HEREDITY IN GASTROENTEROLOGY: A REVIEW

BY

R. B. McCONNELL

From the Department of Medicine, University of Liverpool, and the United Liverpool Hospitals

Attention is drawn to the more important genetic principles which have a bearing on medical problems, and stress is laid on the careful planning necessary if a clinical genetic research project is to produce worthwhile results. There follows a review of the present state of knowledge concerning heredity and various gastroenterological disorders, with suggestions of the lines of research most likely to be rewarding. The view is expressed that the most urgent need is for more knowledge of the genetics of the physiological processes of the gastrointestinal tract.

Physicians have long realized that heredity plays a part in certain conditions. Up to the beginning of this century it was all rather vague, and nothing much could be said other than that in different conditions heredity was either very strong, or only moderately so, or perhaps unimportant. During the past 60 years, however, the study of the mechanisms of heredity, the science of genetics, has made great progress. At first genetics was simple and concerned the effect produced by single genes; applied to medicine it explained the inheritance of many rare diseases which are due to single genes. Gradually it became more complicated and the application of the principles of polygenic inheritance and population genetics began to explain how heredity works in some of the more common conditions. Quite recently the advent of biochemical genetics has uncovered the actual enzymic defect underlying some of the rare single gene diseases, and it may not be long before important advances are made in our understanding of the basic biochemical mechanisms underlying susceptibility to common diseases. Probably the first break through will be in thyroid disorders but diseases of the stomach may not be far behind.

GENETIC PRINCIPLES RELEVANT TO MEDICINE

In this section attention will be drawn to the more important genetic principles concerned with disease and some clinical research techniques and their pitfalls will be described. For more detailed descriptions of these subjects there are available three excellent works (Roberts, 1959a; Childs and Sidbury, 1957; Graham and Lilienfeld, 1958).

GENE ACTION.—Even though the theory of one gene one enzyme is a good working hypothesis and the presence or absence of some genes can be detected by the presence or absence of some chemical substance such as the different haemoglobins or blood group antigens, it must be realized that most genes do not manifest themselves so specifically. Their actions can be modified by numerous factors so that their end-results are variable and lacking in strict specificity (see polyposis). These modifying factors may be environmental or may be other genes, and because of them there may be considerable differences in the clinical picture in different families or even within a family.

A gene may be responsible for an enzyme which is concerned in several metabolic processes and it can, therefore, produce manifold effects. Thus many syndromes affecting several systems of the body have been found to be caused by one gene, for example, galactosaemia with mental deficiency, cataract, hepatomegaly, and jaundice. On the other hand, clinically similar effects can be caused by different genes (see glycogen storage diseas)e.

Another point which must be borne in mind is that environmental influences may simulate the action of genes and produce results (phenocopies) comparable with those effected by genes. This leads to the possibility that amongst the patients with a particular disease there may be some cases genetically determined and others environmental in origin (see pyloric stenosis in infancy). Consequently, genetic entities and clinical entities must be clearly differentiated. A clinical entity or phenotype is arrived at by examining the individual, but a genetic entity or genotype can only be established by a family study.

SINGLE GENE INHERITANCE.—Most conditions which are inherited in a dominant manner are either trivial or without effect on the reproductive rate, or

else they are exceedingly rare. Recessive conditions are usually much more severe and may even be lethal in childhood, the gene being transmitted from generation to generation by the unaffected heterozygotes. In addition, recessive conditions can be relatively common; if the heterozygotes have some selective advantage over both types of homozygote, the gene can reach a high frequency in the population. The best worked out example of this state of affairs in Man is that of the haemoglobin S gene which in certain parts of Africa results in 7 to 8% of children born being affected by the fatal sickle-cell anaemia. The term "polymorphism" is used when two or more forms exist in a population at frequencies above that which could be maintained by recurrent mutation, and the principles underlying balanced polymorphism and natural selection in general are probably of great importance in resistance and susceptibility to disease. This subject will be mentioned again when dealing with the inheritance of fibrocystic disease of the pancreas.

It is becoming more and more apparent that at many genetic loci of Man, the characters determined by the different forms of the gene, the alleles, are neither dominant nor recessive to one another, or at least that dominance and recessiveness are not absolute. Often in the heterozygote both of the alleles are producing an effect, and in double dose in the homozygote an allele has double the effect. When studying a recessive condition in a family it may, therefore, be worth while examining the unaffected relatives very carefully to see if they fall into two classes for some morphological or biochemical trait. If they do, and in a ratio of 2 : 1, that trait may be the single dose expression of the allele which causes the condition when in double dose (see fibrocystic disease of the pancreas).

The genetic terms "expression" and "penetrance" are often used rather loosely in medical papers. It would seem best to reserve the term expression for variability of manifestation, and penetrance for whether or not anything abnormal can be detected. Thus to state that a gene has variability of expression or incomplete expression would mean that its presence in an individual can always be detected but the clinical picture may be incomplete or variable. A gene with incomplete penetrance, on the other hand, could occasionally have no obvious effect whatsoever, and thus, in a pedigree a generation could be unaffected. It is with these meanings that the terms will be used in this paper. Variability of age of onset, like expression and penetrance, is usually due to differences in the environment or to other genes; only if the age of onset falls into two distinct groups is it likely to be determined by single and double doses of the gene.

POLYGENIC INHERITANCE.—In none of the common diseases of Man in which heredity seems to play a part is the pattern of inheritance clear cut. They tend to occur more commonly in some families than others, but many cases occur quite sporadically with no family history and, even when there is a strong family history, the distribution is not of simple mendelian type. The reason for this is that not only are environmental influences important, but that several genes located on different parts of the chromosomes are involved: their inheritance is "polygenic".

One may ask: "What is the difference between polygenic inheritance and inheritance by single genes which are very subject to the influence of other modifying genes?" The difference is only one of degree and tnere is probably no clear-cut dividing line between the two types of mechanism. The writer prefers to use the term polygenic for both types and, in a polygenic system, would describe as a "major" gene any gene which is of great importance in determining the presence or absence of the condition, and, for instance, regards susceptibility to duodenal ulcer as polygenically inherited, probably with several major genes. On much the same evidence, however, Pisot, Dubarry, and Duhamel (1957) regard the inheritance as recessive, involving two pairs of genes, with constitutional and environmental factors modifying the manifestation of the disease. The difference between the two interpretations may only appear semantic, but it implies a different approach to the subject of further research and the importance of identifying the various major and minor genes involved.

Polygenic inheritance is the basis of the inherited element in most normal human characters. When several genetic loci are involved in a character one does not find the clear-cut differences found with single gene inheritance. For instance, with height, which is polygenically determined, a population is found to contain a whole range of heights: it is a graded character with a normal distribution curve tailing off to very small people at one end and very tall at the other, but where one draws the limits of normal is rather arbitrary. Since some common diseases have polygenic inheritance, one might expect them also to be graded characters with no clear-cut dividing line between health and disease. This is obviously not so in the case of cancers in which there must be a critical point, but it may be so in conditions such as duodenal ulcer.

To revert to the illustration of the inheritance of height, the offspring of two tall people will tend to be tall and those of two short people to be short. Since many genetic loci are involved it is quite possible for a short person to have a number of

genes which tend to make him tall but which are swamped by a larger number of genes tending to shortness. The offspring of two such short people would, in fact, on the whole be short, but an occasional one might receive all the tall genes from each parent and be a tall person. Applying this to medicine, one can see that with polygenic inheritance it would be quite possible for a disease to occur in someone with no family history of the condition, even though that disease is wholly genetically determined and quite independent of environmental influences. In practice, however, one should not separate the action of genes from the environment, and a disease can be expected to result from both genetic and environmental influences. The relative size of the genetic and environmental components would vary from case to case, and a few cases might be wholly genetic and a few almost entirely environmental.

CLINICAL GENETIC RESEARCH TECHNIQUES

There are three types of technique available to study whether or not heredity is involved in the aetiology of a disease. They are all fraught with possibilities for the introduction of bias and inaccuracy, and results have to be examined most critically before being accepted at their face value. Before undertaking clinical genetic research, physicians would be well advised to study this aspect of the subject thoroughly, and also seek the advice of an expert in the field.

TWIN STUDY.—The theory underlying twin studies is that if the concordance ratio is higher for monozygotic than for dizygotic twins, a genetic factor is operating. In general this is probably so, though occasionally a higher concordance rate in monozygotic twins may be due to their having a more uniform environment than dizygotic twins. There are, however, more important reasons why papers giving twin analysis may be misleading; for instance, there are the inaccuracies involved in deciding the zygosity of twins, and the possibility that there is a third type, the product of one ovum and two sperms (Platt, 1956). In addition authors often survey the literature in order to get large enough numbers for analysis and it is possible that cases of concordance among "identical" twins are reported more readily than concordance in "non-identical" twins. The ascertainment of the twins by selecting pairs one of whom is ill is also liable to lead to bias. Harvald and Hauge (1956) are using a technique which should avoid the biases inherent in most other twin studies: they are following up a sample of *all* the twins born in Denmark between 1870 and 1910.

PEDIGREE STUDY.—The investigation of the presence or absence of disease over two or three generations of one or a small series of families is of value if the disease is rare, even though information obtained from family members is often inaccurate and may be biased. With common diseases, however, this technique is rarely of value as occasional familial aggregations can be expected by chance alone, and of course, may be the result of nongenetic environmental factors.

STATISTICAL STUDY.—This involves studying the frequency of a disease in relatives of people with the disease and comparing with the frequency in relatives of people who do not have the disease, or comparing with the morbidity or mortality frequencies of the general population. There may be difficulty in eliminating bias from the selection of patients for study, and there is the problem of incomplete ascertainment, quite apart from the inaccuracies and bias of diagnosis based on the recollection of other family members; it is reasonable to suppose that individuals with a disease are more likely to know about relatives having the same disease than are unaffected individuals. The main trouble with this technique, however, is with the controls which are often not matched for age, sex, race, and socioeconomic status. A general population control may be unsuitable as the relatives of patients from a few hospitals may not be representative of an entire country. A solution to these problems may be prospective surveys, in which relatives of patients and suitable controls are followed up each year. The advantages of prospective surveys in eliminating biases have been shown in other fields to outweigh their difficulty, as for example, in the problem of maternal rubella and congenital defects (Hill, Doll, Galloway, and Hughes, 1958).

INTERPRETATION OF RESULTS.—Having definitely established that there is a familial aggregation of a disease, it remains to determine whether it is the result of genetic or environmental factors. This problem will remain difficult as long as the environmental factors in a disease are still completely unknown. Some information can be gained from study of spouses of patients; they share some of the environment but are genetically different from the patient, and, if they have consistently lower frequencies than the relatives, it would provide support for a genetic cause. The interpretation of spouse data is rendered difficult by the fact that mating is not random in human populations. Mating within social, economic, racial, and religious strata (assortative mating) has effects which cannot be accurately measured.

When some environmental factors are known, or even are known not to be of importance, the

distribution of the affected relatives in different generations may provide the answer. For instance, Doll and Kellock (1951), working on duodenal ulcer, a condition known to be independent of social class and occupation, found nearly three times the expected incidence in the fathers. They found it difficult to believe that the fathers had been equally subject to the same adverse influences in their childhood as their children were a generation later, and thought there was little room for doubt that genetic factors were responsible for the increased family incidence. In some cases useful information can be obtained from family data without controls; the study of the incidence of a condition in sibships, divided into those with both parents, one parent, or neither parent affected, can give a clue to the mode of inheritance if a major gene is operating.

IDENTIFYING THE GENES CONCERNED.—If the pattern of inheritance is in keeping with a single gene effect, a biochemical study is indicated. With polygenic inheritance a biochemical approach may also be rewarding, but the biochemical defect also is likely to be polygenically controlled and no clear-cut differences between affected and unaffected would then be found.

Apart from the genes determining rare enzymic defects there are very few commonly occurring genes of which the presence can be detected. It is perhaps remarkable that any of them have been found to be involved in disease, but the ABO blood group genes and the genes controlling secretion of the ABO blood group substances in saliva and gastric juice have been shown to be involved in gastro-intestinal diseases (Roberts, 1959b), and the genes which determine the ability to taste phenylthiocarbamide in thyroid disease (Kitchin, Howel-Evans, Clarke, McConnell, and Sheppard, 1959).

A great many diseases have been studied for a possible relationship with the ABO blood groups, but, with the possible exception of rheumatic fever and carcinoma of the uterus, none has been found and confirmed in any condition outside the alimentary tract. In addition to the established relationships with duodenal and gastric ulcer, carcinoma of the stomach and pernicious anaemia, abnormal blood group frequencies have been found in cirrhosis of the liver, diabetes mellitus, mixed parotid tumour, carcinoma of oesophagus, carcinoma of pancreas, and cholelithiasis. Further studies are needed before it can be decided whether or not these are due to chance.

HEREDITY AND PARTICULAR DISEASES

Some of the conditions which will be dealt with are not diseases solely of the gastro-intestinal tract, but they can all cause lesions in the tract. The amount of space given to a condition will depend, not so much on its frequency and importance, but rather on the degree of uncertainty or the amount of work which has been carried out or on its promise as a subject for further research. The genetic basis of susceptibility to bacterial or parasitic diseases is too large and rapidly expanding a subject for this review. Similarly the collagen diseases affecting the tract are not discussed.

To give all the references to each condition would require too much space, and those given are the most recent reports in readily accessible journals which contain a good bibliography. They are not necessarily the best or fullest articles on the subject. Occasionally, where there has been an outstandingly good article in the past and subsequent work has not added anything of importance, the older reference is given.

Before proceeding it is worth stressing again that these diseases are clinical entities and not necessarily genetic entities. Even in those conditions stated to be due to a single gene, it should not be assumed that all cases of one of them are due to the same gene. As biochemical genetic research progresses it is being shown again and again that a deficiency of any one of several enzymes can lead to the same clinical entity (see glycogen storage disease).

APHTHOUS ULCER.—The familial incidence of this extremely common condition has been investigated without an answer to the problem of whether or not heredity is concerned in its aetiology. Sircus, Church, and Kelleher (1957) found a positive family history in nearly half of their 120 patients, but only 15% had sibs affected. The general population frequency was estimated to be about 20%. On the other hand only 4·1% of the spouses were affected. Farmer (1958) found a positive family history in 39% of 121 patients and the spouse was affected in 18% of the 62 married patients.

APPENDICITIS.—Although family aggregations of appendicectomy have been noted from time to time, there does not appear to have been any statistical study made. As appendicitis may well be more common in particular types of appendix, it would not be surprising if, in fact, hereditary factors are involved. That the anatomy of the organ may be genetically determined is suggested by the report by Downs (1942) of 16 appendicectomies in 22 closely related individuals. In all those operated on there was a band of fibrous tissue binding the appendix to the outer side of the caecum and causing sharp kinking at the base of the organ with constriction of the lumen.

CARCINOMA OF COLON.—The cases of colonic carcinoma occurring in pre-existing familial polyposis are largely determined by the presence of single genes with only slight environmental influence (see polyposis of the intestines). There seems, also, to be a hereditary influence in cases occurring not in association with polyposis, and it is almost certainly polygenic (see Woolf, 1958). In at least one family there may be a major gene without whose presence the disease will not develop. Thus Richards and Woolf (1956) described a family in which 50% of one generation had small adenomatous polyps of the rectum and recto-sigmoid, of similar character, age, and sex distribution to those found in other reported studies of solitary polyps of the colon. There appeared to be a form of dominant inheritance of these polyps, and a relationship between them and the high incidence of carcinoma in the previous generation of this family.

CARCINOMA OF OESOPHAGUS.—This is one of the cancers which has been well studied from the point of view of heredity (Mosbech and Videbaek, 1955), and no evidence was found of any familial tendency. It is, therefore, remarkable that it has been shown that its development can be determined by the presence of a single gene. When Clarke and McConnell (1954) reported a family in which six members had died of oesophageal cancer and postulated a dominant form of inheritance, it is understandable that Steiner (1956) thought the finding was due to chance. Further investigation, however, brought to light an additional family with 12 cases of carcinoma of the oesophagus, and the observation that the cancer developed only in those members of the families who had tylosis (hyperkeratosis palmaris et plantaris). In fact it was calculated that 95% of the tylotics developed the cancer before the age of 65. Tylosis is due to a single gene and there is no doubt that in these families (which are probably related) an unusual and perhaps unique tylosis gene has been responsible for the oesophageal cancer (Howel-Evans, McConnell, Clarke, and Sheppard, 1958).

In the introductory section of this review it was emphasized that environmental factors can mimic a genetic disease. This is an example of a gene mimicking an environmental disease, The tumours in these families were quite indistinguishable clinically and histologically from the usual sporadic oesophageal cancers.

CARCINOMA OF STOMACH.—A great many papers have been published on the role of heredity in gastric cancer, and Graham and Lilienfeld (1958) have made an excellent appraisal of them. In spite of the limitations in the various investigations, the results all tend in the same direction, and suggest that the disease is concentrated in some families more than in others. That this familial tendency is not wholly environmental, but at least partly genetic, is demonstrated by the finding that people of blood group A are about 20% more liable than those of groups O, B, and AB (Roberts, 1957). There is as yet no evidence that the secretor genes are concerned in carcinoma of stomach (McConnell, 1959). The association with pernicious anaemia is further evidence of a genetic effect as there is a strong genetic element in pernicious anaemia.

CHOLELITHIASIS.—A hereditary pre-disposition to gall-stones has been postulated for a long time; Littler and Ellis (1952) found a family incidence of 20%, but the condition is so often symptomless it is difficult to estimate the incidence in the general population. Strong support for a genetic hypothesis has come from twin studies (see Doig, 1957b). The hereditary component is almost certainly not a single gene, but related to cholesterol metabolism which is probably controlled by many genes. One of the genetic loci concerned may be the ABO blood group locus, as Kjølbye and Nielsen (1959) have found an increased frequency of group A in 1,369 patients with gall-stones, suggesting that group A people are about 18% more liable than group O people (see also pancreatitis).

COELIAC DISEASE.—Three systematic studies of the inheritance of coeliac disease have been carried out and each has found affected relatives at a much higher frequency than would be expected from estimates of the frequency of the disease in the general population. It is unlikely that the family concentration is due simply to a common environment as parents were found to have been affected in their childhood.

The absence of any clear-cut mendelian pattern of inheritance suggests that coeliac disease is not caused by the lack of a single enzyme. It is more likely that there is a polygenic predisposition to the development of the intolerance to gluten (see Carter, Sheldon, and Walker, 1959).

CONGENITAL ABNORMALITIES.—The present evidence is in favour of the view that the genetic basis of abnormalities present at the time of birth is much the same as that of diseases developing in later life. Some are due to single gene defects, some have polygenic inheritance, and most of them are the result of both environmental and genetic factors. Rubella in the early weeks of pregnancy is still the only environmental cause of congenital defect which has been definitely established, though maternal age is probably a factor. Even so, the results of genetic

research in many of the commoner congenital abnormalities suggest that, even though heredity is involved, it is unlikely to account for all the cases. For instance, Hirschsprung's disease has been reported several times to have a familial tendency. Bodian, Carter, and Ward (1951) investigated the families of 37 index cases and found four of 37 brothers were affected and none of 28 sisters. This frequency is so much higher than the estimated population frequency of 1 in 50,000-100,000 that it must be concluded that genetic factors play some part in the development of the disease. The inheritance is unlikely to be due to a single gene and is probably polygenic. Alternatively it may be that some cases are genetic and others environmental, and a study of the offspring of patients may be as helpful as it has been with infantile pyloric stenosis (see pyloric stenosis in infancy). The report by Boggs and Kidd (1958) of a brother and sister who had no ganglia or nerves from the duodeno-jejunal junction to the anus may have a bearing on the subject.

Two other congenital abnormalities of the gastrointestinal tract have been reported as occurring in more than one member of a sibship. They are so rare that it is unlikely that more than one case would occur in a family by chance or environmental factors alone, and a genetic basis seems likely. They are congenital atresia of the oesophagus (Sloan and Haight, 1956) and tracheoesophageal fistula (Hausmann, Close, and Williams, 1957).

CONNECTIVE TISSUE DISORDERS.—Two hereditary disorders of connective tissue may lead to gastrointestinal bleeding (see McKusick, 1960). The Ehlers-Danlos syndrome is inherited as an autosomal dominant, i.e., the gene is not located on the X or Y sex chromosomes, but is in one of the other 22 pairs of chromosomes, the autosomes. Pseudoxanthoma elasticum (the Gronblad-Strandberg syndrome) is inherited as a recessive, though the typical retinal changes may be found in the heterozygotes.

Berlyne and Platt (1960) have drawn attention to the fact that in most recorded families with pseudoxanthoma elasticum the affected have either been all males or all females. This raises the possibility of partial sex linkage, the locus being on the part of the X chromosome which pairs with the Y chromosome. If this were proven it would be the first demonstration in the human sex chromosomes of crossing-over (the exchange of nuclear material by the X and Y chromosomes), a process which many geneticists think does not take place.

CROHN'S DISEASE.—The occurrence of more than one case of regional ileitis in a family has been reported in about 30 instances. Whether or not the disease is sufficiently common for this to be due to

chance is uncertain. Certainly there does not seem to be a strong hereditary tendency. More remarkable than the slight familial aggregation of this disease, however, is its association with ulcerative colitis within families. This may be due to cases of Crohn's disease of the colon being misdiagnosed as ulcerative colitis (Lockhart-Mummery and Morson, 1960), but if the diagnoses are accepted it suggests the possibility that the two clinical entities may have a common basis (see Houghton and Naish, 1958). As both conditions are probably heterogeneous it may be that within them there is a single condition with quite a strong genetic basis. Further progress will probably have to await improved clinicopathological subdivision of both diseases, though a detailed study of the features of the disease in the families in which they both occur might be revealing.

DUODENAL ULCER.—Of the common non-infective diseases of Man, duodenal ulcer has been the most successfully investigated from the genetic point of view. Twin studies led to the conclusion that there may be an inherited basis of the condition (Doig, 1957a), and an excellent statistical survey (Doll and Kellock, 1951) left little doubt that the family aggregations are, in fact, due to a genetic component and not to the members of families having a common environment. (More detailed comments on the genetic basis of duodenal ulcer will be found in the sections entitled "Polygenic Inheritance", "Interpretation of Results", and "Gastric Ulcer".) In such a common condition the study of individual families, because they have a high concentration of the disease, does not contribute to answering whether or not genetic factors are involved; after a genetic basis has been confirmed, however, such families can be supposed to have a large number of the genes underlying susceptibility and might be suitable for more detailed investigation to try to uncover the actual genes concerned and their mode of action.

Confirmation that there is a genetic basis, and that the inheritance is polygenic has come from the demonstration of two of the genetic loci concerned. These are the ABO blood group locus and the locus which determines whether or not the ABO antigens are secreted in saliva and gastric juice. Group O people are about 40% more liable than are those of groups A, B, or AB, and non-secretors are nearly 50% more liable than secretors (Roberts, 1957). If the characters are considered together it is found that people who are both group O and non-secretor are about two-and-a-half times more liable than the least susceptible people, the secretors of groups A, B, and AB (Clarke, Evans, McConnell, and Sheppard, 1959). The O gene and the non-secretor gene

seem to work independently, as, even amongst non-secretors, group O people are significantly more liable than those of the other blood groups (McConnell, 1960).

The mechanism by which these blood group genes influence susceptibility to duodenal ulcer is not yet known. The fact that they are also concerned in carcinoma of the stomach and pernicious anaemia suggest that they play a part in the physiology of the upper gastrointestinal tract as well as in its pathology. Knowledge of gastric physiology, apart from the mechanisms controlling acid production, is still too scanty for any conclusions to be drawn regarding the probable function of the high concentrations of blood group antigens in gastric juice. It may be that their action has an immunological basis, or possibly the blood group genes are pleotropic and concerned in a biochemical process unconnected with the production of antigens. A clue to the mode of action might be found if more was known of the environmental conditions causing duodenal ulcer. Conversely, discovering the mode of action of the antigens should reveal the important environmental factors.

How many other genetic loci are concerned in the genetic basis of duodenal ulcer is uncertain, but it would be reasonable to suppose that genes determining differences in anatomy and, perhaps, differences in personality, may be playing a part. Some idea of the size of the blood group contribution can be given by the data which mean that, if it were not for the non-secretor and O genes, that is, if the whole population were secretors of groups A, B, and AB, there would be 20% fewer ulcers in England. This does not imply that 20% of all ulcers are caused by these genes without the aid of the environment. Environmental factors must be of supreme importance in the overall incidence in the population, and be responsible for the remarkable increase in the past 100 years, as the genes in the population cannot have changed appreciably during that time. If two populations are under similar environmental stress, however, that with the higher proportion of group O people should have a higher incidence of duodenal ulcer. The data from Great Britain suggest that this may indeed be so, the further north the higher the proportion of group O people and probably also the higher the incidence of duodenal ulcer. The genetic implications of the work on duodenal ulcer and islet-cell tumours of the pancreas are at present uncertain, but will be discussed under that heading.

FIBROCYSTIC DISEASE OF THE PANCREAS (MUCO-VISCIDOSIS).—In children it is probable that this condition is always inherited as an autosomal recessive trait, and caused by the same gene in double dose. The possibility of several different genes being able to cause the disease has not been ruled out, but the variable clinical picture is more likely to be due to the single gene being modified in its expression by other genes and by the environment (see Smoller and Hsia, 1959). The relationship of adult mucoviscidosis to the formerly fatal disease of childhood is still uncertain both from the clinical and genetic points of view.

It is because the disease was so often fatal before reproductive age and yet it is so frequent in the population (most estimates being about 1 : 1,500 of all life births) that its genetic basis has been of particular interest. If all cases are, in fact, due to the same gene, the frequency of this gene in the population must be about 3%, much too high a level for it to have reached unless it has conferred some selective advantage on its bearers. Since those who were homozygous for it died before reproduction, the advantage must have been, and may still be, enjoyed by the heterozygotes, the 6% of the population who carry one dose of the gene. There is probably a state of genetic polymorphism similar to that of the haemoglobin S gene in Africa; whilst the advantage of one dose of the HbS gene is known to be a degree of resistance to malaria, the advantage of one fibrocystic gene is not known. If further work on the detection of the heterozygote carriers by tests of the electrolyte content of sweat results in a reliable method which can be applied to large numbers of people, it will then be possible to investigate for this hypothetical advantage. Until it is known it will be impossible to assess whether or not the community as a whole is going to benefit from the rise in the gene frequency which will follow the successful treatment of children with fibrocystic disease so that they live and reproduce.

Very little is known of the actual grouping of the genes on human chromosomes, but the gene for ovalocytosis is on the same chromosomes as the Rh blood group locus, and there is also genetic linkage between the nail-patella syndrome and the ABO blood group locus. The possibility that the gene for fibrocystic disease may be linked with the MN blood group locus has been studied by Steinberg and Morton (1956). Confirmation or denial of this will become much easier when the heterozygote carriers of the gene can be scored.

GASTRIC ULCER.—The present position regarding the genetics of gastric ulcer is rather confused, possibly because the disease may not be as distinct a clinical or genetic entity as is duodenal ulcer. Doll and Kellock (1951) showed that duodenal and gastric ulcers tend to be inherited independently and,

at least in clinical genetic research, the two types of ulcer should not be considered together as "peptic ulcer". Taking all gastric ulcers together there is an increased incidence of blood group O, not as marked as in duodenal ulcer, but implying an increased risk in group O people of about 20% (Roberts, 1957). There have been a number of reports of a relationship between group O and ulcer of particular parts of the stomach, but no conclusion can be drawn from them at present (Doll, Swynnerton, and Newell, 1960). The secretor frequency has been tested in only one small series (McConnell, 1960) and, though it does not differ significantly from controls, it may be that non-secretors have some increased risk, though again not nearly so marked as for duodenal ulcer.

GLYCOGEN STORAGE DISEASE.—Hepatomegaly, due to the deposition of excessive amounts of glycogen, has now been shown to be due to defects in at least three enzymes, namely, glucose-6-phosphatase in Von Gierke's disease (liver and kidney), amylo-l : 6-glucosidase in glycogen disease of liver and muscle, and amyl-l : 4 → 1: 6-transglucosidase in glycogenosis with hepatic cirrhosis. Enzymic studies have so far failed to reveal the nature of the underlying abnormality in glycogen disease of the heart (see Harris, 1959).

Von Gierke's disease is inherited as a simple autosomal recessive, and the heterozygote carriers of the gene can be detected by elevated glucose-6-phosphate and fructose-6-phosphate levels in the red cells. It is possible that some cases of "familial hepatic cirrhosis" may in reality be examples of glycogenosis with hepatic cirrhosis (Andersen, 1956).

HAEMOCHROMATOSIS.—The occurrence of the complete clinical picture of haemochromatosis in more than one member of the same family is not common, but it occurs sufficiently frequently to suggest that there is a genetic basis to the disease. It is found in sibs and in parent and child combinations.

Studies of plasma iron levels in the relatives of patients suggest that the underlying biochemical defect, the increased rate of iron absorption, may be determined by a single dominant gene; thus half the adult male relatives have an anomaly of iron metabolism.

Various external factors may be important in precipitating clinical symptoms and influencing the severity of the disorder. The most obvious of these is menstruation which can account for the disease occurring almost exclusively in males even though the gene is probably on one of the autosomes and not on the sex chromosomes.

The juvenile type of haemochromatosis, in which both males and females are affected equally, may be due to two doses of the same gene which causes the more frequently seen disease of late onset (see Debré, Dreyfus, Frézal, Labie, Lamy, Maroteaux, Schapira, and Schapira, 1958; Pirart and Gatez, 1958).

HEPATIC CIRRHOSIS.—There do not appear to have been any studies made of a possible genetic component of the susceptibility of the liver to alcohol and other environmental hazards. Familial hepatic cirrhosis is usually inherited as a recessive character, and is probably heterogeneous in aetiology. In some families it is associated with abnormal glycogen storage (Andersen, 1956), whilst in others there may be an upset of amino-acid metabolism (Still, 1955).

In primary biliary cirrhosis no familial aggregation has been noted, but the disease is still of uncertain aetiology; Sherlock (1959) speculates on the possibility that it may be a sensitivity reaction to some drug or a hormone produced at the menopause. She points out that the sensitivity of certain persons to this type of reaction might, as with other sensitivities, be genetically determined.

HEPATOLENTICULAR DEGENERATION (WILSON'S DISEASE).—This inborn error of metabolism, which is inherited as a recessive (see Bearn, 1953), has been the subject of much biochemical study. The particular enzymic defect has not yet been identified but it seems that the serum copper/caeruloplasmin copper ratio may be of primary importance in the pathogenesis (see Bearn, 1957).

INTUSSUSCEPTION IN CHILDHOOD.—There would appear to be a definite family aggregation of acute intussusception in childhood, but whether this is due to genetic factors or to the common environment is not known, MacMahon (1955) estimated the risk to sibs of an affected child to be between 15 and 20 times the incidence in the general population.

JAUNDICE (NON-HAEMOLYTIC).—There are several clinically distinct familial causes of non-haemolytic jaundice, and the number is being rapidly enlarged.

Neonatal Hepatitis (Giant-cell Type).—This has been studied in 38 families by Hsia, Boggs, Driscoll, and Gellis (1958), and their data are consistent with an autosomal recessive mode of inheritance. They do not, however, rule out an intrauterine factor as being responsible.

Familial Non-haemolytic Jaundice with Kernicterus (Crigler-Najjar Type).—This has probably an autosomal recessive mode of inheritance. Childs and

Najjar (1956) demonstrated that it is due to a metabolic block at the stage of bilirubin conjugation with glucuronic acid, the defect probably being in the enzymic system of the microsomes of the liver.

Familial Non-haemolytic Jaundice (Gilbert's Disease) is probably inherited as a dominant, the gene having incomplete penetrance. It may be that there is the same defect of bilirubin conjugation as in the disease with kernicterus, the differences in the age at onset and severity of the disease being due to their being heterozygous and homozygous for the same gene (see Arias and London, 1957).

Dubin-Johnson Syndrome (Congenital Hyperbilirubinaemia with Pigment in the Liver).—This syndrome may be inherited as an autosomal dominant, having been found in siblings and also in mother and son (Beker and Read, 1958).

PANCREATIC ISLET TUMOURS.—The role of heredity in insulin-secreting and non-insulin-secreting tumours has yet to be fully worked out. That there is a definite genetic component is suggested by the families with multiple adenomas of the pancreatic islets, parathyroids, and pituitary (Moldawer, Nardi, and Raker, 1954). It may be fortuitous that there is a high incidence of duodenal ulcer in these families with adenomatosis of endocrine glands, as there is with hereditary hyperparathyroidism (Jackson, 1959), but, in view of the well-founded association of ulcer and islet cell tumours, it seems quite possible that unrecognized hereditary endocrinopathies may be responsible for some of the familial aggregations of duodenal ulcer.

PANCREATITIS.—Hereditary chronic relapsing pancreatitis is now a well-founded clinical entity and it appears to be inherited as a dominant trait. The gene is autosomal but has not full penetrance (see Gross and Comfort, 1957). Whether or not there is a hereditary influence in the sporadic form of this disease is uncertain. Even though the onset in the familial form is younger than is usual in the sporadic, the clinical picture is similar in other respects and it may be significant that in the families most of the affected persons have been unaware of the occurrence of the disease in their relatives.

A possible association of relapsing pancreatitis with hereditary hyperparathyroidism has been reported (Jackson, 1958). Seven members of a family had hyperparathyroidism and two brothers with recurring pancreatitis were relieved of their symptoms by removal of solitary parathyroid adenomas. The familial association of parathyroid adenomas with pancreatic islet tumours (*q.v.*) is more well-founded.

There may be a relationship between familial

cholelithiasis and familial pancreatitis (Rinaldo and Baltz, 1957).

PERNICIOUS ANAEMIA.—The literature contains many reports of striking concentrations of pernicious anaemia within single families, and twin studies have also suggested an inherited basis. Statistical studies have left little doubt that there is a strong inherited tendency to the disease. That this inheritance is polygenic is shown by the finding that people of group A are more likely to develop the disease than are those of group O, B, or AB (Roberts, 1957). Callender and Denborough (1957) found a remarkably high incidence of ABO non-secretors in their female patients; they did not, however, compare this incidence with that in their female controls and its significance awaits further investigation (see McIntyre, Hahn, Conley, and Glass, 1959).

POLYPOSIS OF THE INTESTINES.—A large number of families have been recorded in which intestinal polyposis is inherited as a dominant trait. In classical polyposis coli, occurring without any obvious associated lesions in other parts of the body, the responsible gene is of high penetrance (Reed and Neel, 1955). In the syndromes in which there are associated lesions, the genes are also of high penetrance though they do not always express themselves fully. The associated lesions occur without polyposis, but polyposis is not found in individuals free from other lesions. The following are probably distinct genetically as well as clinically: Polyposis coli with epidermoid cysts, fibromas, and osteomas (Gardner and Richards, 1953); polyposis coli with multiple sebaceous cysts (Oldfield, 1954); and intestinal polyposis with mucocutaneous pigmentation, the Peutz-Jeghers syndrome (Dormandy, 1957).

The possibility of a genetic basis of the common solitary polyps of the colon and rectum is uncertain, but is discussed with carcinoma of the colon.

In familial polyposis without associated superficial lesions it would be useful to have a marker gene on the same chromosome as, and close to, the gene responsible for the condition. The result of the New Zealand family study by Veale (1958) suggested that there may be such genetic linkage with the MNSs blood group genes. If this is confirmed it will be possible in some families to recognize soon after birth who has and who has not inherited the polyposis gene.

PYLORIC STENOSIS IN INFANCY.—Studies of hypertrophic pyloric stenosis in twins have shown no increased concordance in monozygotic when compared with dizygotic twins (MacMahon and McKeown, 1955). This suggests that the disease is

due to an environmental influence. On the other hand, it was found (McKeown and MacMahon, 1955) that the incidence of the disease in the off-spring of people who had had it in childhood is as high as 6·9%, and in half of these offspring the affected parent was the mother. It would seem that most cases of hypertrophic pyloric stenosis are environmental in origin and occur predominantly in males, but that some cases may have a genetic basis and that these occur about equally in males and females.

STEATORRHOEA.—In the many patients diagnosed as idiopathic steatorrhoea who are suffering from adult coeliac disease, the role of heredity is presumably similar to that in childhood coeliac disease. The remainder may contain examples of genetic entities, but none has yet been discovered with the possible exception of the deficiencies of sugar-splitting enzymes. Bergqvist (1951) reported idiopathic steatorrhoea in a woman and her daughter and possibly also in her sister and son, but because of the knowledge gained since then it is now doubtful from what condition they were suffering.

STOMAL ULCER.—As most patients developing a stomal ulcer have been operated upon for duodenal ulcer, it would not be surprising to find in them a high frequency of blood group O. Doll *et al.* (1960) have, however, found that their group O frequency is even higher than that in duodenal ulcer patients. As there is probably a more direct relationship between stomal ulcer and acid than between duodenal ulcer and acid, this finding is in favour of there being a connexion between the ABO genes and gastric acidity, and that this is the reason for the increased risk of group O people of developing stomal ulcer.

SUGAR-SPLITTING ENZYME DEFICIENCY.—Amongst the causes of diarrhoea in children, three have been demonstrated as being due to deficiency of the sugar-splitting enzymes—lactase, invertase, and maltase (see Weijers, van de Kamer, Mossel, and Dicke, 1960). Though there is no information yet of any family studies, the fact that these are specific enzyme deficiencies makes it likely that they are due to single gene defects.

ULCERATIVE COLITIS.—It is as yet uncertain whether or not heredity plays a part in ulcerative colitis. Houghton and Naish (1958) review the literature and describe five families from one area with more than one case. If their estimate of the incidence in the population is correct, they think these familial aggregations are unlikely to be due to chance. It is possible, however, that the disease is commoner than they estimate and a statistical survey with good controls is needed (see also Crohn's disease).

VASCULAR MALFORMATIONS AND VASCULAR TUMOURS.—*Hereditary capillary purpura* (*Von Willebrand's disease*), in which the defect is apparently confined to the walls of the capillaries which contract inadequately on injury, is usually inherited as an autosomal dominant character (Horler and Witts, 1958).

Hereditary Haemorrhagic Telangiectasia (*Osler-Rendu disease*).—This is inherited as a simple autosomal dominant with good penetrance. There is some evidence suggesting that the type of lesion is also inherited; thus arteriovenous aneurysms are common in some affected families and never occur in others. Such differences may be due simply to varying expression of one gene, but are more likely to be due to different alleles, or even genes at different loci (see Annotation, 1957).

Haemangiomas of Small Intestines.—These have been reported by Bandler (1960) as occurring in five members of a family, and examination of the pedigree suggests an autosomal dominant mode of inheritance. The tumours were cavernous of diffuse expansive type and involved the greater part of the small intestine. In one of the individuals there was mucocutaneous pigmentation somewhat similar to that of the Peutz-Jeghers syndrome.

The angiomatosis of the small intestine, which is sometimes a part of Turner's syndrome, is presumably due partly to the missing sex chromosome which is the primary cause of the gonadal agenesia, and partly to autosomal or environmental factors modifying the expression of the genetic defect (see Annotation, 1959).

WHIPPLE'S DISEASE.—In such a rare condition as Whipple's disease the discovery of two instances of the disease in brothers makes it very likely that there are genetic factors involved. Gross, Wollaeger, Sauer, Huizenga, Dahlin, and Power (1959) have noted that out of 77 cases reported, at least six have had diabetic relatives and that mental illness also seems unusually prevalent among the relatives. They think it possible that some, if not all, patients with Whipple's disease may inherit some metabolic or other abnormality which predisposes them to this affliction.

INDICATIONS FOR FURTHER RESEARCH

Some aspects of this subject were dealt with in the symposium organized by the Gastroenterological Research Group on "The Genetic Approach to the Study of Gastrointestinal Disease" (Annotation, 1960).

With the rare conditions which are probably due to a single gene defect, a biochemical approach is likely to be the most profitable. When the actual enzymic defect has been revealed, there is a possibility of effective prophylactic and curative therapy. Morphological abnormalities, however, are likely to be sequelae of genetically induced chemical changes during early embryonic development, and the chemical abnormality may no longer be detectable after birth.

With the more common conditions in which both heredity and the environment seem to be concerned, it may be that progress will be made by studying both genetic and environmental factors at the same time. For instance, in spite of many surveys of the various stresses to which duodenal ulcer patients have been subjected compared with controls, there is still no convincing evidence of any particular environmental factor being important. Now that the genetic basis of the susceptibility is partly understood, a further such survey might be more rewarding. Instead of simply comparing ulcer patients with normals it is now possible to make a comparison of the stresses of patients who have succumbed in spite of having the highest resistance (secretors of blood groups A, B, and AB) with those of people who have not developed an ulcer in spite of having the least resistance (group O non-secretors).

After decades of study of environmental factors, there is still a large number of diseases of uncertain aetiology, and a genetic approach is now appropriate in many of them. In particular, well-planned statistical surveys are needed in ulcerative colitis, cholelithiasis, cirrhosis of the liver, pancreatitis, steatorrhoea, appendicitis, haemorrhoids, and Crohn's disease.

A whole new field of clinical genetic research has been opened up by the discovery that the drug isoniazid is metabolized at a different rate by different people (Evans, Manley, and McKusick, 1960). The application of pharmacogenetic research to gastroenterological problems could explain why some patients respond to treatment better than do others.

The discovery that the ABO blood group genes are concerned in several disorders of the gastrointestinal tract has drawn attention to a large gap in physiological knowledge. It is quite unknown why saliva and gastric juice should have such high concentrations of the blood group antigens, but their presence cannot be fortuitous, and they must be serving some purpose. It is not even known which cells of the gastric mucosa produce the antigens, nor what are their breakdown products in the intestines. The solution of such basic physiological problems is probably necessary before the mechanism by which the blood group genes influence disease can be understood.

Perhaps the most pressing need is for more knowledge of the genetics of the physiological processes of the gastrointestinal tract. Further studies are required on the secretions of the gastric mucosa. Here at least it has been demonstrated that there is considerable variation between individuals, the range in normal people has been measured and family studies have suggested that, as would be expected, there is a genetic basis to the amount of acid which can be secreted. Sievers (1959) has made a start in trying to identify the genes concerned, and he suggests that the ABO blood group genes may be involved, not so much with the secretion of acid *per se*, as with the entire secretory activity of the gastric mucosa. Not only does this work need to be extended using normal people who have been scored for secretor status as well as blood grouped, but similar genetic investigations made of other biochemical processes, and such things as the motility of the gut.

Man is such an adaptable organism that most processes will be found to have a wide range of activity in a normal population, and the range will be genetically determined. The work of Goodman, Luke, Rosen, and Hackel (1959) is an example; studying twins they found a significant genetic influence, not only on the rate of flow, the *p*H, and amylase activity of saliva, but also on the number of microorganisms in the mouth. Some of those who are at present regarded as patients with disease entities may turn out to be individuals who have a physiological activity of a grade which is apparently pathological, but which is in reality at one end of a normal distribution curve. The first step is the study of the variation in a population, then the study of the variation within families and the identification of the gene/enzyme systems determining the variation. When such knowledge is available the basic pathology of disorders can be understood and the way will be open to really effective therapy.

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