supply the missing hormone and so enable the patient to resume normal life, and, in some cases, to marry and beget children. But the administration of insulin, even over long periods, although it may ameliorate the symptoms, does not remove the pancreatic defect on which diabetes depends (except, possibly, when given at a very early stage). Since diabetes is, to a certain extent, an hereditary disease—that is, a disease which shows a familial incidence—this means that, unless steps are taken to prevent the handing on of this pancreatic defect to offspring, the saving of the lives of a number of individuals liable to suffer from diabetes may lead to unfortunate results from the racial point of view. No one will regard with equanimity the possibility of breeding and rearing a race of citizens who throughout life are dependent on the continued use of insulin for their well-being.

Again, if we take the case of hypothyroidism, we are not justified in thinking that, when we have shown a certain defect (for example, cretinism) to be associated with lack of iodine in the water or food, we have explained its occurrence. This discovery, though useful, only pushes the solution of the problem one stage further back; we still want to know what are the antecedent genetic factors which predispose to this endocrine functional defect. The attainment of fuller knowledge about the physiology of the pancreas and of other endocrine glands is vitally necessary, but we also want fuller knowledge concerning the physiology of the germ cells—that is, the cells which transmit these special defects in certain organs.

In thus speaking of diabetes as the result of an hereditary pancreatic defect I do not wish to suggest that this is the whole of the story concerning this disease. We know, for instance, that while insulin promotes the taking up by the tissues of the sugar in the blood, adrenaline also assists in the liberation of sugar from the liver, where it has been stored in the form of glycogen. The posterior pituitary gland also aids in the manufacture of fat from the sugar, while thyroxine stimulates the oxidation of the sugar by the tissues. Hence we are concerned not only with the pancreas, but with the harmonious working of other endocrine glands in diabetes. At present we do not know to what extent genetic factors may also be concerned in their departure from healthy function.

The same seems also to be true to a certain extent in hypothyroidism. No doubt the thyroid defect which we recognize clinically as cretinism or myxoedema is associated with lack of iodine. But this only means that in some individuals the thyroid gland is less successful in dealing with minute quantities of iodine than it is in others, and this difference may depend on genetic factors.

Certain facts, such as, for example, the high incidence of cretinism in certain Swiss valleys, in which extensive inbreeding of the population has occurred, do point to the importance of hereditary factors. Moreover, a number of cases have been recorded of the birth of twins in which one twin has been a cretin and the other normal. Here the ante-natal environment—that is, the supply of iodine and maternal hormones—has been the same in both twins.¹ If such twins are of the binovular kind and not "identical" then the suggestion is that the germ cells from which they originated were of different genetic constitution in respect of thyroid efficiency.

The same thing happens in connexion with the pituitary gland. Instances have been recorded² in which one twin was an achondroplastic dwarf and the other was normal. The case mentioned by the late Sir F. Treves, of the so-called elephant man, though not a twin, is of interest here. This man had an enormous bony overgrowth and skin hypertrophy affecting the bones of the skull, trunk, and limbs. The pituitary was very large. I had an opportunity of seeing and photographing him at Leicester at an early stage in his illness. The deformity then was much more marked on the right side of the head and trunk; the left arm and leg were only very slightly affected. This hemilateral difference in the effect of the pituitary secretion must have been due to a greater receptivity of the tissues on the right side of the body to the pituitary hormone, and this leads naturally to a discussion of the important question of tissue susceptibility to both internal and external environmental stimuli. Dr. Eric Pritchard, in a letter to Dr. Allan Warner, reports three cases of achondroplasia in twins; in each case only one twin was affected, the other was normal.*

OTHER EXAMPLES OF TISSUE SUSCEPTIBILITY TO HORMONIC STIMULI

While the regulation of the functional activities of the organism by endocrine influences has been greatly emphasized in recent years, at any rate in vertebrate physiology, certain facts still remain which suggest that the circulation in the blood stream of certain internal secretions is not by itself adequate to explain the entire phenomena in all cases. I have already alluded to the striking differences in physiological reaction shown by binovular twins—that is, twins from different germ cells—when reared under similar ante-natal and post-natal conditions. These differences are, I suggest, due to a dissimilar genetic constitution.

Now the same or a like kind of genetic dissimilarity is sometimes seen in the way the tissue cells react to the same hormonal influence on the two sides of the body. In a lecture on "The Genetic Significance of Hemilateral Asymmetry in the Vertebrate Organism," delivered at the University of Birmingham in May, 1932, instances were given showing asymmetry of secondary sex characters in birds. At the Birmingham meeting of the British Association in 1913 a gynandromorphic pheasant was shown with male plumage and a well-developed spur on one side, and female plumage and no spur on the other. An ovotestis was also present. In this case it is difficult or impossible adequately to explain the asymmetric distribution of secondary sex characters by a hormonal secretion circulating equally on both sides of the body. There must be some difference in the capacity of the epidermal tissue cells to react to the secretion formed by the sex glands—some difference, that is, in "maleness" or "femaleness" on the two sides, dependent on chromosomal or gene differences in the constitution of the tissue cells. Further, the embryological evidence shows that this irregular or asymmetric distribution of character, or cell potentialities, takes place at a very early stage in the division of the ovum—that is, at the time when the growth of the embryo is being determined on a bilateral plan. Lillie³ and Juhn have suggested that this asymmetry depends on a difference in the growth rate of the feathers in relation to the hormonal threshold on the two sides of the body.

* Contribution to a discussion on genetics at the meeting of the British Association, Leicester, 1933.

¹ See also "Mongolism in Twins," *Lancet*, April 15th and August 12th, 1933.

Then we have the left-sided growth of the spur in certain female fowls. If a four-toed breed, such as the Game or Andalusian, is crossed with a five-toed breed like the Houdan or Silky Fowl, a condition of genetic instability may arise. The hybrid chickens of the F1 and F2 and later generations often show asymmetric toe development. In certain cases female birds may develop a spur on one leg only, and more frequently on the left side. In such cases, by cross breeding, a condition of somatic asymmetry has been brought about in which the tissues on the two sides of the body differ in responsiveness to the hormonal stimulus. Professor Crew* has recorded the case of a fowl in which there were marked skeletal and other differences on the two sides. The bird was a male hybrid from a Light Sussex and Rhode Island cross, and the asymmetric bone development suggested a difference in tissue susceptibility to the pituitary hormone on the two sides of the body.

Corresponding differences have also been observed in the human subject. I have already mentioned the case of the "elephant" man, and other examples are also given in my Birmingham lecture.

Gynandromorphism in Insects.—In insects and some other invertebrates the development of the secondary sex characters is determined by chromosomal or gene agencies, and hormonal stimuli play little or no part. As Julian Huxley has said† the development of the sex characters in the higher vertebrates is under the control of a two-switch mechanism—chromosomal and hormonal. In insects, on the other hand, the second mechanism is absent, and the development of the secondary sex characters—for example, the male antennae—is under the control of the chromosomal mechanism only. This is well shown in the case of gynander ants and butterflies.

ACQUIRED IMMUNITY AND GENETIC FACTORS

Now if this hypothesis of a difference in receptivity to hormonal influences in the tissues on the two sides of the body be well founded, then we should expect to find an unequal or asymmetrical response to other stimuli, besides those elaborated by the sex gonads. It is true that the skin eruptions which result from the circulation in the blood stream of the toxins of disease organisms, such as the virus of the exanthematous fevers, are, for the most part, symmetrically distributed on both sides of the body. But medical men have not been on the look out for asymmetrical distribution in such cases. Further, they would be of somewhat rare occurrence. It may be, therefore, that when closer attention is drawn to the subject more cases of asymmetrical distribution will be recorded.

I must explain that we are not now concerned with the immunity to certain diseases which characterizes some species of animals and certain races of mankind. Such inborn capacities to resist invasion are the outcome of prolonged racial experience of disease, and depend on genetic factors. The acquired immunity which depends on individual experience of disease, though not based on germ cell variation and selection, yet throws some light on the way in which the somatic tissues—for example, the defensive cells—transmit the newly acquired character of immunity to their cell descendants, though not to offspring. I say not to offspring because we know that the acquired immunity which follows an attack of small-pox or measles is not handed on to children. At the same time we also know that the acquired immunity which follows recovery from small-pox is persistent and usually lifelong, while that which follows vaccinia is only temporary. The same thing is seen in other infective diseases. Thus the immunity which follows recovery from a localized staphylococcal infection, accompanied with suppuration, is often very evanescent, while that which follows an attack of one of the virus diseases, such as measles, is usually lifelong, though even in measles the evidence shows that the persistence of the immunity varies in different families. That is to say, it has a genetic basis.

* See *Journal of Genetics*.

† *Science of Life*, p. 374.

What is the meaning of this difference? Does it depend on the fact that the reaction in the localized form is mainly concerned with cytoplasmic cell elements, while in the generalized form it reaches and affects the nucleus and the nuclear heredity mechanism of the cell? In an interesting article on immunity in the virus diseases C. H. Andrewes³ suggested that "the immunological properties of viruses are probably related to the small size and the intra-cellular parasitism of these agents." If for "intracellular" we read "intranuclear" parasitism, then the causal relation between intranuclear invasion and the transmission of the immune state to cell descendants in the virus infections becomes more readily understood.

The element of minute size in a virus infection as compared with a bacterium or coccus may explain why the former can pass through the nuclear membrane while the coccus or bacterium can only act on the cytoplasm of the cell. The presence of so-called nuclear inclusion bodies in the case of certain virus infections, herpes, varicella, etc., affords evidence that the nucleus is affected in these diseases. E. V. Cowdry⁴ finds inclusion bodies in the nuclei of the liver cells in experimental monkeys in yellow fever, but does not regard it as proved that these actually represent the virus. The essential point is, however, that the nuclear heredity mechanism of the cell must be affected before the adaptive response made by the cell to the disease organism—that is, the immune state—can be handed on to the cell descendants of the individual cell, or cells, which make the response. In the acquired immunity reaction the capacity to resist re-invasion is so handed on. We know, for instance, that after recovery from such an attack the individual remains immune. At the same time we also know that this immunity is not handed on to the germ cells of the same individual, for his children are born susceptible to the disease.

Now there is some recently acquired evidence that the secretions of some of the endocrine glands play a part in keeping the defensive mechanism of the body up to the mark in resisting infection. We also know that some vitamins, especially vitamin A, exercise a very important influence in the same direction. Although the subject of acquired immunity does not bear very directly on the genetic side of endocrine physiology, there can, I think, be little doubt that a study of the way in which somatic cells (for instance, thyroid cells in relation to iodine and the cells of other endocrine organs) react to environmental stimuli, and a fuller knowledge of the mechanism by which such reactions are handed on to later generations of these somatic cells, are matters of great importance. The moral to be drawn from the observations I have brought forward surely is this: that physiology, pathology, and genetics have many important points of contact, and can mutually assist each other.

REFERENCES

- ¹ Armstrong, H.: *British Medical Journal*, 1928, i, 1106.
- ² Warner, A.: *Ibid.*, 1928, ii, 983.
- ³ Andrewes, C. H.: *Lancet*, 1931, i, 989.
- ⁴ Cowdry, E. V.: *Amer. Journ. of Path.*, March, 1933, p. 149.
- ⁵ Lillie, F. R.: *Science*, lxxiv, 387.

The medical and biological section of the first congress of the Association pour la Documentation Photographique et Cinématographique dans les Sciences, which was held in Paris at the beginning of October, devoted special sessions to the preparation of surgical films and radiology. Among the subjects demonstrated by cinematographic films were a plastic mammary operation, cataract extraction, excision of a skin cancer, plastic surgery of the face, resection of the megacolon, tissue culture by Dr. Carrel of New York, Caesarean section, gastrectomy, a normal confinement, and subtotal hysterectomy. Discussions centred round the technique of reproducing such operations by films suitable for demonstration to clinics, and the most recent developments of radiological and cinematographical apparatus.