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Sir Archibald Garrod's "Inborn Errors of Metabolism"

IV. Pentosuria

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"In many cases neurasthenic symptoms and neuralgic pains have been prominent. Others have been perfectly well when once freed from the restrictions of a diabetic regimen. Concerning the real nature of the malady, we can only say that it is an anomaly in the intermediary metabolism, rather analogous to cystinuria and alkaptonuria than to diabetes." *Essential Pentosuria in Two Brothers*, T. C. Janeway, 1906.

INTRODUCTION

UNTIL JANEWAY (1906) DESCRIBED the nineteenth and the first American case of pentosuria, the recognition of this disease had been almost limited to a few German clinics. Janeway's critical and scholarly article, from which comes the above quotation, indicates his familiarity with Garrod's (1902) précis of his concept of the inborn errors, though the latter did not mention pentosuria. Perhaps the quoted lines suggested to Garrod the inclusion of pentosuria with albinism, alkaptonuria and cystinuria as the inborn errors of metabilism. Garrod's contribution to the study of the disease was otherwise slight, since he had never seen a case, and at the time he wrote, the basic facts were hopelessly confused. He called it then, and later (Garrod, 1923), "the least known member of the group." The same kind of delay in comprehension and the same perpetuation of uncertainties in the medical literature that characterized the histories of the other inborn errors of metabolism (Knox, 1958) has plagued the study of pentosuria. It is still today less certainly known than the record shows when critically evaluated. It is still not known whether the neurasthenic symptoms are part of the disease or, as Janeway so nicely implied, the result from the threat of diabetes. Many texts leave the impression that pentosuria may not even be a disease entity, but a condition with many causes.

Well over 200 cases of chronic or essential pentosuria (also called xyloketosuria and xylulosuria) have now been described. There were 163 of these known by 1943 (Derivaux). Except for the first thirty or so cases known in Garrod's time that were imperfectly studied, and except for some minor and usually temporary excretions of various pentoses in certain situations, almost all of the known instances of pentosuria conform to the characteristic pattern of a single disease entity. This consists of the constant urinary excretion from infancy throughout life, almost independent of

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changes in diet, of about 2.0 to 3.5 g. per day of the reducing sugar, *L*-xylulose. There are no notable metabolic or clinical abnormalities, and the affected individuals have a normal life expectancy. The condition is inherited through a single autosomal recessive gene. It is almost entirely limited to Jews, but a few patients of non-Jewish Mediterranian or European origin have been described. There is a singular lack of reviews which discuss these several facets of the pentosuria problem, but articles by Janeway (1906), Greenwald (1922, chemical), Margolis (1929, clinical), Lasker, Enklewitz & Lasker (1936, genetics), and Lasker (1950, chemical) are authoritative considerations of their special fields.

ORIGIN OF THE CONFUSION ABOUT THE NATURE OF PENTOSURIA

The Identification of the Pentose: Like cystine and homogentisic acid, pentose was first found in the urine of patients with hereditary diseases. Blumenthal (1895) found a reducing substance in the urine of a patient in 1880, but this was not identified as a pentose until such substances had been recognized from plant sources and soon thereafter in the urine of the pentosuric described by Salkowski and Jastrowitz (1892). Then the pentose was recognized in the original case. But again like cystine and homogentisic acid, it now seems probable that the nature of the pentose was at first erroneously determined. Neuberg (1900), whose bizarre results in the study of cystinuria have already been described (Knox, 1958), isolated racemic arabinose from the urine of one of Salkowski's cases. "The most remarkable fact of all in regard to pentosuria is the optical inactivity of the excreted sugar (Garrod, 1909)". Such a substance almost always occurs in biological systems in one or the other of its optically active forms. The structures of the sugars in question are shown in Figure 1. All of them reduced Benedict's solution, the routine test which led to their discovery. The pentose was recognized and distinguished from glucose when it could not be fermented by yeast and by the formation of a relatively soluble, low melting osazone, but methods for distinguishing between the very similar pentoses were in their infancy. The optical rotation of xylulose is so low that, with the low concentrations of the pentose in the urine, the lack of optical activity in the urine led to the assumption that an inactive sugar was present. This initial uncertainty about the structure of the pentose was subsequently confounded by inconsistencies in the description of the enantiomorphs by the old prefixes *d*- and *l*-, referring to the optical rotation, and the modern prefix of *D*- or *L*-, which ignores the rotation and indicates the structural

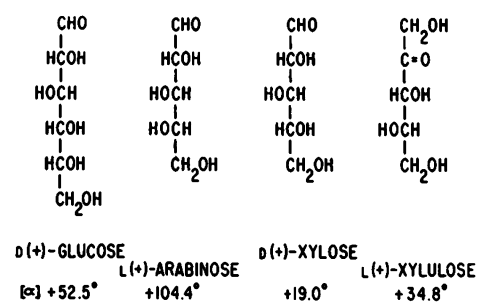

FIG. 1. Structures, *D*- or *L*- designations, and specific optical rotations [α] of some sugars related to the *L*-xylulose (xyloketose) excreted in pentosuria.

relationship of the compound to *D*- or *L*-glyceraldehyde. Zerner and Waltuch (1913) first developed a method based on a marked elevation of the melting point of the osazone when both optical forms were present, which indicated that the urinary sugar was optically active and was not arabinose. They sought to mitigate Neuberg's attack on their work by conceding that there might be two kinds of pentosuria, but the three patients they could check excreted a sugar like the one they had identified. The urinary sugar was promptly thereafter identified as xyloketose (xylulose) by Levene and LaForge (1914). This identification was confirmed in four patients (Greenwald, 1930). After incorrect designation of the optical form in the latter two papers was corrected (Greenwald, 1933), it was clear that the pentose found in the urine of most patients was *L*(+)-xylulose. Lasker (1950) admits on "seemingly good evidence" five reports of the excretion of racemic arabinosuria. The last was in 1928, but one of these cases examined by modern methods forty years later excreted xylulose (Barnes & Bloomberg, 1953). After a simple clinical method for identifying xylulose was developed, depending upon the reduction of Benedict's solution at 55° (Lasker & Enklewitz, 1933), the urinary pentose of another patient who 28 years earlier was thought to excrete arabinose was shown to excrete xylulose (Cohen & Gershenfeld, 1936).

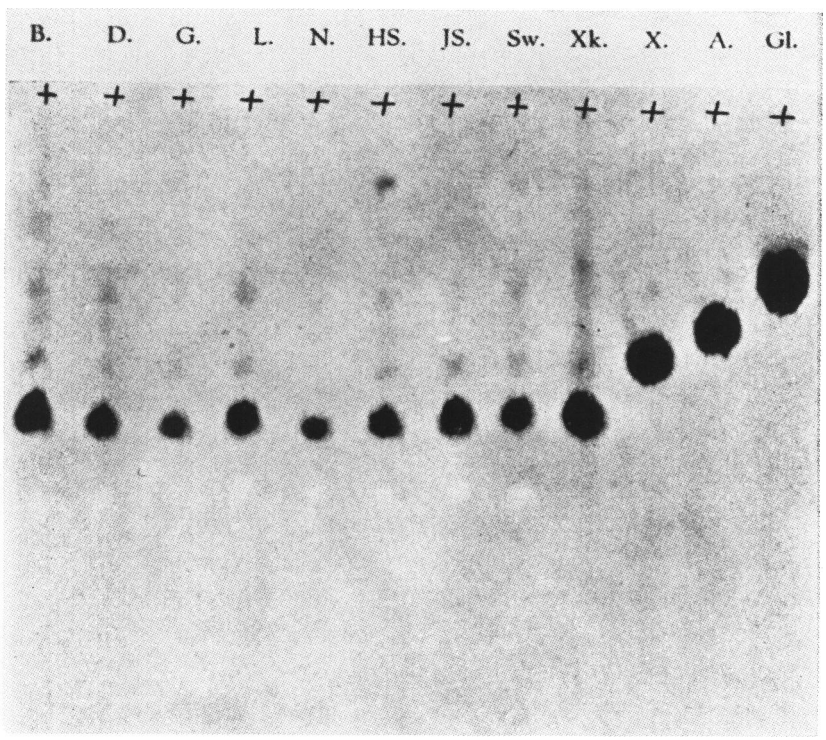

FIG. 2. Photograph of the chromatogram of reducing substances in eight specimens of pentosuric urines and four reference sugars applied at the marks (+). Xk = xyloketose (xylulose), X = xylose, A = arabinose, Gl = glucose. The base line represents the solvent front. (From Barnes and Bloomberg, 1953)

The surety and simplicity with which urinary pentoses can be identified by modern methods is illustrated by the reproduction in Figure 2 of Barnes' and Bloomberg's chromatograph of the urines of their eight patients. B is the patient believed to excrete racemic arabinose on the basis of early chemical studies (Aron, 1913). This method, and column chromatography which has permitted the demonstration that a pentosuric subject also excretes several hundred mg. of *L*-arabitol (Touster & Harwell, 1958), can eliminate any further uncertainty about the chemical anomaly in pentosuria.

PENTOSURIAS OTHER THAN XYLULOSURIA

DL-Arabinosuria: The existence of *DL*-arabinosuria is questionable. No case has been reported since 1928 and of those reported earlier only seven were supported by significant chemical evidence. All were obtained by this same method. One of these has been shown by modern methods to excrete xylulose. It is tempting to attribute these results to inadequate methods, but the derivatives and two separated forms isolated by Cammidge and Howard (1920) from the urines of three of their seven patients cannot be easily ignored. Numerous efforts to prepare similar compounds from known xylulose-containing urines have been unsuccessful. Not one case of arabinosuria has been found among 73 cases of pentosuria studied by Lasker (1950). If arabinosuria exists at all, it is extraordinarily rare and the fact that it does exist must be proved by modern methods.

Intermittent and Drug-Induced Pentosurias: Margolis reviewed nine cases in whom pentosuria appeared to be acquired. The possibility that low levels of pentose excretion would have been missed in previous urine examinations is very real. The first case of chronic pentosuria occurred in a morphine addict, as did the second. In the first case when the morphine was stopped, the pentosuria remained, but in the second case the pentosuria disappeared when the morphine intake was discontinued. With the exception of the pronounced xylulosuria caused by amidopyrine administration (Margolis, 1929), it is probable that the pentosurias reported in patients taking drugs represent drug-conjugated glycuronates which appear in the urine and give the pentose reaction.

Pentosuria in Diabetes: The high frequency of pentose excretion by diabetics which was formerly recorded has not been substantiated. It is also established that pentosurics rarely have abnormal glucose metabolism. Pentosurics frequently give a family history of diabetes, but both conditions are common in Jews. If both diabetes and pentosuria appear in the same individual, they do so as distinct metabolic entities.

Alimentary Pentosuria: It is an undoubted fact that pentose excretion occurs when a normal man is fed some pentose in an amount above the normal tolerance for that particular sugar. Such studies have usually been performed with *L*-arabinose or *D*-xylose. The same result can follow over-ingestion of certain fruits rich in pentose. Seventeen of 18 individuals who drank 1.5 liters of apple juice developed a temporary pentosuria (Johnstone, 1906). Xylose and arabinose are said to be excreted in such alimentary pentosuria from natural foods, but no convincing chemical evidence of the structure of the excreted sugar appears to be available. Alimentary pentosuria is also much more readily produced in some individuals than in others. The coexistence

of renal glycosuria with alimentary pentosuria produced by a diet which did not cause pentosuria in other individuals was reported by Dunsky and Lawrence (1947). Since xylose is reabsorbed in the kidney tubule by the same transport system that acts on glucose (Shannon, 1948), it should not be surprising that the renal glycosurics who lack this system would also readily excrete the pentose.

The excretion of trace amounts of pentoses, amounts several orders of magnitude smaller than those concerned in pentosuria have recently been described in normal man (Futterman and Roe, 1955), in neuromuscular disease (Tower, Peters, and Pogowelskin, 1956), and in cold-stressed or thyroid treated rats (Roe and Coover, 1950). There is no possibility of confusion between these variations in the very small normal output of pentose and the large amounts characteristic of pentosuria. It is apparent that essential pentosuria can be distinguished from all the above conditions by the demonstration of a chronic excretion of gram amounts of the chemically identified pentose, *L*-xylulose.

FREQUENCY

Pentosuria is without doubt uncommon, so that its occurence in more than one sib of a family indicates its familial nature. But there are two quite different estimates of the frequency of pentosuria in the population. Greenwald (1922), and later Margolis (1929), enumerated the urine examinations reported by various workers and the number of pentosurics found. There was a total of about 20 cases from 20,000 urines examined, for an incidence of one in 1,000. It is probable that the population examined had an unusually high percentage of individuals in whom some defect of metabolism was suspected. A less selected population was the nearly 131,000 applicants for life insurance and company employees whose urines were examined over a period of one and one half years (Larson, *et al.* 1937). Thirty-one individual cases of pentosuria were found for an incidence of 1 in 4,000. But approximately 11 urinalyses were made by the field medical examiners of the same company for each urinalysis made in the home laboratory. When this is taken into consideration the incidence of pentosuria would appear to be 1 in 50,000. Only urines containing 0.25 per cent or more reducing substance ("1+" or "2+" Benedict reactions) were tested for pentose in this study, and since pentosuria of 0.1 per cent is not uncommonly reported, the incidence was probably underestimated. It should be noted that the incidence of pentosuria found in studies of this type should be proportional to the percentage of Jews in the population examined. The true incidence must lie somewhere between 1 in 5,000 and 1 in 50,000 people.

The identification of one "non-pentosuric" subject who normally excreted traces of xylulose (60 mg. compared with less than 1 mg. per day by controls), suggests that the incidence of pentosuria might be greatly increased if sufficiently sensitive methods were used for its detection (Touster, Hutcheson, and Rice, 1955). The existence of such individuals clearly separated from the normal individuals on the one hand and from chronic pentosurics on the other could indicate an "incompletely recessive" gene for pentosuria manifested in the heterozygous individuals as has been found for cystinuria (Harris, Mittwoch, Robson, and Warren, 1955).

Pentosuria has been diagnosed at all ages after early infancy and there is no doubt

that it is a life-long abnormality at least after the first two years of life. The youngest patients on which the diagnosis had been made were children of 18 months (Garrod, 1923) and 20 months (Protas, 1934). It may not be surprising that earlier diagnoses remain unreported since the occasions for tests by which this symptomless disorder could be recognized would rarely occur in early infancy. On the other hand, the anomaly might appear only after a certain stage of biochemical maturation. Lack of information of this type is unfortunate. Even if the condition were not strictly congenital, this would not lessen the case for its genetic control.

HEREDITY

The familial occurrence of pentosuria was noted after the first few cases were discovered. Nine of the nineteen cases collected by Janeway occurred among the sibs of four families. Garrod (1909) contented himself with observing that "evidence is accumulating of the occurence of pentosuria in brothers and sisters, and no evidence of its transmission from parent to child has yet been recorded." By 1923 Cammidge and Howard (1920) had observed a father and son in a Greek family and an uncle and nephew in a Jewish family, all with pentosuria. For only one of these, the uncle, was chemical evidence presented that the sugar was *DL*-arabinose. Greenwald (1922) favored multiple causes of the several varieties of pentosuria which might exist, while Margolis (1929) was convinced of a marked hereditary factor, more because of the high incidence among Jews, than because of familial occurrence. Lasker, Enklewitz, and Lasker (1936) published the only serious genetic analysis of pentosuria, a study of twenty pentosuric families. They cited the occurence of pentosuria in two generations of the two families reported by Cammidge and Howard. Reference was made to other published pedigrees showing two affected great aunts and a great uncle of one propositus and four children and a grandmother affected in another family. Other familial instances of pentosuria occurred only among sibs, except in one of their families.

The genetic study of Lasker *et al* was wisely restricted to the pentosuric families observed by them and proved to excrete *L*-xylulose. No instances of arabinosuria were encountered. The twenty families examined contained 37 pentosurics. Ten of these were new cases found among 34 brothers and sisters of pentosuric propositi. The disease was present in the children of ten families in which neither parent showed evidence of the disease. There was one instance of direct transmission from parent to child and this was also the only instance of marriage of first cousins. The ratio of affected to unaffected sibs after substraction of the propositi approximated 1 to 3. The findings were consistent with the transmission of pentosuria by a single recessive gene of relatively high frequency. The preponderance of males among pentosurics which had been observed in all studies was again observed. The suggestion by Margolis that many pentosurics were discovered at the examinations for life insurance where more males than females presented themselves was strikingly confirmed by the ratio of 31 males to 1 female that was found in the survey of life insurance applicants already described. There was no significant difference in the number of males and females among the new patients discovered from the propositi. It was concluded that the inheritance of pentosuria was most probably determined by a single autosomal recessive gene.

CLINICAL ASSOCIATIONS

It is definitely established that pentosuria is a separate entity from diabetes and shares few, if any, of its symptoms. This does not prevent the usual patient from being subjected to attempts to exclude or even to treat diabetes. Marble (1947) summarized the usual experience of the pentosuric: "Not infrequently, the sequence of events in their histories has been about as follows: sugar in small amounts has been found in the urine at a routine examination and the diagnosis of diabetes made, followed by institution of treatment with a restricted diet, with or without insulin; then with some the non-diabetic nature of the disorder has become evident because of lack of hyperglycemia, and the diagnosis of renal glycosuria or other benign glycosuria is made; and finally the correct diagnosis of pentosuria has been established following more careful study of the type of sugar excreted in the urine."

Migraine affected the patient described by Margolis (1929) and this impelled him to undertake a conscientious examination of the clinical details described in published cases. He believed there was a particular habitus found in most cases of pentosuria. This was characterized by neurasthenia in 77 per cent, a clinical catch-all which includes nervousness, fatigue, fleeting pains and dizziness; headaches, often of the migraine type, in 27 per cent of the cases; and some "vagotonic" symptoms like spastic constipation and bradycardia in a small number of the remaining cases.

Various writers have attributed such symptoms to racial temperament, or to the fear of diabetes. It is impossible to reach a decision about associated symptoms of pentosuria on the data available. Some thought should be given to a possible favorable effect of a gene which has a high frequency in a segment of the population. The mortality of 72 pentosurics followed for an average of 14.5 years per individual did not differ significantly from that predicted by the life tables (Lasker, 1955). The causes of death when known were not unusual. Pentosuria would appear to have no serious physiological effect, if any.

PHYSIOLOGICAL CHEMISTRY OF THE PENTOSES

The identification of a reducing sugar in the urine of certain patients, occurring without relationship to diabetes, was long a source of wonderment to physiologists. When the identification of the sugar was changed from the optically inactive but biologically occurring arabinose, to the optically active but relatively unknown xylulose, it then became conceivable that such a sugar might in some way arise from the body's metabolism. The relative constancy of the excretion of pentose (the amount is apparently related only to body size) provided few clues to the origin of the substance. Janeway, and Cammidge and Howard found that the pentose excretion was decreased by low protein diets or starvation and increased by high protein diets. Garrod (1923) concluded that the pentose was probably derived from the protein and that glucosamine was its most likely parent substance. Greenwald (1922) suggested one of the five-carbon amino acids as the source. The variation in the degree of pentosuria with the content of protein in the diet has not been universally confirmed, and this approach withered.

Margolis discovered that the drug, amidopyrine, caused the excretion of large,

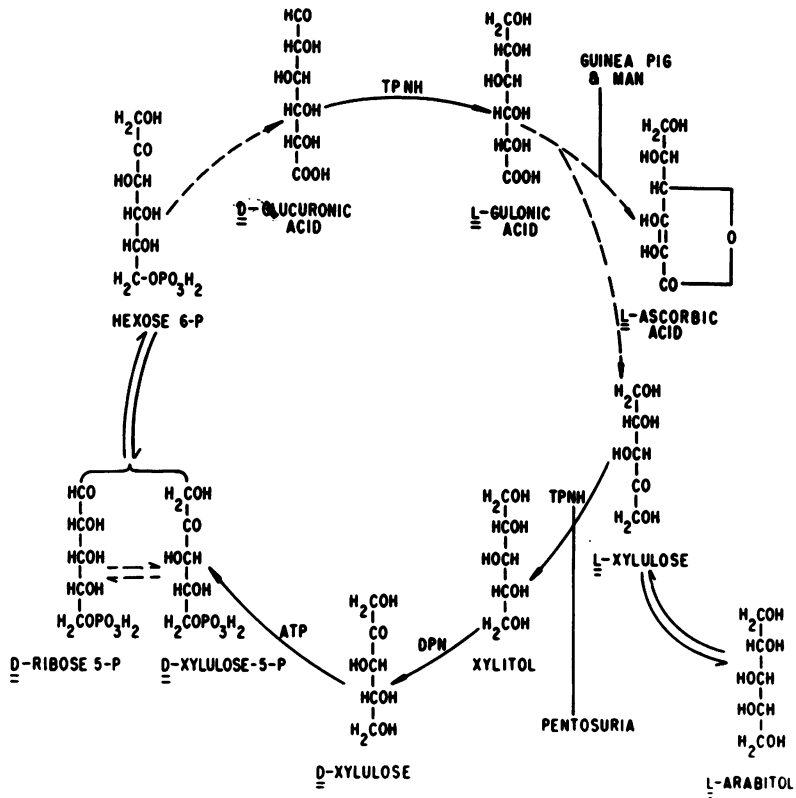

FIG. 3. Glucose-pentose cycle showing possible blocks in pentosuria (and in ascorbic acid synthesis in man).

extra amounts of pentose, at least equal in amount to the weight of drug given. This led to the eventual elucidation of pentosuric metabolism. He noted periodic increases of up to 2 g. in the amount of pentose excreted by his patient (who suffered from migraine). Eventually, he correlated the periods of increased excretion with the ingestion of amidopyrine taken to relieve the headaches. No pentose excretion followed amidopyrine ingestion by normal individuals or non-pentosuric patients with migraine. This curious but important lead has been amply confirmed (Margolis, 1929; Lasker and Enklewitz, 1933; Enklewitz and Lasker, 1935; Flynn, 1955). The extra pentose is *L*-xylulose. Enklewitz and Lasker (1935), acting on the theory that the glucuronogenic effect of amidopyrine (which is partly excreted in conjugation with glucuronate) caused the increase in pentose, found that administration of glucuronolactone itself caused extra xylulose excretion. However, it was less than half as effective as amidopyrine. Touster, Hutcheson and Rice (1955) pointed out that a gram of amidopyrine can cause the excretion of almost 2 g. of xylulose, yet less than half of the drug is excreted as the conjugated glucuronate. It is unlikely that a glucuronogenic effect could explain these results. Probably the drug inhibits some enzyme and channels hexose to pentose (and to ascorbic acid in animals (see Fig. 3)).

The possibility of controlling pentose formation to some extent led to the recognition of the place of xylulose in intermediary metabolism, but this would not have occurred had suggestions such as that of Everett (1946) been seriously considered. Since feeding glucuronic acid to normals did not lead to pentose excretion, it was suggested that the pentosuric patient had an *abnormal* enzyme system which decarboxylated glucuronic acid to yield xylulose. Similar suggestions, that xylulose could be an abnormal metabolite instead of a normal one, were also offered to explain the occurrence of homogentisic acid in alkaptonuria. Recent discoveries of pentose metabolism have demonstrated that *L*-xylulose is a normal intermediate with enzyme systems which form it and remove it (Horecker and Hiatt, 1958).

The steps of a new glucose cycle now known to occur in most tissues and involving the intermediary formation and removal of *L*-xylulose is shown in Figure 3. This series of reactions embraces those forming glucuronic acid and ascorbic acid (except in man and guinea pig where this step is blocked). *L*-xylulose is apparently formed in the course of recycling glucuronic acid to reform glucose. Attempts to determine whether the block in pentosuria was between *L*-xylulose and xylitol or between xylitol and *D*-xylulose (the enzymes for both steps are known (Hollman and Touster, 1957)), led to the discovery that *L*-arabitol was also excreted by pentosurics (Touster and Harwell, 1958). Xylitol excretion was expected if the block was located after this compound. The results do not clearly localize a metabolic block, but they suggest that if there is indeed a metabolic block in pentosuria, it is more likely to exist immediately after *L*-xylulose, as indicated in Fig. 3. The conversion of isotopically labelled glucuronolactone to labelled ribose in normal individuals, but not in pentosurics (Hiatt, 1958), demonstrated the functioning of this cucle in man and strongly supported the location of some discontinuity or block beyond *L*-xylulose in the pathway shown.

RENAL OR METABOLIC ORIGIN OF PENTOSURIA

It is known that a renal defect can account for the excretion of a metabolite in abnormal amounts and produce nearly the same picture as that which Garrod attributed to the inactivity of an enzyme. Such renal defects can be specific, life-long and determined by a single gene, the same as an enzyme defect. Cystinuria, one of Garrod's original examples of inborn errors of metabolism, as well as uric acid excretion by Dalmatian coach hounds and renal glucosuria in man are now known to occur in this way (Knox, 1958). It is necessary to see whether the renal mechanism, which has not been seriously considered for pentosuria, has been effectively ruled out. The nature of such a renal defect is the failure of a specific renal tubular transport system, so that after a substance is filtered out of the blood stream by the glomeruli, along with all the other simple compounds present, it is not reabsorbed by the tubule for conservation in the body. The exceedingly large volume of blood filtered each day and then concentrated by water reabsorption means that the urine of one day may contain some grams of the substance, even though its level in the plasma is always very low. In contrast to a metabolic block, in which the substance accumulates in the body to levels which overflow the kidney's capacity to conserve it, the blood level of the substance in a primary renal defect will be normal or low instead of elevated. Given the same blood level of the substance,

more will be excreted in the urine if there is a renal defect than if there is an enzyme deficiency. The renal defect does not prevent the metabolism in the body of that fraction of the substance which escapes filtration through the kidney. Some experimental data in the literature bear on these points of differentiation between a metabolic and a renal defect in pentosuria.

Garrod (1909) described the administration of arabinose to a pentosuric. Since no extra pentose was excreted following an oral dose of *L*-arabinose, it was apparent that the pentosuric could metabolize this sugar while he was at the same time excreting a pentose. Garrod referred to the similarities between this result and that obtained in cystinuria. The explanation for the latter condition is now known. It is a renal defect and not a metabolic block. Fischer and Reimer (1930) demonstrated that there was also no difference between normals and pentosurics in the amounts of xylose found in the blood or urine after an oral dose of xylose. Very little was excreted in either type of individual, and then only when the blood level was over 60 mg. per cent, which must be the approximate "renal threshold" for xylose. The coexistence of renal glucosuria with an easily evoked xylosuria in one patient has already been mentioned (Dunsky & Lawence, 1947), but this would be expected to occur in all renal glucosurics, if looked for, since the same renal transport system handles xylose and glucose. However, it is now clear that neither arabinose or xylose is excreted in essential pentosuria. Their metabolism and renal physiology may not be relevant to what happens to xylulose.

Greenwald (1931) could not get any of his four pentosurics to take xylulose as part of an experiment, and had to content himself with the demonstration that dogs readily metabolized this pentose excreted by pentosurics. Enklewitz and Lasker (1933) were more persuasive. Five grams of *L*-xylulose isolated from pentosuric urine was fed to a pentosuric and caused only 0.5 g. of extra pentose excretion. None was excreted by a normal control individual after the same dose. This result makes it clear that a pentosuric can metabolize *L*-xylulose almost as effectively as can normal individuals, assuming equal abilities to absorb the sugar.

The crucial information, short of measurements of the renal clearance of *L*-xylulose in normal and pentosuric individuals, is the blood level of xylulose. It is apparently quite low. Flynn (1955) was able to detect it chromatographically only by heavily loading the deproteinized plasma from a pentosuric onto the paper. The amount present was increased after a dose of glucuronolactone which increased the excretion of xylulose. Such a rise after administration of a precursor is compatible with either mechanism for the disease. Unfortunately, no attempt was made to see if xylulose in the plasma of a normal individual was more or less than in the pentosuric. If it could be assumed that there normally must be moderately high levels of xylulose in the blood before it is excreted, as is true for xylose, glucose and a number of other sugars, then it could be deduced from the data of Flynn and that published by Fischer and Reimer (1930) that pentosuria occurred because of a renal defect. In the latter experiments pentose, as measured by a method that would have included xylulose, was undetectable in the plasma of either normal or pentosuric individuals (the fasting values before xylose tolerance curves).

There is not now sufficient evidence to identify pentosuria as the failure of a

specific renal transport system for xylulose, but this possibility has not yet been excluded. It remains a reasonable possibility which must be tested directly, even with the evidence for a metabolic block recently presented by Hiatt (1958). This failure of labelled glucuronolactone to give rise to labelled ribose in a pentosuric may have alternate explanations not now apparent.

CONCLUSION

Pentosuria research has not been unusual, in comparison with the studies of the three other hereditary diseases singled out by Garrod, in the confusion which has masked the real advances. Critical evaluation of the work accumulated in the fifty years after pentosuria was called an inborn error of metabolism reveals it to be a disease entity whose main properties are well-established. There remain some uncertain questions on which further observation would be desirable, and the paramount question of a renal or an enzymic mechanism is still to be decided. The possible occurrence of arabinosuria, though it would be a separate entity if it exists at all, can now be readily determined by chromatography of the urine of all pentosurics. This is the procedure of choice for diagnosis, in any event. A more intensive study to identify any frequently associated but probably minor abnormalities is clearly indicated. The possibility of some selective advantage which the heterozygotes of pentosuria may possess has also been raised. Identification of the heterozygotes, which may be possible if the individual who excreted several hundred mg. of xylulose was one, would simplify this study and would also provide some measure of the gene frequency of this disease, which is apparently quite common among the Jewish population.

Some dissatisfaction with the utility of Garrod's concept of the inborn errors of metabolism might be voiced on the basis of the fragmentary and uncertain descriptions of these diseases commonly available. The current reviews (Knox, 1958) of the four diseases first singled out by Garrod (1908) show that, on the contrary, there is no ground for criticism. The concept of a specific functional protein under hereditary control has guided two generations of investigators to reach at last some understanding of each of the disease mechanisms. Any deficiency in the subject must instead be attributed to the oftentimes shallow and uncritical consideration which these diseases have received in the medical literature. The strength and fertility of Garrod's concept of the inborn errors of metabolism is also manifested by its continued utility in medicine and science. This has been shown by the intensive study the first four diseases have received, and by the adoption of the same hypothesis in that signal advance in physiological genetics called the "one gene—one enzyme" hypothesis. The continued addition of new disease entities also has proved that the slightly modified concept of Garrod embraced an etiologically distinct group of diseases. Fifteen years after his Croonian Lectures, Garrod (1923) added porphyria and steatorrhea (now separated into idiopathic steatorrhea and cystic fibrosis of the pancreas) to the original four inborn errors of metabolism. The mere enumeration of those since added to the list by others would serve no useful end. It is long and rapidly growing longer. The original concept, now modified to admit the hereditary control not only of enzymes, but also of other functional proteins such as the discrete

renal transport systems, the hemoglobins, the blood cell antigens and the plasma proteins, covers all of those many conditions which are best called the hereditary molecular diseases, and in which all clinical aspects of the disease can be referred to the hereditary molecular defect of one species of protein.

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