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NUTRITION AND METABOLIC DEFECTS

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Historical aspects of inborn errors of metabolism

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Chemical basis of individuality

An inborn error of metabolism is a metabolic defect caused by an abnormality in one or more genes. An abnormality present at birth is not necessarily inborn: the foetus may acquire congenital disease such as syphilis or deformity through intra-uterine injury. Of more direct nutritional interest are the diseases of the newborn that occur through administration of substances to the pregnant woman: malformations of infants may be caused by the antivitamin aminopterin (Warkany, Beaudry & Hornstein, 1959) or by tolbutamide given to a diabetic mother (Larrson & Sterky, 1960); the analogue of vitamin K, naphthaquinone, can cause hyperbilirubinaemia and even kernicterus in the newborn (Crosse, Meyer & Gerrard, 1955; Allison, 1955; Meyer & Angus, 1956).

Until a century ago, physicians paid a great deal of attention to constitution in disease. From ancient times it has been known that a tendency to a certain disease is inherited since certain diseases run in families and tend to be commoner in persons of particular constitutions. The Hippocratic work, *Περὶ Χυμῶν*, states: 'As to the modes of diseases, it is possible by enquiry to discover that some are inborn, others due to the country, others to the body, and some due to food and the condition of the disease or seasonal.' It was easy to recognize that structural defects could be inherited, such as extra fingers, hare-lip or achondroplasia. Other inherited abnormalities, such as haemophilia or colour-blindness, appeared to be functional rather than structural. As knowledge advanced, the distinction between structure and function became less: albinism, at first regarded as an inherited structural abnormality of hair, became recognized as very probably caused by insufficiency of the enzyme tyrosinase. As we shall see later, this may be a structural defect at the molecular level. A remarkable book was published in 1814 (Adams, 1814) which distinguished diseases that were inherited from those that were familial but not inherited; it also distinguished between dominant and recessive inheritance, and

recognized that inherited disease was frequently precipitated by environmental factors. We must now define what is inherited and what contributed by environment.

By constitution of a person is implied his inborn qualities of body and mind; his constitution therefore is the result of the genes he receives from his parents, and the word is synonymous with genotype and temperament. One such quality embraced in constitution is a person's physique, usually classified following Sheldon (1940) by degrees of ectomorphy, mesomorphy or endomorphy. The last is the inherited tendency to be circular, but has to be distinguished from the obesity resulting from acquired overeating. Constitution or genotype is in fact altered by environmental factors to determine a person's phenotype; such factors include overeating, malnutrition, alcohol, worry, bacteria. Aristotle (*Categories*, ch.8) recognized that 'The healthy are so called by virtue of possessing an inborn capacity not to be affected easily by chance events and the unhealthy by virtue of having an incapacity not to be affected.' A person may be unusually susceptible to disease through either his constitution or his phenotype. But in the former event his inherited susceptibility may not become manifested in actual disease unless some environmental agent acts upon him as in the instance of infections. Indeed, haemophilia can be regarded as an inherited susceptibility to disease, injury being the agent that provokes the actual disease. Constitution is the soil that determines the action of the environmental factor—the seed. Many of us harbour tubercle bacilli or pneumococci or Klebs–Loeffler bacilli without developing tuberculosis or pneumonia or diphtheria. The cause of anterior poliomyelitis is not the virus, but the entry and multiplication of the virus in a predisposed body, and in this predisposition many factors—inherited or acquired by such environmental agents as nutrition and previous infection—play a part.

This predisposition to a disease is sometimes called diathesis, though there has been much confusion about a diathesis being inborn or acquired. Ryle (1926), for instance, defined diathesis as 'a transmissible variation in the structure or function of tissues . . .', but later apparently changed his mind when he misquoted his original definition as 'a variation . . .' (Ryle, 1948). A diathesis is a condition of the body, whether inborn or acquired, that causes it to be chronically predisposed to a certain disease. Further, the distinction between diathesis and idiosyncrasy is often not clear. An idiosyncrasy is an abnormal reaction to a stimulus, whether inborn or acquired, positive or negative. Idiosyncrasies therefore include allergic reactions, and they can be acquired or lost.

Idiosyncrasies to food have been recognized from earliest times, and are exemplified by the statement of Lucretius (1495) that what is one man's meat may be another man's poison. Urticaria may follow ingestion of oysters or crabs, strawberries or raspberries, eggs or cow's milk; such idiosyncrasies can be familial. Less frequently, abnormal reactions may follow the ingestion of honey, meat, nutmeg, apples, parsley, figs, peas or wheat flour. Perhaps the most remarkable instance of the last is David Waller (Overton, 1855) who, allegedly because his mother had trouble with bread when he was a foetus, could not ingest wheat flour in any amount without the onset of intense itching, colic and vomiting; the smell of flour affected him, but this

idiosyncrasy was not neurotic since it was produced by a very small quantity of flour surreptitiously introduced into a soup which he was assured contained none.

Uroscopy

Although throughout the centuries intelligent doctors noted idiosyncrasies as interesting peculiarities and paid great attention to constitution and diathesis as important factors in the causation of disease, little real understanding was possible until the advent of the sciences of biochemistry and genetics. Biochemistry may be regarded as starting with so-called Paracelsus (1493–1541). We may briefly consider a single aspect of his work, chemical examination of the urine, in view of its direct importance to various inborn errors of metabolism. The inspection of urine, uroscopy, played an outstanding part in ancient and mediaeval medical practice. The ancient Sumerian word for a physician was *asu*, 'a man who understands water.' The Pythagoreans, as is shown in the Hippocratic works, recognized the prognostic value of urines of different colours. In ancient Hindu Brahmin medicine, Suśruta (5th century A.D.) recognized diabetes mellitus as *madhumeha* or honey-urine, and noted the symptoms of thirst, foul breath and languor. In the 13th century Walter Agilon abandoned the customary classification of diseases by parts of the body, from head to foot, and instead recognized four regions in the urinal which, from top to bottom, were supposed to represent the head, chest, abdomen and urogenital system. Mysticism and nonsense followed unchecked until Paracelsus declared that no information could be obtained from urine without its chemical examination by extraction, coagulation and distillation. To this sound principle of chemical analysis his pupils added unrealistic scholastic rules which were castigated by James Hart (1625) and by the greatest follower of Paracelsus, Van Helmont. Though black and red urines had been known from antiquity, the former most commonly caused by the methaemoglobinuria of malaria ('blackwater fever') and the latter by haematuria usually from calculus, about this time urine that blackens on standing was recognized by G. A. Scribonius (1584), Schenck (1609) and Zacutus Lusitanus (1649) (all quoted by Garrod, 1923). Lommius (1560) regarded black urine as an index of extreme heat. In the more charitable forms of treatment, heroic attempts were made with baths, cold sops, purges and blood-letting to cool the fiery heat of the viscera that charred and blackened the bile; less fortunate boys underwent more drastic methods to drive out the devil. Fortunately alkaptonuria is a very rare anomaly. Perhaps the most interesting account is that given by Marcet (1823) in his *Account of a singular variety of urine, which turned black soon after being discharged*. In the urine from this boy, which blackened his nappies from birth, 'the colouring matter in question, whatever the nature of its basis may be, is developed either by the addition of an alkaline salt, or by the spontaneous evolution of alkali from the urine itself.' The great chemist Prout analysed some of the black substance and concluded it was an unknown acid, 'melanic acid'. In 1858 Bödeker (1859) found a reducing substance other than sugar in the urine of a patient, and he gave it the name of 'alcapton', consciously derived by a barbaric hybrid of

the arabic 'alkali' with the Greek *κάπτεω*. But the greatest contribution was made by Sir Archibald Garrod to whose genius tribute must now be paid.

Sir Archibald Garrod and Mendelism

Garrod was the son of Dr A. E. Garrod who performed an historic experiment in 1854 to demonstrate the increased amount of uric acid in the blood of patients with gout, and his daughter is Professor Dorothy Garrod, the Cambridge archaeologist. He was physician to St Bartholomew's Hospital and to the Hospital for Sick Children before becoming Regius Professor of Medicine in the University of Oxford. As a paediatrician he was particularly well able to recognize the occurrence of abnormalities in an infant and in its sibs and parents; as a lecturer in chemical pathology he could attempt to interpret those abnormalities in biochemical terms. In 1899 he added four cases to the twenty-three recorded examples of alkaptonuria (Garrod, 1899), and noted its 'very special liability . . . to occur in children of first cousins' (Garrod, 1902). That was a year before the rediscovery of Mendel's work in 1900, and it is as surprising that the significance of Mendel's combination of arithmetic and peas was not realized for 35 years as it is that the work of Garrod was ignored for a rather longer period by geneticists except Bateson, who introduced the word 'genetics'. After that rediscovery, Bateson (1902) enthusiastically disseminated Mendelism; and Garrod became a close friend of his and of Hopkins, in the course of his brilliant combination of biochemistry and genetics. In 1908 he delivered four Croonian Lectures (Garrod, 1908*a-d*), and the following year extended them in his classical monograph (Garrod, 1909). In this he added to alkaptonuria three other 'inborn errors of metabolism': albinism, cystinuria and pentosuria. Alkaptonuria was the first condition in lower animals or man shown to follow Mendel's laws of heredity.

At this time, 1909, katabolism was regarded as simple combustion, and the metabolic fires burnt brightly or low. Bence-Jones (1865) had published his *Diseases of Suboxidation*, but Bouchard (1882) in particular popularized *Maladies par Ralentissement de la Nutrition*. Since certain conditions—such as obesity, diabetes and gout—tended to occur together, it was supposed that all combustion was equally slowed—of aliments, glucose and purines. Garrod (1909) emphasized 'metabolism in compartments' or by steps: 'If any one step in the process fail the intermediate product in being at the point of arrest will escape further change, just as when the film of a biograph is brought to a standstill the moving figures are left foot in air'.

In 1923 Garrod published a second edition of his monograph (Garrod, 1923), dedicated to Hopkins; in this he added two further diseases, congenital porphyrinuria and congenital steatorrhoea, and he elaborated his clear conception of the mechanism of inborn errors of metabolism: '. . . in the case of each of them the most probable cause is the congenital lack of some particular enzyme, in the absence of which a step is missed, and some normal metabolic change fails to be brought about . . . If the lack of a special enzyme be in each instance the underlying factor, it is to be expected that they should behave as Mendelian recessive characters'.

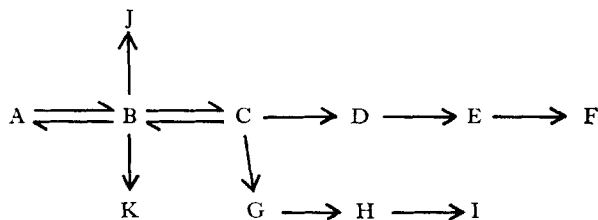
Garrod recognized that other inborn errors of metabolism would be discovered; indeed he suggested some other possibilities such as xanthine calculi. Paper chromatography made possible rapid advances in detecting urinary abnormalities, and other analytical refinements together with the elucidation of metabolic pathways have made it desirable to widen Garrod's title into inborn molecular diseases. Beadle (1945) enlarged Garrod's concept into that of 'one gene-one enzyme', and the term 'molecular disease' was first introduced by Pauling (1955). He speculated that the disease sickle-cell anaemia might be caused by an abnormal haemoglobin, and in 1949 he and his associates demonstrated this (Pauling, Itano, Singer & Wells, 1949). He has generalized from this that all or nearly all hereditary diseases may be molecular diseases in the sense that the amino acids in a protein (such as an enzyme or haemoglobin) are arranged slightly wrongly so that an abnormal compound is formed: he believes for instance that an abnormal gene manufactures an abnormal enzyme which is structurally different from the normal one and because of this difference does not serve as an effective catalyst. Functional abnormalities therefore have a structural basis.

Biochemical genetics

To understand this concept better we must briefly consider the action of genes. The hereditary material is deoxyribonucleic acid (DNA) which occurs in filaments which are the basis of chromosomes. Segments of these filaments are genes. The filaments have a helical backbone of the pentose and phosphate parts of DNA with four bases (adenine, guanine, cytosine and thymine) pointing inwards from the backbone and cross-linking (adenine to thymine, and guanine to cytosine) by hydrogen-bonding between two such helices. Replication of DNA occurs by the double helix unwinding, and each filament then serves as a template on which nucleotides condense and polymerize to form a complementary chain. DNA in the nucleus directs the synthesis of template RNA which then diffuses into the cytoplasm where it in turn directs the synthesis of protein. A mutation producing an abnormal gene can therefore cause an inherited abnormality in the arrangement of amino acids in a protein. This has been beautifully demonstrated in the extensive recent work on abnormal haemoglobins. For instance, Ingram (1956) showed that in sickle-cell haemoglobin only 2 out of 600 amino acid residues differ from those in normal adult human haemoglobin. Pauling (1960) believes that 'Since there are hundreds of thousands of species of animals, it is probable that there are hundreds of thousands of different kinds of haemoglobin', but the probability is greatly lessened if one remembers that many species have no haemoglobin. However, in the last 12 years more than twenty abnormal human haemoglobins have been found. I have mentioned Pauling's belief that the genetic absence of an enzyme probably occurs through the gene giving rise to a protein in which the amino acids are not in the correct order so that the compound does not have catalytic activity. It is, however, also possible that the template coding does not make 'sense', so that no protein can be formed. But in either event, the abnormality is a structural one at the molecular level. At this level there is no clear distinction between structure and function.

Mechanisms of metabolic disorders

We must now consider briefly the simplest mechanisms whereby abnormal metabolism may arise from the defective production of an enzyme. We may consider a metabolic sequence as follows:



Block between C and D. If the enzyme that converts C into D is absent, at least four consequences may cause disease.

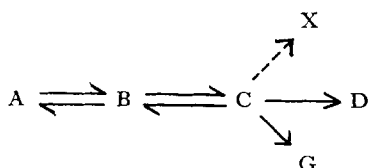
(1) Lack of D, E, F. Examples are: (a) albinism, in which melanin cannot be formed from tyrosine; (b) familial goitre in which tri-iodothyronine cannot be formed; (c) hypoglycaemia in von Gierke's disease through lack of glucose-6-phosphatase.

(2) Accumulation of C. Examples are: (a) homogentisic acid in alkaptonuria which by oxidative polymerization stains urine, cartilage and other mesenchymal tissues; (b) L-xylulose in pentosuria, another of Garrod's inborn errors; (c) glycogen storage diseases caused by lack of muscle or liver phosphorylase.

(3) Accumulation of A or B. The high glycogen and high lactate of von Gierke's disease are examples.

(4) Production of normally minor substances, G, H, I. Such metabolites, usually produced only in traces, occur in increased amounts in phenylketonuria and maple-syrup-urine disease.

Production of a mutant enzyme.



This is theoretically possible. An abnormal gene might give rise to an abnormal enzyme that catalyses a reaction that does not normally occur (C into X). It is possible that familial primary amyloidosis is an example.

Defects in rate of metabolic sequence. (1) Block between C and G might produce more D, E, F, or this might occur through excessive production of the enzyme that converts C into D. (2) The rate of reaction may be affected by altered amounts of permeases or other systems that affect the rate of passage of substrates into cells or metabolites from cells. In diabetes mellitus, for example, there is a twofold metabolic disturbance: there is decreased permeability of the membrane of muscle to glucose

through lack of insulin, and there is decreased phosphorylation of glucose within the cells through its inhibition by hormones such as those of the adrenal cortex and anterior pituitary.

Expression and therapy

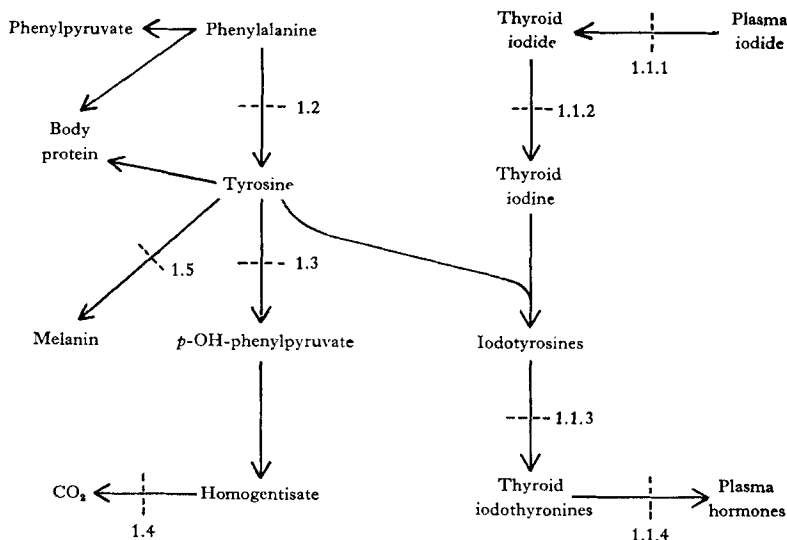
The expression of the metabolic error in the form of disease may vary. Some, such as pentosuria or tyrosinosis, give rise to no symptoms. Others, such as errors of blood coagulation or drug-induced haemolytic anaemia, give rise to symptoms only under certain conditions, such as trauma or drugs. Others, such as alkaptonuria or acatalasia or gout, may give rise to mild symptoms and signs. Others, such as phenylketonuria or Wilson's disease, may be severe or lethal. Finally, the defect may be so severe that survival is impossible and stillbirth results.

Therapy in specific instances in this Symposium is discussed by other speakers. There are four main methods. First, the precursor, A, may be decreased by dietary means, as in phenylketonuria. Secondly, the product (D, E, F) may be supplied by mouth or injection, as when thyroid hormone is administered in familial goitre. Thirdly, environmental changes may be made, as to avoid trauma in haemophilia or certain drugs in drug-induced haemolytic anaemia. Lastly, a substance that has accumulated in unusual amount may be reduced, as when administration of penicillamine or British Anti-Lewisite (BAL) causes excretion of stored copper in Wilson's disease, or when cystine stones are prevented by copious draughts of water.

Classification of inborn metabolic disorders

The following classification of inborn metabolic disorders largely follows the excellent recent monograph edited by Stanbury, Wyngaarden & Fredrickson (1960).

(1) Amino acid metabolism (Fig. 1)



The numbers refer to classification (see above)

Fig. 1. Enzymic defects concerned with tyrosine and iodine.

(1.1) Familial goitre may result from five different enzymic defects. First, the thyroid gland (and salivary glands and gastric mucosa) may fail to trap iodide. Secondly, a peroxidase may fail to oxidize trapped iodide to iodine which is essential for combination with protein. Thirdly, the coupling of iodotyrosines to form iodothyronines and thyroxine may not occur. Fourthly, the breakdown of stored thyroglobulin may not occur. Lastly, an abnormal thyroid protein may be formed.

(1.2) Phenylketonuria is caused by insufficiency in the liver of phenylalanine hydroxylase.

(1.3) Tyrosinosis, of which only one case has been described, is probably caused by insufficient tyrosine transaminase.

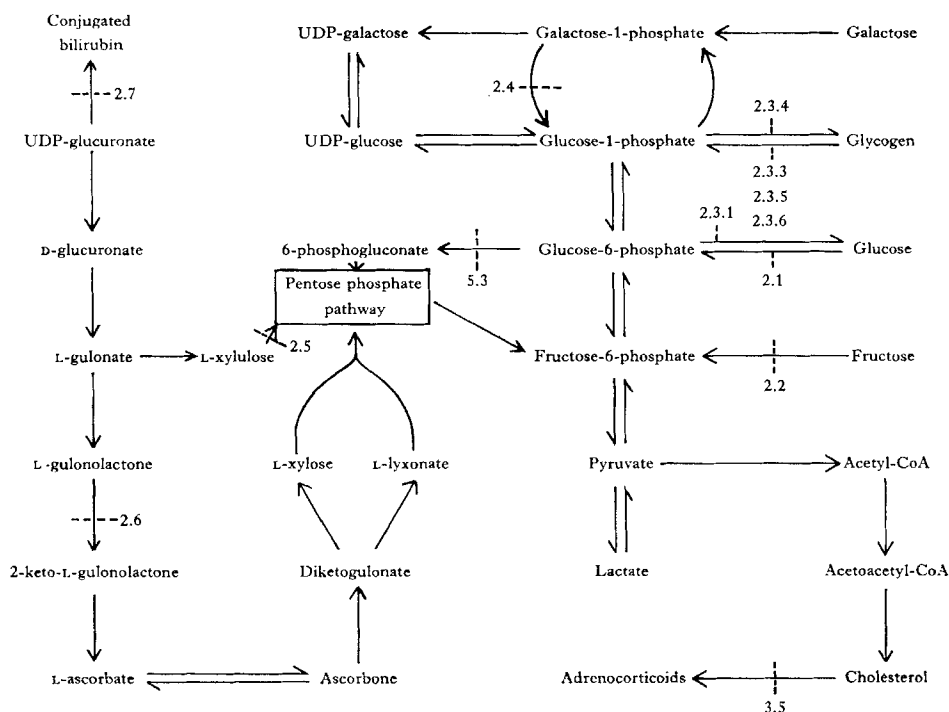
(1.4) Alkaptonuria is caused by insufficient homogentisate oxidase.

(1.5) Albinism is caused by the failure of melanocytes to form tyrosinase.

(1.6) Primary hyperoxaluria and oxalosis are caused by a metabolic defect with overproduction of oxalate, perhaps from glyoxylic acid.

(1.7) Maple-syrup-urine disease is characterized by excretion in the urine of the keto acids from leucine, isoleucine and valine.

(2) Carbohydrate metabolism (Fig. 2)



The numbers refer to classification (see p. 7)

Fig. 2. Enzymic defects concerned with carbohydrate metabolism.

(2.1) Diabetes mellitus, the potentiality to develop which is inherited, has been mentioned above.

- (2.2) Fructosuria may occur either from insufficient liver fructokinase or perhaps from insufficient fructose-1-phosphate aldolase.
- (2.3) Glycogen deposition diseases can occur from every enzymic deficiency that causes storage of glycogen: (2.3.1) glucose-6-phosphatase (von Gierke's disease); (2.3.2) unknown; (2.3.3.) debranching enzyme; (2.3.4) branching enzyme; (2.3.5) muscle phosphorylase; (2.3.6) liver phosphorylase.
- (2.4) Galactosaemia is caused by insufficient galactose-1-phosphate uridyl transferase.
- (2.5) Pentosuria results from a block in the glucuronic acid pathway beyond L-xylulose.
- (2.6) Scurvy results from dietary insufficiency of L-ascorbic acid combined with absence of the enzyme that oxidizes L-gulonolactone to 2-keto-L-gulonolactone, a tautomeric form of L-ascorbic acid. This enzyme is absent in primates, guinea-pigs and certain other animals.
- (2.7) Hyperbilirubinaemia occurs in various forms which are not properly understood. Failure to conjugate bilirubin occurs.
- (3) Lipid metabolism
- (3.1) Essential familial hyperlipidaemia comprises two forms, hyperlipaemia and hypercholesterolaemia.
- (3.2) Infantile amaurotic family idiocy (Tay-Sachs) has excess gangliosides.
- (3.3) Sphingomyelinosis (Niemann-Pick).
- (3.4) Cerebrosidosis (Gaucher).
- (3.5) Adrenogenital syndrome results from defective formation of adrenocorticoids from cholesterol (Fig. 2).
- (4) Purine and pyrimidine metabolism
- (4.1) Gout probably occurs through overproduction of uric acid.
- (4.2) Xanthinuria may occur through insufficient xanthine oxidase.
- (4.3) Orotic-aciduria has only been described once.
- (4.4) β -amino-isobutyric-aciduria.
- (5) Blood and blood-forming tissues
- (5.1) Porphyrrias occur in various forms of which the commonest is erythropoietic porphyria in which an enzymic defect in the formation of erythrocytes causes Type I porphyrins to be formed in increased amounts.
- (5.2) Hereditary spherocytosis is caused by deficiency of high-energy phosphate bonds in the walls of erythrocytes.
- (5.3) Drug-induced haemolytic anaemia is caused by old erythrocytes having insufficient glucose-6-phosphate dehydrogenase to maintain structural integrity of the cell after administration of certain drugs, such as the antimalarial primaquine or of fava beans.
- (5.4) Hereditary methaemoglobinaemia has not been fully categorized biochemically.
- (5.5) Haemoglobinopathies and thalassaemia include sickle-cell disease which has already been discussed.

- (5.6) Blood-clotting factors may be defective and so cause haemophilia, Christmas disease and several others.
- (6) Metal metabolism
- (6.1) Haemochromatosis in its primary form is caused by excessive absorption of iron for an unknown reason.
 - (6.2) Wilson's disease is accompanied by decreased synthesis of the copper-protein caeruloplasmin.
 - (6.3) Periodic paralysis is accompanied by passage of potassium ions from plasma into muscle.
 - (6.4) Adynamia episodica hereditaria is similar in some respects to the last.
 - (6.5) Pseudohypoparathyroidism is accompanied by low plasma calcium and phosphate.
- (7) Deficiency of plasma enzymes or proteins
- (7.1) Hypophosphatasia is accompanied by low serum alkaline phosphatase.
 - (7.2) Acatalsia is accompanied by deficiency of catalase in blood and tissues.
 - (7.3) Hereditary hypoproteinaemias include agammaglobulinaemia and albuminaemia.
- (8) Defects in renal tubular transport
- (8.1) Familial hypophosphataemia and vitamin D-resistant rickets have not been fully characterized biochemically.
 - (8.2) Fanconi syndrome is probably caused by defective tubular reabsorption of glucose, amino acids, phosphate and bicarbonate.
 - (8.3) Renal glycosuria may be caused by defective tubular reabsorption of glucose.
 - (8.4) Renal tubular acidosis is accompanied by urinary loss of calcium and potassium.
 - (8.5) Vasopressin-resistant diabetes insipidus is not understood.
 - (8.6) Glycinuria appears to be caused by deficient reabsorption of the four dibasic amino acids, cystine, lysine, arginine and ornithine.
 - (8.7) Hartnup disease is accompanied by aminoaciduria, and deficient formation of nicotinic acid from tryptophan.

Conclusion

That diseases have primary and secondary causes has been recognized for more than 20 centuries; alternatively these may be called predisposing and precipitating factors. Some of them are inborn and others acquired, and the former were discussed by Garrod (1931) in an essay on diathesis. There may be an inherited defect in the machinery of the body which only becomes apparent when some normally trivial environmental factor (such as sunlight, drugs or diet) enhances it and disease results. Or there may be relative weakness or strength in the machinery which determines whether some major environmental factor will cause disease or not; and a single defect in the machinery can produce different diseases under the stress of different environmental factors, just as a single environmental factor can in association with

different constitutions produce different diseases. It is therefore not surprising that certain disorders tend to be associated, such as coronary thrombosis with obesity, gout, diabetes mellitus, duodenal ulcer and gall-stones. Since obesity is associated with all these except duodenal ulcer, we may look a little more into the possible nature of these associations.

It is well known to all workers on nutrition that malnutrition predisposes to infections. A well-known exception is that monkeys with deficiency of thiamine are less susceptible to infection by the virus of poliomyelitis than are normal monkeys. With deficiency of essential fatty acids (EFA) I believe this increased susceptibility—which is very marked—may be caused at least partly by the structural damage that occurs in cellular and other membranes, allowing the organism to gain access more easily (Sinclair, 1958). This structural defect probably causes the duodenal ulcers found in rats with such deficiency, since the abnormal mucosa is more easily affected by hydrochloric acid. In hamsters with this deficiency gall-stones are found. Let us suppose we could take three men who are constitutionally at extremes of somatotype, and induce a relative EFA deficiency in all three. The ectomorph—thin and energetic in body, restless and worrying in disposition, with hyperchlorhydria—conforms to the ulcer diathesis, and would tend to develop duodenal ulcer, particularly if a male, since EFA requirement is much greater in male animals until after reproductive life. The endomorph—obese and slothful in body, placid and self-confident in disposition—might tend to get gall-stones, from the epithelial desquamation in the gall-bladder, particularly if a female up to late middle-age if oestrogens increase the excretion of cholesterol into the gall-bladder. The mesomorph—athletic and muscular in body, strong-willed and extroverted in disposition—would tend to develop coronary thrombosis, particularly if a male for the reason already stated. Hence, although we can recognize physically and psychologically constitutions that conform to an ‘ulcer type’, or ‘gall-stone type’ or ‘coronary-thrombosis type’, there is overlapping in them: if our mesomorph worries and therefore has unusual amounts of hydrochloric acid in his duodenum he may develop duodenal ulcer as well as coronary thrombosis. Considerations such as these may explain in the future not only the association of apparently unrelated diseases, but also the as yet unexplained prevalence of certain diseases in the two sexes (such as males being much more prone to coronary thrombosis, atherosclerosis, duodenal ulcer, gout and females to obesity, gall-stones, hyperthyroidism, purpura haemorrhagica).

As we recognize and treat, partly dietetically, inborn errors of metabolism, we must remember what a disservice we may be doing to the community as a whole. Until recently phenylketonurics have tended to be imbeciles, so that they may spend their days in mental hospitals and not breed. If all babies’ nappies were tested soon after birth by a simple chemical test, about forty cases a year in Great Britain might be detected and 1% of all present idiots saved. But these people would breed and the prevalence of this inborn error would increase. By medical research we are making it possible for bad genes to be passed on that would otherwise tend to be removed. By the use of X-rays and the increased hazard of radiation from ‘fall-out’ and other

sources we are increasing mutations, most of which are bad. We may therefore confidently predict that the human race will deteriorate unless we take steps to eliminate bad genes and preserve the good.

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Clinical aspects of inborn metabolic defects

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The clinical viewpoint

Metabolic diseases involve interference with the use or disposal of nutritive material in vital processes that may affect the whole body or only certain cells. Many of the diseases that I shall mention are described in other chapters of medical text books than the one headed *Diseases of Metabolism*, for example, some in the haematological and some in the neurological sections.

The practitioner's viewpoint is quite different from that of the scientist. The aim of the scientist is to know fully, of the clinician to act successfully, even if he does not