A SURVEY OF SOME HEREDITARY METABOLIC DISEASES

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It has been recognized for many years that there are a few entities in which a characteristic combination of clinical and chemical abnormalities is genetically transmitted. The number of diseases and apparently harmless metabolic anomalies which have been recognized as belonging to this group has increased considerably since Garrod in 1902²⁵ described alkaptonuria as an 'inborn metabolic error'; and there are others such as diabetes mellitus, the causation of which appears to be at least partly hereditary. The original hypothesis of a genetically determined enzyme block has proved a fruitful one, and it has received experimental support from the study of the specific blocks in metabolism which occur in mutant strains of micro-organisms such as *Neurospora*. Some inherited chemically characteristic diseases are due to a failure of specific renal tubular re-absorptive processes and presumably result ultimately from an abnormality of the enzymic mechanisms which effect active transport across these cells.

All enzymes are probably proteins and the inborn enzyme defects are therefore specialized examples within the group of diseases which are due to inherited abnormalities of protein synthesis. Limitation of space prevents a discussion of other inherited protein abnormalities such as the haemoglobinopathies, the congenital plasma protein deficiencies and the deficiencies of the blood-clotting factors. The renal tubular reabsorption defects (e.g. cystinuria) have also been omitted for this reason.

DISORDERS OF AMINO-ACID METABOLISM

Alkaptonuria

In this disorder of aromatic amino-acid metabolism there is a congenital deficiency of the enzyme homogentisic acid oxidase which converts homogentisic acid (2 : 5-di-hydroxyphenyl acetic acid) to maleyl aceto-acetic acid. The disease was documented from the clinico-pathological and genetic aspects by A. E. Garrod, who also cor-

rectly forecast that it was due to a failure of the single enzymatic reaction which normally opens the benzene ring of the aromatic amino-acids.^{25, 26, 27, 55, 58} Homogentisic acid forms a brown or black polymer on oxidation; this reaction occurs readily and is accelerated by alkali. It interferes in the Benedict's and Fehling's tests for urinary glucose with the formation of an orange precipitate and a dark brown supernatant solution, but the tests for glucose which do not depend upon the reducing properties of the sugar are unaffected. Normal blood and urine do not contain detectable amounts of homogentisic acid and the level in alkaptonuric patient's blood (about 3 mg. per 100 ml.) is so low as to be near the lower limit of measurement by the available procedures.⁶⁶

Alkaptonuria may be detected in infancy by the characteristic dark staining of the urine-soiled napkins. In later life, usually after the age of 40, the cartilages, tendons, ligaments and sclerae become demonstrably pigmented ('ochronosis'). This is first apparent clinically as a bluish-grey discoloration of the auricular and nasal cartilages and superficial tendons. The affected cartilages feel abnormally rigid and the earliest scleral deposits take the form of brown triangular areas which have their bases directed towards the corneoscleral junction; the sclerae subsequently acquire a uniform grey tint. Brown pigmentation of the 'butterfly' area of the face, over the thenar and hypothenar eminences and of the nails as well as a dark discoloration of the ceruminous and sebaceous secretions has been described and pigmentation of the bones, kidneys and of atheromatous plaques may be apparent at necropsy. Similar pigmentation occurs in chronic phenol poisoning ('carbolic ochronosis'). Alkaptonurics characteristically develop osteoarthritic lesions in the spine and large joints of the limbs. The intervertebral discs are thin and calcified and ectopic calcification may develop in bursae and tendon sheaths. The depth of pigmentation of the cartilage of the affected joints is not necessarily

directly proportional to the severity of the osteoarthritis, and carbolic ochronosis is not particularly associated with articular degeneration.

Most cases of alkaptonuria display a recessive (or homozygous) pattern of inheritance as judged by the occurrence of multiple cases of the disease in individual sibships, the parents being overtly normal, and an incidence of parental consanguinity which is greater than that prevailing generally in the population from which the families are drawn, the abnormal gene being rare. In these families the affected members are homozygous and their parents are heterozygous for the abnormal gene concerned. A few pedigrees have been reported,⁴³ in which the disease appears to have a dominant (or heterozygous) pattern of inheritance; in these families affected individuals appear in successive generations, and the incidence of parental consanguinity is no greater than that encountered generally in the population. This genetic heterogeneity suggests that there may be two biochemical lesions which can give rise to alkaptonuria. It is probable that the detailed biochemical studies which have resulted in the formulation of the current concept of the aetiology of the disease have all been performed on the commoner recessive variety. Alkaptonuria appears to be about twice as common in males as it is in females in both genetic types, but no satisfactory explanation of this has so far been advanced.

Phenylketonuria (Phenylpyruvic Oligophrenia; Phenylpyruvic Amentia)

Folling²³ recognized that mental deficiency was sometimes associated with the presence of large amounts (0.5-1 g. daily) of phenylpyruvic acid in the urine, and it has been shown that this association exists in about one-half to one per cent. of all mental defectives.

The vast majority of cases are of imbecile grade and have abnormal electroencephalograms. Epileptiform attacks and 'organic' neurological signs (usually extrapyramidal) have been reported in about 30% and 60% of cases respectively.⁵¹ Stature and head size are only slightly reduced, the skin and hair tend to be fairer than the average for the population from which the cases are drawn, and the blood adrenaline level is said to be abnormally low.

The aetiological biochemical lesion is a deficiency of one component of the phenylalanine hydroxylase enzyme system.^{64, 90} Abnormally high levels of phenylalanine are found in the blood and cerebrospinal fluid, and abnormal metabolites of this amino-acid are excreted in the urine. Phenylpyruvic acid is one of these and is easily detected by the green coloration which it produces when ferric chloride solution is added

to the acidified urine. The urine also contains some tryptophane derivatives whose presence, as well as the lowered blood and urine levels of 5-hydroxytryptamine and 5-hydroxyindole acetic acid respectively, could be explained on the basis of defective tryptophane hydroxylation.

The pattern of inheritance is recessive and the individuals who are heterozygous for the abnormal gene concerned (e.g. the parents of affected homozygous individuals) can be detected by their impaired ability to metabolize a test dose of phenylalanine normally as judged by the rate of disappearance of the amino-acid from the blood plasma.⁴⁸ The fasting plasma phenylalanine levels in the heterozygous subjects are also slightly higher than normal. Low phenylalanine diets are currently being tried therapeutically on the assumption that the abnormally high concentrations of phenylalanine or one of its metabolites are responsible for the neuropsychiatric disorders. They need to be given from earliest infancy and although the obvious chemical abnormalities of the body fluids can be corrected in this way, and the fits and electroencephalographic abnormalities abolished, their efficacy in promoting completely normal mental development is still under long-term assessment.^{56, 95}

Tyrosinosis

The recognition of this third inborn metabolic error of aromatic amino-acid metabolism rests upon the description of a single case of Medes⁶¹ in which large amounts of tyrosine and *p*-hydroxyphenylpyruvic acid were excreted in the urine. The condition was associated with myasthenia gravis, but in view of the lack of evidence that other myasthenics have any similar metabolic disturbance it is generally accepted that the association was a fortuitous one, and that tyrosinosis itself has no clinical manifestations apart from the urinary abnormality. Medes's⁶¹ results suggest that a metabolic block exists between *p*-hydroxyphenylpyruvic and homogentisic acids.

Albinism

This is a relatively common inborn metabolic error, albinos constituting about 1 in 20,000 of the population of Great Britain. There is an inherited failure to form melanin due to the absence of tyrosinase from the melanocytes. The pinkish white photosensitive skin, white hair, translucent iris, nystagmus, photophobia and defective vision are well known clinical findings. The failure of pigment synthesis may not be complete, and in one genetically distinct (sex-linked) type the only albinotic change is found in the eye ('ocular albinism'). The commoner generalized form appears to be inherited as an

autosomal (non-sex-linked) recessive character, although the situation is complicated by the fact that there is more than one abnormal gene which may, when present in double dose (homozygosity) give rise to the condition. Thus albino parents who are homozygous for different abnormal genes can beget non-albino children, the latter being heterozygous for different genes responsible for albinism.

Goitrous Cretinism

The clinical association of non-endemic cretinism and goitre is uncommon and three distinct biochemical lesions, each representing a block at different stages of thyroid hormone synthesis, have been identified as causes of this syndrome.^{38, 49, 81, 82} The available data are compatible with these conditions being due to the operation of rare recessive autosomal genes.

Hartnup Disease

Baron, Dent, Harris, Hart and Jepson⁵ reported the clinical association of a pellagra-like rash, mental deficiency, neurological manifestations of varying severity (cerebellar ataxia, nystagmus, involuntary movements) and a renal amino-aciduria which, although generalized, does not involve all the amino-acids to the same degree.²⁰ The urine also contains unusual amounts of indole compounds related to tryptophane (indolylacetic acid, indolylacetyl glutamine and indican). Three sibs showed the full syndrome and one other (the youngest) had amino-aciduria only; the parents, who were normal, were first cousins. Other similar cases have been identified.⁴⁷ It has not been finally decided whether this disease results primarily from a block at some stage in the metabolism of tryptophane with secondary deficiency of nicotinic acid or whether it is primarily a disorder of amino-acid transport.³⁹

Maple Sugar Urine Disease

In this disease high levels of the branched-chain amino-acids valine, leucine and isoleucine are found in the blood and urine, whereas the levels of threonine, serine and alanine are exceptionally low,⁹³ and it has been suggested that the underlying abnormality is a failure to metabolize the branch-chain amino-acids normally. The affected children fail to thrive from the age of a few days; spasticity, opisthotonos and irregular jerky respirations are associated with feeding difficulties, inanition and death during the first weeks of life. The urine smells characteristically of maple sugar: this is thought to be due to certain α -hydroxy acids which are present; the post-mortem appearances are non-specific. The available evidence is compatible with this disease

also being due to the operation of a rare recessive gene.⁶²

Argininosuccinic Aciduria

This disease is characterized by the presence of argininosuccinic acid in the urine, blood and cerebrospinal fluid. Argininosuccinic acid is an intermediate compound in the ornithine cycle of urea formation,⁷⁰ and its relatively high cerebrospinal fluid level in the disease has suggested that it may be formed in the central nervous system due perhaps to a block in some hitherto unrecognized metabolic process; the blood and urine urea levels are normal.^{1, 21, 92}

Allen *et al.*¹ described the disease on the basis of their study of two sibs (aged three and six years respectively) whose parents were unrelated. Both children had grossly abnormal electroencephalograms and were severely mentally retarded, although they had apparently developed normally during the first year of life, and there was no definite evidence of microcephaly. One patient was epileptic, and motor inco-ordination with choreo-athetoid features was present for several weeks after a series of fits. Friable hair, cardiac systolic murmurs and elevated serum alkaline phosphatase levels were noted in both cases.

β -aminoisobutyric Aciduria

Some otherwise normal people excrete about 50-200 mg./24 hours of β -aminoisobutyric acid in their urine as opposed to the much smaller amounts which are normally present. There is evidence that this represents a harmless inborn anomaly of thymine metabolism, although its mode of inheritance has not been elucidated.³⁹

Cystathioninuria

Harris, Penrose and Thomas⁴⁰ found large amounts of cystathionine, an intermediary in methionine metabolism, in the urine of an elderly mental defective, and increased amounts of the same amino-acid were found in the patient's liver and kidney tissue post mortem, although there was no evidence that it accumulated in the blood. Cystathionine cannot be detected in the urine of normal subjects, but a clinically normal nephew and brother of the propositus excreted amounts which, although less than those excreted by the propositus, were still appreciable. These observations suggest that cystathioninuria may be due to a genetically determined metabolic lesion which results in a failure to convert cystathionine to homoserine and cystine.

Primary Hyperoxaluria

Primary hyperoxaluria, which has a recessive

pattern of inheritance,*⁷⁶ causes severe progressive urolithiasis and nephrocalcinosis beginning in childhood and is characterized by a continuous high urinary excretion of oxalate, much of which is derived from glycine. About the same degree of isotope dilution occurred between the precursor glycine (labelled with ¹³C) and the urinary oxalate in patients with primary hyperoxaluria and a normal subject; this suggests that the fundamental abnormality in primary hyperoxaluria is a failure to degrade glyoxylate normally to formate and carbon dioxide with secondary over-production of oxalate, rather than excessive metabolism of glycine via the pathway:¹⁷

Such a metabolic lesion need involve only a small part of the normal glycine metabolic turnover in order to produce the amount of oxalate which patients with this disease excrete.⁹¹ The alimentary absorption of oxalate is not excessive and there is no evidence of a primary renal defect in these cases.² Numerous calcium oxalate monohydrate crystals are found in the walls of small muscular arteries and arterioles, the rete testis, the myocardium, the growing regions of bones and, less extensively, in other tissues as well as in the kidneys at necropsy.^{32, 77} It has not proved possible to determine clinically the stage in the evolution of the disease at which the extrarenal deposition of oxalate ('oxalosis') begins and the precise level of the urinary oxalate excretion cannot be correlated with the age at which obvious stone formation begins or with its rate of progression; the prognosis is, however, bad.³⁷ It appears that the blood oxalate level is not grossly elevated except at a very late stage in the evolution of the disease.¹⁸ Small amounts of oxalate have also been found in cerebrospinal fluid collected at post mortem, none being detectable in appropriate control material.^{37, 77}

DISORDERS OF CARBOHYDRATE METABOLISM

Galactosaemia

Infants with this recessively inherited metabolic defect appear normal at birth, but after a few days of milk feeding become lethargic, vomit and fail to thrive; abdominal distension and hepatomegaly develop and there is a prolonged period of neonatal jaundice. Should they survive infancy,

* Shepard, Krebs and Lee's⁷⁸ report raises the possibility that a rare dominant variety of the disease may exist. The studies which form the basis of this review were performed on the recessive type.

mental retardation, stunted growth, cataracts and hepatic cirrhosis become apparent. Proteinuria, a generalized amino-aciduria and high concentrations of galactose in the blood and urine are the obvious chemical accompaniments. The disease is due to a deficiency in the enzyme system, which converts galactose-1-phosphate to glucose-1-phosphate; this can be demonstrated in the patient's erythrocytes as well as in isolated liver tissue. The crippling effects of this metabolic lesion can be prevented by the administration of a galactose-free diet from earliest infancy, which is achieved by the use of protein hydrolysates or proprietary lactose-free milk preparations. The affected children acquire tolerance for small amounts of milk as they grow older.⁴⁵

Essential Pentosuria (L-xyloketosuria)

The first reported case of this condition was that of Salkowski and Jastrowitz in 1892⁷³ and it was one of the four original, inborn metabolic errors described by Garrod. Only traces of L-xyloketose (L-xylulose) can be demonstrated in the blood of these patients and apart from the excretion of several grams of L-xyloketose (L-xylulose) daily there are no clinical or chemical abnormalities. Most of the patients are of Central European Jewish descent and the pattern of inheritance is recessive (homozygous). No abnormalities have so far been demonstrated in the subjects who are presumably heterozygous for the abnormal gene. Essential pentosuria should be distinguished from the transient secondary pentosuria (D-arabinosuria) which follows the ingestion of large amounts of fruit. Pentoses reduce Benedict's reagent so that most cases of essential pentosuria are found during the course of routine medical examination.

L-xylulose is a normal metabolic intermediate in one of the pathways of glucose metabolism; its further metabolism is via the pentose-phosphate cycle as a result of which its carbon atoms may be reincorporated into glucose. D-glucuronic acid is another intermediate on this pathway of glucose metabolism and the administration of glucuronogenic drugs increases the excretion of L-xyloketose in essential pentosurics and causes it to appear in the urine of normal subjects; ribulose is also excreted under these circumstances.⁶ There may be some as yet incompletely explored connection between L-xyloketose and ascorbic acid metabolism for the biosynthetic pathways from glucose to both compounds appear to be identical as far as their immediate precursor.

Essential Fructosuria

This recessively inherited biochemical anomaly

also produces no untoward clinical manifestations. The urine contains fructose only when this sugar is present in the diet, the patient's ability to metabolize a test dose of fructose is diminished, and the parents who are presumably heterozygous for the abnormal gene are not demonstrably abnormal. It has been suggested that fructosurics are unable to metabolize the fraction of the dietary fructose which is normally metabolized directly to lactic acid.⁷²

Congenital Deficiency of Erythrocyte Glucose-6-phosphate Dehydrogenase

The red cells of patients in whom acute haemolysis follows the administration of primaquine, sulphanilamide, acetanilide, naphthalene, thiazosulphone, phenylhydrazine, menaphthone and fava beans are deficient in glucose-6-phosphate dehydrogenase activity and contain abnormally small amounts of reduced glutathione. The reduced glutathione content of the erythrocytes decreases further when an haemolytic crisis is induced and *in vitro* incubation of a 'sensitive' individual's red cells with acetylphenylhydrazine also diminishes their reduced-glutathione content.¹³ The affected males inherit the condition from their mothers only, and the clinical manifestations are more severe in males and in females who are homozygous for the gene than in the corresponding heterozygous females.

Hereditary Spherocytosis

Erythrocyte glycolysis is defective in this disease,⁶⁷ and Tabechian, Altman and Young⁸⁴ have suggested that this involves the step 2-phosphoglycerate → phosphoenolpyruvate which is normally catalyzed by enolase. The mode of inheritance is dominant, but a few cases have been reported whose parents were proved to be haematologically normal; these might be the results of fresh mutations or represent a different metabolic lesion which causes spherocytosis.

Hereditary Non-spherocytic Haemolytic Anaemia

This newly-recognized condition which is characterized by mild intermittent haemolytic icterus and other symptoms attributable to episodic intravascular haemolysis is considered on the basis of recent biochemical studies to be due to another abnormality of intraerythrocytic glucose metabolism which has a dominant pattern of inheritance.⁶⁵

The Glycogen-storage Diseases

The polysaccharide glycogen has a molecular weight of several million and is composed entirely of glucose units which are linked together to form

a multibranched structure. It functions as a carbohydrate store to which glucose may be added, or from which it may withdrawn by lengthening or shortening the polysaccharide chains. Glucose storage begins with the conversion of glucose-6-phosphate (formed by the reaction of glucose and adenosinetriphosphate under the influence of hexokinase) to glucose-1-phosphate by phosphoglucomutase. Glucose-1-phosphate is built on to the pre-existing core of the glycogen molecule by phosphorylase; inorganic phosphate is liberated and removed by oxidative phosphorylation. The 'brancher' enzyme ('amylo-(1:4→1:6) transglucosidase') comes into action when about eight successive glucose residues have been added and effects a branch point in the glycogen molecule. The successive actions of phosphoglucomutase and the brancher enzyme build up an arborescent structure. Glucose mobilization follows a similar, but reversed, pattern—phosphorylase hydrolyses the outer polysaccharide chains until the branch points are reached; these are hydrolyzed by the 'debrancher' enzyme ('amylo-1:6-glucosidase') and another series of glucose residues are made accessible to the action of phosphorylase. The immediate product of phosphorylase action is glucose-1-phosphate which accounts for about 92% of the glycogen hydrolyzed (the remainder emerging as free glucose). Phosphoglucomutase converts glucose-1-phosphate to glucose-6-phosphate which is converted to free glucose by glucose-6-phosphatase in liver and kidney tissue. In muscle, where there is no glucose-6-phosphatase, glucose-6-phosphate is either converted to lactic acid or completely metabolized.

The condition described by von Gierke⁸⁶ in which there is abnormal glycogen storage in the liver and kidneys only, results from glucose-6-phosphatase deficiency and is now referred to as 'Type 1 glycogen-storage disease.' It occurs in a severe form, associated with extremely low liver glucose-6-phosphatase levels,¹⁶ and in a clinically milder form in which the enzyme deficiency is of smaller degree. The severely affected infants fail to thrive, have gross hepatomegaly and readily become hypoglycaemic and ketotic. The glucose tolerance curve is flat and the hypoglycaemia is unaffected by adrenaline. Death from intercurrent infection in early childhood is usual and the customarily recommended regime of frequent high protein feeds does not seem to influence the course of the disease. Patients with the milder variant may survive to adult life and they may ultimately have few disabilities. Type 1 glycogen-storage disease has a recessive mode of inheritance, whether the two sub-types should be regarded as the same genetic entity appears to be uncertain.

Hsia⁴⁷ has shown that the presumed heterozygous carriers of the abnormal gene have elevated levels of glucose-6-phosphate and fructose-6-phosphate in their erythrocytes.

In Type 2 glycogen-storage disease the polysaccharide accumulates in the myocardial, smooth and skeletal muscle fibres. The heart is enlarged and globular, there are left axis deviation and ischaemic changes in the electrocardiogram, and the patients usually die from heart failure in infancy. The pattern of inheritance is recessive, but nothing is known of the underlying enzymic defect.

In Type 3 glycogen-storage disease¹⁵ the glycogen has abnormally short outer chains due to deficiency of 'debrancher' enzyme⁵³ and glycogen deposits occur in the hepatic, myocardial and skeletal muscle cells. Hepatomegaly, cardiomegaly, macroglossia, fasting hypoglycaemia and sometimes generalized progressive muscular weakness are apparent clinically. In some cases the latter feature may be so prominent that the disease resembles amyotonia congenita.⁵⁷

In the fourth type of glycogen-storage disease the glycogen molecules have abnormally long chains of glucose residues between the branch points;¹⁵ this is believed to be due to a deficiency of the 'brancher' enzyme. The physical properties of this abnormal glycogen resemble those of amylopectin (a starch polysaccharide); it accumulates in the liver parenchyma and the cells of the reticuloendothelial system. The manifestations of diffuse hepatic cirrhosis dominate the clinical picture, the blood sugar is normal, there is no ketosis and the response to adrenaline is sub-normal. Chemical investigation of the glycogen isolated from a liver biopsy specimen has been used to confirm the diagnosis.^{54, 59} The disease progresses at a variable rate and it seems that patients may survive to the age of about ten years; it may be that some cases which have been labelled 'familial hepatic cirrhosis' have been examples of Type 4 glycogen-storage disease.

Although cases of glycogen-storage disease can be conveniently classified into these four groups,¹⁵ Calderbank, Kent, Lorber, Manners and Wright¹² have encountered two sibs, one with glucose-6-phosphatase deficiency, the other with 'debrancher' enzyme (amylo-1 : 6-glucosidase) deficiency.

DISORDERS OF LIPID METABOLISM

Idiopathic hyperlipaemia is characterized by gross elevation of the neutral fat and fatty acid fractions of the serum lipids, the cholesterol and phospholipid fractions being only slightly raised.

The α_1 , α_2 and β_1 -globulin fractions of the serum proteins are elevated.

Burger and Grütz¹¹ described the juvenile variety of the disease as a syndrome of acute attacks of abdominal pain, with cutaneous xanthomatosis and milky whiteness of the serum under fasting conditions. The yellowish pink 'eruptive' xanthomata are surrounded by an inflammatory-looking red halo; they occur most commonly on the buttocks, back and limbs, but may be generalized, and the oral mucosa may be involved. Hepatosplenomegaly may be present and fever with a polymorphocytosis accompanies the acute episodes. The occurrence of the latter cannot be correlated with changes in the blood lipid level. A low fat diet or long-term heparin administration diminish the serum turbidity, restore the plasma protein electrophoretic pattern to normal and cause the gradual disappearance of the cutaneous xanthomata. Burger-Grütz's disease has a recessive pattern of inheritance, some of the presumably heterozygous subjects have slightly increased serum lipid levels.⁹

Thannhauser⁵⁵ has described an adult variant of the disease in which there may be few abnormalities apart from the hyperlipaemia, and denies that these cases suffer from angina or myocardial infarction at an unusually early age. The co-existence of cutaneous xanthomata and some impairment of glucose tolerance in adult idiopathic hyperlipaemia sometimes results in these cases being confused with examples of xanthoma diabetorum.

Familial hypercholesterolaemic xanthomatosis appears to be due to excessive cholesterol synthesis. The serum cholesterol level is greatly elevated, but the other plasma lipids are normal or only slightly increased. It is unrelated to normocholesterolaemic xanthomatosis (eosinophilic xanthomatous granuloma, lipid granuloma, Schüller-Christian's syndrome), which is probably not genetically determined except in the acute generalized form (Letterer-Siwe's disease).⁵⁵

In familial hypercholesterolaemic xanthomatosis the cutaneous lesions ('xanthoma tuberosum et planum') have an orange-yellow colour, a 'velvety' consistency and vary in diameter from a few millimetres to several centimetres. They occur mainly on the eyelids, on the extensor surfaces of the limbs and on the buttocks. Non-pigmented subcutaneous xanthomatous deposits also occur. Tendon-xanthomata, which are a feature of this disease, occur most commonly in the tendo Achilles, the patella tendon and the extensor tendons of the fingers. Death due to the cardiovascular complications of extensive atheroma may occur at an early age. Hypercholesterolaemia is the constant and may be the only feature of the

disease, the cutaneous and cardiovascular manifestations being variable.

The genetic analysis of familial hypercholesterolaemia is rendered difficult by the normal, but variable, rise in the serum cholesterol with age. It appears to be transmitted in a dominant fashion, and it has been suggested that patients with extensive cutaneous lesions or marked atheroma at an early age are homozygous for the abnormal gene.

The Disorders in which Cerebrosides, Sphingomyelins and Gangliosides Accumulate

The ceramides are the amides of sphingosine (an amino-alcohol) with a higher fatty acid; the sphingomyelins are choline or ethanolamine phosphoric acid esters of the ceramides, and they differ from one another in respect of the fatty acid component of the ceramide moiety. The cerebrosides consist of a ceramide, the fatty acid of which is linked to a galactose or glucose residue. The cerebrosides of normal tissue consist almost entirely of galactocerebrosides and only small amounts are present in cells other than those of the nervous system. The ceramides appear to be intermediate in the biosynthesis of both the sphingomyelins and the cerebrosides:

The gangliosides are related compounds, the exact structures of which are not known. They contain a ceramide linked to glucose, galactose, chondrosamine and neuraminic acid (a polyhydroxy amino-acid), and have been isolated from some normal tissues.

In both the adult and infantile forms of Gaucher's disease, either glucocerebrosides alone or a mixture of galactocerebrosides and glucocerebrosides accumulate in the reticuloendothelial cells. This is attributed to imbalance of the intracellular enzymes which effect the interconversion of the ceramides and cerebrosides.⁸⁵ The adult form of Gaucher's disease usually presents in late childhood or early adult life, and may be compatible with relatively little disability. In this type Gaucher cells (cerebroside-containing

reticuloendothelial cells) are found mainly in the spleen, which is usually very large, the liver and bone marrow; bone pain and deformities, blood dyscrasias and brown pigmentation (most commonly involving the face, backs of the hands and anterior aspects of the legs) are characteristic clinical findings. In the relatively rare infantile type the child usually seems normal at birth, but hepatosplenomegaly, cyanotic attacks, neurological manifestations and poor mental development are soon apparent, and death is usual during the first year of life. Numerous Gaucher cells are demonstrable in the thymus, adrenal, intestinal lymph follicles and lungs, as well as in the organs which are involved in the adult variety. Gaucher cells have not been found in the nervous tissue as opposed to the meninges of these patients. The ganglion cells of the brain are distended, but do not contain abnormal amounts of cerebrosides. Pedigrees suggesting both dominant and recessive patterns of inheritance for Gaucher's disease have been described.^{47, 85} These apparent genetic differences have not been correlated with possible minor chemical differences in the cerebrosides. There is a suggestion that infantile and adult forms of the disease may be genetically distinct.⁴⁷

Niemann-Pick's disease in which sphingomyelin accumulates in the reticuloendothelial cells is attributed to imbalance of the intracellular enzymes which effect the metabolic turnover of phospholipids. Clinical abnormalities usually become apparent when the infant is about three months old, hepatosplenomegaly results in gross abdominal distension with wasting, anaemia, muscle hypotonia, mental retardation, yellowish-brown cutaneous pigmentation, generalized lymphadenopathy and progressive blindness and deafness. The macula lutea shows a cherry-red spot in about 50% of cases. 'Foam cells' (sphingomyelin-containing histiocytes) are often present in the peripheral blood (*cf.* the invariable absence of Gaucher cells from this situation) and the plasma phospholipid level is low. Foam cells have been detected histologically in virtually every organ except the central nervous system and the skin. The ganglion cells of the brain and retina are swollen and degenerate, but this is not due to an abnormal accumulation of sphingomyelin within them. The sphingomyelin content of the brain is normal although differences between the fatty acid composition of specimens prepared from normal brain and specimens prepared from the brains of patients with Niemann-Pick's disease have been reported. The ganglioside content of the brain is increased and it seems that this is responsible for the apparent distension of the ganglion cells. Patients with the rare adult form of the disease are usually unaware of

their disease until it is detected during a routine examination. The lungs, liver and spleen are the most extensively involved organs, and pulmonary infiltration may cause diffuse pulmonary fibrosis with cor pulmonale. It has been suggested that Nicmann-Pick's disease has a recessive pattern of inheritance, patients with the infantile form being homozygous for the gene concerned, those with the adult variant being the corresponding heterozygous individuals; further genetic studies of this disease are, however, needed.

Tay-Sachs disease (infantile amaurotic familial idiocy) occurs mainly in Jews and has a recessive pattern of hereditary transmission. It is characterized chemically by the accumulation of very large amounts of gangliosides in the central nervous system in the absence of visceral sphingomyelin accumulation. The possibility that the ganglioside content of the brain may be increased in other genetically-determined degenerative diseases of the nervous system has not been investigated.⁸⁵ Cases of Tay-Sachs disease appear normal at birth, but delayed mental development, fits, amaurosis and the classical 'cherry-red' spot in the region of the macula lutea are apparent by the age of six months; and they usually die during the first two years of life.

The Porphyrrias

The porphyrias are primary disorders of porphyrin synthesis, and they should be distinguished from the porphyriurias in which the increased urinary and faecal porphyrin excretion is a secondary phenomenon (e.g. when there is abnormally active erythropoiesis). Porphyrin biosynthesis takes place according to the following simplified scheme:

Stage 1: One molecule of glycine and one molecule of succinate combine to form δ -aminolaevulinic acid. This reaction only occurs if the succinate has been activated by Coenzyme-A ('succinyl Coenzyme-A').

Stage 2: Two molecules of δ -aminolaevulinic acid combine to form one molecule of porphobilinogen. This compound contains the five membered 'pyrrole' ring which occurs in the porphyrins.

Stage 3: Four molecules of porphobilinogen combine to form uroporphyrin. Two isomeric uroporphyrins can result at this stage and are described as belonging to 'Series I' and 'Series III.' The physiologically important porphyrins belong to Series III and normally only small traces of Series I porphyrins are formed.

Stage 4: Uroporphyrin III forms coproporphyrin III by loss of the carboxyl groups from four of its eight side chains.

Stage 5: Partial dehydrogenation of two of the

side chains converts coproporphyrin III to protoporphyrin III.

Stage 6: Haem is formed from protoporphyrin III by the insertion of one atom of ferrous iron per molecule.

Acute Intermittent Porphyria

Attacks of severe intestinal colic, constipation and episodic neurological manifestations (pain, hypoaesthesia, paresis, fits, coma and psychiatric symptoms) sometimes accompanied by fever and hypertension, and beginning at puberty, are characteristic of this disease. The onset of an acute attack can sometimes be traced to barbiturate administration; pregnancy also appears to affect the disease adversely. The urine is dark red (port-wine coloured) during the acute episodes and contains large amounts of porphobilinogen and δ -aminolaevulinic acid; small amounts of the zinc complexes of Series I and III uroporphyrins and coproporphyrins are also present. There is no urinary abnormality until the first attack and relatively low levels of porphobilinogen and δ -aminolaevulinic acid excretion are found between the attacks. It is suggested that the uroporphyrins and coproporphyrins are formed secondarily from excreted porphobilinogen when this reaches very high levels. Necropsy shows patchy demyelination of the peripheral nerves and in the central nervous system.

The biochemical lesion has not been identified, it may be that the conversion of porphobilinogen to uroporphyrin III is blocked, or there may be a defect in the balance of synthesis and utilization of δ -aminolaevulinic acid via other metabolic pathways so that it accumulates and is converted to porphobilinogen in the liver. The clinical manifestations cannot be accounted for by the known pharmacological properties of porphobilinogen or δ -aminolaevulinic acid.^{34, 50} Affected individuals and asymptomatic porphobilinogen excretors are believed to be heterozygous for the gene concerned.^{33, 87, 88, 89} Only symptomatic treatment is available for the acute attacks, although Goldberg³³ has suggested that corticotrophin or cortisone may be helpful if given early in the attack.

Congenital Porphyria

Large amounts of Series I porphyrins, which cannot be utilized or metabolized in the normal way, are synthesized in this disease. They accumulate in the bones, teeth, erythrocytes and skin and are excreted in the urine and bile; the urine does not contain porphobilinogen or δ -aminolaevulinic acid. The bones and teeth, which are reddish-brown, and the urine fluoresce in ultra-violet light. The skin is abnormally photosensitive and bullous eruptions (hydraea aestivale),

which heal slowly and leave considerable scarring and deformity, occur on the exposed skin surfaces. A chronic haemolytic anaemia possibly due to erythrocyte-photosensitivity is usually present and there may be splenomegaly. Porphyria congenita is thought to be due to the operation of a rare recessive gene for which the patients are homozygous.⁷⁵ These investigators also make the novel suggestion that two series of erythrocytes and erythrocyte-precursors exist in the same patient, porphyrin synthesis being abnormal in one series and normal in the other.

Porphyria Cutanea Tarda

The clinical manifestations of porphyria cutanea tarda are intermediate between those of acute intermittent porphyria and porphyria congenita, but they are less disabling. Attacks of intestinal colic and cutaneous photo-sensitivity with vacciniiform lesions of the exposed skin areas begin in early adult life, but neurological manifestations are rare and less severe than those which occur in acute intermittent porphyria. During remissions, large amounts of protoporphyrin and coproporphyrins are excreted in the faeces; this diminishes during the acute exacerbations of the clinical manifestations when large amounts of Series I and Series III uroporphyrins and coproporphyrins appear in the urine. Porphobilinogen is absent from the urine except possibly terminally. It has been suggested that the metabolic lesion in porphyria cutanea tarda involves the step:

Protoporphyrin III → haem

and that the acute manifestations are related to episodic disturbances of hepatic function which inhibit the biliary excretion of the abnormal pigments.^{35, 36, 71} It seems likely that the cases which have been described under this title may comprise more than one entity.⁸⁹ Adequate genetic studies require faecal as well as urinary porphyrin analyses in order to detect asymptomatic cases. Where this has been done the results have suggested a dominant pattern of inheritance.⁴⁴

Hereditary Coproporphyrin

Large amounts of coproporphyrin III are excreted in the urine and faeces in this apparently recessively-inherited anomaly.⁸ There are no symptoms such as occur in the other porphyrias, although it has been suggested that there may be a predisposition to riboflavine deficiency.

The Congenital Methaemoglobinaemias

In these conditions the iron of an appreciable proportion of the circulating haemoglobin is trivalent (methaemoglobin or ferrihaemoglobin).

They have to be distinguished from secondary methaemoglobinaemia due to phenacetin, antipyrine, acetanilide and nitrates.

Gibson-Harrison Type ('Congenital Idiopathic Methaemoglobinaemia')

This condition results from an inborn deficiency of the enzyme system which normally keeps the iron of haemoglobin in the divalent state (ferrohaemoglobin). The chemical conditions within the erythrocyte, particularly on the venous side of the circulatory system, are such as to favour the conversion of ferrohaemoglobin to ferrihaemoglobin and a small proportion (about 0.4%) of the total circulating haemoglobin is in this physiologically inert form.⁶⁸ Ferrihaemoglobin accounts for between 10 and 45% of the total circulating haemoglobin in congenital, idiopathic methaemoglobinaemia, the patients have life-long histories of cyanosis and there may be slight compensatory polycythaemia.⁴ Apart from an inconstant association with mental defect,⁹⁶ there is usually no disability associated with the condition. Intravenous injection of ascorbic acid or of methylene-blue temporarily relieves the cyanosis; these two substances appear to act in different ways.^{28, 29} The oxygen dissociation curve is shifted to the left; a similar shift is observed in haemoglobin solutions containing methaemoglobin *in vitro*, and has been attributed to interaction between haemoglobin and methaemoglobin. If this explanation is correct, the observation suggests that methaemoglobin is present in all the erythrocytes rather than being segregated in some of them. If the two pigments were segregated into different cells there could be no interaction between them and the oxygen dissociation curve would have a normal shape.

The data of Gibson and Harrison³⁰ are compatible with a recessive pattern of inheritance, but Codounis¹⁴ studied a family whose pedigree suggested dominant transmission. The enzymic defect was not investigated in the latter family so it is uncertain whether these cases were of the Gibson-Harrison type, although the cyanosis was relieved by ascorbic acid and by methylene-blue.

Horlein-Weber Type⁴⁶

This variety is due to an abnormality of the globin moiety of haemoglobin which is thought to make the iron atom unduly easily oxidizable so that the rate of production of ferrihaemoglobin exceeds the capacity of the erythrocyte-reducing systems. Between 15 and 25% of the haemoglobin is in the form of ferrihaemoglobin, and this is unaffected by vitamin C and methylene-blue. The pattern of inheritance is dominant;

the abnormal haemoglobin ('haemoglobin M') has characteristic electrophoretic properties.

The Congenital Hyperbilirubinaemias

Crigler-Najjar Type^{19, 74}

Glucuronide synthesis, including the formation of bilirubin glucuronide (conjugated or direct reacting bilirubin) is grossly defective in these patients due to a recessively inherited deficiency of glucuronyl transferase. The patients, who are deeply icteric by the second day of life, become spastic and choreoathetotic and die in early childhood. Their serum bilirubin consists virtually entirely of unconjugated (indirect reacting) bilirubin. Subjects (the parents and some sibs), who may be presumed to be heterozygous for the abnormal gene but are not jaundiced, show some impairment of their ability to make glucuronide conjugates.

Gilbert Type^{3, 31, 63}

This is a benign condition in which intermittent jaundice is usually first noticed during the second or third decades. There is a small increase in the circulating unconjugated bilirubin, and the mode of inheritance appears to be dominant. Impaired glucuronide synthesis has been demonstrated, and the Gilbert and Crigler-Najjar types of congenital hyperbilirubinaemia are presumably closely related to one another.

Dubin-Johnson Type²²

Patients with this condition suffer no disability apart from intermittent icterus which is usually first noted in early life. The hyperbilirubinaemia is due to the presence of increased amounts of conjugated bilirubin so there is bilirubinuria. The aetiology of this condition is uncertain, it appears to be familial; the liver looks greenish-black on macroscopic examination and the liver cells contain brown iron-free and bile-free pigment of uncertain composition.⁵²

Gout

The purine moieties of the nucleic acids are synthesized in the body from glycine and other small molecules (formate, CO₂ and NH₃) via 4-amino-5-imidazole-carboxamide ('AIC'), the structure of which is:

Normally, the endogenous urinary uric acid is derived mainly from nucleic acid catabolism and

to a lesser extent via an alternative ('shunt') pathway which appears to leave the main route after the 4-amino-5-imidazole-carboxamide stage:

The underlying abnormality in gout appears to involve excessive uric acid production via the 'shunt' pathway, but the precise nature of the metabolic lesions has not been elucidated.^{7, 78, 83, 97} In contradistinction to this, the increased uric acid production which may give rise to gouty manifestations in patients suffering from such diseases as polycythaemia rubra vera and myeloid leukaemia results from increased nucleic acid turnover.⁹⁸

The occurrence of multiple cases of gout in a given family is well recognized, but except for a preponderance of male cases the pedigrees, as judged by the clinical manifestations, are usually irregular, and apparently sporadic cases are common. The distribution of plasma urate levels among the relatives of gouty patients has been studied by several groups of workers. Smyth, Cotterman and Freyburg⁸⁰ concluded that hyperuricaemia was an inherited character which appeared in subjects who were heterozygous for the gene and about 10% of these develop clinical gout, for some, as yet, unexplained reasons. If this is correct the rare cases in which very severe gout develops in early life might be homozygous for the abnormal gene concerned. The data of Hauge and Harvald⁴² do not, however, fit this relatively simple hypothesis.

Hypophosphatasia

Patients with this disease, which resembles rickets clinically and radiologically, have low serum and tissue alkaline phosphatase activities, and excrete large amounts (100-200 mg/l.) of ethanolamine phosphate in the urine. Ethanolamine phosphate occurs in the cells of many tissues, but only trace amounts which could be derived from the breakdown of cephalins are normally present in the urine, and there is no evidence that it normally has any specific function in connection with bone formation.

The clinical severity of the disease appears to be very variable, ranging from skeletal abnormalities which are sufficiently severe to be apparent radiologically *in utero* to minor deformities which are only detected in later child-

hood or adult life.^{24, 69} It appears that the overt cases of hypophosphatasia are homozygous for a rare abnormal gene; the heterozygous individuals have been identified by their small but significantly raised ethanolamine phosphate excretion. The wide variation in the normal serum alkaline phosphatase level makes this parameter unsuitable as a means of identifying the heterozygotes, although the average values for groups of these subjects have been found to be lower than those of control subjects.⁴¹

Cusworth and Dent²⁰ reported that an adult patient with hypophosphatasia had a low plasma threonine level, a small excretion of proline and increased excretions of taurine, threonine and serine. The relationship of these results to the other chemical features of the syndrome is not apparent.

Congenital Serum Pseudocholinesterase Deficiency

Some otherwise normal individuals have abnormally low levels of serum pseudocholinesterase activity and are therefore unduly sensitive to the muscle-relaxant drug, suxamethonium.⁶⁰ This trait has a recessive pattern of inheritance and is due to the formation of an enzyme protein with catalytic properties which differ from those of its normal counterpart.³⁹

Congenital Adrenal Hyperplasia

There is a failure to complete the synthesis of cortisol (hydrocortisone) in congenital adrenal hyperplasia and cases of this condition can be classified clinically into three groups:

1. Those with virilization only.
2. Those with virilization and inability to retain sodium.
3. Those with virilization and hypertension.

Progesterone is hydroxylated at carbon atoms numbers 17, 21 and 11 to form hydrocortisone;¹⁰ although not necessarily in this order.⁹⁴ The excretion products of the adrenocortical steroids have either 21 or 19 carbon atoms. The latter (the 'adrenal 17-ketosteroids') are androgenic. Failure of progesterone hydroxylation prevents the synthesis of hydrocortisone, the level of circulating adrenocorticotrophic hormone is increased and the gland is stimulated to produce abnormal amounts of the incompletely hydroxylated precursor substances which are degraded in part to 17-ketosteroids. A high circulating level of these androgens beginning during intrauterine life produces pseudohermaphroditism in girls and macrogenitosomia praecox with hypoplastic testes in boys.

In the commonest type of congenital adrenal hyperplasia, virilization is the only manifestation,

and the urinary excretions of 17-ketosteroids and 3 α , 17 α , 20 α -pregnantriol (a derivative of 17 α -hydroxy-progesterone) are high. The anatomical abnormalities are apparent in the affected girls at birth, but boys do not usually show clinical evidence of virilization until they are about one year old. Untreated patients grow rapidly in early childhood but are of less than average height in adult life, due to premature epiphyseal fusion. The costal cartilages calcify at an unusually early age. The continued parenteral administration of cortisone to suppress the abnormal adrenocorticotrophin output brings about normal somatic growth and secondary sexual development provided that it is begun in early infancy. The dosage should be such as to maintain a 17-ketosteroid excretion level which is normal for the patient's age. Some treated male patients have fathered apparently normal children, but treated females have very low fertility (although few of those who have been treated with cortisone from infancy have yet reached puberty). The pattern of inheritance is recessive and females appear to be more commonly affected than males, although this may only reflect the fact that the genital abnormalities are more striking in females. Some presumably heterozygous members of the families have been shown to excrete somewhat larger amounts of 3 α , 17 α , 20 α -pregnantriol after the administration of adrenocorticotrophin than normals.

The patients who are unable to retain sodium develop an Addisonian crisis-like state when they are about two weeks old and soon die, unless they are treated with desoxycorticosterone or fludrocortisone as well as with cortisone. This acute episode may be precipitated by an intercurrent infection or by surgery as may similar episodes in the children who have survived infancy. There is evidence that it is the hydroxylation of carbon atom number 21 which is defective in both of these groups of cases, although the severities of the virilizing and sodium-losing syndromes do not parallel one another.

In the third group, the hypertension begins in the first years of life, there appears to be inability to hydroxylate carbon atom number 11, and abnormal amounts of powerful salt-retaining steroids (e.g. 17 α -desoxycorticosterone) are produced. Treatment with cortisone acetate by injection abolishes the hypertension and restores normal development.

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