## NEWS AND VIEWS

# Sex Determination Reconsidered

THERE have been many theories of sex determination. The idea that the *X* and *Y* sex chromosomes could control the differences between the sexes by differentially regulating the rate of cell division and thus the rate of development of embryos, suggested by Dr Ursula Mittwoch on page 446, seems very much more simple than many of its predecessors. There have been a great many suggestions of how the differences between males and females could be determined both in animals and plants. In 1908, J. A. Thomson, in his book *Heredity*, made the famous observation that " . . . the number of speculations as to the nature of sex has been wellnigh doubled since Drelincourt in the eighteenth century brought together two hundred and sixty-two 'grandes hypotheses' . . .".

Thomson was writing near the time of the discovery of the sex chromosomes in insects, which provided genetically determined differences—the *X* and *Y* chromosomes, one noticeably longer than the other—that could be seen under the microscope. It was rather later that the mammalian sex chromosomes were described, and now, of course, it is known that the presence of two of the larger *X* chromosomes determines the development of a female, whereas the possession of one *Y* chromosome causes the animal to be a male. Mendel's work had been discovered in 1900 and the confusion of theories was increased by many subsequent attempts to explain sex determination according to the laws of Mendelian inheritance, with their implications that genetic determinants segregate independently when the gametes are produced, and recombine freely with one another at fertilization.

In the 1920s C. B. Bridges proposed that sex differentiation depends on a balance between one set of genes which determine maleness and another set which determine femaleness. This theory of genic balance was based on work with the fruit fly *Drosophila melanogaster*, in which the *Y* chromosome causes the sperm to be motile, but does not seem to be necessary for sex determination, which is controlled by the ratio of the number of *X* chromosomes to autosomes. With a diploid set of autosomes, two *X* chromosomes determine a female, and one determines a male, and intersexes are possible. To explain this, Bridges suggested that the *X* chromosome of *D. melanogaster* contains genes which determine a female and the autosomes contain genes which determine a male.

This theory has since been extended to man, in whom, of course, intersexes are also known. This was in spite of the fact that nobody seemed to be sure what all the genes were doing. Dr Mittwoch now wishes boldly to cast away the idea of genes which determine sex and consider again the effects of the whole sex chromosomes. She has collected evidence from various sources to show how the presence of extra chromosomes can affect quantitative differences, such as the number of dermal ridges on the fingers. Such differences are likely to depend on rates of growth and ultimately on rates of cell division.

On the basis of her evidence Dr Mittwoch suggests that perhaps the *X* chromosome reduces the rate of mitosis and the *Y* chromosome increases it, thus affecting the growth of the embryo. In such conditions the mammalian gonad, which at first is not distinguishable as male or female, could develop into an ovary or testis according to its rate of development, the testes, which anyway begin to differentiate before the ovaries, being the result of the more rapid development.

The idea that extra chromosomes, whether sex or autosomes, can affect rates of growth might help to explain various conditions such as Mongolism—an extra autosome. Individuals with this chromosomal abnormality are smaller at birth than babies with the normal forty-six chromosomes, while the condition *XYY* has been associated with extra tall men. It will be interesting to see how such ideas are received by the cytogenetic world.

METABOLIC DISEASES

# Vitamin $B_{12}$ Dependency

from our Medical Biochemistry Correspondent

INBORN errors of metabolism occur when an abnormal gene causes the production of an enzyme protein so different from the normal enzyme that it has lost its catalytic activity. The consequences of this loss may be slight, showing up only when certain drugs are administered, or they may be lethal. Identification of the block often reveals a lot about normal metabolism, and suitable treatment can sometimes enable people to live normal lives if the condition is detected very early.

An interesting new condition which was described last year now seems to be treatable if the patient is given large doses of vitamin $B_{12}$. Rosenberg, Lilljeqvist and Hsia (*New England J. Med.*, **278**, 1319; 1968) reported that a retarded eight month old boy with metabolic acidosis was excreting large quantities of methylmalonic acid and long chain ketones in his urine. At times his blood also contained a high concentration of glycine. High concentrations of protein in the diet or administration of the branched chain amino-acids valine and isoleucine increased the quantities of methylmalonic acid and ketones in the urine. Methylmalonic acid usually appears in the urine in large amounts only in vitamin $B_{12}$ deficiency, but this child showed no signs of the usual anaemia and his serum contained reasonable amounts of vitamin $B_{12}$. They postulated that this condition of methylmalonic aciduria was caused by a defect in the $B_{12}$-dependent enzyme which

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