ESSENTIAL PENTOSURIA IN TWO BROTHERS.[1]

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Historical. Salkowski and Jastrowitz, in 1892, first observed the excretion in the urine of an optically inactive sugar which did not ferment with yeast. This they identified as a pentose,[2] by the melting point of its osazon. In 1895, Blumenthal reported two more cases from Salkowski's laboratory. Since that time additional observations have brought the number of indubitable instances of this metabolic anomaly to seventeen, all but a few of which are from Salkowski's laboratory, or the first medical clinic in Berlin. One true case and several questionable ones have come from Italy, and a careful study of two patients from Norway; but no single instance has yet been reported in the British, French, or American literature. The condition is evidently rare, but may frequently have escaped detection or publication.[3]

Apart from its theoretical interest, pentosuria is of importance clinically because of its confusion with diabetes in almost every recorded case—an error which, once the existence of pentosuria is in mind, may be easily avoided.

After a careful study of the original reports the seventeen cases reported by the following observers seem to me unquestionable: Salkowski and Jastrowitz[4] (Case I), Blumenthal[5] (Cases II and III), Bial[6] (Cases IV and V), Meyer[7] (Case VI), Luzzatto[8] (Case VII), Blumenthal[9] (Case VIII), Brat[10] (Cases IX and X), Bendix[11] (Case XI), Bial[12] (Cases XII, XIII, XIV, and XV), and

[1] Read at a meeting of the Association of American Physicians, Washington, D. C., May 15 and 16, 1906.

[2] The pentoses are sugars containing five carbon atoms; the better known grape sugar, fruit sugar, etc., being hexoses with six. The various members of the group differ from one another in the position of attachment of the OH groups, as do dextrose, levulose, and galactose, for instance, among the hexoses. Pentoses are common in the vegetable kingdom, in fruits and stems especially. The most important ones are l-arabinose and l-xylose. In the animal body, pentoses are present in the nucleoproteids, that of the pancreas and of the liver having been identified as l-xylose.

[3] One case I know has been definitely studied by a member of this Association, Prof. E. K. Dunham, though never put on record.

[4] Centralbl. f. d. med. Wissenschaft, 1892, xxx, 337.

[5] Berl. klin. Woch., 1895, xxxii, 567.

[6] Ztschr. f. klin. Med., 1900, xxxix, 473.

[7] Berl. klin. Woch., 1901, xxxviii, 785.

[8] Festschrift f. P. Albertoni, Bologna, 1901; Beiträge z. chem. Physiol. u. Pathol., 1904-5, vi, 87.

[9] Die deutsche Klinik, 1902, No. 71–72, Amer. edit., Modern Clinical Medicine, Diseases of Metabolism, p. 262.

[10] Ztschr. f. klin. Med., 1902, xlvii, 499.

[11] Münch. med. Woch., 1903, liii, 1551.

[12] Berl. klin. Woch., 1904, xli, 552.

Klercker[1] (Cases XVI and XVII). In addition, von Jaksch[2] refers to a case he has had under observation for some time and is about to publish. This with Dunham's unpublished case and my two would make twenty-one cases in all.[3]

The cases of Reale and of Colombini, included by Bendix in his monograph, but with some doubts, I do not think can be admitted as chronic pentosuria, on account of the disappearance of the pentose after a short time. In Reale's case, also, the differentiation from glycuronic acid was not carefully made. Neuberg mentions d'Amato as publishing a case, but this was an example of pentosuria accompanying severe pancreatic diabetes.

In all the above cases except Luzzatto's the pentose was optically inactive; and in one, Neuberg succeeded in isolating the r-arbinose. Luzzatto, in his second paper, described the osazon he obtained as dextrorotary to the same degree as that of l-arabinose. Whether this is a unique case, with the excretion of l-arabinose alone, or possibly an alimentary pentosuria accompanying the chronic r-arabinose excretion, as has been described, does not seem to me proved.

Personal Observations. The two cases observed by me are a reproduction of those already on record and I report them in brief as showing the usual clinical history.[4]

Case I.—Male, aged twenty-eight years, married, a salesman. Born in Germany. His father died, aged sixty-two years, of angina pectoris; mother aged thirty-two years, of some liver trouble. The mother suffered from migraine. Three brothers and five sisters are living and healthy, except that one brother has a little "sugar" also.[5]

The patient had tuberculous glands of the neck operated on eight years ago, and catarrhal jaundice at the age of eighteen years, but no other illness. He has never been robust, and has suffered from headaches as long as he can remember. During the period of observation he had a sharp attack of renal colic. He was refused life insurance five months ago because of "sugar," and has been on a rather restricted diet since. Sugar had been found, however, as long as a year ago.

Physical examination was wholly negative.

Urine, 1050 c.c., in twenty-four hours; specific gravity, 1028; highly acid, without albumin, but reducing Fehling's solution, and giving a doubtful bubble in the fermentation tube prepared without

[1] Nord. med. Arch., 1905, xxxviii, abt. ii, S. 1. 55.

[2] Zentralbl. f. innere Med., 1906, xxvii, 145.

[3] Since this paper was read, Blum (Ztschr. f. klin. Med., 1906, lix, 224) has reported two additional cases without family tendency; Kaplan (New York Med. Jour., 1906, lxxxiv, 233) has reported a case of intermittent pentosuria and glycosuria, which, though not true chronic pentosuria, is of much interest; and Johnstone (Edin. Med. Jour., 1906, lxii, 138) has reported a case from von Jaksch's clinic.

[4] I wish to thank my father, Dr. E. G. Janeway, and the family physician, Dr. H. A. Bernstein, for the privilege of studying these patients.

[5] I have not been able to examine the remaining brothers and sisters. One uncle has no pentosuria.

special care as to air bubbles in the urine. This was on a diet containing considerable bread, milk, and fruit.

He was put on a proteid-fat diet, plus 120 grams of toast, to test his tolerance, and the trace of sugar remained unchanged, even after he developed a slight Gerhardt reaction. After a short time the lack of relation between his reported sugar excretion and his diet was so evident that I suspected the presence of pentose, and looked for it. The orcin test was strongly positive, as was the phloroglucin test. Nylander's reagent gave a light-brown color. The reduction of Fehling's solution did not occur for a few minutes after boiling, and then the change of color was sudden to a greenish yellow throughout.

During almost daily observations for two months no positive evidence of fermentation was ever obtained, no rotation of polarized light, and the pentose color and spectroscope reactions were always positive. One hundred grams of dextrose at a single dose failed to produce the slightest glycosuria, as evidenced by fermentation or the polariscope. The phenylhydrazin test was always positive. The osazon was obtained from a large quantity of urine, concentrated *in vacuo*, and its melting point found to be 154 to 158° C. For assistance with this I have to thank Prof. John A. Mandel. The nitrogen content of the osazon has not yet been determined, as all the substance is being used by Prof. Mandel and Dr. Levene, in the attempt to isolate the pure arabinose.

The daily amount of reducing substances excreted was estimated as dextrose, by titration with Pavey's solution—which seems to me rather preferable to Knapp's solution, used by others for this purpose—and found to vary between 2.46 and 4.2 grams, calculated as dextrose.

A study of the effect of diet was made, of a rather unsatisfactory character, because the patient could not control quantities as well as might be desired, but with careful collection of all urine over a long period. The average of the daily estimations by the above method showed the following:

	Average sugar excretion as grams dextrose.
Purin-free diet, 3 days (milk, eggs, rice, toast)	2.56
Ordinary mixed diet, 7 days	3.3
High purin diet, 5 days (much sweetbread, liver and kidney)	3.6
Purin-free diet, 2 days	2.88
Ordinary mixed diet, 2 days	3.1

CASE II.—Brother of Case I, aged twenty-seven years, single, manufacturer. Born in Germany. The patient had meningitis severely at the age of three years; pneumonia as a child, and again three years ago; operations on the nose during the last three years. Has never applied for life insurance. In January of this year he began having headaches like his brother. The urine was examined and sugar found. Restricted his diet for a time only. Correction

of astigmatism cured his headaches. Complained of some palpitation and nervousness, and that he was not very strong.

Physical examination was wholly negative. His urine showed the presence of a non-fermentable optically inactive sugar, giving a typical orcin reaction. The melting point of the osazon was 160 to 162° C. The patient came under observation only a couple of weeks ago, but the amount of urine and of reducing substance, as dextrose, is exactly similar to the other case, from 2.46 grams on a purin-free diet to 3.95 grams on a diet high in nucleins.

I hope to be able in the future to undertake a more complete study of these cases, as well as an investigation of the remaining members of their family.

PRESENT STATE OF OUR KNOWLEDGE OF PENTOSURIA. Three different types of pentosuria have so far been observed, the distinctions between them being important. Alimentary pentosuria, analogous in every way to alimentary glycosuria, occurs whenever large amounts of vegetables or fruits containing pentosanes are eaten, though it is usually very slight. Von Jaksch (*loc. cit.*) has just called attention to its frequency in patients who take much of the pure fruit juices—apple, for instance. Alimentary pentosuria is distinguished, apart from its transitory character and evident cause, by the polariscopic reaction, no optically inactive vegetable pentose being known.

A second group contains those rare cases of severe diabetes in which the inability to burn carbohydrates extends to the pentoses as well as the hexatomic sugars. I have not personally observed this, though on the watch for it during the past winter, but authentic cases like d'Amato's are on record. This group, also, has no real relation to essential pentosuria.

The third group, chronic pentosuria, occurring without reference to the pentoses of the food, and persisting unchanged for years, is a very difficult problem in intermediary metabolism. The definite facts thus far ascertained are as follows:

The sugar excreted is the optically inactive r-arabinose (with the possible exception of Luzzatto's Case VII). This is the only known occurrence of an optically inactive sugar anywhere in nature. It, therefore, cannot be derived from the vegetable pentoses, nor from the l-xylose of the food nucleins. Blumenthal[1] says that he and Bial have found the arabinose in the blood.

The amount excreted is small and fairly uniform in the various cases, from 0.2 to 0.6 per cent., as a rule. Blumenthal's Case VIII, with 1 per cent., is the highest on record. The urine quantity in no case has been excessive. The specific gravity is somewhat increased, and the acidity usually marked.

In a few cases small amounts of glucose have appeared from time

[1] Deutsche Klinik, loc. cit.

to time (Cases I and XVI, possibly IX), but tests with 100 grams of glucose have shown no diminished tolerance for this sugar. In my first case I am unable absolutely to exclude a trace of glucose, in the period before the discovery of pentose, but I consider its presence highly improbable.

The power of burning dextrose has been normal in all the cases examined (Cases IV, XI, XVI, XIX, and my Case I). The tolerance for other carbohydrates has also been tested by Bial[1] and by Klercker,[2] who found levulose, galactose, and, the former, l-arabinose, as fully utilized.

He also found no increase in pentosuria after feeding 500 grams of thymus. Further experiments with inactive galactose are necessary, in the light of Neuberg's theory.

The nuclear metabolism has not been increased, as measured by the excretion of purin bodies and of phosphorus,[3] hence[4] the source of the pentose cannot be an abnormal nuclear destruction, as was to be expected from other considerations.

Klercker, as well as I, have found a diminished pentose excretion on a milk or purin-free diet; Klercker obtained his lowest figures during hunger. He also found a certain parallelism between total nitrogen and pentose in the urine. Blumenthal also states that he and Meyer have found that a meat diet increased the nervous disturbances in these patients, and a milk diet was particularly advantageous. These facts would seem to point toward some relation between the abnormal production of r-arabinose and the activity of metabolic processes.

A family predisposition seems well-marked (Cases IX and X, XI, XII and XIII, XVI and XVII, and my two). The nineteen cases represent only fourteen families, and this question of heredity was not studied with most of the other patients.

The relation to morphine and cocaine addiction, at first supposed, because of Salkowski's original case, has not been substantiated. Reale's and Colombini's patients were of this character, but were not true chronic pentosurics.

In many of the 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.

DIAGNOSIS. The recognition of new cases of pentosuria must depend largely upon clinicians, who should be conversant with the simple tests necessary to establish the diagnosis as a probability.

[1] Verhandl. d. XIX Cong. f. in. Med., 1901, p. 413.
[2] Nord. med. Arch., 1905, xxxviii, Abt. II, p. 1 and 55.
[3] Die Pentosuria, Stuttgart, 1903, p. 49.
[4] Loc. cit.

Any urine which reduces Fehling's solution in an atypical way, the color remaining unchanged for a minute or so after boiling and then suddenly turning a greenish yellow or muddy orange throughout, should be subjected to further tests. If it yield good crystals with the ordinary phenylhydrazin test, does not ferment with yeast, and is optically inactive, pentose is probably present.

The orcin test, with the precautions urged by Brat,[1] should be used, whenever there is any suspicion. To 3 c.c. of urine add 5 c.c. of concentrated HCl, specific gravity 1.19, and a knife-point-full of orcin. With a thermometer in the test-tube, heat on a water-bath at 90 to 95° C for two or three minutes. In the presence of pentose a green precipitate will form, which should be taken up with amyl alcohol and examined spectroscopically, an absorption band in the orange and contiguous red being typical of pentose. Too prolonged heating may split up the conjugate glycuronic acids, which will then give the reaction, and are the only possible sources of confusion. (Menthol and turpentine glycuronic acids break up spontaneously, but may be recognized at once by their odor.) Heating over the direct flame may fail to produce the typical reaction when pentose is present; but, if the other method is impossible, may be resorted to for ruling out pentosuria. I have also found that very concentrated urines often give a gummy red precipitate, which obscures the green, and these should be diluted one-half.

When the orcin test is positive[2] [3] the absolute proof must be sought in the preparation of the osazon, with phenylhydrazin. If the melting point of this be found about 156 to 160° C., and its N. content about 17.07 per cent., then the diagnosis is beyond question. This must, of course, be left to a competent chemist.

Clinical Significance of Essential Pentosuria. No patient with pentosuria has been under surveillance a sufficient length of time to speak with absolute certainty of its course or prognosis. No bad results have yet been noted, though Blumenthal considers it possible that the increase in circulating sugar may conduce to arteriosclerosis, as in diabetes. There is, of course, no loss of an important foodstuff, as in the latter disease, and the prognosis is certainly better than in the mildest diabetes. In life insurance, I think this should be the attitude toward such cases. It is in life insurance examining that the condition should be most often found, and it is a gross injustice to class these people with diabetics.

The only treatment consists in carefully explaining to the patient the difference between his ailment and diabetes, and the removal of any previous dietetic restrictions he may have been subjected to.

[1] Ztschr. f. klin. Med., 1902, xlvii, p. 499.

[2] For the differential diagnosis of the various carbohydrates of the urine, see F. C. Wood, Chemical and Microscopic Diagnosis, 1905, New York, p. 548, or F. Blumenthal, Pathologie des Harnes, 1903, p. 112.

[3] Otori, Ztschr. f. Heilkunde, 1904, xxv, p. 12, found that he could detect the presence of arabinose by this method in dilution as low as 0.05 per cent.

LITERATURE.

The full literature of the subject with excellent critical reviews may be found in the following publications:

Bendix, E. Die Pentosurie, Stuttgart, 1903.

Neuberg, Carl. Die Physiologie der Pentosen and Glukuronsaüre Ergeb. d. Physiol., 1904, iii, p. 373.

Klercker, K. O. Studien über die Pentosurie, Nord. med. Arch., 1905, xxxviii, Abt. ii, p. 1 and 55.

The best clinical article is that on Pentosuria by F. Blumenthal, Modern Clinical Medicine, Diseases of Metabolism, 1906, p. 262.

THE VALUE OF MASSIVE DOSES OF THE SALICYLATES IN THE DIAGNOSIS AND TREATMENT OF ACUTE ARTICULAR RHEUMATISM.

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For the last six years, in the treatment of acute articular rheumatism at the Lakeside Hospital, the tendency has been to a progressive increase in the dosage of sodium salicylate employed. Beginning with ten grains every two hours or fifteen grains every four hours, the amount used has been increased to ten grains, fifteen grains, or even twenty grains hourly in the endeavor to secure the drug effect as promptly as possible. This massive salicylate dosage has seemingly been of such value in the prompt and sure control of symptoms that an analysis of the hospital cases so treated has been undertaken in a critical review of the question. In the review it has seemed only fair, in order, if possible, to learn the exact effect of these large doses, to exclude certain classes of cases. For this reason, all patients who showed an acute complication on admission to the hospital and those in whom, on admission, the temperature was normal, probably due to medication at their homes, have been omitted. Children below twelve years of age have also been excluded on account of the difficulty of classifying these according to dosage. All other cases are included in the analysis.

These exclusions leave seventy-four cases of adults admitted with joints acutely inflamed and temperatures elevated. The discussion of the effects of the large doses of the salicylate, an administration of 240 grains, or more, in the twenty-four hours being considered a large dose, will be divided into two heads, therapeutic and diagnostic.

Therapeutic Effects. The routine method of treatment has consisted of giving the sodium salicylate every hour, if the patient was awake, in doses varying from 10 to 20 grains, until the toxic symptoms appeared, the attendants being alert to recognize the appearance of deafness and tinnitus, as an index of full drug effect; the salicylate was then stopped, to be resumed when the symptoms