REVIEWS

THE GENETICS OF MAN. A review of ten books on Human Genetics. C. D. Darlington.

The task of genetics which now faces us is to use our understanding of heredity and variation as a means of defining the relations of organisms with their environments—and often with their past and future environments as well. Little less than a total picture of life is thus offered to us as our goal. The different methods by which we approach this goal vary from one organism to another and for a long time man had seemed to be the most difficult of all to approach.

Why? Until recently where man was concerned the methods of Galton and Mendel stood in lonely isolation. The possibilities of chromosome study were unrealised. The uses of biochemistry were undeveloped. The history of man, the geography of his dispersal, the origin of his breeding systems, were all unexplored. His relations with infectious disease, and with the various agents he used to combat it, the role of natural selection and the effects of artificial medical selection, these were all problematical and disconnected.

Publications in medical genetics have however multiplied in volume and importance during these last years. They have radically changed the position. They arise from improved techniques and improved teaching as well as from the diminishing scope of non-genetic medicine. The ten publications here reviewed are evidence of the great activity which has been set on foot. What we see before us is, very clearly, a mass of detail, a body of information and, less clearly, certain guiding or warning principles.

The work of Vogel is a monumental treatment. It will provide the teacher with ample materials for reference although its weight and variable type sizes will discourage continuous reading. Clarke's book although smaller and directed to the clinician is almost as comprehensive. Both are highly condensed and deserving of high praise. But it should be said that it will be difficult for the reader, as it seems to have been for the authors, to stand back from the picture they have presented and see the whole thing in perspective. This is partly because the thing has itself grown so much bigger and its ramifications have spread so much further while the authors have been actually engaged on their task. But it is also partly because medical work on human genetics must often be perplexing to the non-medical reader and vice versa. It is worth considering why.

Genetics, including Human Genetics, is concerned with classifying effects according to their causes, the possibility of remedy being usually remote and frequently excluded. Medicine on the contrary is concerned with classifying effects with a view to their remedy. It relegates the investigation of causes to a separate department obscured by the name *ætiology* and confused by the term *congenital*. These are words which, we may note, are not included in Dr. Clarke's glossary. Medical teaching and terminology are thus imbued with a notion of the priority of results which is repugnant to genetics, and can scarcely be explained or excused to the geneticist.

We are often uneasily aware of this conflict concealed in the presentation of medical and human genetics. Although the genetic point of view which

demands a classification by causes, is continually gaining new successes, the medical point of view, which demands a classification by effects, dictates the ideas that are used and thus impedes the discovery of causes. In the extreme case of the Johns Hopkins notes (which show what happens when many authors fail to capture an editor) it leads to incoherence. Moreover in medicine, superimposed on the heredity, development, and infection known to ordinary biology, with all their variations, are other causal systems, those concerned with treatment. They include the new studies of pharmacogenetics and radiation biology, discussed by Clarke, which introduce their own genetic sequences of reaction. Thus the whole scope and purpose and internal connections of medical science are being shifted by the impact of genetics. It is not surprising therefore that the attempt to introduce genetics into medicine, urgent as it is, and still only at the beginning, encounters even greater difficulties than have been encountered in what were the purer sciences of botany and zoology.

The remedy for this situation is clear particularly from the study of Vogel. It is that a series of books is now needed covering the dozen or so main fields of interest in human genetics. The materials for such works are made available in the other volumes we have before us. Each of the six joint works, symposia or conferences (5-10) covers a wide range of medical genetic problems. The most novel of these concern the chromosomes and the biochemistry of man.

The last three items (8-10) deal almost exclusively with the recent discoveries about human chromosomes which are conveniently summarised in the two text books and the three symposia. To understand their value it is necessary first to generalise their conclusions.

Visible abnormalities in the number and structure of chromosomes in human populations may be put in three fractions according to the time at which they take effect, as follows :—

(i) *The inviable and invisible fraction* ($3x$, $2x-1$, etc.) : triploid or monosomic embryos which as a rule fail to survive gestation and lead to abortion ;

(ii) *The viable and visible fraction* ($2x+1$): trisomic and also Y-deficient embryos which at least partly survive gestation and lead to physical and sexual defects in all degrees after birth.

(iii) *The fertile and postponed fraction* : interchanged and also XXX and XYY embryos which lead to no noticeable defects in the first generation but only to abnormalities in a proportion of the succeeding generations.

The total frequency of the three classes is probably between one and two per cent. of all conceptions in man and thus agrees with that in outbreeding plants and animals generally. The mode of action of the unbalanced sex chromosome complements has however shown itself to be quite different from anything previously known. Extra Y chromosomes, beyond one, and extra X chromosomes beyond two, appear to have a reduced or even neglibible effect (tables 1 and 2).

This property is discussed by Stern (in Ashley Montagu) in a closely reasoned study showing its connection with Muller's theory of dosage compensation in *Drosophila*. It now appears however that there is a contrast between man and the fly in this respect which may be more instructive than

the comparison. For in man the lack of effect of extra X-chromosomes is combined with a condensation of these chromosomes, or part of them, in the resting nucleus. They are liable to behave as inactive heterochromatin behaves, producing what we may call, after their discoverer, Barr bodies. In *Drosophila* this situation applies not just to extra elements, as in man, but to all such elements. Thus different methods are used in the cells of different organisms for correcting the effects of genes in the sex chromosomes when they are unbalanced. This is not surprising in view of the different methods of evolutionary divergence of sex chromosomes in mammals, insects, flowering plants and elsewhere. But it raises new problems for the student of human and mammalian genetics.

To one of these a solution has been found in the illuminating hypothesis of Mary Lyon published since these books appeared. On this view the inactivation of one or other of the two X-chromosomes would be expected in female mammals. The expectation is verified, not in man, but in the cat and the mouse. But, in addition, there is an alternation of the chromosomes inactivated in cell lineages owing to which mosaics arise (M. F. Lyon, 1962, *Am. J. Hum. Gen. 14* : 135). The investigation of this mosaic action is itself likely to have far-reaching effects—beginning with the tortoiseshell cat.

There are other significant features of these chromosome unbalances. One is their connection with autosomes whose nucleolar attachment would be expected to give rise to irregular chiasma formation and hence non-pairing at meiosis. This error, which is chiefly responsible for the mongoloid 21-trisomic, largely arises at meiosis in women. A second is their connection with sex chromosomes and hence with sexual abnormalities which largely arises from failure of pairing at meiosis in men. This connection is probably due to the shortness of the pairing segment which alone provides for chiasma formation between X and Y in the heterozygous sex.

Let us not forget, in this regard, that chiasma frequency is subject to genotypic control. Therefore non-disjunction should, as Benirschke finds (*Cytogenics*, *1* : 75, 1962), run in families.

A third feature is the frequent connection of chromosome mosaics in the body with the production of telocentrics and isochromosomes. These are contributed by one or both arms of the X and perhaps, although they would usually escape detection, also of Y. They are expected to have weak centromeres with lagging at mitosis. Mosaics are indeed supposed to arise by mitotic errors but dispermy cannot always be excluded. They can apparently take the form of gynandromorphs (*e.g.* T. Kemp, 1952, *Genetics and Disease*, fig. 19).

Mosaics have two other significances which are generally overlooked. First, they demonstrate that secondary sexual characters in man have a basis which is in part localised in the cells as well as in part diffusible by hormones. Secondly, if the egg in which they occur splits into two, it will give non-concordant one-egg twins. For in a mosaic egg the two products of splitting will differ in their chromosome complements. In this case they cannot be " genetically identical " as one-egg twins are assumed to be by all our authors—including Gedda and Shields, who are as innocent of misgivings in this matter as if they were living in the time of Galton.

It may be thought that chromosomally discordant one-egg twins are too rare to matter. But what we may call cytoplasmic, or at least non-nuclear,

discordance as revealed by mirror-imaging, and also by the incidence of left-handedness, is far from rare and far from trivial (*cf.* Sutton *et al.*, 1962, *Am. J. Hum. Gen.*, *14* : 52). Whether these non-nuclear differences are increased by delay in splitting of the egg we do not know (*cf.* Bateman, 1960, *Nature*, *187* : 339). In these circumstances it is fallacious to speak of one-egg twins as identical. Nuclear differences must exist where there are

TABLE 1

Sex chromosome combinations in man classified according to their double modes of origin through non-segregation (XX/O and XY/O) and non-separation (X_3/X/O/O) at meiosis

		Male contributions (sperm)			
		O	X	Y	XY
Female contributions (eggs) †	O	die	Turner XO	die	(XY)*
	X	Turner XO	**XX**	**XY**	Klinefelter XXY
	XX	(XX)*	X_3	Klinefelter XXY	Klinefelter (X_3Y)
	XXX	(X_3)	(X_4)	Klinefelter (X_3Y)	Klinefelter (X_4Y)
Apparent sex		♀		♂	

* Normal products of abnormal origin : expected to be very rare.
† Irregularities probably increasing with the age of the mother.

Notes: (1) Normal combinations in heavy type.
(2) Rare types, from a double error, giving less than 0·1 per cent. of conceptions in brackets.
(3) The Klinefelter type becomes more emphatic as the number of X-chromosomes increases.
(4) Turner and Klinefelter sexual types can arise as gene combinations with apparently normal XX and XY chromosome complements : they have normal intelligence.

mosaics. Non-nuclear differences must exist where there is mirror-imaging of structure or behaviour.

Thus the primary opposition between heredity and environment which underlies all genetic analysis, evidently breaks down in the very comparison which is most used to establish it, that between one- and two-egg twins. What is internal and genetic in the egg before splitting is partly external and environmental to its own halves after splitting. And the two halves are not genetically identical in respect to the cytoplasm when the splitting is not symmetrical (Darlington, 1954 : *Caryologia*, *6* : 370).

Thus also it is wrong to conclude that differences between one-egg twins are always and entirely due to the action of the environment. They are often partly due, and can be entirely due, to internal causes.

Chromosome abnormalities in man thus turn out to be of profound importance equally in relation to the practice of medical diagnosis and of eugenics, to theories of human behaviour, to cellular and endocrine physiology, and to the study of evolution.

The next field of interest is that of the biochemistry of genetics in man. This now touches medicine over as wide a field as do the chromosomes.

TABLE 2

Sex chromosome combinations classified according to their character and consequences

X \ Y	O	Y	YY	Barr bodies
X	XO Turner * dwarf, subsexual, sterile ±m.d. (infrequent through low viability)	XY normal ♂	XY_2†	O
XX	XX normal ♀	XXY Klinefelter ‡ oversized subsexual, sterile±m.d. (2 per cent. of all m.ds)	X_2Y_2 (as XXY)	1
XXX	X_3† ±subsexual physically variable all m.d.	X_3Y (as XXY)	—	2
X_4	X_4 (as X_3)	X_4Y (as XXY)	—	3
Apparent sex	♀	♂		

* Class includes partial deletions of X and also mosaics.

† Sexually fertile but likely to produce abnormal sex ratios and frequent abnormal progeny.

‡ Normal male embryo when in a triploid.

Notes: (1) Subsexual, with failure of development of ovaries or testes and corresponding failure of secondary sex characters.

(2) m.d., mentally deficient.

And its connections with the genetics of microorganisms, and through them with the fundamental problems of biosynthesis, are continually becoming more evident.

The biochemistry of human variation clarifies a number of fundamental genetic problems. It has revealed the specificity and localisation of the amino-acid substitutions in hæmoglobin. It has also shown the range of more diffuse changes in the amino-acid and carbohydrate defects expressed in the constitution of urine. The diverse metabolic effects of these changes may be concealed under formal discussions of dominance and penetrance and expressivity. But they may also be related to the absence of the strict mendelian situation in an outbreeding organism. And when we look at these variations in relation to the new chromosome work we see that the

investigators ought not to disregard the assumption of diverse and graded origins from the extreme specificity of individual nucleotide substitutions to gross structural change with deficiencies, position effects and recognisable whole chromosome losses. Nor ought we to disregard the fact that these gradations, represented at the levels of both the chemically specific gene and the whole chromosome, are already related to variation in human behaviour. For, as Ginsburg has very well shown (1958, *Persp. Biol. Med.*, *1* : 397) a large part of our knowledge of the genetics of behaviour in man has biochemical connections.

Summing up, the publication of these books and symposia marks a turning point in the development of genetics not only in man but also in the most general sense. For the first time we can say that in one species, which happens to be our own, genetics has established connections with the whole biology and with the whole history of the species. The possibilities of this momentous situation are thus opened for discussion and for exploitation.

1. *Lehrbuch der Allgemeinen Humangenetik*. By Friedrich Vogel. Springer, Berlin-Göttingen-Heidelberg. 1961. Pp. 753. 333 figs., 1 plate. Price DM 88 (1.59 Kg.)
2. *Genetics for the Clinician*. By C. A. Clarke. Blackwell, Oxford. 1962. Pp. 294 (with glossary). Price 47s. 6d.
3. *Twins in History and Science*. By Luigi Gedda. Charles C. Thomas, Springfield, Illinois. 1961. Pp. 240. 168 figs. Price £5.
4. *Monozygotic Twins Brought Up Apart and Together*. By J. Shields, with a foreword by Eliot Slater. Oxford University Press. 1962. Pp. 264. Price 50s.
5. *Clinical Aspects of Genetics*. Ed. F. Avery Jones. Proc. Confce. at R.C. Phys. Introd. by Sir R. Platt, March 1961. Pitman, London. Pp. 190. Price 25s.
6. *Medical Genetics* (1958-1960). Ed. V. A. McKusick. Journal Book of Johns Hopkins School of Medicine. (Seminars with bibliographies). Henry Kimpton, London. 1961. Pp. 534. 71 figs. Price 108s. 6d.
7. *British Medical Bulletin* (Vol. 17, No. 3). Human Genetics : 16 original articles. Introd. by Sir R. Platt. British Council, London. 1961. Pp. 177-263. Price 20s.
8. *Genetic Mechanisms in Human Disease*. Chromosomal Aberrations. Ed. M. F. Ashley Montagu. Thomas, Springfield, Illinois. 1961. Pp. 592. Price £7. 16s.
9. *Chromosomes in Medicine*. By J. L. Hamerton (ed.) M. L. Barr, D. H. Carr, C. M. Clarke, C. E. Ford, M. Fraccaro, D. G. Harnden, P. E. Polani, R. W. Smithells, and N. D. Symonds. Heinemann. Pp. 231. Price 40s.
10. *The Human Chromosome Newsletter*. No. 7 Ed. by D. G. Harnden and P. A. Jacobs. Medical Research Council, Edinburgh. August 1962. Pp. 25.

THE STATISTICAL PROCESSES OF EVOLUTIONARY THEORY. P. A. P. Moran. Clarendon Press, Oxford, 1962. Pp. vii + 200. 38s.

Mathematical genetics started out in a small way early in this century when such writers as Jennings, Weinberg and Bernstein made important pioneering contributions to the mathematics of various situations encountered