# PAPER 19

19. Carter, C. O. (1969). Genetics of common disorders. *Br. Med. Bull.*, **25**, 52–57

## COMMENTARY

Paper 19 is included because of the novelty of the hypothesis proposed to explain some of the common congenital malformations. The multifactorial threshold hypothesis depends on genetic predisposition and assumes an interaction between polygenic inheritance with intrauterine environmental factors. In most cases, however, very little is known about the actual mechanisms involved. Prevention of the common congenital defects should therefore become possible if couples genetically at risk could be protected from the triggering environmental factors. For this reason, individual gene loci and the environmental factors involved need to be identified (Carter, 1976).

The validity of this model has recently been questioned by Melnick and Shields (1976) who suggested 'allelic restriction' as an alternative model to account for the more common congenital malformations, in particular those occurring with a high frequency in the population and with relatively few families 'showing an atypical type of vertical transmission'.

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# GENETICS OF COMMON DISORDERS

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Genetic and part-genetic disorders may be subdivided into those determined by chromosome abnormality; those determined by mutant genes of large effect; those determined by maternal–foetal incompatibility; and those determined or partly determined by extremes of "normal" variation caused by alleles at many gene loci.

The incidence at birth of conditions due to chromosome abnormalities depends essentially on the mutation rate and the intra-uterine mortality of those affected. These conditions are nearly all severe, or at any rate substantially reduce reproductive fitness, and so there are few second-generation cases. Such disorders are not uncommon at conception and, since major chromosome anomalies are present in about 1 in 4 spontaneous abortions, it may be estimated that about 1 in 25 conceptions is affected by such a major chromosome abnormality. Because of this high intra-uterine loss, only a minority of conditions due to chromosome anomalies have an incidence of the order of 1 in 1,000 or more at birth. This minority includes Down's syndrome and the sex-chromosome anomalies, Klinefelter's syndrome and the XXX syndrome.

Single-gene-determined conditions, if at all serious, are also likely to have their incidence largely determined by the mutation rate at the gene locus concerned. Gene mutation rates are known to be low; few, if any, are higher than 1 in 10,000. Therefore of the individual conditions caused in this way, if serious, almost all have an incidence of less than 1 in 10,000. Milder single-gene conditions may have a high incidence; there is reasonable evidence, for example, that Dupuytren's contracture, which has a population incidence of almost 1 in 6, is a dominant condition (Ling, 1963). The few serious single-gene-determined conditions that have incidences of more than 1 in 1,000 are those where there is heterozygote advantage. A proved example is sickle-cell anaemia, where the heterozygote advantage is in resistance to malaria; and a probable example is congenital microcytosis. In Britain the commonest serious single-gene-determined disorder is cystic fibrosis of the pancreas, which has a population incidence in this country of the order of 1 in 2,000 (Pugh & Pickup, 1967; Hall & Simpkiss, 1968).

Mother–child incompatibility is also a mechanism which could give conditions with an incidence of more than 1 in 1,000, as it does with haemolytic disease of the newborn. Recently and remarkably it has been shown that sensitization of the rhesus-negative mother by the rhesus-positive child is largely preventable (Clarke, 1968).

The genetic element in most common disorders, however, is neither chromosome abnormality nor mutant gene of large effect, but very probably an underlying polygenically[1] determined and continuously distributed genetic predisposition with a threshold beyond which individuals are at risk. Conditions determined in this way may be persistently common even if those affected have a low reproductive fitness, provided that there is also selection against extreme deviants for the genetic predisposition in the direction opposite to that of those affected with the disorder.

The hypothesis of polygenic inheritance has been made more plausible in recent years by the discovery of polymorphism at many gene loci—that is to say that, at many gene loci, allelic genes are present with frequencies that cannot be readily explained by mutation (Harris, 1966; Lewontin, 1967). It is almost inevitable with such polymorphism that variation for any character which is not a direct product of gene action will have a continuous distribution that is polygenically determined. It is also very probable that, where many genes are concerned, the phenotypic expression of some at least of them will vary with differences in the environment.

## 1. Polygenic Variation: Continuous and Discontinuous

Polygenic inheritance is best established for characters showing continuous variation, such as stature, intelligence or blood pressure. Here, however, extremes in normal variation will not always be regarded as disease. The very short and the very tall probably have reduced physical and physiological efficiency, but are not considered to have any disease. Individual types of dwarfism are recognized as diseases, but here, as in achondroplasia or the severest forms of spondylo-epiphysial dysplasia, inheritance is due to single genes. As regards intelligence, the label of mental retardation is given to the subnormal and this label has social relevance, but is artificial; and, once again, when pathology is present the abnormality is usually determined by a single gene or by environmental factors. In the case of blood pressure, the label hypertension is given for extreme deviations to the right of the distribution; such a label has clinical and prognostic significance, but again is artificial except where this hypertension is secondary to renal or other abnormality (Hamilton, Pickering, Roberts & Sowry, 1954), or where there is (as some have argued, Platt (1959)) evidence that the hypertension is due to a single-gene effect.

In recent years, however, it has become apparent that some discontinuous traits that are clearly pathological appear likely to be inherited as the result of a polygenic predisposition and a threshold beyond which individuals are at risk. Environmental factors also play a part in the aetiology of almost all these conditions. More than 30 years ago, Wright (1934) showed that polydactyly in the guinea-pig was probably inherited in this way. He concluded that alleles at at least 4 gene loci were involved.

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[1] Such genetic predisposition has been called "polygenic" or "multifactorial". I prefer to use the term "polygenic" with reference to the genetic predisposition and the term "multifactorial" to include environmental as well as the genetic factors. The term polygenic is not intended to imply the existence of any special class of genes called polygenes.

### 2. Common Congenital Malformations

Examples of common conditions that appear to be determined in this way are provided by those congenital malformations that have an incidence at birth of at least 1 in 1,000. These are now the predominant cause of stillbirth and of infant mortality. The common malformations in Britain are listed in Table I, with their approximate incidence per 1,000 total births and their sex ratio. There is, however, much racial and geographical variation in the incidence of congenital malformations (Stevenson, Johnston, Stewart & Golding, 1966).

**TABLE I. Malformations with incidences of at least 1 in 1,000 total births**

| Malformations | Incidence/1,000 | Sex ratio (male : female) |
|---|---|---|
| Down's syndrome | 2 | 1.0 |
| Cleft lip (± cleft palate) | 1 | 1.8 |
| Pyloric stenosis | 3 | 5.0 |
| Talipes equinovarus | 3 | 2.0 |
| Congenital hip dislocation | 1 | 0.15 |
| Spina bifida cystica | 2.5 | 0.8 |
| Anencephaly | 2 | 0.4 |
| Congenital heart defects | 4 | 1.0 |

Down's syndrome is a case apart, being determined by a chromosome abnormality. The genetics of the other conditions have much in common and their family patterns strongly suggest polygenic inheritance interacting with environmental factors.

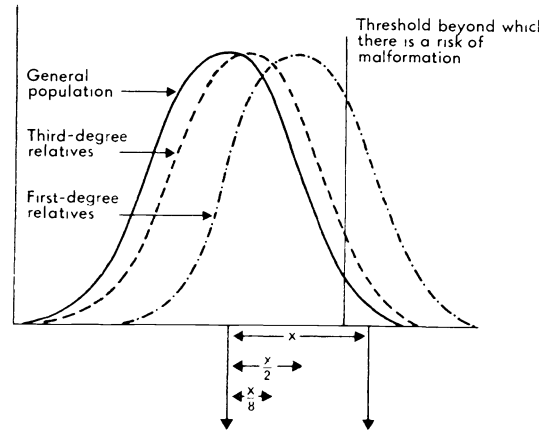
The best family data available are those for cleft lip and palate, since reliable family histories are fairly easy to obtain, and almost all cases come to operation, so that the affection in relatives is readily documented. Three large-scale studies are available, from Denmark (Fogh-Andersen, 1942), Utah (Woolf, Woolf & Broadbent, 1963) and from London (J. A. F. Roberts, A. Buck and C. O. Carter, personal communication, 1968). The London study was in particular designed to provide information on offspring of index patients. The findings are shown in Table II.

This family pattern is not easily interpreted as being due to single-gene inheritance. Recessive inheritance is made unlikely by the close resemblance of the proportion of sibs and of children affected. Dominant inheritance is made unlikely by the sharp fall in the proportion affected as one passes from monozygotic co-twins to first-degree relatives (represented by sibs and children) and again as one passes from first- to second- (represented by aunts and uncles, and nephews and nieces) to third-degree relatives (represented by first cousins). With dominant inheritance one may expect a reduction by about 0.5 with each of these steps, since the proportion of relatives sharing the dominant gene with index patients is unity for monozygotic co-twins, 0.5 for first-degree, 0.25 for second-degree and 0.125 for third-degree relatives. (Few patients would be affected as the result of a fresh mutation, since on the hypothesis of dominant inheritance it must be assumed that the manifestation rate is low.)

**TABLE II. Proportion of relatives affected in three large family studies of cleft lip (with or without cleft palate)**

| Relatives | Denmark (%) | Utah, USA (%) | London (%) | Incidence relative to that of the general population |
|---|---|---|---|---|
| First-degree relatives | | | | |
| Sibs | 4.9 | 4.6 | 3.2 | ×40 |
| Children | — | 4.3 | 3.0 | ×35 |
| Second-degree relatives | | | | |
| Aunts and uncles | 0.8 | 0.7 | 0.6 | × 7 |
| Nephews and nieces | — | 0.8 | 0.7 | × 7 |
| Third-degree relatives | | | | |
| First cousins | 0.3 | 0.4 | 0.2 | × 3 |

**FIG. 1. Model for polygenic inheritance of cleft lip, with, or without, cleft palate**




x: deviation of mean of malformed individuals from the population mean

The findings, however, are very much those that one would expect with polygenic inheritance with a threshold beyond which there is a risk of malformation (see fig. 1). The distribution of the polygenic predisposition for the general population will on an appropriate scale be Normal,[2] and this is illustrated by the continuous curve in the diagram. First-degree relatives will have a curve of distribution about a mean approximately half-way between that of the general population and the index patients beyond the threshold. This will bring a substantial proportion of them beyond the threshold, and so at risk of developing the malformations. Second-degree relatives would have a distribution about a mean shifted to the right by approximately one-quarter of the distance between the mean of the general population and the index patients. Third-degree relatives would have a distribution about the mean approximately one-eighth of the distance from the population mean towards that of the index patients. This representation is over simplified. The distribution in relatives would not be Normal on the scale which gives Normality in the general population (Edwards, cited by Falconer, 1967); the variance in relatives would probably be rather less than in the general population; the manifestation rate would probably increase as the geno-

[2] The capital letter N here and elsewhere in this paper refers to observations whose statistical variation is describable by the Normal (Gaussian) Distribution Function.—ED.

**TABLE III. Family patterns for some common congenital malformations**

| | Cleft lip with or without cleft palate | Talipes equinovarus | Congenital dislocation of hip (males only) | Congenital pyloric stenosis (females only) | Spina bifida and anencephaly |
|---|---|---|---|---|---|
| General population | 0.001 | 0.001 | 0.002 | 0.005 | 0.008 |
| Monozygotic twins | × 400 | × 300 | × 200 | × 80 | — |
| First-degree relatives | × 40 | × 25 | × 25 | × 10 | × 7 |
| Second-degree relatives | × 7 | × 5 | × 3 | × 5 | — |
| Third-degree relatives | × 3 | × 2 | × 2 | × 1.5 | — |

type deviates further beyond the threshold; but the errors introduced are not large.

On this simple hypothesis, assuming that 3 in 1,000 of the population are beyond the threshold and that one of the three is clinically affected (giving an incidence of 1 in 1,000), the proportion beyond the threshold of first-, and second- and third-degree relatives respectively would be approximately × 30, × 8 and × 3 that of the general population. This fits well with the findings for cleft lip and palate.

Similar, but less complete, data are available for other congenital malformations: for example, pyloric stenosis (C. O. Carter and K. A. Evans, personal communication, 1968), talipes equinovarus (Wynne-Davies, 1964), congenital dislocation of the hip (Record & Edwards, 1958; C. O. Carter and J. A. Wilkinson, unpublished work, 1968), spina bifida cystica and anencephaly (Record & McKeown, 1950; Williamson, 1965; Carter, David & Laurence, 1968), and these are summarized in Table III, the data for spina bifida being those of Carter *et al.* (1968). The least complete data for relatives other than sibs are those for anencephaly and spina bifida, where family history is least reliable and documentation, for example for stillbirths, is difficult for second- and third-degree relatives.

Modern family studies of specific congenital heart malformations are only just becoming available (Zoethout, Bonham Carter & Carter, 1964; Nora, McNamara & Fraser, 1967; Emanuel, Nichols, Anders, Moores & Somerville, 1968; E. M. Williamson, personal communication, 1968; Wilkins, 1969). These and older studies based on questionnaires (Lamy, de Grouchy & Schweisguth, 1957; Campbell, 1965) indicate recurrence risks to later sibs of between 1% and 3%. For example, Nora *et al.* (1967) found the risk of similar defect in the sibs of patients with atrial septal defect (ostium secundum type) to be a little over 3% and E. M. Williamson (personal communication, 1968) found a proportion of a little over 3% affected in both sibs and children. The population incidence of atrial septal defect is estimated to be about 0.5 per 1,000 births, so that first-degree relatives have about 60 times the population incidence.

### 3. Tests for Polygenic Hypothesis

Family patterns determined by polygenic inheritance have several other features which may be used to test the hypothesis (see Penrose, 1953; Edwards, 1960; Carter, 1961b, 1964; Newcombe, 1964; Vogel & Krüger, 1967).

i. The risks in relatives compared with those of the general population would be expected to be absolutely greater, but proportionately less, as the population incidence of the malformations increases; this is well seen in Table II. For example, assuming the higher population incidence, 2/1,000 beyond the threshold, and again a manifestation rate of those at risk of 1 in 3, which would be appropriate for congenital dislocation of the hip in females, the expected relative risks for first-, second- and third-degree relatives would be × 25, × 6 and × 2.5. This is similar to the ratios actually observed. Assuming a still higher population incidence, 5/1,000, and again a manifestation ratio of 1 in 3, which would be appropriate in males for infantile pyloric stenosis, the relative incidences would be × 12, × 4 and × 2, which are again in good agreement with those actually found.

As the proportion of the population at risk rises, the decline in the proportion affected as one passes from first- to second- to third-degree relatives becomes progressively less useful in distinguishing polygenic from dominant inheritance. This test would be more useful for neural-tube malformations in a low-incidence area such as Japan than in the United Kingdom.

ii. In contrast to the usual situation with single genes, in polygenic inheritance the risk to relatives will vary from family to family. Therefore the risk will be increased where there are already two affected in a family. This is seen, for example, with anencephaly and spina bifida, where the risk to later offspring is about twice as great for mothers who have already had two affected children, compared with those who already have had one such child (Carter & Roberts, 1967). In contrast, with a recessive condition such as cystic fibrosis of the pancreas the risk remains 1 in 4 whether the mother has already had one, two or even three affected children. Again, with cleft lip, where parent and one child is already affected the risk to subsequent children rises from 3–4% to over 10% (Fogh-Andersen, 1942). With pyloric stenosis also there are indications of a substantial rise in the risk where one parent and a child are already affected.

iii. With polygenic inheritance one would expect that the more severe degrees of malformation would carry a relatively higher risk to relatives. This is seen, for example, with cleft lip. When combining the Danish data of Fogh-Andersen and the London data (J. A. F. Roberts, A. Buck and C. O. Carter, personal communication, 1968), the risk to subsequent sibs after a child with unilateral cleft lip is about 2.5%, but after bilateral cleft lip and palate is nearly 6%. Similarly with aganglionic megacolon (Hirschsprung's disease) the risk to sibs increases with the length of the aganglionic segment (Bodian & Carter, 1963).

iv. An extension of the test of increasing risk with increasing severity is provided by the malformations in which the sex ratio deviates markedly from unity. Patients of the more rarely affected sex will tend to be more extreme deviants from the population mean and so the risk to their relatives will be correspondingly higher (Carter, 1961a). In pyloric stenosis the ratio is 5 males to 1 female and the proportion affected among relatives of girl index patients is more than three times higher than amongst the relatives of affected boys. This is best seen in the offspring of index patients, and the data (C. O. Carter and K. A. Evans, personal communication, 1968) are summarized in Table IV.

v. An increase in parental consanguinity is also to be expected with polygenic inheritance, since a consanguinous marriage is a form of assortative marriage. For common conditions the small increase in parental consanguinity

**TABLE IV. Proportion of those affected among children of patients with pyloric stenosis**

| | Affected, and total, children of patients with pyloric stenosis | |
|---|---|---|
| | Sons | Daughters |
| 330 boy index patients | 19 : 346 (5.5%) | 8 : 337 (2.4%) |
| 239 girl index patients | 20 : 103 (19.4%) | 7 : 96 (7.3%) |

expected, a 50–100% increase, is little less than that expected for recessive conditions, though with rare conditions recessive inheritance implies much higher consanguinity rates.

### 4. Common Diseases

Family data on the common diseases of adult life have not on the whole been collected as extensively as for congenital malformations, and such studies involve difficulties in definition, diagnosis, and correction for the unexpired risk of developing the disease, which hardly arise with congenital malformations. Nevertheless the family patterns in several instances appear similar to those for the common malformations and examples are provided by the major psychoses, early-onset ischaemic heart disease, rheumatoid arthritis, ankylosing spondylitis and diabetes mellitus.

*Major psychoses.* The data on schizophrenia and manic depressive psychosis (Stenstedt, 1952; Kallmann, 1953; Ödegård, 1963; Winokur & Pitts, 1965) suggest that for these two major types of psychosis, the risk to first-degree relatives is of the order of 10–15%. In comparison each has a life-time population risk of 5–10/1,000. In the case of schizophrenia this risk to children applies even when they have been separated from the schizophrenic parent at birth (Heston, 1966). The risk to sibs appears to be about doubled when one parent is also affected (Winokur & Pitts, 1965). The proportion of monozygotic co-twins of index patients also affected is of the order of 50%. Both the family data and the twin data show that the polygenic predisposition tends to be specific for one or other major type of psychosis and not for both. The reproductive fitness of the patients, especially of schizophrenics, is reduced. It has been plausibly argued for schizophrenia (Irving, Gottesman & Shields, 1967) that this and other findings are more consistent with polygenic than single-gene-determined inheritance. The same arguments apply with equal strength for manic depressive psychosis.

*Ischaemic heart disease.* The studies of Gertler & White (1954), Rose (1964) and Suri, Singh & Tandon (1966) suggested that the first-degree relatives of patients with ischaemic heart disease had only about 2.5 times the risk of a control population of dying of ischaemic heart disease. However, a more elaborate analysis (Slack & Evans, 1966) has shown that, for unselected patients with early-onset ischaemic heart disease ("early onset" being defined as before the age of 55 years in men and 65 years in women), deaths in first-degree relatives were on average about 6 times the expected number in the general population. It is known that, in a small proportion of cases, such a disease is associated with a single-gene-determined condition, "pure hypercholesterolaemia" (Epstein, Block, Hand & Francis, 1959; Nevin & Slack, 1968). These cases, however, are not sufficiently common to contribute much of the familial concentration for unselected patients (Slack & Evans, 1966). For the years under consideration the risk of death from early-onset ischaemic heart disease in the general population is about 15/1,000 in males and 10/1,000 in females, so that the sixfold increase in first-degree relatives is compatible with a polygenic element in the—no doubt multifactorial—aetiology of ischaemic heart disease.

*Rheumatoid arthritis.* Family data for rheumatoid arthritis are available from a number of surveys (Miall, 1955; Lawrence & Ball, 1958; de Blécourt, Polman & de Blécourt-Meindersma, 1961), as aiso are data for ankylosing spondylitis (Stecher, 1957; de Blécourt *et al.* 1961; Emery & Lawrence, 1967). For rheumatoid arthritis, with a population incidence of perhaps 20–30/1,000, Lawrence and Ball found an increase of close to fourfold in first-degree relatives, and the results from the other two studies are comparable. For the rarer condition, ankylosing spondylitis, the risks in relatives compared to those in the general population are understandably higher. The population incidence in north-east Europe is of the order of 2/1,000 in men and 0.4/1,000 in women. In the 1961 survey of de Blécourt *et al.*, based on 74 male and 26 female index patients, the incidence in relation to that of the general population was × 35, × 10 and × 3 the population incidence in first-, second- and third-degree male relatives and about × 100 the population incidence in first-degree female relatives. The situation appears similar to that with pyloric stenosis, but a full comparison cannot be made because the relatives were not subdivided according to sex of index patient. Recently Emery & Lawrence (1967) have reported a further family study in which approximately 7% of first-degree male and 2% of first-degree female relatives were affected with clinical ankylosing spondylitis, i.e., approximately × 35 and × 50 the incidence in the general population of that sex. These authors make the point that the best genetic hypothesis to explain the finding is a polygenic one, and they apply Falconer's techniques (see section 5) to estimate "heritability".

*Diabetes mellitus.* The early studies of the family histories of patients with diabetes mellitus were interpreted as indicating that the condition was determined by a single gene, some regarding the condition as a dominant and others as a recessive one. Pincus & White (1934) suggested that diabetes was a recessive condition. Harris (1949) suggested that those patients with early onset (before the age of 40 years) were homozygotes and those with later onset were heterozygotes for the gene responsible. Lamy, Frézal & de Grouchy (1957) put forward an essentially similar hypothesis: that patients with severe diabetes, whether of early or late onset, were homozygotes and milder cases were heterozygotes. Later, however, they preferred a hypothesis closer to polygenic inheritance (Lamy, Frézal & Rey, 1961). Single-gene inheritance is perhaps an attractive idea when the abnormality is suspected to be in a single plasma protein. Single-gene determination, however, has never seemed plausible to clinicians. The absence of any clear dividing line between normal and abnormal blood-sugar curves, the change in the renal threshold for glucose and the change in blood-sugar curve with increasing age, the absence of any suggestion of bimodality in the sugar-tolerance curves of either controls or the first-degree relatives of diabetics (see, e.g., Thompson, 1965), the obvious importance of environmental factors (especially diet) in the cases of late onset, all suggest that, if a single gene were concerned, its manifestation

must be much influenced by other genetic and by environmental factors.

Recessive inheritance is, in fact, made unlikely by the consistent finding that the incidence of diabetes in parents and children (when corrections have been made for age) is as high as in sibs. Dominant inheritance is made unlikely by the finding that the risks to sibs of diabetic patients is more than twice as high when one parent is also diabetic as when neither parent is diabetic (Harris, 1949; Steinberg & Wilder, 1952; Thompson & Watson, 1952). When both parents are diabetics the risk is further increased; thus Cooke, Fitzgerald, Malins & Pyke (1966) found that 7 in 57 (12%) children of couples with diabetes of onset before the age of 40 are diabetic.

Polygenic inheritance is compatible with the family findings, though it may well be that the factors concerned with early-onset severe diabetes are different from those in late-onset mild diabetes. The population incidence in the survey of the family history of diabetes made by a working party in Birmingham (College of General Practitioners, 1965) is shown in Table V below, by age-group compared with the incidence in siblings. The age distribution in siblings is not shown, but it is assumed to be similar to that in the index patients. Similar ratios are seen in the study of Simpson (1964), in which the age distribution of the sibs, but not the index patients, is given.

**TABLE V. The relative incidence of known diabetes in sibs of diabetics and in the comparable general population**

**(Data from College of General Practitioners (1965))**

| Age-group (years) | Population incidence per 1,000 | Relative incidences in sibs of diabetics |
|---|---|---|
| 0–29 | 2 | × 24 |
| 30–49 | 4 | × 6 |
| 50–69 | 13 | × 2.4 |
| 70–80 | 21 | × 1.5 |

### 5. Correlation between Relatives and Heritability

Falconer (1965) has shown that it is possible to estimate the regression of relatives on index patients (or correlation of relatives and index patients) for the liability to disease (liability including both genetic and environmental predisposing factors) for threshold characters, if it be assumed that the genetic element in the liability is polygenic. The information needed is the incidence of the condition in the general population and the incidence in particular types of relatives. Assuming that the liability is normally distributed (and as the scale is an arbitrary one it may be assumed to be such that the distribution will be Normal), from the incidence in the general population the deviation of the threshold from the population mean may be estimated, also the mean deviation of affected individuals. Further, Falconer (1965) has noted that, with due reservations, it is then possible to make estimates of the heritability of the condition in the sense of the proportion of the variance of the liability which is determined by additive genetic variance. For example, for a condition where the variation in liability is entirely determined by additive genetic variance, and so heritability is 100%, the regression of first-degree relatives on index patients would be 0.5, for second-degree relatives 0.25, and for third-degree relatives 0.125. This corresponds to the number of genes that the relatives are likely to have in common with the index patients. When the regressions are less, the estimated heritability is correspondingly reduced below 100%. Any difference in the variance in the general population and the relatives does not affect this estimate of regression (Smith, cited by Falconer, 1967).

Using Falconer's procedure on cleft lip and palate, and taking the figures shown in Table II, the regression of first-degree relatives on the index patients would be 0.38, for second-degree 0.19, and for third-degree 0.084, implying heritabilities of 76%, 76% and 67%. The incidence in monozygotic twins, based on only small and perhaps unrepresentative series, also suggests a heritability of the order of 80%.

Estimates of heritability from sib regressions will be too high if non-additive genetic variance (due to dominance or epistasis) is present; however, this is not the case with regression of child on index patient. Perhaps more important in human material, the estimates of heritability will be too high if there is similarity of relatives due to the environmental differences within families being less than those between families. The greatest effect of this source of error will be on the regression for monozygotic co-twins, then for sibs, then for children and least perhaps for second- and third-degree relatives. In the case of cleft lip, however, estimates are similar for all types of relatives.

On the same principle, estimation of regression coefficients for first-degree relatives for some of the other common conditions considered above are: pyloric stenosis, males only, 0.3 (heritability about 60%), females only, 0.45 (heritability about 90%); talipes equinovarus, 0.3 (heritability about 60%); congenital dislocation of the hip, females only, 0.35 (heritability about 70%); spina bifida cystica, 0.3 (heritability about 60%). For the major psychoses, a population incidence of 1% and a risk for first-degree relatives of 10% implies a regression coefficient of about 0.4 and a heritability of about 80%. For early-onset ischaemic heart disease, a population risk of about 1% and a sixfold increase in first-degree relatives implies a coefficient of 0.3 and a heritability of about 60%. For rheumatoid arthritis, the findings of Lawrence & Ball (1958) imply a regression of about 0.35 and a heritability of about 70%. For ankylosing spondylitis, a regression of 0.4 for males implies a heritability of about 80%. For diabetes mellitus, a regression of about 0.35 implies a heritability of about 70% for cases with onset before the age of 30 years, but a regression of 0.15 implies a heritability of only about 30% for cases with onset of the condition after the age of 50–70 years.

While these estimates of heritability are to be considered as upper limits of the true heritability, they do indicate that the genetic component of all these common diseases, if polygenic, may be a substantial one.

### 6. Conclusions

The investigation of the genetics of common disorders should not stop at the stage of the polygenic hypothesis. There is a need to discover the individual gene loci involved. In the case of duodenal ulcer, the *ABO* locus and the secretor locus are known to be involved, but they account for only about 3% of the increased risk to sibs (Roberts, 1965). There is also need to discover the mechanisms by which genetic predisposition acts, the nature of the additional environmental factors, and the way these interact with the genetic predisposition. Some success has been achieved in these last aims, for example,

with congenital dislocation of the hip (Carter & Wilkinson, 1964). Much too is known of the additional environmental factors concerned in the aetiology of ischaemic heart disease.

Where the heritability of a condition is high, however, it implies that ultimate prevention will usually, though not necessarily, depend on special environmental prophylaxis for those known to be genetically predisposed, rather than on measures of prophylaxis applied to the whole population. Further, where inheritance is polygenic it is unlikely, in contrast to the situation with single-gene-determined diseases, that a search for a single biochemical abnormality underlying the condition will be profitable (Vogel & Krüger, 1967).

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