Progress report

Genetics and gastroenterology

The decade since the last review of this subject in Gut has seen considerable advances in many aspects of genetics, including the influence of heredity on disease. Compared with some specialties gastroenterology has few disorders with simple Mendelian inheritance, but in most of its conditions there is some hereditary influence. Some of the best human data illustrating a quantitative type of disease liability are those on hypertrophic pyloric stenosis and Hirschsprung's disease, and the discovery of two of the genes of the genotype giving susceptibility to duodenal ulcer is still unique. There is growing realization that both heredity and environmental factors are concerned in the aetiology of most disorders.

Blood Groups and Alimentary Physiology

It is still not clear what part the ABO blood group genes and the genes at the secretor, H, and Lewis loci play in alimentary physiology. It would seem likely that they are concerned via their control of the arrangement of the sugars on the molecules of the mucus of the upper part of the tract. Yet one would not expect such slight variations between the different group specific molecules to affect their physicochemical properties. Furthermore, the discovery of the close relationship between the serum content of jejunal alkaline phosphatase and the ABO blood group and secretor status suggests that the blood group genes are pleiotropic. In addition to their well known, and possibly unimportant, effect on the serological specificity of glycoproteins, these genes may be concerned in more fundamental processes such as the transport of lipids across cell membranes. Whether or not they influence maximal gastric acid output in healthy people is still in doubt.

Hypertrophic Pyloric Stenosis

There has been a most rewarding study of the offspring of people who were treated in infancy by Rammstedt's operation. The data show the quantitative nature of the hereditary influence. It is apparent from the 4:1 sex ratio of the condition that the female baby is more resistant to any initiating environmental factors. Yet it was found that the disease developed in some 19% of the sons and 7% of the daughters of female patients, compared with only about 5% of the sons and 2.5% of the daughters of male patients. Among the sibs the proportion of affected was lower than in the offspring, but again the risk was higher in the sibs of female patients.

The most likely genetic explanation of these data is that liability to pyloric stenosis is polygenic and modified by sex in such a way that girls require much more genetic liability before they develop the clinical condition. Because of the concentration of autosomal genetic factors in an affected
female her offspring will receive a greater number of these genes than do the offspring of an affected male.

**Hirschsprung’s Disease**

Several systematic family studies have been made and the striking result is that the proportion of affected sibs is significantly higher with long-segment cases than with short-segment ones. For instance, Bodian and Carter⁹ found eight affected in 63 sibs of long-segment cases and only 10 in 318 sibs of short-segment cases. Another interesting result concerned sex ratios, the proportion of affected brothers being higher than affected sisters (nine in 173 boys and one in 145 girls) of short-segment patients, while in the sibs of long-segment patients the sex ratio was more nearly unity (five of 35 brothers and three of 28 sisters). Finally, in most of the investigations there has been found a remarkable consistency in the length of aganglionic bowel within families¹⁰,¹¹.

These data have many features in common with those concerning hypertrophic pyloric stenosis, in which there is a similar sex ratio. They are consistent with a quantitative genetic effect. A polygenically determined susceptibility to environmental factors is the most likely explanation. The association with mongolism may indicate a chromosomal factor¹⁴.

**Gastric and Duodenal Ulcer**

Convincing evidence of the separate inheritance of gastric and duodenal ulcer was found by Doll and Kellock¹⁵. Added weight for their conclusions has been given by blood group data, patients with concomitant gastric and duodenal ulcers and those with antral ulcers having the high frequency of group O found in duodenal ulcer patients, whilst chronic ulcers of the mid-third of the stomach are not associated with any particular blood group or secretor status¹⁴,¹⁵.

Two of the genes concerned in duodenal ulcer have been identified, the gene which determines blood group O and the gene for non-secretion of blood group substances in saliva and gastric juice. Data collected all over the world have confirmed that blood group O people are about 35% more liable to duodenal ulcer than people of groups A, B, and AB. It has also been amply confirmed that non-secretors are about 50% more liable¹⁵,¹⁸. People who are both group O and non-secretor (the most susceptible type) are about 2.5 times more liable than the people who are least at risk, the secretors of groups A and B¹⁷. The association with group O has been found to apply particularly to those patients whose ulcers have bled or perforated¹⁸,¹⁸, indicating that group O may influence severity of ulcer. The high group O frequency in stomal ulcer⁸⁰ could be merely a reflection of the high group O frequency in bleeding and perforating ulcers, because many of the stomal ulcers have developed in patients who had had a partial gastrectomy following bleeding or perforation⁸¹.

**Crohn’s Disease and Ulcerative Colitis**

There has been a large number of reports of two or more people in one family having Crohn’s disease²⁸,²⁹,³⁴, and there have been several investiga-
tions of the familial incidence in series of patients with ulcerative colitis. Burch et al. analysed the age pattern in seven clinical series, and concluded that the disease is confined to genetically predisposed persons. They distinguished two groups, early-onset patients who differ genetically and clinically from late-onset patients though the two genotypes may well have certain alleles in common.

For many years there have been reports of both Crohn's disease and ulcerative colitis occurring in the same family. At first it may have been possible to attribute these reports to misdiagnosis or coincidence, but it must now be admitted that these two relatively uncommon diseases, diagnosed according to accepted criteria, occur together in the same family too often to be due to chance. Almy and Sherlock collected reports of 17 families in which both diseases are known to have occurred. A family has been reported with four cases of Crohn's disease in one sibship, and another in a cousin. In the same family, ulcerative colitis occurred in a cousin and a nephew.

Further, both diseases are associated with ankylosing spondylitis, both in individuals and in families. The spondylitis cannot be regarded as a complication of the intestinal diseases, since symptoms of arthropathy come first in the majority of cases.

The most likely explanation of the relationship between Crohn's disease and ulcerative colitis is that the two polygenic systems which determine liability to the two diseases may have a number of genes in common. Overlapping genotypes may also explain the association with ankylosing spondylitis.

Polyposis

Although there is much that is not clear about polyps of the gastrointestinal tract, there is fairly general agreement that there exist at least three genetically distinct types: (1) familial polyposis of the colon; (2) the Gardner syndrome—polyps of small and large intestines with osteomata, fibromata, and sebaceous cysts, and (3) the Peutz-Jeghers syndrome—generalized gastrointestinal polyposis with melanotic spots of the buccal mucosa, lips, and digits. In addition, there are probably other inherited varieties of polyposis; some of the more distinct entities are as follows: (4) discrete polyps of the rectum and colon; (5) colonic polyposis and tumours of the nervous system; (6) colonic polyposis with sebaceous cysts; (7) multiple polyps of the colon and stomach; and (8) colonic polyposis with development of a duodenal polyp.

Coeliac Disease

Coeliac disease of childhood has an incidence in the general population which is much less than that found in the sibs and other relatives of patients with the complaint. The pattern of cases is consistent with polygenic inheritance of susceptibility to damage by gluten and other environmental agents. The heritability has been calculated at about 44%.

Adult coeliac disease occurs in the relatives of childhood cases sufficiently often to suggest that it is determined by the same polygenic system. In fact, most patients with coeliac disease presenting in adult life have probably had
the condition in a mild form in childhood and a long remission has been brought to an end by pregnancy, an infection, or some other non-specific factor.

The Disaccharidase Deficiencies

When the first descriptions appeared of children suffering from diarrhoea due to deficiency of sugar-splitting enzymes, it seemed that each specific deficiency was likely to be due to a single defective gene. Normally in childhood there are about six different enzymes present in the intestinal brush border—lactase, trehalase, and a number of maltases, one of which is invertase or sucrase—but they are not always deficient singly. Patients have been reported in whom various combinations of the enzymes have been deficient\textsuperscript{41,42}.

The hereditary nature of most of these enzyme defects is now established. In saccharose and glucose-galactose intolerances examination of the parents’ enzymic activities has given results intermediate between those of normal people and of the affected children, confirming recessive inheritance. Similarly in invertase-isomaltase deficiency parents had reduced activity of both invertase and isomaltase whereas lactase and trehalase activities were normal. Isolated invertase or isomaltase deficiency has not been described, and it is likely that these two enzymic activities are possessed by one polypeptide.

With isolated lactase deficiency the mode of inheritance is not so certain. In one series of 18 affected children there were three pairs of sibs, but parental consanguinity has not yet been reported.

Lactase deficiency in adults is a common condition which seems to be acquired. There is little evidence to indicate a hereditary element other than the considerable differences which have been found in people of different races\textsuperscript{41,42}. In fact, it seems likely that lactase deficiency is the normal state in most of adult mankind, the enzyme only persisting into adult life in Europeans and others who have kept cattle for several thousand years\textsuperscript{43}.

Gallstones

There is a high familial incidence of gallstones\textsuperscript{44}, but it is uncertain how much more common it is in the relatives of patients than in the general population. The weight of evidence suggests an incidence two or three times that in the general population. When the index cases are children in whom gallstones have developed, the familial incidence is exceptionally high, in keeping with the hypothesis that there is polygenic inheritance of liability to gallstone formation.

Pancreatitis

Pancreatitis may occur with hereditary hyperparathyroidism, hereditary hyperlipaemia, gallstones, and inherited bile or pancreatic duct anomalies. Alcoholism is a major factor in other cases, but in many the aetiology is obscure. The part played by heredity is uncertain, but in reported series there have often been cases with a positive family history.

In addition, there have been a number of reports of families in which many members have had chronic relapsing pancreatitis\textsuperscript{45,46}. In the first families
reported from the Mayo Clinic in 1952 there seemed to be a dominant mode of inheritance. Since then, however, many of the pedigrees have shown a degree of incomplete penetrance and a variability of expression more in keeping with polygenic inheritance. Many cases are so mildly affected that propositi do not know that other cases exist among their relatives. In some, but not all, families aminoaciduria is found.

The most outstanding clinical difference between the familial cases and the sporadic is the earlier age of onset of most of the familial cases, and the weight of evidence is in favour of there being a hereditary form of chronic relapsing pancreatitis determined by a major gene and independent of the commoner cases of idiopathic pancreatitis in which there may also be a genetic element.

Liver Diseases

Cirrhosis of the Liver
Apart from galactosaemia, Wilson’s disease, and haemochromatosis, there are genetic factors involved in the aetiology of infantile hepatic cirrhosis, and possibly of congenital hepatic fibrosis which resembles cystic disease of the liver47. There is no simple pattern of heredity however. Juvenile cirrhosis has quite a marked familial tendency and in adult portal cirrhosis48,49 there seems to be an increased family incidence in the cases which are not related to the heavy consumption of alcohol. In the latter a suggestion of an increased incidence of colour blindness has not been substantiated, nor has an association with blood group A. Studies of relatives for antinuclear factor and hypergammaglobulinaemia have suggested that the hereditary influence may be due to the inherited factors concerned in autoimmunity.

There is still considerable controversy about whether haemachromatosis is a genetic disease50,51, an inborn error of iron metabolism with abnormal intestinal absorption of iron, or is merely portal cirrhosis with increased iron due to drinking wines and other iron-rich food52,53. Studies of liver biopsies and of iron stores in relatives of patients showing the features of haemachromatosis, including diabetes and the typical skin pigment, do however make it very likely that it is a genetically determined entity.

The liver and pancreatic changes of haemochromatosis are preventable by regular venesection, and a detailed investigation of relatives to detect latent or early cases should be a regular measure of preventive medicine. It is sufficiently important to justify liver biopsy of apparently healthy young adults, but this may not be necessary if careful desferrioxamine tests are carried out.

Recurrent cholestatis has been reported in sibs on several occasions54. Byler’s disease is a much more serious type of intrahepatic cholestasis55,56. It is usually fatal during the first decade of life. Features are early onset of diarrhoea, attacks of jaundice, hepatosplenomegaly, and dwarfism. It is probably a recessive disorder and was first demonstrated in the inbred Old Order Amish in Pennsylvania. Kaye’s disease is a similar cholestatic disorder in which itching predates the jaundice which begins before 2 or 3 years of age. Biliary atresia, neonatal giant-cell hepatitis, and galactosaemia are three causes of neonatal jaundice. In the first there is little evidence of hereditary factors, but in the other two there is recessive inheritance47.
The Hereditary Hyperbilirubinaemias

In addition to Gilbert's disease, which has dominant inheritance, another benign unconjugated hyperbilirubinaemia (Arias type) seems to have recessive inheritance57. There is impaired glucuronyl transferase activity58. Also with recessive inheritance is the severe unconjugated Crigler-Najjar syndrome.

It is possible that the Dubin-Johnson and Rotor syndromes are due to the same gene, as in several families examples of both syndromes have occurred59. It may be that variability of expression of the gene accounts for the lack of liver pigment in the Rotor syndrome. Heredity is dominant, but the gene has incomplete penetrance with many sporadic cases.

Carcinoma of the Oesophagus

There has been a follow-up study of the Liverpool families in which carcinoma of the oesophagus is inherited in a dominant manner, occurring only in the tyloitic members of the families. Six more cases of the cancer have occurred in the 12 years since the previous report60. In addition, other instances of carcinoma of the oesophagus occurring in tyloitics were reported61.

R. B. MCCONNELL

Department of Medicine,
The University of Liverpool

References


