CHAPTER X

PENTOSURIA

PENTOSURIA is the least conspicuous and least clearly defined of the six anomalies here discussed. We know less of its nature than we appeared to know twelve years ago, for the more recent researches have tended to confuse rather than to clear the issues, and points which appeared to have been settled once for all are now subjects of controversy. It is even doubtful whether under the collective name of pentosuria several distinct errors of metabolism have not been included.

Our knowledge of the sugars of the pentose group is of recent acquisition, and dates back only a few years further than the discovery of pentosuria. It was in the year 1887 that Kiliani [1] showed that arabinose, the sugar of gum arabic, which had previously been classed as a hexose, was a member of a different class of sugars from any which had up till then been thoroughly investigated, and that its molecule contained only five carbon atoms, its formula being $C_5H_{10}O_5$. Not long afterwards Wheeler and Tollens [2] found that the wood sugar, xylose, was a second member of the group, and since then other pentoses have been recognized or obtained, including ketoses, and a series of methylpentoses of which rhamnose is the best known.

In 1892 Salkowski and Jastrowitz [3] described the case of a young man, neurasthenic and a victim of the morphine habit, whose urine gave the reduction tests for sugar, did

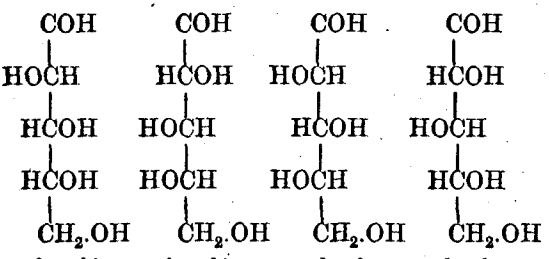
[1] *Berichte der deutschen chemischen Gesellschaft*, 1887, xx. 339.

[2] *Annalen der Chemie und Pharmacie* (Liebig's), No. 254, 1889, pp. 304, 320.

[3] *Centralbatt für die medicinischen Wissenschaften*, 1892, xxx. 337.

not ferment with yeast, was optically inactive, but yielded an osazone the melting-point of which was 159° C. This melting-point suggested that the sugar present was a pentose, although no compound of that class had previously been recognized as a product of animal metabolism, nor as a constituent of animal tissues. Further investigation confirmed this conjecture, and thus was laid the foundation of our knowledge of pentosuria. Soon afterwards Hammarsten[4] demonstrated the presence of a pentose in the pancreas, and since then the presence of such a substance in the nucleo-proteins of various tissues and organs has been proven.

Like other sugars the pentoses exist in dextro- and lævo-rotatory forms, and also in optically inactive, racemic, combinations. The structures of the isomeric arabinoses and xyloses are represented by the following formulæ:



d-arabinose. l-arabinose. d-xylose. l-xylose.

The names l- and d-arabinose and xylose express their affinities to the l- and d-series of hexose sugars respectively, and not their own optical properties. As a matter of fact, both l-arabinose and l-xylose, the forms usually met with in nature, are dextrorotatory. The pentoses are abundantly represented in vegetable structures, not as such, but in the form of complex anhydrides known as pentosanes.

The power of the normal human organism to destroy

[4] *Zeitschrift f. physiol. Chemie*, 1894, xix. 19.

pentoses is very limited, and quite small doses, such as one gramme of arabinose or even less, lead to the appearance of some of the sugar in the urine. Different observers have found that the fractions excreted varied widely, and the destruction may be in part effected in the alimentary canal before absorption.

Seeing that many vegetable foods are rich in pentosanes it is not surprising that some degree of alimentary pentosuria is occasionally induced by their free consumption, but the quantities excreted after the eating of such fruits as plums and cherries, even in abundance, are very small, and delicate tests are required for their detection. Such an alimentary pentosuria, which is wholly distinct from the so-called essential pentosuria, is little likely to lead to diagnostic errors, but von Jaksch [5] has found that when the unfermented fruit juices, which are popular beverages on the Continent, are taken in such quantities as a litre or more, the next passed urine yields Trommer's and Nylander's tests and also the special tests for pentoses. Under such conditions the sugar excreted is the l-arabinose contained in fruits and the urine rotates the polarized ray to the right. Hence it is evident that the presence of a pentose in urine, in quantities easy of detection, is not necessarily due to an error of metabolism, but may be of accidental alimentary origin.

Since the anomaly was first described by Salkowski and Jastrowitz upwards of fifty cases of pentosuria have been put on record. Most of these have been met with on the Continent, and most of those recorded in America have been in persons of German or Russian birth. Among patients whose race has been mentioned a large proportion have been Jews, and it would seem that there is a special liability of the Hebrew race to this inborn error. The only cases reported in England, up to now, are those of Cammidge and

[1] *Centralblatt für innere Medicin*, 1906, xxvii. 145.

Howard,[6] of whose seven patients three were Jews, two, a father and son, were of Greek descent, and only two were English by birth and ancestry. The tendency of pentosuria to occur in several members of a family, and the preponderance of males among its subjects have been referred to in Chapter II.

Although pentosuria is known to persist for many years without causing serious impairment of health, the evidence that it dates from birth is far from complete. Nor is this to be wondered at, seeing that it is only detected by the reducing power of the urine, and the urine of infants is seldom tested for the presence of sugar. However Aron [7] has described an unequivocal case in a boy five years of age.

The case recorded by Alexander [8] of a male child of eighteen months was apparently alimentary, for on several occasions the pentose disappeared from the urine when milk was eliminated from the diet.

As to the prognosis of pentosuria it is too soon to speak positively, but the impression prevails among those who have devoted study to the subject that it is not seriously harmful, but the history of alcaptonuria should make us cautious in adopting that view. Some patients have come under observation at the age of sixty years and upwards, and af Klercker [9] had the opportunity of watching his patients, two Jewish brothers, for at least ten years, during which period there was no aggravation of their condition.

Pentosuria is not necessarily associated with any morbid symptoms. In some cases the detection of a sugar in the urine at an examination for life insurance has been the first indication of anything amiss, but this is also true of many

[6] *British Medical Journal*, 1920, ii. 777.
[7] *Monatsschrift f. Kinderheilkunde*, 1913, xii. (orig.) 177.
[8] *Archiv f. Verdauungskrankheiten*, 1918, xxiv. 286.
[9] *Nordiskt Medicinskt Arkiv*, 1905, Afd. ii, Heft 1, pp. 1 and 55. *Deutsches Archiv f. klin. Medizin*, 1912, cviii. 277.

mild cases of diabetes mellitus. In many cases there are symptoms of neurasthenia, and if any morbid condition can be regarded as specially closely associated with pentosuria it is this. However race and racial temperament may here play a not unimportant part, and the diagnosis of diabetes, commonly made, may contribute to this result. Most pentosurics have been supposed to be diabetic and have, at first, to be treated accordingly. Gastro-intestinal symptoms are sometimes prominent, and Alexander [10] has expressed his belief that pentosuria is nothing more than a symptom of digestive disturbance, and neither a congenital anomaly nor a disease *sui generis*.

The question whether there is any connexion between primary pentosuria and diabetes mellitus is of considerable interest and difficulty. It would appear that from the standpoint of the student of metabolism they are absolutely distinct. The power of dealing with glucose is in no way impaired in the pentosuric, and addition of carbohydrates to the diet, or their elimination therefrom does not affect the output of pentose. We still await investigations of the sugar in the blood of pentosurics, and the only observation on this matter which I have met with is that of Blumenthal and Bial,[11] who found a normal content of glucose in the blood of a pentosuric. In the light of recent investigations this observation has not the great importance which they attached to it, for it is by no means the case that all persons who excrete glucose in their urine have an excess of sugar in their blood.

Kulz and Vogel [12] found that some diabetic urines, especially of sufferers from the more severe varieties of the disease, there may be obtained, in addition to glucosazone, an osazone soluble in hot water which has the melting-point

[10] loc. cit., sub 8.
[11] *Deutsche med. Wochenschrift*, 1901, xxvii. 349.
[12] *Zeitschrift f. Biologie*, 1895, xxxii. 185.

and nitrogen content of a pentosazone. Only small yields of this product were obtained when several litres of urine were dealt with, and other observers have failed to find pentose in diabetic urines, and among them Bendix [13] who employed the same method as was used by Kulz and Vogel. The same observers found pentose in the urine of a dog after removal of the pancreas. W. Voit [14] also obtained an osazone with the melting-point of pentosazone, from twelve out of fourteen urines of diabetes of the more severe kinds.

None of the above investigators determined the exact nature of the pentose in question, or whether it was the same sugar as that excreted in primary pentosuria, and special importance attaches to the more recent work of Zlataroff [15] who investigated the urine of a sufferer from a grave form of diabetes, from which he obtained, in addition to glucose, a second sugar which did not yield the ordinary pentose reactions, but which appeared to belong to the pentose group. From 26 grammes of the osazone he obtained 6 grammes of a sugar in crystalline form, which had the percentage composition, and water of crystallization of a methyl pentose, melted at 93° and was shown by its optical rotation to be that known as rhamnose. The urine in question contained 8·8 per cent. glucose and no less than 1·99 per cent. rhamnose. What lends special interest to Zlataroff's result is that this sugar, rhamnose, has never been identified in the urine of a subject of primary pentosuria.

The clinical evidence is still more perplexing. Several of the recorded pentosurics have also excreted glucose, either at intervals or continuously. The original patient of Salkowski and Jastrowitz did so, but in his case the

[13] *Die Pentosurie*, Stuttgart, 1903, p. 55.
[14] *Zeitschrift f. physikal. u. diätet. Therapie*, 1909, xii. 659.
[15] *Zeitschrift f. physiol. Chemie*, 1916, xcvii. 28.

morphine habit, of which he was a victim, may have been the cause of the temporary glycosuria. One of Blumenthal's patients was a glycosuric, as also was one of af Klercker's. The Jewish family described by af Klercker has been investigated more thoroughly than any other. The pedigree which he published includes three generations and no less than eleven members, the urine of all of whom was examined. Two brothers of the second generation were pentosuric. No account of diabetes in the family was forthcoming, but on examination af Klercker found glucose in the urine not only of one of the pentosurics but also in that of their father and a third brother. Schüler's [16] patient had lost a brother and two sisters from diabetes, and the father and brother of one of Rosenfeld's patients were diabetic. We can hardly dismiss, as of no significance, this apparent association of the two derangements of carbohydrate metabolism, but it is possible that the liability of the Jewish race both to diabetes and to pentosuria may play some part in the coincidence.

Only further research can settle the question of the relationship, if any exists, between the two conditions. It is obvious that a pentosuric is not a diabetic, for he is able to deal with ingested glucose as any normal individual can; only when that sugar is taken in doses which overtax the power of a normal man to deal with it does glucose appear in the urine.

Clearly the correct diagnosis of cases of pentosuria is a matter of real practical importance. If it be not made the patient is not only subjected to the distress which the diagnosis of diabetes entails, but is subjected to irksome dietary restrictions which in his case are wholly uncalled for, are quite useless, and when not necessary are certainly undesirable. On the other hand, it is better that a few persons who exhibit an anomaly so rare as pentosuria

[16] *Berliner klin. Wochenschrift*, 1910, xlvii. 1322.

should be erroneously classed as diabetic, than that a diagnosis of pentosuria, on inadequate grounds, should lead to the omission of treatment in a number of cases of true diabetes.

In pentosuria the urine is not excessive in quantity, nor are the symptoms so often prominent in diabetic cases, such as thirst and undue appetite, met with in connexion therewith. The specific gravity of the urine usually varies from 1·025 to 1·035, and when it is boiled with Fehling's solution it reduces as does a diabetic urine containing some 0·5 per cent. of glucose. Many observers have described the reduction as delayed, and as occurring suddenly after the test-tube has been removed from the flame. Urine containing small percentages of glucose may behave in this way, and Bial,[17] who had an exceptionally large experience in this matter, stated that, when fresh, pentose urines may show no such peculiarity of behaviour and that the reduction may occur before the boiling-point is reached. He suggested that the delayed, but sudden, reduction, so often observed, is due to the urine having been kept for some time with the addition of preservative substances, such as toluene or chloroform.

Pentose urines also yield Moore's test for sugar and that of Nylander, although not very strikingly since the amount of the sugar present is never large. They also yield the saffranin test.

With the yeast test no fermentation occurs, and after standing with yeast in a warm place for twenty-four hours the reducing power of the urine is not impaired. This fact was made use of by af Klercker for the elimination of the glucose in one of his cases, but Voit has shown that under certain conditions a small quantity of l-arabinose added to a diabetic urine may be fermented with the glucose.

The urine of most pentosurics has been optically inactive,

[17] *Berliner Klinik*, 1907, Heft 226.

but in a few described by Blumenthal,[18] Luzzatto,[19] and Rosenfeld[20] the urine apparently optically inactive yielded a dextrorotatory osazone.

With the phenyl-hydrazine test a crystalline osazone is obtained, but as it is to some extent soluble in hot water it is only thrown out in crystalline form after the liquid has cooled. In appearance the crystals closely resemble those of phenyl-glucosazone, but whereas the latter after recrystallization melts at 205° C., the melting-point of pentosazone is much lower, between 156° and 160° C. This melting-point supplies one of the most important means of diagnosis of pentosuria, but to ensure complete certainty as to its nature the nitrogen content of the osazone must be estimated. The theoretical amount for a pentosazone is 17·07 per cent. N. Special derivatives of phenyl-hydrazin are helpful for the identification of individual pentoses. Thus di-phenyl-hydrazin yields a characteristic osazone with arabinose.

The special tests which are available for the detection of pentoses are based upon the property which such sugars possess of yielding furfurol when heated with mineral acids. The phloroglucin test is performed as follows: a small quantity of phloroglucin is dissolved in 5 or 6 cubic centimetres of fuming hydrochloric acid, a slight excess remaining undissolved. To one portion of the solution half a cubic centimetre of the urine to be tested is added in a test-tube, and to the other portion an equal quantity of normal urine as control. Both tubes are then placed in a beaker of boiling water. If pentose be present the test containing it quickly assumes a deep red colour from the surface downwards, whereas the normal specimen shows little change.

[18] Eulenberg's *Real-Encyclopädie*, 1908, xxxii. 388.

[19] Hofmeister's *Beiträge*, 1905, vi. 87, and *Archivio Italiano d. Biologia*, 1909, li. 469.

[20] *Medizinische Klinik*, 1906, ii. 1041.

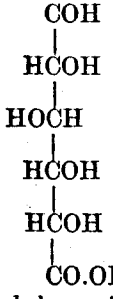
The colour can be readily extracted by shaking with amylic alcohol, and the amylic extract, suitably diluted, shows a spectroscopic absorption band between the Fraunhofer lines D and E—about λ 5425 to λ 5750. More satisfactory for diagnostic purposes is the orcin test. A specimen of urine is warmed with an equal volume of concentrated hydrochloric acid in which sufficient orcin to cover a knife point has been dissolved. A green colour quickly develops if pentose be present and the liquid becomes turbid by the formation of a bluish-green flocculent precipitate. After cooling the precipitate may be taken up with amyl alcohol, which acquires a rich green colour and shows a characteristic absorption band between the solar C and D lines and overlapping the D line—about λ 5850 to λ 6150. A second band nearer to the red end of the spectrum and a fainter band in the green, which are often seen, are not of diagnostic importance.

Bial's[21] modification of the orcin test is very useful for clinical purposes. It is based upon the effect of the addition of ferric chloride in quickening the reaction. The reagent is prepared as follows: 1 gramme of orcin is dissolved in 500 cubic centimetres of hydrochloric acid of specific gravity 1·151, and to the solution 25 drops of a 10 per cent. solution of ferric chloride are added. The liquid when kept in an amber-coloured bottle will preserve its activity for a long period. Five cubic centimetres of the reagent are boiled in a test-tube and, after the tube has been removed from the flame, five drops of the urine to be tested are allowed to run on to the surface of the liquid from a pipette. If pentose be present a green ring appears at the junction of the liquids, and if the tube be gently shaken the green colour spreads through the liquid. With the spectroscope the characteristic absorption band is seen. Care is required that the correct proportions be employed in mixing the

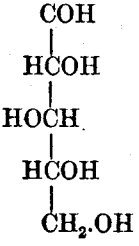
[21] *Deutsche medicinische Wochenschrift*, 1902, xxviii. 253.

reagent, and the hydrochloric acid must be of the prescribed strength. If a pentose urine be not available the efficiency of the reagent may be tested with a dilute solution of gum arabic. I can testify, from my own experience, that the reaction so obtained is a very striking and characteristic one. By its means it is easy to exclude pentosuria in doubtful cases, and it is easily applied in ordinary clinical work. Bial and also Kraft maintain that, if performed in the manner described, the test is diagnostic and is yielded by none but pentose urines. However, for the diagnosis of pentosuria one should not rely upon any single reaction and confirmatory tests should be applied.

The discrimination between pentosuria and glycosuria should present no real difficulty, as glucose does not yield the above colour tests. It is in connexion with glycuronic acid that the risk of error comes in. Glycuronic acid has obvious chemical relationships to the pentoses, as their respective formulæ show. By splitting off carbon dioxide



d-glycuronic acid.



l-xylose.

from it a pentose results, and the acid itself yields the furfurol reactions. Urine containing glycuronic acid may yield the phloroglucin test, but as the acid is almost always in combination in urine, as compound glycuronates, the reactions are not obtained until the combination is loosened.

However, some compound glycuronates, such as the menthol compound, break up spontaneously in urine.

It is not easy to make sure from the writings of those who have had most experience of these reactions whether in clinical work the risk of mistaking a urine containing glycuronic acid for a pentose urine is really great. It is stated that the orcin test is not yielded by compound glycuronates unless heating be unduly prolonged, and although Bial's reagent, if boiled with a urine containing a compound glycuronate, gives the green colour and the absorption band, it is claimed that no risk of confusion exists if the urine be added after the test-tube has been removed from the flame. With free glycuronic acid Paul Mayer [22] obtained crystalline phenyl-hydrazine compounds, one of which had a melting-point like that of a pentosazone, but this is not yielded by compound glycuronates, and in case of doubt an estimation of the nitrogen in the crystalline product will settle the point.

Again, the polarimeter may help in the diagnosis, for all known compound glycuronates are lævorotatory, although the free acid is dextrorotatory, whereas pentose urine is almost always optically inactive. Lastly, patients who excrete glycuronic acid in appreciable quantities are almost always taking some drug which is known to be excreted as a compound glycuronate. Nevertheless there is some doubt whether in certain cases [23] which have been described as examples of pentosuria the reducing property of the urine was not really due to glycuronic acid.

A. Neumann [24] devised a modification of the orcin test which yields distinctive colours and spectra with different sugars, and so serves to distinguish pentoses from dextrose,

[22] *Zeitschrift für physiologische Chemie*, 1900, xxix. 59.

[23] Caporali, *Riforma Clinica e Terapeutica*, 1896, xviii, 13; Colombini, *Monatshefte der praktischen Dermatologie*, 1897, xxiv. 129.

[24] *Berliner klinische Wochenschrift*, 1904, xli. 1073.

lævulose and glycuronic acid, and also renders possible the identification of special pentoses, such as arabinose and xylose.

Lastly, Castellani and Taylor,[25] by an ingenious reversal of the method of distinguishing bacteria by the sugars which they ferment, were able to diagnose a case of pentosuria by the bacteria by which the sugar in the urine was fermented.

Our knowledge of the quantities of pentose excreted by pentosurics is very imperfect. The ordinary Fehling's method of estimation is not applicable to such urines, because the cuprous-hydrate precipitate does not separate satisfactorily, and other methods have to be resorted to, such as Allihn's, Knapp's, or weighing the phloroglucin precipitate. The estimated amounts in individual cases have differed widely—from 1 to 7 grammes in the twenty-four hours—and Neuberg [26] states that all such estimates are too low, sometimes by 100 per cent., because much of the pentose is in combination with urea as a ureide, and the portion so combined does not reduce until the ureide is broken up by heating with an acid. If this be so the quantity estimated—i. e., the uncombined arabinose—may represent no constant fraction of the total amount. Neuberg [26] mentions from 30 to 36 grammes as the figure which may be reached by the day's excretion, which is far more than twice as much as any other recorded estimate with which I am acquainted.

Zerner and Waldtuch,[27] on the other hand, showed that, in the cases which they investigated, the pentose in the urine was free, and not in combination as ureide, and af Klercker thinks that such a combination may take place

[25] *Journal of Tropical Medicine*, 1919, xxii. 121.

[26] *Pathologie des Stoffwechsels* (von Noorden), second edition, 1907, ii. 220.

[27] *Biochemische Zeitschrift*, 1914, lviii. 410.

when the urine is kept, but doubts its presence in fresh urines.

Neuberg[28] first determined the nature of the sugar present in the urine of a pentosuric. He obtained the free pentose in crystalline form from the osazone prepared by treating a large volume of the urine with di-phenyl-hydrazine, and showed that it was racemic arabinose. This discovery was the more remarkable because no racemic sugar had hitherto been found in the animal organism. Moreover, Neuberg and Wohlgemuth[29] found that when 15 grammes of this sugar were so taken by a normal man his urine (which had previously contained no reducing substance, had been optically inactive and had failed to yield the orcin test), acquired after the lapse of four hours strongly reducing properties, was optically active, and gave the pentose reactions. Of the excreted arabinose, to which these properties were due, no less than two-thirds was the lævorotatory d-arabinose, and it was evident that the individual in question had a much greater power of destroying the ordinary l-arabinose than the other form. This was in the early days of our knowledge of pentosuria, and the failure of the urine to rotate the polarized rays was a notable feature of all the earlier cases of the anomaly. Hence, it was assumed, very naturally, that what was true of one pentosuric held good for all, and that the sugar excreted in pentosuria was always racemic arabinose. Even when it was found that in some cases the urine, or the osazone obtained from it, was dextrorotatory, and that no osazone could be got with di-phenyl-hydrazin, as in the cases of Luzzatto and af Klercker, it was supposed that there was an excretion of excess of l-arabinose. Aron,[30] whose patient was a Jewish boy of five years, made a

[28] *Berichte der deutschen chemischen Gesellschaft*, 1900, xxxiii. 2243.
[29] *Zeitschrift für physiologische Chemie*, 1902, xxxv. 41.
[30] loc. cit., sub 7.

thorough examination of the urine which was optically inactive, and satisfied himself that the pentose which it contained was dl-arabinose, as in Neuberg's case. He obtained a crystalline osazone with di-phenyl-methan-di-hydrazine, a reagent introduced by von Braun,[31] which yields osazones only with arabinose, rhamnose, galactose, and mannose.

So the matter stood until the work of Zerner and Waltuch, and of Levene and La Forge, published in 1914, reopened the whole question of the nature of the urinary pentose.

Levene and La Forge [32] found in the urine of a pentosuric a dextrorotatory sugar, and from the properties of the osazone which they obtained concluded that it belonged to the xylose group. Like af Klercker they failed to obtain a di-phenylosazone. They point out that a dextrorotatory pentosazone which when mixed with a lævorotatory xylosazone exhibits a rise of melting-point from 163 to 205 must be regarded as a xylosazone, and their product behaved in this way. A dextrorotatory xylosazone may be derived from d-xylose, from l-lyxose or from the keto-pentose of either of these. The first was excluded by the dextrorotation of the urine, and by the characters of the p-brom-phenylhydrazone prepared, which also excluded l-lyxose, and they considered that all the evidence pointed to a keto-pentose corresponding to l- or d-xylose.

Zerner and Waltuch [33] investigated two pentosurics who were not members of the same family, a fact which adds to the significance of their results. Both urines were optically inactive, but both yielded dextrorotatory osazones. The osazone from the urine of the first patient melted at 162°–

[31] *Berichte der deutschen chemischen Gesellschaft*, 1908, xli. 2169, and 1910, xliii. 1495.

[32] *Journal of Biological Chemistry*, 1913–14, xv. 481; ibid., 1914, xviii. 319.

[33] *Biochemische Zeitschrift*, 1914, lviii. 410.

163°, and was shown by analysis to be a pentosazone, but its dextrorotation did not agree with that of arabinosazone or xylosazone. They considered that arabinose was excluded by the failure to precipitate the sugar by di-phenyl-hydrazine, although the directions of Neuberg were strictly followed, nor by di-phenyl-methan-di-methyl-hydrazine, a still more delicate test for arabinose.

When the urinary osazone was mixed with l-xylosazone the melting-point was conspicuously raised, and they obtained a new substance which melted at 210° and which was undoubtedly dl-xylosazone. Similar results were obtained with the osazone from the second case.

Zerner and Waltuch conclude that in both their cases the sugar excreted is a member of the d-xylose group, but that its exact nature could not be confidently stated. They also believe that the sugar in the urine of the patients of Luzzatto and af Klercker, which failed to yield di-phenyl osazone, cannot have been arabinose.

They think it probable that cases of pentosuria are of at least two distinct kinds ; that in some, such as Neuberg's and Aron's cases, the pentose excreted is racemic arabinose, and in others is a member of the xylose group.

More recently Cammidge and Howard[34] have published the results of their examination of the urine of seven pentosurics. From the di-phenylhydrazone prepared from the urine of three of them they were able to obtain a pure crystalline sugar, optically inactive, which melted at 163°–164°. From this sugar they prepared barium arabonate and r-arabona-lactone, and thus were able to prove that the sugar excreted was dl-arabinose. Additional evidence that they were actually dealing with racemic arabinose was afforded by the fact that they were able to separate the constituent dextro- and lævorotatory sugars from specimens of their optically inactive, crystalline product. The optical in-

[34] loc. cit., sub 6.

activity of the remaining urines, and their behaviour with p-bromphenylhydrazine and di-phenylhydrazine, rendered it highly probable that the same sugar was present in them, and these observations supply very strong evidence that the majority of cases of pentosuria belong to the arabinosuria group.

Hammarsten first demonstrated the presence of a pentose in pancreatic tissue and such a sugar is also present in the nucleo-proteins of other organs. Neuberg identified the pancreatic pentose as l-xylose, and although one would look to this supply as the source of the urinary pentose, such an origin appeared to be excluded by the nature of the sugars in urine and tissues. But the work of Levene has reopened the question of the nature of the tissue pentose also. He demonstrated the presence in the pancreas of d-ribose, and although the question is still controversial, Abderhalden, in the third edition of his text-book, states that as yet the only recognized pentose in nucleic acid is d-ribose. It has been urged that the total quantity of tissue pentose in the body is insufficient to serve as a source of supply, for Grund [35] estimated it at only 10 grammes, and Bendix [36] made it only slightly more. Moreover, Bial and Blumenthal [37] found no increase of urinary pentose after feeding a pentosuric with 500 grammes of calf's thymus, and the uric acid and phosphate excretion of pentosurics affords no evidence of abnormal break-down of nucleo-proteins.

Whilst the nature of the pentoses of the tissues and also of the urine is still open to doubt we cannot hope to make much advance towards the solution of the problems of pentosuria, and the results of the various feeding experiments which have been carried out do not help materially.

[35] *Zeitschrift für physiologische Chemie*, 1902, xxxv. 111.
[36] loc. cit., sub 13.
[37] *Deutsche med. Wochenschrift*, 1901, xxvii. 349.

Alexander [38] found that in the case of the child of 18 months who was under his care the sugar disappeared from the urine whenever milk was eliminated from the diet, and reappeared when it was restored, but in no other case has such a dependence upon diet been demonstrated, although the temporary pentosuria which follows the taking of pentosanes in excess is well known. In the ordinary cases the pentosuria is obviously not alimentary.

Exclusion of carbohydrate from the diet has been shown to have no influence upon the pentose output as estimated by reduction tests, nor is the pentosuric less able to burn dextrose and lævulose than a normal subject. Still more remarkable is the fact, observed by Bial and Blumenthal,[39] that even when 5 grammes of l-arabinose were administered to a pentosuric by the mouth, the amount of the optically active arabinose excreted was no greater than when a like dose is administered to a normal man. Just as a cystinuric destroys cystin given by the mouth, so the pentosuric is able to destroy the usual proportion of a dose of l-arabinose when so given. From this it is clear that, even if any treatment of pentosuria is called for, no good purpose is served by restriction of the carbohydrate, nor even of the pentose intake.

Neuberg [40] suggested d-galactose as a likely parent substance of the racemic arabinose which his pentosuric excreted, but himself points out that the evidence in support of this hypothesis is purely circumstantial, and that no direct proof of its correctness is forthcoming, moreover such an explanation relates only to cases of arabinosuria.

By a series of changes, with glycuronic acid as an intermediate stage, the pentose known as l-xylose can be derived from d-glucose, and l-arabinose stands in a like relation to d-galactose. Moreover, Neuberg quotes

[38] loc. cit., sub 8. [39] loc. cit., sub 37.

[40] *Ergebnisse der Physiologie*, 1904, iii, 1. Abtheilung, 426.

Fischer's observation that, on account of the symmetry of the groupings upon its four middle carbon atoms, d-galactose is readily converted into optically inactive derivatives, mucic acid by oxidation, and dulcite by reduction. By converse treatment these products are reconverted into galactose, but into the racemic form. On this account Neuberg finds it easier to suppose that this particular sugar may be the parent substance of the racemic arabinose of pentosuria. The formation of d-galactose in the animal body is an undoubted fact; lactose, the disaccharide formed from glucose and galactose, is abundantly formed during lactation, and galactose has also been shown by Thierfelder [41] to be the sugar yielded by cerebrin.

So far no conclusive evidence is forthcoming that galactose administered as such by the mouth, or in lactose, has any appreciable effect upon the output of arabinose by a pentosuric, nor are there any recorded observations upon a female pentosuric during lactation. In Aron's case of dl-arabinosuria, elimination of milk from the child's diet had no effect upon the output of pentose. Blumenthal and Bial gave to their patient 100 grammes of galactose by the mouth, not with any idea of testing Neuberg's hypothesis which had not then been put forward, but observed no conspicuous increase of urinary pentose. Otto af Klercker, who gave 100 grammes of lactose to one of his patients, observed a distinct increase of the hourly output of pentose six or seven hours later, but the total day's excretion was in no way excessive. Tintemann [42] observed a slight increase of pentose in the urine after 50 grammes of galactose given on an empty stomach.

Luzzatto observed a definite increase of pentose after 15 grammes of galactose, but no further increase with much larger doses. Erben obtained no increase with 100 grammes

[41] *Zeitschrift für physiologische Chemie*, 1890, xiv. 209.
[42] *Zeitschrift für klinische Medicin*, 1906, lviii. 190.

of lactose, whereas Schüler observed a slight increase after large doses of lactose in both his cases. No experiments with lactose or galactose were made in Neuberg and Aron's cases of dl-arabinosuria, the more important variety from this point of view, but Cammidge and Howard found that neither the administration of lactose, nor the withdrawal of all carbohydrate food had any effect upon the excretion of dl-arabinose by one of their patients.

The feeding experiments of af Klercker,[43] which are the most elaborate hitherto recorded, indicate that primary pentosuria is not wholly independent of diet. His patients were Jews, and the Day of Atonement happened to occur in the course of a series of observations upon one of them. On that day the output of pentose fell promptly to half the ordinary amount, but as he mentions that for a great part of that day the patient took neither food nor drink, presumably the collection of the urine did not coincide with the period of the ritual fast, so it cannot be reckoned as a complete hunger-day. A very conspicuous fall was also observed on the second day of a milk diet, rich in carbo-hydrates, but this was partly attributable to loss of appetite. Obviously observations upon the effect of hunger days upon pentosurics are much to be desired, and may throw important light upon the nature of the anomaly, or anomalies, in question.

Observations which af Klercker carried out on the hourly excretion of pentose and nitrogen revealed a remarkable parallelism of the two curves, which was equally striking whether the patient was upon a mixed, carbohydrate-free or milk diet. The parallelism could not be explained by excretion of pentose in the form of ureide, which could be excluded in these cases. Again, Cammidge and Howard found that, in one of their cases, diminution of proteins in the diet was followed by a fall of the output of dl-arabinose from 3·2 grammes to 0·5 gramme in the day, whereas the

[43] loc. cit., sub 9.

output gradually returned to its former level as the intake of protein was increased.

The obvious explanation of such results would seem to be that the pentose is derived from protein, and if so that glucosamine is its most likely parent substance, but in his later series of investigations of his patients af Klercker found that the administration of 10 grammes of glucosamine, by the mouth, did not cause any increase of the pentose output in either case.

Here the matter rests for the moment, and it will be obvious, from all that has gone before, that we are only at the beginning of the study of pentosuria, or of the pentosurias. However such knowledge as has been accumulated indicates clearly the lines which future research should follow.

Doubtless, as the years go by, other inborn errors of metabolism will be recognized from time to time, and, in all probability, examples of such anomalies are to be found among the past records of rare and exceptional cases. I have little doubt that a young man, whose case was recorded by Schölberg,[44] and who also came under my own observation, was the subject of an unknown inborn metabolic error. His urine, and also that of his father and sister, blackened on standing, and contained from his early childhood the chromogen of a purple pigment which was unlike any other urinary pigment with which I am acquainted.

A case described by Walter Smith,[45] of a young woman whose urine threw down an abundant sediment of leucin, but who showed no other signs of serious illness, also calls for mention. It may well be that among the cases grouped under the heading of 'renal glycosuria' are examples of such an anomaly; and the very rare xanthin calculi, first

[44] *Trans. Pathological Soc.*, 1902, liii. 279.
[45] *The Practitioner*, 1903, lxx. 165.

described by Alexander Marcet[46] more than a hundred years ago, may have their origin in an error of purin metabolism.

So far we only know of those anomalies which are the most conspicuous, and, as we have seen, they are able to teach us much. We may feel confident that each new inborn error which is recognized and studied will serve to throw yet further light upon the workings of the metabolic processes in living things.

[46] *An Essay on Calculous Disorders*, 1817.