hypertrophy. Thus the case falls into Bell's group C. In the elder twin the right deltoid is larger than the left, but this may well be work hypertrophy. His legs are the parts most affected, the facial muscles not at all. Thus his disorder falls into Bell's group B. Both cases fall into Brown's group 2, Tyler and Stephens's group 2, and Stevenson's "autosomal" limb-girdle muscular dystrophy group.

The physical characteristics of the twins were carefully examined in an attempt to establish that they were identical. There was a striking physical resemblance in spite of the marked wasting of the younger twin. The colours of their hair and eyes were the same; their height differed by only $\frac{1}{2}$ in. (1.3 cm.), whilst their biparietal, fronto-occipital, and bizygomatic diameters differed by no more than $\frac{1}{4}$ in. (6 mm.).

Their main blood groups were the same: ABO: A₁; Rh: CDe/cde; MN: M. The subgroups, done by the Blood Group Reference Laboratory, were the same:

	S	P	Lu ^a	Kell	Le ^a	Le ^b	Fy ^a
Case 1 ...	+	+	-	-	-	+	+
Case 2 ...	+	+	-	-	-	+	+

Although the fingerprints of identical twins are not the same, the fingerprints of these twins are of interest. All the impressions of the younger twin were of the type known as "ulnar loop" with the exception of the right forefinger, which was a radial loop, whereas the impressions of the elder twin were all ulnar loops except that of the left forefinger, which was the same pattern as that of the right forefinger of the younger twin—that is, radial.

These findings, although not conclusive, support the opinion of the family that the twins are identical.

It is noteworthy that the younger twin is severely incapacitated, whereas the elder is so mildly affected that he does not realize that he has the disorder. This raises the question of whether there is some environmental factor which determines the severity of the disease.

Boyes *et al.* (1950) found that in several of their cases the onset of the disease was associated with a specific environmental stress, and that a period of unusual physical strain precipitated the onset of the disease in the muscles under stress. Thus in one case the disease started in the shoulder of a woman after working long hours as a waitress carrying trays, and later affected her legs in pregnancy.

In the present cases no such explanation could be found. Both were brought up on the same farm and have lived in the same area since, the younger twin remaining at home and the elder at the age of 17 moving to the farm of an uncle only ten miles away. Their modes of life, nutrition, and work on the two farms were similar.

The two illnesses described by the younger twin as influenza caused marked deterioration on each occasion. It is possible that these illnesses were caused by a particular strain of influenza virus or some unusual type of virus which did not affect the other twin. It is more probable, however, that they were ordinary influenzal attacks, that the other twin has had similar attacks, and that some other unidentified factor has been responsible for the marked difference between the two.

Summary

Muscular dystrophy is reported as occurring in identical male twins now aged 45; in one the disease is severe and incapacitating, but in the other it is so mild that he is unaware that he is affected. No explanation can be given for this difference.

I wish to thank Dr. A. P. Dick for permission to publish these cases and for his help in the preparation of the report; Dr. Helen Dimsdale for her criticisms; Dr. C. B. V. Walker, of the Blood Transfusion Service, Cambridge, and Dr. D. M. Parkin, of the Blood Reference Laboratory, for their opinions in the blood grouping; Mr. P. Graham for the photographs; and the superintendent of the Huntingdonshire County Constabulary for the fingerprints.

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ESSENTIAL PENTOSURIA*

BY

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Essential, or idiopathic, pentosuria is a rare condition which has been included by Garrod (1923) among the inborn errors of metabolism. Its occurrence was first described by Salkowski and Jastrowitz in 1892, but since then only about 200 cases have been recorded in the literature, and only one clinical report dealing with the condition has been published in this country—namely, that of Cammidge and Howard, which appeared in 1920 and described seven cases. The early case reports have been reviewed by Garrod (1923) and Margolis (1929a), and, more recently, Bock (1944) has summarized the features of the condition in a review of the benign meliturias. Since 1944 case reports have been added by Bloomberg *et al.* (1946), Caven (1947), and Barnes and Bloomberg (1953).

The clinical importance of pentosuria depends on the fact that it may be confused with diabetes mellitus. Nowadays, however, when chemical confirmation of a diagnosis of mild diabetes is almost a universal practice, it is more likely to be misdiagnosed as renal glycosuria.

The identification of urinary reducing substances has been greatly facilitated by the introduction of paper chromatography. In the department of clinical pathology at University College Hospital we have been applying this method to identify the reducing substance excreted in cases which appear to have a low renal threshold for glucose. In the course of 4½ years two cases of essential pentosuria have been encountered. These two cases are described here and existing knowledge of the condition is reviewed.

The following methods were used: (1) Qualitative Benedict tests (Flynn *et al.*, 1953). (2) Bial's test (Lasker, 1950). (3) Osazones (Enklewitz and Lasker, 1935a). (4) Blood sugar (Hagedorn and Jensen, 1923). (5) Urine nitrogen (micro-Kjeldahl). (6) Urine xylulose (Lasker and Enklewitz, 1933), using the factor of Greenwald (1930a) for the calculation. (7) Chromatography (Horricks and Manning, 1949), using a 3:2:1.5 *n*-butanol-pyridine-water solvent (Hough *et al.*, 1950) as well as the 4:5:1 *n*-butanol-acetic-acid-water mixture of Partridge and Westall (1948). The paraphenylenediamine reagent of Flynn *et al.* (1953) was used for showing up the sugar spots on the paper chromatograms.

*Based on a communication read at a meeting of the British Diabetic Association on July 17, 1954.

Case 1

A married Hungarian Jewess aged 34 was admitted to University College Hospital under the care of Dr. J. F. Stokes in May, 1950, suffering from infective hepatitis. During her stay in hospital it was noted that her urine gave a yellowish-green reduction of Benedict's reagent.

History of "Glycosuria."—Sugar was first discovered in the urine in October, 1947, when the patient was in University College Hospital under Dr. F. M. R. Walshe, with poliomyelitis. So far as she was aware this was the first time her urine had been tested. She was referred to the diabetic clinic, but failed to attend. She had no symptoms suggestive of diabetes at any time apart from two boils in October, 1949. She had gained 2–3 st. (12.7–19 kg.) in weight in the last three years. Glycosuria had been noted more than once by the several doctors she had consulted in the previous year, but she was told that her blood sugar was normal and that she had renal glycosuria.

There was no family history of diabetes, though the patient recalled that one of her three siblings had once been thought to have sugar in the urine.

FIG. 1.—Blood-sugar curve in Case 1 after 50 g. oral glucose. G₂=yellowish-green reduction.

Investigation of "Glycosuria"

The urine was tested repeatedly over a six-day period. Reduction of Benedict's reagent was found to occur with all specimens, regardless of the time of day; most gave a yellowish-green reduction. Rothera's test was consistently negative.

A glucose-tolerance test was performed, the result being shown in Fig. 1. This shows a normal blood-sugar curve, but sugar is present in all three specimens of urine, the concentration being the same in each.

Paper chromatography of the urine disclosed the presence of a small amount of glucose and glucuronate and a large amount of another substance which we had not previously encountered. This unknown substance moved relatively fast on the chromatogram and was recognized, by the reddish colour produced on spraying with paraphenylenediamine, as being a pentose. The R_F value of this sugar was greater than that of xylose or arabinose, however, and was nearest to that of rhamnose. Subsequently we realized that the sugar must be xylulose (also known as xyloketose), and were able to confirm this by showing that it gave the typical chemical reactions, and had an identical R_F value to that of a synthetic xylulose solution prepared from xylose according to the method of Schmidt and Treiber (1933).

Chemical studies showed that the urine gave a positive Lasker-Enklewitz test (see below), and a positive Bial test. The reducing property of the urine was destroyed by treatment with dilute hydrogen peroxide solution (Enklewitz, 1936), and by heating with strong acid (Enklewitz and Lasker, 1933), but treatment with bromide did not affect the results of reduction tests (Greenwald, 1930a). An osazone was prepared which showed the typical properties of L-xylosazone (Greenwald, 1930a, 1930b; Barnes and Bloomberg, 1953). Direct examination of the urine in the polarimeter did not disclose any optical activity.

The concentration of xylulose was estimated in a random afternoon specimen of urine and was shown to be 0.5 g. per 100 ml. The concentration of other reducing substances present was 0.2 g. per 100 ml. (when expressed as xylulose).

Case 2

A German Jewess aged 55 first attended Professor M. L. Rosenheim's out-patient clinic at University College Hospital in February, 1951, having been referred by her doctor on account of hypertension. Diabetes was said to have been present for 30 years. On examination the only abnormal findings were a blood pressure of 225/130 and a bluish-green reduction of Benedict's reagent on testing the urine. No ketones were present. A diagnosis of benign essential hypertension was made.

History of "Glycosuria."—In 1919, when the patient was aged 24, her urine was tested for the first time. She had been feeling unwell immediately following her father's death, and while in Austria consulted a chemist, who found sugar and acetone in her urine. She had lost much weight, and her cousin, a doctor, diagnosed diabetes. She was put on a strict diet in a clinic at Wiesbaden, and subsequently attended there each year for 12 years. In 1920 she was said to have had a coma. In 1923 she was given two injections of insulin, with severe reactions. In 1933 she gave up going to Wiesbaden and ceased to worry about her diet, as she found she kept well without it. She returned to it, however, before visits to her doctor. In 1936 insulin was tried again and was followed by fairly typical hypoglycaemic attacks. In 1941 she was in hospital in this country on account of pyrexia of unknown origin. Routine testing of the urine revealed sugar, and she was again advised to take insulin, but refused to do so.

It is also noteworthy that she underwent appendicectomy in 1924, left radical mastectomy in 1933, hysterectomy in 1943, and a further gynaecological operation in 1946, all without complications.

FIG. 2.—Blood-sugar curve in Case 2 after 50 g. oral glucose. G₂=yellowish-green reduction.

The family history revealed that her father and her maternal grandfather had been known to have small amounts of sugar in the urine, but none of her five sisters was known to be so affected.

Investigation of "Glycosuria"

A glucose-tolerance test was performed, and the result is shown in Fig. 2. This shows a blood-sugar curve which is just within normal limits, but sugar is present in all three specimens of urine, the concentration being the same in all and unrelated, therefore, to the height of the blood sugar.

The urine-reducing substance was shown by paper chromatography to be a pentose and was subsequently identified,

FIG. 3.—Paper chromatogram of urine sugar from Case 2 with appropriate markers.

as in Case 1, as xylulose. A chromatogram of a later specimen of this patient's urine, with appropriate markers, is reproduced in Fig. 3, and shows the presence of glucuronic acid and xylulose. The large quantity of glucuronic acid in this specimen was due to prior administration of glucurone.

Further tests, carried out in June, 1951, when the patient was admitted to the wards, showed that the condition was in every way typical of essential pentosuria. The results (Figs. 4 and 5) show: (a) that the daily excretion of xylulose is constant at about 3.5 g. a day when no drug is being given, regardless of minor changes in the diet; (b) that xylulose excretion is not affected by feeding fructose; (c) that xylulose excretion is increased by administration of glucurone and amidopyrine; (d) that xylulose excretion is not related to nitrogen output; (e) that xylulose excretion is not related to urine volume; (f) that the rate of xylulose excretion rises more rapidly after glucurone than amidopyrine; and (g) that there is a direct relationship between glucuronate and xylulose excretion.

We were also able to demonstrate xylulose in the plasma by heavily loading protein-free filtrate on to paper chroma-

FIG. 4.—Urine findings during metabolic investigations in Case 2.

FIG. 5.—Correlation between urinary excretion of xylulose and glucuronate in Case 2. (Glucuronate excretion assessed from size and intensity of spot on chromatogram.)

tograms. It was just detectable in the fasting state, but the concentration was increased following administration of glucurone.

Urine specimens were obtained from the one relative resident in this country—a sister—and the first specimen reduced Benedict's reagent and showed xylose on chromatography. This startling finding must be attributed to fruit-eating, for subsequent specimens were sugar-free.

Discussion

Types of Pentosuria

These two cases are typical of essential pentosuria, which is characterized by the constant excretion of small amounts of L-xylulose. Other forms of pentosuria from which this condition has to be distinguished are alimentary pentosuria, in which arabinose or xylose is found in the urine after ingestion of a large amount of fruit or fruit product, and possibly also ribosuria, which has recently been claimed to accompany some cases of muscular dystrophy (Minot *et al.*, 1949; Orr and Minot, 1952).

Features of Essential Pentosuria

The incidence of essential pentosuria has been estimated from insurance records to be 1 in 50,000 (Larson *et al.*, 1937). It is found almost exclusively in people of Jewish lineage, but proved cases have been recorded in non-Hebrews (Barnes and Bloomberg, 1953). There is a distinct familial tendency, and the studies of Lasker *et al.* (1936) indicate that the disorder is inherited as a simple recessive. The condition has been found more often in males, but, as pointed out by Bock (1944), this may merely reflect the fact that more males than females apply for life assurance. It has been discovered at all ages, and persists throughout life. As yet no case has been proved to be present from birth.

The condition appears to be harmless to health. Margolis (1929a) noted that a high proportion of these patients suffered from headaches and were psychoneurotic; such symptoms, however, may have resulted from the patients worrying unduly about their so-called diabetes. In all cases reported by Cammidge and Howard (1920) excess urobilin and amino-acid nitrogen were found in the urine. This finding has not been confirmed by others and there was no amino-aciduria in either of the cases reported here. Excess urobilin was not found in the urine of Case 2 at any time.

The salient feature of essential pentosuria is the continuous excretion in the urine of small amounts of

L-xylulose. Usually 2-5 g. is excreted per day, the amount apparently varying with body weight (Enklewitz and Lasker, 1933); the concentration is always less than 1%. In the early literature arabinose was reported to be the sugar excreted, but later workers have agreed with Levene and La Forge (1914) that L-xylulose is the sugar present. Many cases reported as arabinosuria were in all probability cases of xylulosuria; indeed, two such cases have been proved to be so (Lasker, 1950). Wolfson *et al.* (1949) and Barnes and Bloomberg (1953) have shown by paper chromatography that pentosurics may excrete traces of xylose and other sugars in addition to xylulose.

For a given patient the amount of xylulose excreted is constant from day to day regardless of diet (Enklewitz and Lasker, 1935a). Feeding hexoses or pentoses is without effect (Cohen, 1910; Cammidge and Howard, 1920; Engle-witz and Lasker, 1933; Bloomberg *et al.*, 1946), but fasting for 24 hours has been shown to halve the excretion (Enkle-witz and Lasker, 1933). It has been claimed that the xylulose excreted paralleled the purine and protein content of the diet (Janeway, 1906; Cammidge and Howard, 1920), but Margolis (1929b) was unable to confirm this, and our results in Case 2 do not show an obvious relationship between nitrogen and xylulose excretion. Exercise and admin-istration of thyroid and insulin are without effect on xylulose excretion (Rabinowitch, 1925; Enklewitz and Lasker, 1933), but feeding glucuronic acid or drugs which are excreted as glucuronates—such as amidopyrine and codeine—results in increased excretion (Margolis, 1929a, 1929b; Lasker and Enklewitz, 1933; Enklewitz and Lasker, 1935a), as demon-strated in Case 2.

Metabolic Defect in Essential Pentosuria

Enklewitz and Lasker (1935a) seem to have established that glucuronic acid is the precursor of L-xylulose in pento-surics. Thus feeding them glucuronic acid or drugs excreted as glucuronates leads to increased excretion of xylulose, but feeding conjugated glucuronate is without effect. Moreover, there appears to be a direct relation between the amount of glucuronic acid administered or produced in the body and the extra amount of xylulose excreted. Our results in Case 2 seem to bear this out. It is odd that feeding drugs which are excreted as glucuronates should lead to increased xylulose excretion; presumably they stimulate the formation of more glucuronic acid than is required for their conjuga-tion.

As feeding glucuronic acid to normals does not lead to pentose excretion, the suggestion has been made that pento-suric patients have an abnormal enzyme system which decarboxylates glucuronic acid to yield xylulose (Everett, 1946). There is evidence, however, that L-xylulose may be a normal intermediary metabolite rather than an abnormal one. Thus L-xylulose appears to be metabolized by dogs (Greenwald, 1931; Larson *et al.*, 1939), and in a normal man, after oral administration of 5 g., none could be recovered in the urine in 24 hours (Enklewitz and Lasker, 1933). If L-xylulose is a normal metabolite in man then essential pentosuria could result from a block in the further metabolism of xylulose, for when 5 g. of L-xylulose was fed to a pentosuric an extra 0.5 g. was recoverable in the urine in the next 24 hours (Enklewitz and Lasker, 1933).

The nature of the error in essential pentosuria would appear, then, to be a partial or complete block in the meta-bolism of xylulose—one of the normal derivatives of glucuronic acid metabolism. A possible alternative explana-tion is that there is an abnormally large production of xylulose which overwhelms the mechanism that normally disposes of this sugar.

Diagnosis of Essential Pentosuria

Diagnosis depends on (a) discovering a constant meli-turia; (b) excluding diabetes by demonstration of normal glucose tolerance; and (c) identifying xylulose in the urine. Usually diagnosis is straightforward, but cases have been recorded with a coexistent diabetes (Edelman and Reiner,

1943), with diabetic symptoms (Enklewitz and Lasker, 1935b; Peterman, 1945), and where a reduction by the urine was not found in all specimens (Derivaux, 1943). In the case reported by Peterman the urine sugar was not proved to be xylulose.

Regarding tests for xylulose in the urine, that of Lasker and Enklewitz (1933) is an ideal screening test, as it can be readily performed by the clinician. It is carried out by adding 1 ml. of urine to 5 ml. of Benedict's qualitative reagent, mixing, and placing the test-tube in a water-bath at 55° C. for 10 minutes; if a water-bath is not available the mixture is left at room temperature for 3 or, preferably, 24 hours. The appearance of a yellow precipitate under these conditions is very suggestive of xylulose. Fructose, ascorbic acid, and glucose in high concentration may cause false positives, so confirmation is essential (Lasker and Enklewitz, 1933; Enklewitz, 1936; Barnes and Bloomberg, 1953).

For final identification of xylulose in the urine, paper chromatography provides the most satisfactory test, and is simpler than preparation and purification of osazones for melting-point and nitrogen determinations. With the use

FIG. 6.—Separation of sugars by one-dimensional paper chromato-graphy using 3:2:1.5 *n*-butanol-pyridine-water solvent.

of a butanol-pyridine-water solvent, and a spray reagent which distinguishes pentoses from hexoses, it is possible to identify all the urinary sugars on a one-dimensional chromatogram as shown in Fig. 6. It is likely that with the help of paper chromatography many more cases of essential pentosuria will be discovered.

Summary

Two unrelated cases of essential pentosuria are de-scribed; one masqueraded as diabetes mellitus, the other as renal glycosuria.

Results of metabolic investigations in one case are presented.

The features of the condition are reviewed and the nature of the metabolic defect is discussed.

The simple Lasker-Enklewitz test for detecting xylulose in the urine is described, and attention is drawn to the value of paper chromatography for final identi-fication of the sugar.

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TRUE HERMAPHRODITISM

BY

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An individual who has both ovarian and testicular tissue is a true hermaphrodite. Proof of the presence of both types of gonad in the same individual is histological, as the secondary sex characters may be affected by other factors, such as overactivity of the adrenal cortex.

Adopting these criteria, an examination of the literature has disclosed 59 unequivocal cases of true hermaphroditism, to which two further cases are added below. The further progress of the case originally recorded by Broster *et al.* (1938) is also noted.

Case 1

J. O., the third child of healthy parents of English extraction, was first seen at the age of 16 months, having been brought for determination of the sex. No family history of any endocrine disease or congenital abnormality was forthcoming, except for talipes in the second child. The mother had suffered no illness during the pregnancy.

On examination the child appeared healthy and apparently normal except for the genitalia, which showed the following abnormalities. The phallus, about 3 cm. long, curved downwards and had a hooded prepuce. About 3 cm. behind the phallus lay an orifice into which opened the urethra and a short recess. This recess admitted a probe for 2.5 cm. and presumably represented the lower part of the vagina. The labio-scrotal folds were rugose and contained no testes or hernial sacs.

Investigations.—Urinary 17-ketosteroids, 0.3 mg. a day (this is at the lower limit of assay, and indicates only that the 17-ketosteroid excretion was not increased). X-ray examination of the pituitary fossa showed no abnormality. The epiphysal bone age was 2–3 years—that is, about one year more than the actual age.

Operation.—Mr. L. R. Broster performed a laparotomy on July 17, 1953. A small (4 cm.) uterus was observed, from which ran two Fallopian tubes, terminating in fimbriated ends. In the usual position of the right ovary lay a structure about 2 cm. long, resembling a testis, a portion of which was removed for microscopical examination. No epididymis or other Wolffian elements could be found on either side. The adrenal glands felt normal in size and consistency. Samples of skin were taken from both sides of the abdomen for examination of the somatic nuclei by the method described by Moore *et al.* (1953). Dr. W. E. Evans reported

that the whole of the piece of tissue (8 by 3 mm.) from the right gonad consisted of immature testicular tissue, with seminiferous tubules separated by a loose, clear-celled stroma. Interstitial cells were not identified. A narrow fibrous capsule lay along one edge of the biopsy. The specimen, about 3 by 3 mm., from the left gonad consisted of a strip of young ovarian tissue beneath which was loose fibrous tissue. No ovarian "germinal" epithelium was found on the surface. Several ova were present, each surrounded by rather flattened cells with deeply stained nuclei, apparently derived from the ovarian stroma.

Skin Biopsies.—Professor M. L. Barr reported that a chromatin mass was present in less than 10% of epidermal nuclei. It has been observed (Moore *et al.*, 1953) that, in sections of tissue taken from a normal female, more than 80% of the nuclei seen contain a speck of chromatin on the periphery of the nucleus. In normal males such a mass is seen in less than 10% of nuclei in tissue sections. This observation is in accordance with the difference between the female sex chromosome pattern (XX) and the male pattern (XY). The nuclear picture in this case therefore conforms to the male type.

Case 2

P. F. was first seen in July, 1940, at the age of 20 months. The child had been brought up as a girl, but was already rougher and more masculine in behaviour than the elder sister, who was a normal girl. The patient was a muscular child with a deep voice and of normal intelligence. The phallus was about the normal size for a male of that age, but the urethra terminated at its base. No gonads could be felt in the scrotum, which was split, and a small uterus was palpated rectally.

Investigations.—Urinary 17-ketosteroid excretion, 0.3 mg. a day. Perirenal insufflation gave no evidence of adrenal enlargement.

Operation.—Laparotomy was performed on September 1, 1940, by Mr. L. R. Broster. A small infantile uterus with fimbriated Fallopian tubes was found. Two gonads lay in the position of the ovaries. The left gonad was the size of a pea and the right gonad was slightly larger. No epididymis or vas deferens was seen on either side. Both gonads were removed for microscopical examination.

Professor H. W. C. Vines reported that the left gonad consisted of ovarian tissue and the right gonad of fibrotic testicular tissue.

The child was clearly more male than female in its behaviour, and was therefore brought up as a boy. From the age of 4 years a series of operations were performed to correct the hypospadias. Injections and local inunction of testosterone from the age of 6 years have produced some increase in the size of the penis, which was, however, still smaller than normal when he was last seen in 1951 at the age of 13. He was then psychologically male, but rather shy, tending to cling to his mother.

Unfortunately, it has not proved possible to get in touch with the patient in order to obtain a sample of skin for nuclear examination.

Case 3

B. T. (Broster *et al.*, 1938) was regarded as a female at birth. At the age of 3 years, however, the child's social and legal sex was changed to male. Two years later hair began to grow on the face, legs, and pubis, and the voice cracked. When seen at the age of 9 years the child had a small penis with complete hypospadias and a split scrotum containing no testes. He was psychologically male. At laparotomy on November 30, 1936, at the age of 9, an infantile uterus with tubes was present. The gonads, which were in the position normally occupied by the ovaries, were shown by biopsy to be both ovotestes.

The patient's hypospadias was successfully repaired at the age of 14, and since then injections and implants of testosterone have been given to encourage penile growth.

When last seen, in January, 1954, he had the appearance of a normal adult male except for a small penis and no