MEDICAL PRACTICE

Scientific Basis of Clinical Practice

Management of Inherited Metabolic Disease

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Hitherto, with the exception of galactosaemia and phenylketonuria and occasionally other disorders, clinicians have largely closed their eyes to the possibility that patients with any one of nearly 1,000 diseases, over 100 of them with a precisely known cause, may pass through their hands undiagnosed. And who can blame them? All the diseases are rare, some extremely rare, and there may be no local experience to draw upon; many are rapidly fatal; few can be treated, and those that can usually involve great effort and resource, the reward for which is sometimes dubious; diagnostic tests are often difficult and, in some cases, impossible outside academic centres; and just to know of their existence involves life-long dedication to the library. The present contribution is intended to define some of the problems and provide a framework on to which individual knowledge and experience can be grafted. Though each disease is rare, collectively they account for a significant proportion of disease and, in the field of mental retardation, it has been stated that "in economically advanced populations, known inborn biochemical factors are responsible for somewhat less than 10% of cases."[1]

Nature of Inherited Metabolic Disease

Strictly speaking, inherited metabolic diseases, of which alkaptonuria is the archetype and phenylketonuria the best known, are due to genetically determined defects in the biosynthesis of a particular enzyme, whose activity is reduced to a very low level. More than one kind of defect can occur, affecting the enzyme to differing degrees and several examples of such multiple alleles are known (suxamethonium sensitivity affecting plasma cholinesterase; glucose-6-phosphate dehydrogenase, leading variously to drug-induced haemolytic anaemia, prolonged jaundice in infancy, or almost no clinical involvement at all).

Aetiologically there is no real difference between these and the genetically determined defects of transport processes and these disorders, such as Hartnup disease and cystinuria, are also included. Finally there is hardly any difference between these and the genetically determined protein abnormalities, such as the haemoglobinopathies and bisalbuminaemia, and, while these will not be treated here because their effects are somewhat different, their study has provided many of the concepts forming the basis of the present discussion. In fact there are conditions, such as Wilson's disease, where the defect appears to be one of a protein, caeruloplasmin, but the disease has much in common with other metabolic diseases and the usual method of detecting it depends on the enzymic (p-phenylene diamine oxidase) activity associated with caeruloplasmin.

So far, all genetically determined diseases due primarily to an enzyme deficiency are inherited by recessive or sex-linked mechanisms[2,3] and this rule is holding so well that there is little reason to search for such a cause in conditions showing dominant inheritance. This is because the reserve capacity of enzymes is so great that even half a "genetic dose" is sufficient to meet most metabolic needs; there are therefore no clinical manifestations in the heterozygote.

Clinical Recognition

"Chemical" disease should be diagnosed, like any other disease, for positive reasons rather than because no other cause can be found. Some clinicians have a sixth sense for metabolic disease for which they are unable to account, but which consistently proves to have been reliable—usually at necropsy. There are, however, several clinical situations which should alert to the possibility of particular diseases and these are summarized in Table I.

Still the most important clue, however, is the presence of either a pattern of symptoms or of early and unexplained death in several members of a sibship born to apparently healthy parents. It is still not unusual for the first diagnosed case of a known disease to be the third affected member in the family and there are many instances in sibships of symptom complexes, not described in the literature, whose cause is quite unknown. In such cases a search for a metabolic cause may well be rewarding.

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TABLE I—*Inherited Metabolic Diseases Indicated by a Selection of Clinical Features*

Anaemia
Acetophenetidin sensitivity
Adenylate kinase deficiency
Anaemia hypochromic
Diphosphoglycerate mutase deficiency of red cells
Formiminotransferase deficiency
Glucose-6-phosphate dehydrogenase deficiency
Glutathione peroxidase deficiency
Glutathione reductase deficiency
Glutathione synthetase deficiency
Glycogen storage disease type 7
Hexokinase deficiency
Hexose phosphate isomerase deficiency
ω-Hydroxy isovaleric aciduria
Lecithin-cholesterol acetyl transferase
Methaemoglobin reductase deficiency (NADPH)
Methylmalonic aciduria types 1 and 2
Orotic aciduria
Phosphofructokinase deficiency
Phosphoglycerate kinase deficiency
Propionic acidaemia
Pyroglutamic aciduria
Pyruvate kinase deficiency
Triose phosphate isomerase deficiency

Cyanosis
Acetophenetidin sensitivity
Methaemoglobin reductase deficiency (NADH)

Eye—Cataracts
Angiokeratoma diffuse
Galactokinase deficiency
Galactosaemia-classical
Galactosaemia-Negro
Glycogen storage disease type 8
Hypoxanthine-guanine phosphoribosyl transferase deficiency
Lowe's oculo-cerebro-renal syndrome
Mannosidosis
Mucopolysaccharidosis types 1, 3, 5, and 6

Eye—Ectopia Lentis
Homocystinuria
*Hyper*Lysinaemia
Sulphocysteinuria

Eye—Macular Spot
GM1 Gangliosidosis type 1
GM2 Gangliosidosis types 1, 2, and 3
Neimann-Pick disease

Eye—Retinal Pigmentation
Angiokeratoma diffuse
Cystinosis type 2
aβ-Liproteinaemia
Refsum's disease

Geographical Origin
Glucose-6-phosphate dehydrogenase (Mediterranean and Negro)
Tyrosinaemia (Quebec)
Refsum's disease (Norway)

Hair
Arginino-succinic aciduria

Hepato(spleno)megaly
Arginino-succinic aciduria
*hyper*Bilirubinaemia type 2 and Shunt
Byler's disease
Dibasic amino aciduria type 2
Diphosphoglycerate mutase deficiency of red cells
Fructose intolerance
Galactosaemia-classical
GM1 Gangliosidosis type 1
GM3 Gangliosidosis
Gaucher's disease type 3
Glutathione reductase deficiency
Glycogen storage disease types 1, 3, 4, 6, and 8
Granulomatous disease due to leucocyte malfunction
an α-Lipoproteinaemia
Mannosidosis
Mucopolysaccharidosis types 1, 2, and 3
Niemann-Pick disease
Porphyria congenital
Pyruvate kinase deficiency
Wolman's disease

Jaundice
*hyper*Bilirubinaemia type 2, Shunt and transient familial neonatal
Byler's disease
(Carotinaemia)
Crigler-Najjar syndrome
Galactosaemia-classical
Glucose-6-phosphate dehydrogenase deficiency
Glutathione synthetase deficiency
Hexokinase deficiency

Mental Symptoms and Subnormality
See M in column 2 of Table II

Neurological Degeneration
See N in column 2 of Table II

Odour
β-Hydroxy isovaleric acidaemia
Maple-syrup-urine disease; classical and intermittent
Methionine malabsorption
Phenylketonuria
Sidbury syndrome
Smith-Strang disease
Trimethylaminuria
*iso*Valeric acidaemia

Renal Calculi
Cystinuria types 1, 2, and 3
Oxalosis types 1 and 2
Xanthinuria

Skin Eruption
Hartnup disease
Phenylketonuria

This requires a general approach, in the first instance, by chemical methods designed to probe groups of related compounds.

Some of the simple side-room systems of detecting known diseases employ methods general enough to include a wide range of conditions. Those described by Perry *et al.*[4] and Buist[5] test for phenols, sulphur compounds, reducing substances, tyrosine derivatives, amino acids, keto acids, acid mucopolysaccharides, protein, and some other compounds. The comprehensive system of Berry *et al.*[6] was designed to allow, using the simplest laboratory equipment, the diagnosis of cystinosis, cystinuria, galactosaemia, glycinuria, Hartnup disease, histidinaemia, homocystinuria, Hurler's syndrome, Lowe's syndrome, phenylketonuria, tyrosinosis, and several other disorders of amino-acid and carbohydrate metabolism. Chromatographic screening systems have been described for amino-acids, organic acids, purines, phenolic acids, indoles, sugars,[7] and, more recently, for purines.[8]

More sophisticated techniques include automatic amino-acid analysis,[9] prolonged chromatography combined with spectrophotometry,[10] and gas-liquid chromatography. The latter technique can be combined with mass spectrometry for identification of the compounds, and a system has recently been devised by which a biological fluid can be subjected to eight different gas-liquid chromatography systems, designed to separate different groups of chemicals, and any peak from these instruments can be analysed by mass spectrometry and the result compared, by means of a computer, with similar data from an increasing number (already tens of thousands) of known compounds.[11] Such a system has already lead to the recognition of three new diseases—methylmalonicacidaemia, β-methylcrotonyl glycinuria, and pyroglutamic aciduria. Many countries have one or more centres with apparatus suitable for this kind of analysis.

Sources of Information

Once a disease is suspected of being metabolic, on either clinical or chemical grounds, the vast literature must be explored for more detailed information and, usually, if anything is to be achieved, this must be done within hours or a day or two. Present systems of information retrieval are wholly inadequate for this purpose but at least a start can be made. The most compendious sources on known diseases are the textbooks by Stanbury, Wyngaarden, and Fredrickson,[12] and Hsia and Inouye.[13] In addition it is essential to be able to refer to McKusick,[14] which lists 789 recessive and 149 sex linked human disorders, giving a brief clinical description and the most useful literature sources for further information. (The recessive and sex linked disorders are potential "inborn errors of metabolism"; the book also lists 944 dominantly inherited disorders which are not.)

The next most useful works are the books by Eastham and Jancar,[15] Crome and Stern,[16] Mehnert and Förster,[17] and Lamy *et al.*,[18] and the series of monographs published for the Society for the Study of Inborn Errors of Metabolism.[19-26] Indexes of signs and symptoms are, surprisingly, not available. Good lists are contained in *Recognizable Patterns of Human Malformation*[27] and in *Atlas of Mental Retardation Syndromes*,[18] but both of these are concerned with much besides inherited metabolic disease and only certain of the latter are included.

The subject lends itself to a system of computer-assisted diagnosis and an approach is being made towards this. A programme has been devised for matching a symptom complex against a matrix of signs and symptoms against individual cases of known diseases, but it will be some time before sufficient data can be put into the matrix for even a preliminary evaluation of its usefulness. Meanwhile a system which is proving useful is to maintain as a card index a check list of disorders, recording for each disease whether or not it usually presents with each of four groups of clinical features, mental subnormality, neurological disease, eye defects, and "other features," such as skeletal abnormality. hepatosplenomegaly, etc. The present state of knowledge concerning treatment is also assessed in four categories ranging from "established" to "none" and recorded on the card with any other information not yet included in the standard reference works referred to.

Since speed of action is so often important, clinicians should have a list of the centres in their country known to be actively interested in this area of disease for, though a centre may not have personal experience of a particular disorder, it is likely to know who has and, at least, it will appreciate the inquirer's need to telephone rather than to write a letter. Those who do not appreciate the need to be prepared are likely, instead, to be too late.

Care of a Clinically Diagnosed Patient

The detailed requirements for the management of patients in whom a specific diagnosis has been made vary with the disease. Several forms of treatment have been proposed and in Table II, column 3 an attempt has been made to assess whether the treatment is either of established value, has been proposed and preliminary results are promising, or whether it should be regarded as purely experimental at this stage. There are still

TABLE II—*Clinical Features and Investigational Possibilities of some Inherited Metabolic Diseases*

Disease	Clinical Features	Treatability	Heterozygote Tests	Antenatal Diagnosis	Enzyme
Acetophenetidin sensitivity (20030)	2, o-anaemia, methaemoglobinaemia	Est.			
Acid phosphatase deficiency (20095)	4, n, o-vomiting		Enz.	+	Acid phosphatase (E.C. 3.1.3.2)
Acrodermatitis enteropathica (20110)	4, o-skin, diarrhoea	Est.			
Adenylate kinase deficiency (20160)	4, o-anaemia	Nil	Enz.		Adenylate kinase (E.C. 2.7.4.3)
Adrenal hyperplasia type 1 (20170)	4, o-virilization, hypertension	Est.	Est.		Steroid 21-hydroxylase (E.C. 1.14.1.8)
Adrenal hyperplasia type 2 (20180)	4, o-virilization, hypertension	Est.			Steroid 11β-hydroxylase (E.C. 1.24.1.6)
Adrenal hyperplasia type 3 (20190)	4, o-salt loss	Est.			β-Hydroxysteroid dehydrogenase (E.C. 1.1.1.51)
Adrenal hyperplasia type 4 (20200)	4, o-hypospadias	Est.			
Adrenal hyperplasia type 5 (20210)	4, o-virilization	Est.			Steroid 17α-hydroxylase
hyper β-Alaninaemia (23740)	4, n	Nil			
Albinism type 1 (20310)	3, e-depigmentation, o-skin	Nil			o-Diphenol oxidase (E.C. 1.10.3.1)
Albinism type 2 (20320)	2, o-skin	Nil			
Albinism with haemorrhagic diathesis and pigmented cells in the reticuloendothelial system (20330)	3, o-skin colour, bleeding	Nil			
Albinism-deafness syndrome (30070)	3, o-Skin, Deafness	Nil			
Albinism, ocular (30050)	3, e-depigmented fundus, nystagmus	Nil			
Albinism ocular (Forsius-Eriksson type) (30060)	3, e-depigmented fundus, nystagmus	Nil			
Aldosterone deficiency (20340)	4, 0-fever, dehydration	Est.			
Alkaptonuria (20350)	3, n, e-ochronosis. o-black urine, arthritis	PP			Homogentisate oxygenase (E.C. 1.13.1.5)
*hyper*Ammonaemia type 1 (23720)	4, m, n, o-vomiting	PP		N	Ornithine carbamoyltransferase (E.C. 2.1.3.3)
*hyper*Ammonaemia type 2 (23730)	4, m, o-vomiting	PP			Carbamoylphosphate synthase (E.C. 2.7.2.5)
Anaemia, hypochromic (30130)	4, o-anaemia	Exp.			δ-Aminolaevulinic acid synthetase
Angiokeratoma, diffuse (30150)	3, e-cataracts, retinal pigmentation, o-skin, renal and, pulmonary failure	Nil			Ceramide trihexoside α-galactosidase (E.C. 3.2.1.22)
Antitrypsin deficiency (20740)	3, o-respiratory failure	Nil	Enz.		
Argininaemia (20780)	3, m, n	Nil		N	Arginase (E.C. 3.5.3.1)
Argininosuccinic aciduria (20790)	3, m, n, o-hepatomegaly, hair	Exp.		N	Argininosuccinate lyase (E.C. 4.3.2.1)
Aspartyl-glycosaminuria (20840)	3, m, o-skin	Nil			2-acetamido-1-(β¹-L-aspartamido)-1, 2-dideoxy-glucosidase
Ataxia, intermittent (20880)	3, n	Nil	Enz.		Pyruvate decarboxylase (E.C. 4.1.1.1)
*hyper*Bilirubinaemia type 2 (Dubin-Johnson) (23750)	3, o-jaundice, hepato-megaly	Exp.			
*hyper*Bilirubinaemia-shunt (23780)	2, o-splenomegaly, jaundice	Nil			
*hyper*Bilirubinaemia, transient familial neonatal (23790)	2, o-jaundice	Est.			
Blue diaper syndrome (21100)	4, m, n, c-constipation	Nil	Indir.		
Byler's disease (21160)	4, o-diarrhoea, jaundice, hepatosplenomegaly	Nil			
Carnosinaemia (21220)	4, m, n	Nil			Carnosinase
Carotinaemia, familial (11530)	2, o-skin, carotinaemia	Nil			
*a*Catalasaemia, Japanese (20020)	3, o-gum hypertrophy	Nil	Enz.		Catalase (E.C. 1.11.1.6)
*a*Catalasaemia, Swiss (20020)	3, o-gum hypertrophy	Nil	Enz.		Catalase (E.C. 1.11.1.6)
Chediak-Higashi syndrome (21450)	4, e-photophobia, o-skin, infections	Nil	Indir.		
Chloride diarrhoea (21470)	4, o-diarrhoea	Exp.			
Citrullinuria (21570)	4, m, n, o-vomiting	Exp.			Argininosuccinate synthetase (E.C. 6.3.4.5)
Crigler-Najjar syndrome (21880)	4, o-jaundice	Nil			UDP-glucuronyltransferase (E.C. 2.4.1.17)
Cystathioninuria (21950)	1			N	Homoserine dehydratase (E.C. 4.2.1.15)
Cystinosis type 1 (21980)	4, e-photophobia, o-bone	Exp.	Indir.		
Cystinosis type 2 (21990)	3, e-photophobia, retinal pigmentation	Exp.			
Cystinosis type 3 (22000)	1, e-crystals in cornea	Nil			
Cystinuria type 1 (22010)	2, o-calculi	Est.	Indir.		
Cystinuria type 2 (22010)	2, o-calculi	Est.	Indir.		
Cystinuria type 3 (22010)	2, o-calculi	Est.	Indir.		
Diabetes insipidus, nephrogenic (30480)	3, o-dehydration	Est.	Indir.		
Diabetes insipidus, neurohypophyseal type (30490)	3, o-dehydration	Est.			
Dibasic amino-aciduria type 1 (12600)	1	Nil			
Dibasic amino-aciduria type 2 (22270)	4, m, o-diarrhoea, hepto-megaly, vomiting	Exp.			
Diphosphoglycerate mutase deficiency of red cells (22280)	3, o-splenomegaly, haemolytic anaemia	Nil			Diphosphoglyceromutase (E.C. 2.7.5.4)
Disaccharide intolerance type 1 (22290)	4, o-diarrhoea	Est.			β-Fructofuranosidase (E.C. 3.2.1.26)
Disaccharide intolerance type 2 (22300)	4, o-diarrhoea	Est.			β-Galactosidase (E.C. 3.2.1.23)
Disaccharide intolerance type 3 (22310)	4, o-diarrhoea	Est.			β-Galactosidase (E.C. 3.2.1.23)
Dysautonomia (22390)	3, e-alachrymia, corneal anaesthesia, o-sweating	Nil			
Farber's lipogranulomatosis (22800)	4, m, n, o-skin	Nil			
Fatty metamorphosis of viscera (22810)	4, n, o-muscle	Nil			
Formimino transferase deficiency (22910)	3, m, o-anaemia	Nil			Formimino transferase
Fructose 1,6-diphosphatase deficiency (22970)	3, n, o-acidosis	Nil			Hexose diphosphatase (E.C. 3.1.3.11)
Fructose and galactose intolerance (22950)	3, n	Est.			
Fructose intolerance (22960)	4, m, o-hepatomegaly, vomiting, hypoglycaemia	Est.			Ketose-1-phosphate aldolase (E.C. 4.1.2.7)
Fructosuria, benign (22980)	1	Nil			Fructokinase (E.C. 2.7.1.4)
Frucosidosis (23000)	3, m, n, o-bone	Nil		N	α-L-Fucosidase
Galactokinase deficiency (23020)	3, e-cataract	Est.			Galactokinase (E.C. 2.7.1.6)
Galactosaemia, classical (23040)	4, m, e-cataract, o-jaundice, hepatomegaly	Est.	Enz.	+	Galactose-1-phosphate uridyltransferase (E.C. 2.7.7.10)
Galactosaemia, Duarte (23040)	1	Nil	Enz.		Galactose-1-phosphate uridyltransferase (E.C. 2.7.7.10)

TABLE II—*Continued*

Disease	Clinical Features	Treatability	Heterozygote Tests	Antenatal Diagnosis	Enzyme
Galactosaemia, Negro (23040)	3, m, e	Exp.			Galactose-1-phosphate uridyltransferase (E.C. 2.7.7.10)
GM1 Gangliosidosis type 1 (23050)	4, m, n, e-macular spot, o-hepatosplenomegaly, bone	Nil	Enz.	N	GM1 ganglioside β-galactosidase (E.C. 3.2.1.23)
GM1 Gangliosidosis type 2 (23060)	3, m, n	Nil		N	GM1 ganglioside β-galactosidase (E.C. 3.2.1.23)
GM2 Gangliosidosis type 1 (27280)	4, n, e-macular spot	Nil	Enz.	+	β-Acetylglucosaminase A (E.C. 3.2.1.30)
GM2 Gangliosidosis type 2 (26880)	4, n, e-macular spot	Nil	Enz.		β-Acetylglucosaminase A and B (E.C. 3.2.1.30)
GM2 Gangliosidosis type 3 (23070)	3, m, n, e-macular spot	Nil			β-Acetylglucosaminase A (E.C. 3.2.1.30)
GM3 Gangliosidosis (24550)	4, m, n, o-splenomegaly	Nil			GM3 ganglioside-β-galactosidase (E.C. 3.2.1.23)
Gaucher's disease type 3 (23100)	3, o-splenomegaly	Nil	Enz.	N	Cerebroside β-glucosidase (E.C. 3.2.1.21)
Glucose-galactose malabsorption (23160)	4, o-diarrhoea	Est.			
Glucose-6-phosphate dehydrogenase deficiency (30590)	2, o-haemolytic anaemia, jaundice	Exp.	Enz.	N	Glucose-6-phosphate dehydrogenase (E.C. 1.1.1.49)
Glutathione peroxidase deficiency (23170)	2, o-haemolytic anaemia	Nil			Glutathione peroxidase (E.C. 1.11.1.9)
Glutathione reductase deficiency (23180)	3, n, o-haemolytic anaemia, hepatosplenomegaly	Exp.			Glutathione reductase (E.C. 1.6.4.2)
Glutathione synthetase deficiency (23190)	3, o-haemolytic anaemia, jaundice	Nil			Glutathione synthetase (E.C. 6.3.2.3)
*hypo*Glycaemia due to deficiency of glycogen synthetase (24060)	4, m, n	Nil			UDP-glucose-glycogen glucosyl transferase (E.C. 2.4.1.11)
*hyper*Glycinaemia, isolated (23830)	4, m, n	Exp.			
Glycogen storage disease limited to heart (23210)	3, o-heart	Nil			
Glycogen storage disease type 1 (23220)	3, o-hepatomegaly, hypoglycaemia	PP	Indir.		Glucose-6-phosphatase (E.C. 3.1.3.9)
Glycogen storage disease type 2 (23230)	3, o-cardiomegaly, muscle weakness	Nil	Enz.	+	α-1:4-glucosidase
Glycogen storage disease type 3 (23240)	3, o-hepatosplenomegaly	Exp.		N	Amylo-1:6-glucosidase (E.C. 3.2.1.33)
Glycogen storage disease type 4 (23250)	4, o-hepatosplenomegaly	Nil	Enz.		α-glucan branching glycosyltransferase (E.C. 2.4.1.18)
Glycogen storage disease type 5 (23260)	2, o-muscle pain	Nil			Glycogen phosphorylase (E.C. 2.4.1.1)
Glycogen storage disease type 6 (23270)	3, o-hepatomegaly, hypoglycaemia	PP	Enz.		Glycogen phosphorylase (E.C. 2.4.1.1)
Glycogen storage disease type 7 (23280)	2, o-muscle pain, haemolytic anaemia	Nil			Muscle phosphofructokinase (E.C. 2.7.1.11)
Glycogen storage disease type 8 (30600)	3, m, n, e-cataract, o-hepatomegaly	Exp.			Liver phosphorylase kinase (E.C. 2.7.1.38)
Granulomatous disease due to leucocyte malfunction (23370)	3, o-hepatosplenomegaly, skin, lymphadenitis	Nil			Glutathione peroxidase (E.C. 1.11.1.9)
Granulomatous disease due to leucocyte malfunction (30640)	4, o-hepatomegaly, splenomegaly, skin lymphadenitis		Indir.		
Hartnup disease (23450)	3, m, n, o-skin	Exp.			
Hexokinase deficiency (23570)	3, o-haemolytic anaemia, jaundice	Nil			Hexokinase (E.C. 2.7.1.1)
Hexose phosphate isomerase deficiency (23575)	3, o-haemolytic anaemia	Nil			Glucose phosphate isomerase (E.C. 5.3.1.9)
Histidinaemia (23580)	2, m	PP			Histidine ammonia-lyase (E.C. 4.3.1.3)
Homocystinuria (23620)	3, m, e-ectopia lentis, o-marfanoid, thrombosis	PP	Indir.	N	L-serine dehydratase (E.C. 4.2.1.13)
Homocystinuria (23620)	3, o-bone	Exp.			N^5-methyl tetrahydrofolate methyl transferase
β-Hydroxy-isovaleric aciduria and β-methyl crotonylglycinuria (21020)	3, n, o-anaemia, odour	Exp.			β-methylcrotonoyl-CoA carboxylase (E.C. 6.4.1.4)
Hydroxykynureninuria (23680)	4, m	Nil			Kynureninase (E.C. 3.7.1.3)
Hydroxylysinuria (23690)	3, m, n	Nil			
Hydroxyprolinaemia (23700)	3, m, o-haematuria, hyperactive	Exp.			Hydroxyproline oxidoreductase
Hypoxanthine-guanine phosphoribosyl transferase deficiency (30800)	4, m, n, o-cataract	Exp.	Indir.	+	Hypoxanthine-guanine phosphoribosyl transferase (E.C. 2.4.2.8)
Iminoglycinuria (24260)	1	Nil			
Indolyl-acroyl-glycinuria with mental retardation (24290)	3, m	Nil			
Isoniazid inactivation (24340)	1	Nil			
Ketoaciduria with mental deficiency (24510)	3, m, n, o-hypogonadism	Nil			
Krabbe disease (24520)	4, n	Nil	Enz.		Galactocerebroside-β-galactosidase (E.C. 3.2.1.23)
Lactic acidosis (24540)	4, m, n	Exp.			
Lecithin-cholesterol acetyl-transferase deficiency (24590)	3, e-corneal deposits, o-anaemia	Nil			Lecithin-cholesterol acyltransferase
Lipase deficiency (24660)	3, o-steatorrhoea	Exp.			Lipase (E.C. 3.1.1.3)
an α-Lipoproteinaemia (20540)	3, o-hepatosplenomegaly, tonsils	Exp.	Enz.		α-Lipoprotein
a β-Lipoproteinaemia (20010)	4, n, e-retinal pigmentation, o-red cells, malabsorption	Exp.			β-Lipoprotein
Lowe's oculo-cerebro-renal syndrome (30900)	4, m, n, e-cataracts, nystagmus, o-muscle, bone	Nil	Indir.		
*hyper*Lysinaemia (23870)	3, m, e-ectopia lentis	Exp.			Lysine-ketoglutarate reductase
Lysine intolerance (24790)	4, n, o-vomiting	PP			L-Lysine: NAD oxido-reductase
*hypo*Magnesaemic tetany (30760)	4, n	Exp.			
Mannosidosis (24850)	4, m, e-cataract, o-hepatosplenomegaly, bone	Nil		N	α-Mannosidase (E.C. 3.2.1.24)
Maple-syrup-urine disease (24860)	4, m, o-odour	Nil	Enz.	+	Keto acid decarboxylase
Maple-syrup-urine disease, intermittent (24860)	3, m, odour				Keto acid decarboxylase
Metachromatic leucodystrophy with mucopolysacchariduria (24990)	4, m, n	Nil			
Metachromatic leucodystrophy (25010)	4, m, n	Nil	Enz.	+	Cerebroside sulphate sulphatase (arylsulphatase A) (E.C. 3.1.6.1)
Methaemoglobin reductase deficiency (NADPH) (25070)	2, o-anaemia	Nil			Methaemoglobin: NADPH oxidoreductase
Methaemoglobin reductase deficiency (NADH) (25080)	3, m, o-cyanosis	Exp.			Methaemoglobin: NADH oxidoreductase
*hyper*Methioninaemia (23890)	4, o-liver	Exp.			
Methionine malabsorption (25090)	4, m, o-odour, diarrhoea	Exp.			
Methylmalonic aciduria type 1 (25100)	4, m, o-vomiting, anaemia	Exp.			Methylmalonyl-CoA mutase (E.C. 5.4.99.2)
Methylmalonic aciduria type 2 (25110)	4, m, o-vomiting, anaemia	Exp.			Methylmalonyl-CoA isomerase
Mucopolysaccharidosis type 1—Hurler (25280)	4, m, e-cataract, o-bone, hepatosplenomegaly	Nil		+	
Mucopolysaccharidosis type 2—Hunter (30990)	4, m, o-bone, hepatomegaly	Nil			
Mucopolysaccharidosis type 3—San Filippo (25290)	4, m, e-cataract, o-bone, hepatomegaly	Nil			
Mucopolysaccharidosis type 4—Morquio (25300)	3, o-bone	Nil			
Mucopolysaccharidosis type 5—Scheie (25310)	3, e-cataract	Nil			
Mucopolysaccharidosis type 6—Maroteaux-Lamy (25320)	3, e-cataract, o-bone	Nil			

TABLE II—*Continued*

Disease	Clinical Features	Treatability	Heterozygote Tests	Antinatal Diagnosis	Enzyme
Myeloperoxidase deficiency (25460)	3, o-candidiasis	Exp.			Myeloperoxidase
Necrotizing encephalopathy (25600)	4, m, n, o-acidosis	Exp.			Pyruvate carboxylase (E.C. 6.4.1.1)
Niemann-Pick disease (25720)	4, m, n, e-macular spot, o-hepatosplenomegaly	Nil		+	Sphingomyelinase
Orotic aciduria (25890)	3, o-anaemia	Exp.	Enz.		Orotidylic decarboxylase (E.C. 4.1.1.23)
Oxalosis type 1 (25990)	3, o-calculi	Nil			2-oxoglutarate: glyoxylate carboligase
Oxalosis type 2 (26000)	2, o-calculi	Nil			D-glyceric dehydrogenase
Pentosuria (26080)	1				Xylitol: NADP oxidoreductase (E.C. 1.1.1.10)
Phenylketonuria (26160)	3, m, o-skin	Est.	Indir.		Phenylalanine-4-hydroxylase (E.C. 1.14.3.1)
*hypo*Phosphataemia (30780)	3, o-bone	Exp.			
*hypo*Phosphatasia (14630)	3, o-bone	Nil			Alkaline phosphatase
*hypo*Phosphatasia (Phosphoethanolaminuria) (24150)	4, o-bone	Nil	Enz.		Alkaline phosphatase
Phosphofructokinase deficiency	2, o-haemolytic anaemia	Nil			Red blood cell phosphofructokinase (E.C. 2.7.1.11)
Phosphoglycerate kinase deficiency (31180)	2, o-haemolytic anaemia	Nil	Enz.		Phosphoglycerate kinase (E.C. 2.7.2.3)
Porphyria-congenital (26370)	4, o-splenomegaly, skin	Nil			Uroporphyrinogen III cosynthetase
Prolinaemia type 1 (23950)	2, m, o-haematuria, deafness, fits	Exp.			L-Proline:NAD (P) 5-oxidoreductase (E.C. 1.5.1.2)
Prolinaemia type 2 (23950)	3, m, o-fits	Nil			Δ^1pyrroline-5-carboxylate dehydrogenase (E.C. 1.5.1.2)
Propionic acidaemia (23200)	4, o-anaemia	Exp.			Propionyl-CoA carboxylase (E.C. 6.4.1.3)
Pyridoxine dependency (26610)	3, n	Est.			Glutamate decarboxylase (E.C. 4.1.1.15)
Pyroglutamic aciduria	4, m, n, o-anaemia, vomiting	Nil			
Pyruvate kinase deficiency (26620)	4, o-splenomegaly, haemolytic anaemia	Exp.			Pyruvate kinase (E.C. 2.7.1.40)
Refsum's disease (26650)	3, n, e-retinal pigmentation, o-skin	Exp.	Enz.	N	Phytanic acid oxidase
Saccharopinuria (26870)	3, m	Nil			
Sarcosinaemia (26890)	3, m	Nil	Indir.		Sarcosine dehydrogenase
*hyper*Serotoninaemia (23960)	3, n, o-rage, flush				
Smith-Strang disease (27050)	4, m, o-odour	Nil			
Sulphocysteinuria (27230)	4, n, e-ectopia lentis	Nil			Sulphite oxidase (E.C. 1.8.3.1)
Suxamethonium sensitivity, dibucaine type (27240)	2, o-drug sensitivity, apnoea	Est.			Cholinesterase (E.C. 3.1.1.8)
Suxamethonium sensitivity, fluoride type (27240)	2, o-drug sensitivity, apnoea	Est.			Cholinesterase (E.C. 3.1.1.8)
Suxamethonium sensitivity, silent type (27240)	2, o-drug sensitivity, apnoea	Est.			Cholinesterase (E.C. 3.1.1.8)
Thyroid dyshormonogenesis type 1 (27440)	4, m, o-goitre	Est.			
Thyroid dyshormonogenesis type 2A (27450)	4, m, o-goitre	Est.			
Thyroid dyshormonogenesis type 2B (27460)	4, m, o-goitre	Est.			
Thyroid dyshormonogenesis type 3 (27470)	4, m, o-goitre	Est.			
Thyroid dyshormonogenesis type 4 (27480)	4, m, o-goitre	Est.			Iodotyrosine dehalogenase
Thyroid dyshormonogenesis type 5 (27490)	4, m, o-goitre	Est.			
Triose phosphate isomerase deficiency (27580)	3, n, o-haemolytic anaemia	Nil	Enz.		Triosephosphate isomerase (E.C. 5.3.1.1)
Trypsinogen deficiency (27600)	3, o-oedema, malnutrition	Exp.			Trypsinogen
Tryptophanuria (27610)	3, m, n, o-skin	Nil			
T-substance anomaly (27620)	3, m	Nil			
Tyrosinaemia (27670)	4, o-liver, bone	Exp.			p-Hydroxyphenylpyruvate hydroxylase (E.C. 1.14.2.2)
Tyrosine transaminase deficiency (27660)	3, m	Exp.			Tyrosine aminotransferase (E.C. 2.6.1.5)
Tyrosinosis (Medes) (27680)	3, o-muscle	Nil			
*iso*Valeric acidaemia (24350)	4, n, o-vomiting, acidosis, odour	Nil			Isovaleric acid CoA dehydrogenase
Valinaemia (27710)	3, m, o-vomiting	Exp.	Indir.	N	Valine transaminase
Wilson's disease (27790)	3, n, e-kayser-fleischer rings, o-liver	Est.	Indir.		Caeruloplasmin (p-phenylene diamine oxidase)
Wolman's disease (27800)	4, o-hepatosplenomegaly	Nil			Acid lipase (E.C. 3.1.1.3)
Xanthinuria (27830)	2, o-calculi				Xanthine oxidase (E.C. 1.2.3.2)
Xeroderma pigmentosum (27870)	3, o-skin	Nil			Nucleic acid repair enzyme
Xylosidase deficiency (27890)	3, n	Nil			β-Xylosidase (E.C. 3.2.1.37)

Such a table can be neither complete nor wholly accurate. It may be scanned either for the disease or for symptoms. It does not contain sufficient information for diagnosis and is only intended to lead to further sources of information.

Disease.—The alphabetical system adopted is that of McKusick,[14] modified to accord with British spelling. Prefixes indicating quantity—for example, hyper- hypo-, a- and Greek letters—are ignored for listing purposes. The number in brackets is that of McKusick;[14] those starting with 2 and 3 are recessive and six-linked respectively.

Clinical features.—The severity of the condition is graded 1-4. 1 = totally benign, 2 = benign in the absence of a precipitating agent such as a drug, 3 = mild to moderate, 4 = severe to lethal. The main presentation is indicated by m = mental subnormality, n = neurological degeneration, e = eye abnormalities, and o = other features. The last two are subdivided.

Treatment is regarded as Est. = established, PP = proposed and with promising initial trials, Exp. = still experimental, and Nil = none proposed.

Heterozygote tests.—Enz. = based on enzyme assay, Indir. = indirect—that is, loading tests and other studies.

Antenatal diagnosis.—The criteria for this are not yet established with certainty in any instance. + = success in some cases, N = enzyme is present in amniotic cells and therefore an affected fetus might be expected to be associated with cells deficient in the enzyme.

Addendum to Table II

Since preparing Table II the following diseases have been noted as suitable for inclusion in a subsequent revision. Several names suggest the diagnostic features and further information can be obtained from McKusick.[14]

Addison's disease and spastic paraplegia (20150)
Alaninuria with microcephaly, dwarfism, enamel hypoplasia, diabetes mellitus (20290)
Amaurotic family idiocy, juvenile (Batten, Vogt-Spielmeyer) (20420)
Amino aciduria with mental deficiency, dwarfism, muscular dystrophy, osteoporosis, and acidosis (20480)
β-Aminoisobutyric aciduria (21010)
*hyper*Calciuria (23810)
Cephalin lipidosis (21280)
Cerebral cholesterinosis (21370)
Cholesterol ester storage disease of liver (21500)
*hyper*Cystinuria (23820)
Dyggve-Melchior-Clausen disease (22380)
Enterokinase deficiency (22620)
Glycoprotein storage disease (23290)
Glyoxylase type 2 deficiency (23320)
Gout (30620)
Hooft's disease (23630)
Leber's optic atrophy (30890)
*hyper*Lipidaemia type 5 (23840)
*hyper*Lipidaemia type 6 (23850)
Lipidosis, juvenile dystonic (24680)
Lipid transport defect of intestine (24670)
*hyper*Lipoproteinaemia type 1 (23860)
*hypo*Magnesaemia (24130)
Megaloblastic anaemia responsive to folic acid, ataxia, mental retardation, and convulsions (24930)
Mucolipidosis type 1 (25240)
Mucolipidosis type 2 (25250)
Mucolipidosis type 3 (25260)
Nephrosis, congenital (25630)
Neurovisceral storage disease with curvilinear bodies (25700)
Peroxidase and phospholipid deficiency in eosinphils (26150)
*hyper*Phosphatasia with mental retardation (23930)
Phosphoglycerate kinase deficiency of erythrocyte (26170)
*hyper*Pipecolataemia (23940)
Polysaccharide, storage of unusual (26360)
Pseudo-hypophosphatasia (26440)
Pseudo-vitamin D deficiency rickets (26470)
Renal tubular acidosis (26710)
Renal tubular acidosis type 2 (31240)
Renal tubular acidosis type 3 (26720)
Renal tubular acidosis with progressive nerve deafness (26730)
Rubinstein syndrome (26860)
Sea-blue histiocyte syndrome (26960)
Sialuria (26990)
Sidbury syndrome (27000)
Sulphatidosis, juvenile, Austin type (27220)
Trimethylaminuria (27570)
*hyper*Uricaemia, ataxia, deafness (30720)
*hyper*Uricaemia, infantile, with abnormal behaviour and normal hypoxanthine guanine phosphoribosyl transferase (24000)
*hyper*Uricaemia, lipodystrophy and neurologic defect (24010)
Vitamin B_{12} metabolic defect (27740)
Vitamin-D dependent rickets (27750)
Wolman's disease with hypolipoproteinaemia and acanthocytosis (27810)
Xanthurenicaciduria (27860)

many diseases for which no useful proposals for treatment have been made.

The commonest approach has been to provide a diet deprived of an offending constituent, the greatest experience having been obtained with the treatment by this means of phenylketonuria and galactosaemia. These same basic diets are susceptible to alteration to suit other metabolic disorders (for example, histidinaemia and tyrosinosis) and several manufacturers are willing to co-operate in meeting the special requirements of particular patients. Sources of special diets are listed in Table III.

The completely synthetic diet developed by Winitz *et al.*[29] for metabolic studies of astronauts provides a basis for endless variation to suit particular diseases.

The basic diet for the condition will inevitably be highly artificial and it is important not to neglect the supplementary factors. Early experience with phenylketonuria, where growth retardation and severe degrees of skin excoriation sometimes occurred, led to the discovery that an unusually wide range of vitamin and mineral supplements was necessary for satisfactory progress.[30] It is customary to add to all artificial diets all the essential vitamins in the form of Ketovite Tablets and Ketovite (Supplement) Liquid (Paines and Byrnes) and, to most diets, a mineral mixture based on that of Westall,[31] such as Maple Syrup Mineral Mixture (Scientific Hospital Supplies Ltd.). Infants not receiving natural milk may also be deprived of adequate amounts of calcium. These considerations are still being overlooked in other clinical situations calling for artificial diets.[32 33] The pocket book by Wood[34] contains valuable practical information on this and other aspects of infant nutrition. Other artificial supplements that may also find a place in treating certain diseases include low molecular weight glucose polymers and medium-chain triglycerides (see Table III).

Finally, of the greatest value in the successful management of these forms of treatment is a close liaison between the biochemist (to monitor the treatment), the dietician (who should meet the parents regularly to discuss feeding problems), and the social worker (to deal with problems in the home where the treatment should be established, if not from the outset, at the earliest possible time).

TABLE III—*Sources of Special Diets*

Only *initial* diets are included (satisfactory for a week or two). Information about alternative foods, such as low protein bread and biscuits should be obtained from the dietitian. The Maple Syrup Mineral Mixture (SHS) is of general value and can be added to some of the other diets with advantage.

Disorder	Preparation	Manufacturer
Galactosaemia	Cow and Gate LL Food	U
	Galactomin Formula 17 or 18	U
	Nutramigen	MJ
	Velactin	W
Histidinaemia	Albumaid Histidine Low	SHS
	Aminex Biscuits	L
	HF 2	U
Homocystinuria	Albumaid X Methionine	SHS
	Aminex Biscuits	L
Lactose intolerance	Cow and Gate LL Food	U
	Galactomin Formula 17 or 18	U
	Prosobee	MJ
	Sobee	MJ
	Velactin	W
Maple syrup urine disease	Maple Syrup Mineral Mixture	SHS
	MSUD Aid	SHS
Methioninaemia	Albumaid X Methionine	SHS
	Aminex Biscuits	L
	Formula LPTM(2)	U
Phenylketonuria	Albumaid X P	SHS
	Aminex Biscuits	L
	Aminogran	AH
	Cymogran	AH
	Lofenalac	MJ
	Minafen	U
	PK Aid No. 1	SHS
	PK Aid No. 2	SHS
Prolinaemia	MP1 HPD	SHS
Tyrosinaemia	Albumaid X Phenylalanine and Tyrosine	SHS
	Aminex Biscuits	L
	Formula LPT(1)	U
	Formula LPTM(2)	U

Other Preparations of Value

	Preparation	Manufacturer
Medium chain triglycerides	Alembicol D	LK
	MCT 1 Milk	U
	MCT Oil	MJ, SHS, U
	Portagen	MJ
Fat emulsion	Prosparol	BDH
Glucose polymers	Caloreen	SHS
	Gastrocaloreen	SHS

Manufacturers

UNITED KINGDOM OFFICES

AH Allen and Hanburys Ltd., Bethnal Green, London E2 6LA (Tel: 01-739 4343)

BDH B.D.H. Pharmaceuticals Ltd., Birkbeck Street, London E.2 (Tel: 01-739 3451)

L Liga Infant Food Ltd., Liga House, 23 Saxby Street, Leicester LE2 0NL (Tel: 0533-57748)

LK E. J. R. Lovelock, Oaklands House, Oakland Drive, Sale, Manchester M33 1WS (Tel: 061-962 4423)

MJ Mead Johnson Laboratories, Langley, Slough SL3 6EB (Tel: 0753-43261)

SHS Scientific Hospital Supplies Ltd., 38 Queensland Street, Liverpool 7 (Tel: 051-709 3588)

U Unigate Foods Ltd. (Cow and Gate, Trufood products), 40 Stoke Road, Guildford, Surrey (Tel: 0483-68181)

W A. Wander Ltd., 42 Upper Grosvenor Street, London W1X 9PG (Tel: 01-499 3931)

INTERNATIONAL AND OVERSEAS OFFICES

LK *Italy.*—Alembic Oil Italiana s.r.l., Piazza Della Vittoria 4, 16121 Genoa, Italy (Tel: 566570, Genoa)

U *International.*—Unigate International Division, Bythesea Road, Trowbridge, Wiltshire, U.K. (Tel: Trowbridge 3611)
Italy.—Medifood, S.R.L., Specialità Dietoterapeutiche, Sede ed amministrazione, Via Balbi, 31/1, 16126 Genoa, Italy.
Yugoslavia.—Belje Trufood Infant Nutritian Service, Vukorvarska 312, Osijek, Yugoslavia.

L *Australia.*—Tomasetti & Son Pty. Ltd., 634, Graham Street, Port Melbourne, Australia (Tel: 64.4221)
Belgium.—Betterfood N.V., Kapelsesteenweg 753, B-2070-Ekeren-2, Belgium (Tel: 03-64.25.50)
Canada.—Messrs. TOP's Importing Limited, Box 190, Grimsby, Ontario, Canada (Tel: 416-945.5436)
Eire.—Messrs. LIGA Ireland Ltd., 61, Middle Abbey Street, Dublin-1, Eire (Tel: 48956)
France.—"CODIME" S.à.r.l. Comptoir d'Importation et d'Exportation, 4, rue Guillaume Léfèbvre, Roubaix-Nord, France (Tel: 73.14.63)
Germany.—LIGA Nahrungsmittel G.mbH, Moltkebahnhof, 51-Aachen, West Germany (Tel: 50.59.11)
Holland.—Liga Fabrieken n.v., P.O. Box 27, Roosendaal, Holland (Tel: 1650-34940)
Italy.—LIGA Italia s.r.l., Via Valsugana 37-39, Lainate-20020, Italy (Tel: 937.02.62)
Jordan.—Elias Bakhit Stores, King Hussein Street, Amman, Jordan (Tel: 22560)
Lebanon.—S.E.C.R. Societe d'Entreprises Commerciales et de Representations, Rue al-Moutrane, Beyrouth, Lebanon (Tel: 242401-236889)
Malta.—Strand Palace Store, 203 B, Old Bakery Street, Valletta, Malta G.C. (Tel: 26540)
Norway.—Norsk Medisinaldepot, Dag Hammarskjldsv 58, Oslo-1, Norway (Tel.: 2243.50)
South Africa.—Prima Vera Trading Co., P.O. Box 49, Pretoria, South Africa (Tel: 70-9134)
South America.—Handelmaatschappij J. L. Jong & Kiem N.V. P.O. Box 272, Paramaribo, Suriname, South America (Tel: 6644-5-6)
Spain.—Inibsa S.A., Anevida Sarriah 130-132, Barcelona-17, Spain.
Sweden.—Aktiebolaget Hollandska, Vanadisvagen 29, 113.23 Stockholm, Sweden (Tel: 33.23.75-33.84.82)
Switzerland.—Barbezat & Cie, 2114-Fleurier-Ntel, Switzerland (Tel: 038-91315)

MJ *Austria.*—Frika, Pharmazeutische Fabrik GmbH., Postfach 43, A-1091 Vienna, Austria (Tel: Frikachemie 34.76.21)
Belgium.—Mead Johnson Benelux S.A., 77-79 rue Berkendael, Brussels 6, Belgium (Tel: 45.38.60)
Canada.—Mead Johnson Laboratories, 95 St. Clare Avenue West, Toronto 7, Ontario, Canada (Tel: 416.921)
Denmark.—R. Baungaard & Co., Naerumgaard No: 10, Naerum, Denmark.
France.—Laboratoires Allard, 10, Avenue de Messine, Paris 80, France (Tel: Laboallard 522.62.50)
Germany.—Paul Lappe, GmbH, Deutsche Bristol GmbH, Rosenstrasse 10-20, 5060 Bensberg b. Koeln, Germany (Tel: Lapperemedia 64184)
Norway.—Norsk Medisinaldepot, Postboks 766, Ulvenceien 58, Oslo, Norway.
Sweden.—Kemi-Intressen, Aktiebolag Chemical Limited, P.O. Box 16363, 10327 Stockholm 16, Sweden (Tel: Sodium 23.59.60)
Switzerland.—Globopharm Ag., Seestrasse 200, Kusnacht, Zurich, Switzerland
U.S.A.—Bristol Myers Co. International Division, 2404, Pennsylvania Avenue, Evansville, Indiana, 47721, U.S.A.

Opportunity for Experimental Therapy

Dietary restriction is by no means the only approach to therapy and in disorders of many essential amino-acids may not even be feasible. Excretion of homocystine and of hydroxyproline has been facilitated (in the, as yet, unproved belief that this will be to the advantage of the patient) by inhibiting re-absorption of these amino-acids by the renal tubule, the first by adminis-

tering arginine intravenously,[35] the second by adding glycine to a normal diet.[36]

Experiments have been performed in animals with enzymes enclosed in semipermeable microcapsules, blood being shunted through a column of these.[37] Urease has been used to treat uraemia in dogs[37] and catalase for treating acatalasaemic mice.[38] Patients have been treated with parenteral injections of enzymes —for example, glycosidase for glycogen storage disease,[39 40] uricase for hyperuricaemia.[41] The results with both techniques are encouraging. Serious attempts at organ transplants have been made for haemophilia in dogs[42] and for Gaucher's disease in man.[43] Opportunities come so rarely and often there is so little to offer as an alternative that, provided suitable facilities exist for meaningful studies to be made, novel forms of treatment can be justified and indeed may be the only way in which real progress will ultimately be made.

Neonatal Screening

In most cases, where an established treatment is available, it is of crucial importance to begin this before clinical damage has occurred. Ideally, galactosaemia and maple syrup urine disease should be treated from birth and phenylketonuria before 3 months. This has led to the introduction over wide areas of early detection programmes of varying complexity from the Phenistix (Ames Co.) test for phenylketonuria—once nearly universal in the Western World but now considered inadequate —through chromatographic tests for o-hydroxyphenylacetic acid and some related phenolic acids;[44] Guthrie and Susi's[45] microbiological tests for phenylketonuria, which are claimed to be adaptable to the detection of up to 16 disorders,[46] automated fluorimetric determination of plasma phenylalanine for phenylketonuria;[47] to paper chromatographic procedures for whole blood[48] or plasma.[49 50] Our own experience with the latter technique[51] suggests that histidinaemia and prolinaemia may be as common as phenylketonuria. The yield from a population of 1 million (20,000 births per year) has been 7 diagnoses per year. The operation of such a scheme has involved each year about 50 children making an average of three outpatient visits each and admitting eight children to hospital for further investigation or treatment.

Screening programmes have also been attempted for galactosaemia,[52 53] but ideally these should be applied to cord blood and not delayed for even the minimum of six days called for by the Medical Research Council Working Party on Phenylketonuria for phenylketonuria screening.[54]

Antenatal Detection

The development of techniques for amniocentesis has encouraged the thought that an affected fetus might be recognized from the composition of the amniotic fluid, the microscopic (light or electron) and staining characteristics of the cells it contains, the specific enzyme activity of the cells before or after they have been cultured or, in the case of sex-linked disorders, the nuclear sex of the cells. The purpose is to recognize the condition early enough for the safe induction of abortion where there is no treatment or, where treatment can be given, to introduce this at the earliest possible stage. There have been some successes with a variety of diseases—enough, unfortunately, to cause enthusiasm to outstrip knowledge—and it is necessary to review some of the uncertainties still to be removed before these techniques can be relied upon.

There are still insufficient data on the composition of amniotic fluid at different periods of gestation and the initial promise that pregnanetriol determination is of value in the recognition of the adrenogenital syndrome in utero[55] remains controversial.[56, 57] The determination of enzyme activity in amniotic cells is fraught with uncertainties. Many of the cells in the fluid as collected are dead and enzyme activity referred to cell numbers, protein content, nucleic acid content, or even to the activity of another enzyme will be affected by the number of dead cells in the sample. Sutcliffe and Brock[58] have shown that the activity of five enzymes in uncultured amniotic cells is so low that a little contamination by erythrocytes can affect the result. To overcome this, cells have been cultured so that determinations can be made on living cells but, apart from the delay this introduces, it is found that the enzyme content is affected by the degree of confluence of the cell cultures.[59]

Since cells from a fetal heterozygote are expected to have less than normal enzyme activity, it will be necessary to define the values in the homozygous affected fetus very precisely. It is most important that these methods of recognizing affected subjects do not fall into disrepute with either medical practitioners or their patients through too hasty or over-enthusiastic application.

Examination of the cells themselves may be of value and Hug[60] *et al.* (1970) have reported vacuoles in amniotic cells associated with Pompe's disease (glycogenosis type II). Metachromatic staining of amniotic cells has also been of value in some hands in the antenatal diagnosis of the mucopolysaccharidoses (Danes and Bearn,[61] 1967) but this too has not received universal acceptance (Taysi[62] *et al.*, 1969) and it remains to be seen whether later modifications (Danes[63] *et al.*, 1970) will be more satisfactory.

In column 5 of Table 2 those diseases for which an abnormal fetus has been recognized prior to birth are indicated. For several enzyme deficiency diseases the appropriate enzyme has been shown to be present in normal amniotic cells. In the presence of an affected fetus, therefore, it might be expected that a deficiency of the enzyme will be demonstable when the opportunity arises to test this. These conditions are also indicated in Table 2, column 5. For the time being, however, where the results of such tests are used as an indication for abortion after adequate explanation to the parents, the abortus should always be examined to discover whether or not the prediction was correct.

Heterozygote Detection

The selection of cases for further investigation by amniocentesis can be helped if it is known that both parents are heterozygotes for the disease. If they have had an affected child then this is not in doubt but if their anxiety arises from a more remote family history an attempt should first be made to establish their status. Moreover, normal siblings of an affected child often desire to know the risk of the disease to their own children. Though in no instance can heterozygotes be determined with certainty there are several conditions for which tests have been devised (Table II, column 4) and some of these show a considerable ability to discriminate the heterozygote from the normal homozygote. For example, phenylalanine-loading tests for phenylketonuria can discriminate in 96% of cases and an enzyme test for galactosaemia in 96·8%.

These tests have not been the subject of very intensive study but there is now a much greater need for them and there is likely to be considerable progress in the quality and range of this type of investigation. In general the tests become more discriminating if the enzyme can be studied directly, especially if its activity can be related to that of another, unaffected, enzyme rather than to cell counts or to protein concentration. Unfortunately not all enzymes are present in such accessible cells as erythrocytes, leucocytes, skin or cultured skin "fibroblasts." Nevertheless, in some instances even needle biopsy of liver or kidney might be justified to establish the genetic status of the subject if it can be shown that analysis of these tissues will give more reliable information than the simpler less direct tests.

Conclusion

Inherited metabolic disease is a field of medicine for which the present system of medical care, based on family practitioner, consultant paediatrician, district general hospital, and regional reference laboratory is not well adapted. The problem is characterized by a large number of moderately rare but specific clinical entities for which unusual methods of investigation and

treatment are required. Expressed in this way it becomes clear that there may be other medical fields (say, unusual but specific virus infections or immunological diseases) for which the present discussion may provide some common solutions.

It is recommended that a few (say, five for a population of 50 million) specialist centres should be established with common systems of communication and access to systematically maintained stores of information. The centres would begin by sharing responsibility for specialized techniques of investigation and treatment, decentralizing these as the need arose. Research into the best methods of communication between such centres and the medical community at large should be undertaken. Only in this way can the ever increasing number of specific diseases be realistically encompassed, and the establishment of such a system may provide lessons for other branches of medicine. There is a real danger at present that the uncoordinated extension by laboratory-based enthusiasts of the more comprehensive screening programmes already established in Manchester, Birmingham, and a few other towns will create problems of management which clinicians have barely begun to consider.

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