Hereditary tyrosinaemia

Clinical, enzymatic, and pathological study of an infant with the acute form of the disease

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Carson, N. A. J., Biggart, J. D., Bittles, A. H., and Donovan, D. (1976). *Archives of Disease in Childhood*, 51, 106. **Hereditary tyrosinaemia: clinical, enzymatic, and pathological study of an infant with the acute form of the disease.** A clinical, enzymatic, and pathological study of an infant with the acute form of hereditary tyrosinaemia is presented. Treatment with a diet low in methionine, tyrosine, and phenylalanine was unsuccessful. A selection of specific and non-specific hepatic enzymes, obtained at necropsy within one hour of the infant's death at 9½ weeks, were studied to try to throw light on the basic defect. The major pathological findings were those of a peculiar hepatic fibrosis associated with bile retention and an abnormal grouping of hepatocytes, islet-cell hyperplasia of the pancreas, and dilatation of the proximal renal tubules. Death was precipitated by bronchopneumonia and liver failure.

The difficulty in diagnosing the acute form of tyrosinaemia is pointed out, especially in differentiating it from hereditary galactosaemia (transferase deficiency) and hereditary fructosaemia. All three may present with the same clinical symptoms and liver lesions, and the distinction must be made by enzyme studies and by therapeutic trial.

Hereditary tyrosinaemia, a rare metabolic disorder with its onset in infancy or early childhood, was first described by Baber (1956) and linked with an abnormality in tyrosine metabolism in 1957 (Sakai and Kitagawa, 1957a, b). It presents clinically in two forms.

Firstly, an acute form with symptoms occurring within a few weeks or months of birth and characterized by rapidly progressive cirrhosis, bleeding diathesis, hypoglycaemia, and renal tubular dysfunction. In addition there is a generalized aminoacidaemia with especially high concentrations of tyrosine and methionine accompanied by an overflow aminoaciduria. Death invariably ensues from liver failure associated with infection or bleeding, or both, within the first year of life.

Secondly, a subacute or chronic form of the disease in which the initial symptoms are generally manifest before 12 months of age. This form is

more common, and affected infants present with failure to thrive, gastrointestinal symptoms, hepatic cirrhosis, and multiple renal tubular defects associated with secondary rachitic changes. The amino acid abnormality is usually confined to tyrosine, but there may be a rise in methionine in the terminal phase of the disease. Death usually occurs within the first decade.

Both forms of the disorder seem to be inherited as autosomal recessive traits (Gentz, Jagenburg, and Zetterström, 1965). Opinions on the nature of the primary defect differ. The defect in tyrosine metabolism is due to reduced activity of the tyrosine hydroxylating enzyme p-hydroxyphenylpyruvate oxidase (pHPPA oxidase) (La Du and Gjessing, 1972), and some authors have claimed that this represents the primary defect with the abnormality in methionine metabolism occurring secondary to the severe liver dysfunction (Gentz *et al.*, 1965; Halvorsen *et al.*, 1966). However, Perry *et al.* (1965) believe that the defect in methionine is the primary one and that the disturbance in tyrosine metabolism

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is secondary. A third hypothesis is that the primary defect is neither tyrosine nor methionine metabolism and is as yet unrecognized (Woolf, 1966; Gaull *et al.*, 1970; La Du and Gjessing, 1972).

This report describes the case of a young infant who presented with the acute fulminating type of hereditary tyrosinaemia and in whom dietary treatment was unsuccessful. The death of the infant enabled a wide range of hepatic enzymes, not so far studied in any one patient, to be assayed and a detailed necropsy study to be made.

Case report

The patient, a 7-week-old boy, was born at term with a birthweight of 3118 g and fed on cow's milk with cane sugar. At about 3 weeks of age his mother noticed an unpleasant sweetish smell from his motions and body similar to that in a sib who had died, aged 2 months, a few years previously with a liver disease. Jaundice became apparent at 6 weeks. At 7 weeks he developed a high temperature and bruising was noted over his right thigh and later over his lower abdomen. He was admitted to hospital.

On admission he weighed 4660 g. He was slightly jaundiced and very irritable with a temperature of 38.3°C , and a very pronounced, unpleasant sweet smell, similar to rotten cabbage, was noted from his body. Respirations were 38/min and shallow. The liver was 2 fingerbreadths below the costal margin and of firm consistency. The spleen was not enlarged and there was no evidence of ascites. An umbilical hernia was present and some craniotabes was noted. Bruising and swelling were present across the lower abdomen and right thigh. He had a grossly purulent nasal discharge and over the next 24 hours respiratory distress was more pronounced. He was treated initially with intravenous glucose and ampicillin and cloxacillin. Because the findings at the necropsy of his sister had suggested the disorder described by Perry *et al.* (1965) as hypermethioninaemia he was started on a low methionine diet two days after admission. There were 3 healthy sibs in his family and a history of possible consanguinity five generations before.

Investigations. Chest x-ray examination showed irregular collapse of the basal segments of the left lower lobe with two further subsegmental areas of collapse around the left hilum. There was no skeletal abnormality. Coagulation activity was less than 1%. Plasma fibrinogen was 1.0 g/l, the Fibrindex test was slightly prolonged, and no circulating anticoagulant was noted. Hb was 12.1 g/dl and the white cell count was $22 \times 10^9/\text{l}$ ($22\,000/\text{mm}^3$). Biochemical findings before treatment were as follows: serum bilirubin 177 $\mu\text{mol/l}$ (10 mg/100 ml), alkaline phosphatase 533 KA-U/l, aspartate aminotransferase 156 units/l, glucose 1.4 mmol/l (25 mg/100 ml), albumin 35.0 g/l (3.5 g/100 ml), total protein 50.0 g/l (5.0 g/100 ml), and urea 1.7 mmol/l (10.2 mg/100 ml). Sodium, potassium, chloride, bicarbonate, cholesterol, calcium, inorganic phosphate,

urate, ammonia, and lactate dehydrogenase levels were normal. The amino acid levels in the plasma, cerebrospinal fluid (CSF), and urine are shown in Tables I and II. In a generalized aminoacidaemia the most pronounced rises were in methionine concentration followed by tyrosine, ornithine, arginine, phenylalanine, lysine, proline, and threonine in that order. Amino acid levels in the CSF were also generally raised, mostly so in taurine, glutamine, methionine, tyrosine, and histidine. An overflow type of generalized aminoaciduria was present and tyrosyl metabolites, p-hydroxyphenylacetic acid (pHPAA), and p-hydroxyphenyllactic acid (pHPLA) were present in high concentration in the urine. No p-hydroxyphenylpyruvic acid (pHPPA) was noted but this may have been due to delay in testing for this substance. Mellituria was present with fructose, galactose, and sucrose identified chromatographically. The amino acids were estimated by ion exchange chromatography using a Standard Technicon Amino-Acid Analyser.

Dietary treatment. The initial diagnosis was made in the Regional Hospital, Galway, and treatment with a low methionine diet instituted two days after admission at the age of 8 weeks. One week later the infant was transferred to the Royal Belfast Hospital for Sick Children, where facilities were available for monitoring this type of treatment. The low methionine diet was continued and phenylalanine and tyrosine were also restricted. A special amino acid mixture was prepared* which contained no methionine, phenylalanine, or tyrosine. A restricted quantity of these amino acids was given as cows' milk, which supplied about 50 mg/kg of phenylalanine and of tyrosine, and 20 mg/kg of methionine. The carbohydrate was in the form of a polyglucose polymer (Caloreen*) and the essential fat given as Prosparol† (50% arachis oil in water). On restricting the methionine intake the peculiar smell, notably lessened. However, despite the special diet, the baby's condition deteriorated, the abdomen became distended, respiratory distress increased, and the temperature rose to 38.2°C . Jaundice did not increase and was never severe at any stage of the illness. He died aged 9½ weeks with terminal pneumonia and liver failure. A special diet had been given for a total of 11 days, the low methionine diet being given for 6 days, and a low methionine, phenylalanine, tyrosine diet for the last 5 days. The diet resulted in a dramatic decrease in the urinary excretion of amino acids, tyrosyl metabolites, and disappearance of urinary sugars. On the low methionine diet a general reduction was noted in plasma amino acid levels with the exception of threonine, glycine, alanine, cystine, phenylalanine, and histidine, which rose. The tyrosine level remained unchanged. After a further 5 days on the low methionine, phenylalanine, tyrosine diet the level of all plasma amino acids fell, that of the branched chain amino acids valine, leucine, and isoleucine substantially.

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TABLE I

Amino acid levels in plasma and cerebrospinal fluid (CSF) of patients with acute tryosinaemia

	Plasma ($\mu\text{mol/l}$)				CSF ($\mu\text{mol/l}$)	
	Normal range*	On admission	After 7 day's treatment	After 11 days' treatment	On admission	Mean of 13 normals†
Taurine	57-115	7	4	7	520	05.3
Aspartic acid	4-20	85	46	Trace	NE	2.9
Hydroxyproline	25	6	5	7	Trace	NE
Threonine	42-95	798	1260	NE	396	26.6
Glutamine	57-467	930	698	NE	+ + + +	455
Serine	79-112					
Glutamic acid	23-250					
Citrulline	12-30	2	4	4	Trace	2.1
Proline	68-148	1168	642	103	162	Trace
Glycine	117-223	596	1116	60	278	8.5
Alanine	137-305	1462	1420	172	466	28
Valine	128-283	446	448	34	162	14.3
Cystine	45-77	22	37	9		Trace
Methionine	11-16	1456	352	35	200	3.2
Methionine sulphoxide	—	67	Trace	4	72	—
Isoleucine	28-84	169	79	14	63	5.0
Leucine	56-178	284	206	21	114	12
Tyrosine	31-71	978	972	44	303	7.9
Phenylalanine	26-61	652	1440	22	139	7.5
Ornithine	27-86	618	414	70	109	8.4
Lysine	71-151	1316	932	104	200	18.6
Histidine	24-85	294	616	67	423	11
Arginine	23-86	866	592	68	129	14.2

* Scriver and Davies (1965).

† Van Sande *et al.* (1970).

NE, not estimated.

Hepatic enzyme studies. The liver was removed within one hour of the patient's death and immediately stored at -20°C . Control livers were obtained from 'cot death' infants with no obvious lesion found at necropsy and stored at -20°C within three to six hours of death. The results of the hepatic enzyme assays carried out on the patient and on the controls are shown in Tables III-V. Three main groups of enzymes were studied; general liver enzymes, including those with cytoplasmic, lysosomal, microsomal, and mitochondrial location (Table III); specific enzymes of the tyrosine, methionine, and lysine pathway (Table IV); and specific enzymes involved in fructose and galactose metabolism (Table V).*

Among the general liver enzymes assayed (Table III) the activities of the patient's aspartate aminotransferase, lactate dehydrogenase, and isocitrate dehydrogenase were similar to those of the controls. There was a striking reduction in alanine aminotransferase activity, which was confirmed in three different liver homogenate preparations. The activities of the alkaline phosphatase, acid phosphatase, and cholinesterase enzymes were greater than those of the controls, the alkaline phosphatase activity particularly being raised. In general, the specific enzymes studied in the patient had a lower level of activity than the control samples (Tables IV and V). There was defi-

cient activity of the tyrosine pathway enzyme, pHPA oxidase, the trans-sulphuration enzymes cystathionine synthase and cystathionase, of lysine oxoglutarate reductase, and of the fructose-1-P and fructose-1, 6 diP aldolases. Only tyrosine-L-oxoglutarate aminotransferase, the lysine pathway enzyme saccharopine dehydrogenase, and galactose-1-P uridyl transferase activities lay within the control range.

Pathology. Necropsy was performed within one hour of death. All internal organs were examined grossly and microscopically. Only those organs that showed pathological changes are reported on here.

The baby weighed only 3500 g and had a crown-heel length of 55 cm. There was mild icterus and generalized subcutaneous oedema. The only external abnormality was a small umbilical hernia.

Lungs. Terminal bronchopneumonia.

Liver. Weight 175 g. The parenchyma was deeply bile-stained with no apparent nodularity. The gallbladder communicated with a patent biliary duct system. Histology of the liver showed the normal architecture completely disrupted, owing to an unusual grouping of hepatocytes, into small and irregularly shaped acinar formations, some of which had central lumens (Fig.). These lay embedded in a diffuse fibrous stroma infiltrated by occasional lymphocytes,

*Details of methods used may be obtained from N.A.J.C.

TABLE II

Amino acid levels in urine of patient with acute tyrosinaemia and in controls

	Urine levels ($\mu\text{mol/mg creatinine}$)			
	On admission	After 4 days	Control	Control
Taurine	0.57	Trace	3.45	0.6
Aspartic acid	0.35	—	—	0.1
Hydroxyproline	7.7	—	—	—
Threonine	110.0	27.8	0.58	0.54
Glutamine	46.2	12.7	1.1	1.4
Serine	119.1	3.0	1.1	1.6
Glutamic acid	1.1	34.0	0.04	0.21
Proline	0.75	—	0.04	0.21
Glycine	107.5	13.0	2.60	2.79
Alanine	38.7	11.2	1.06	1.37
Valine	2.40	—	0.02	0.27
Cystine	3.5	—	0.22	0.22
Methionine	1.5	—	—	0.28
Isoleucine	—	—	—	0.16
Leucine	1.48	—	—	0.20
Tyrosine	10.2	4.1	0.24	0.37
Phenylalanine	37.0	1.1	0.16	—
Ornithine	21.0	9.9	—	0.12
Lysine	67.0	58.7	0.36	0.58
Arginine	7.4	1.4	0.62	0.10
Methionine sulphoxide	0.80	1.0	—	—
Histidine	74.4	22.0	1.82	1.28
Homocystine	—	22	—	—
Cystathionine	—	—	—	—
Ethanolamine	—	—	0.62	0.44

TABLE III

General liver enzyme activity in patient with acute tyrosinaemia and in normal control infants

Enzyme	Patient (age 9½ w)	Infant controls aged			
		2 d	3 w	4 w	5 w
Aspartate aminotransferase (nmol/min per mg protein)	643	600	637	677	639
Alanine aminotransferase (nmol/min per mg protein)	25	259	796	702	879
Lactate dehydrogenase (nmol/min per mg protein)	1607	1255	927	1976	1302
Isocitrate dehydrogenase (nmol/min per mg protein)	283	203	313	374	310
Alkaline phosphatase (nmol/min per mg protein)	69.1	14.0	9.9	6.1	6.6
Acid phosphatase (nmol/min per mg protein)	69.0	34.3	25.1	26.0	26.0
Cholinesterase (units/min per mg protein)	1.47	0.72	1.37	1.08	1.30

neutrophils, and eosinophils. One section included a solitary regenerative micronodule composed of hepatocytes with small intracytoplasmic fat droplets. Elsewhere fatty change was not a feature and no excess glycogen was demonstrable. Bile and haemosiderin pigments were prominent in most of the hepatocytes and numerous bile thrombi blocked the canaliculi. The portal tracts showed no excess of fibrous tissue and there was no bile duct proliferation.

Pancreas. Weighed 16 g. In several sections there was a pronounced increase in the number of islets as compared with age-matched controls. Several islets were unusually large. Within each islet the normal relative proportions and distribution of α , β , and δ cells appeared to be maintained (Gomori acid fuchsin stain). No increased mitotic activity or degenerative changes were seen in any of the islets. The exocrine system appeared normal.

TABLE IV

Activity of enzymes of tyrosine, methionine, and lysine pathways in patient with acute tyrosinaemia and in normal infants and adult controls

Enzyme	Patient (age 9½ w)	Infant controls aged				Adult controls	
		2 d	3 w	4 w	5 w	1	2
pHPPA oxidase (nmol/min per mg protein)	0.9	5.8	19.0	2.3	—	—	—
Tyrosine-L-oxoglutarate aminotransferase (nmol/min per mg protein)	62.3	46.6	23.0	262.7	32.7	—	—
Cystathionine synthase (nmol/hour per mg protein)	7.2	10.1	37.2	16.4	46.0	—	—
Cystathionase (nmol/hour per mg protein)	3.9	18.5	17.5	64.5	53.8	—	—
Lysine oxoglutarate reductase (nmol/hour per mg protein)	73	—	—	—	—	333	355
Saccharopine dehydrogenase (nmol/hour per mg protein)	79	—	—	—	—	369	91

TABLE V

Activity of enzymes of fructose and galactose pathway in patient with acute tyrosinaemia, in control infants, and galactosaemic infants

Enzymes	Patient (9½ w)	Infant controls aged:		Galactosaemic infant
		4 w	5 w	
Fructose-1-6-diP aldolase (μmol/hour per mg protein)	0.9	3.2	3.7	—
Fructose-1-P aldolase (units/mg protein)	0.8	3.7	3.7	—
Galactose-1-P-uridyl transferase (nmol/min per mg protein)	4.9	5.1	2.0	0.13

Kidneys. Right, weighed 45 g, left, 50 g. Each was swollen, showing cortical pallor and an increased cortico-medullary ratio of 1:2. Renal vessels were patent. Histological examination showed mild variability in size of the glomeruli but they were normocellular with no basement membrane thickening. The juxtaglomerular apparatus was not hyperplastic and there was no excess granularity. The tubular epithelium in all zones was intensely eosinophilic and granular. Tubular dilatation was only of moderate severity and confined mainly to the proximal convoluted segments. Small round amorphous globules were present within these and may have been proteinaceous in nature.

Discussion

There are many reasons for the presence of increased plasma and urinary tyrosine levels accompanied by the excretion of tyrosyl metabolites. In the differential diagnosis of so-called 'acute hereditary tyrosinaemia' only those diseases presenting within the first year of life associated with hepatorenal dysfunction need be considered.

Nonhereditary tyrosinaemia and methioninaemia have been described in acute and chronic

liver disease associated with cirrhosis (Levine and Conn, 1967) and with neonatal hepatitis (Carpenter, 1968; Yu, Walker-Smith, and Burnard, 1971). Here the levels of tyrosine and methionine revert to normal with recovery of hepatic function. In the hepatic form of glycogen storage disease (von Gierke's Disease) the diagnosis is established by finding an increase in tissue glycogen content together with a marked deficiency of hepatic glucose-6-phosphatase activity (Howell, 1972). Increased activity of this enzyme has been reported in a patient with hereditary tyrosinaemia (Silverberg, 1967).

The distinguishing feature in classical galactosaemia is the absence of galactose-1-P-uridyl-transferase in red blood cells and in hepatic tissue. The microscopic appearance of the liver may show a striking similarity to that found in acute tyrosinaemia. Normal activity of red cell galactose-1-P-uridyltransferase has been reported in patients with hereditary tyrosinaemia (Gaull *et al.*, 1970; Halvorsen *et al.*, 1966) and in the present study.

The disorder most likely to be confused with the

FIG.—Section of liver showing diffuse fibrosis and acinar groupings of hepatocytes. Few lymphocytes seen within fibrous background. (Haematoxylin and eosin. $\times 175$.)

acute form of hereditary tyrosinaemia is fructosaemia. Clinically they may be indistinguishable. Both have a generalized aminoacidaemia and aminoaciduria of similar pattern and in each disorder fructosuria may be present. Liver biopsy may show a similar disturbance in liver architecture (Odièvre, Gautier, and Rieu, 1969). In fructosaemia a fructose-free diet results in striking clinical improvement and a reduction in the aminoacidaemia and aminoaciduria with the rapid disappearance of fructosuria when present. There is a severe deficiency in the activity of hepatic fructose-1-P-aldolase (0 to 12% of normal) with a less severe reduction in fructose-1-6 diP-aldolase activity (approximately 25% of normal) (Froesch, 1972). However, in the patient with hereditary tyrosinaemia reported here a moderate decrease in the activity of both these enzymes has been found. Recently the activity of fructose-1, 6-diphosphatase has been reported as deficient in patients with the clinical and biochemical features of the classical form of hereditary fructosaemia (Bakker *et al.*, 1974; Baerlocher *et al.*, 1971; Hülsmann and Fernandes, 1971).

Treatment. In the acute type of hereditary tyrosinaemia the results of dietary therapy have been largely unsuccessful, even when the diet has been started within the first month of life, and most

infants die within the first year (Laroche *et al.*, 1967; Bodegard *et al.*, 1969). The diet in our patient was started at the age of 8 weeks. A dramatic improvement in the renal tubule handling of amino acids resulted, but the effect on the plasma amino acid abnormalities and the clinical state was disappointing. A temporary form of the disease has been described (Gaul *et al.*, 1970; Harries *et al.*, 1969; Pickering and Bower, 1972) in 3 infants in whom liver function and the amino acid abnormalities reverted to normal after some months of dietary treatment and continued so on a normal diet. A low phenylalanine, tyrosine, and methionine diet would therefore seem profitable in all cases of acute tyrosinaemia.

Pathology. Renal tubular dilatation, pancreatic islet hyperplasia, and a peculiar diffuse hepatic fibrosis with pseudoacinar groupings of hepatocytes form the triad of histopathological features seen in most cases of hereditary tyrosinaemia. They were present in our case, but the spongiform degeneration of the brain which has been described was not demonstrable in several routine brain sections. Neither was there any gross or histological evidence of rickets, but its development seems to be age-dependent, occurring in children who survive longer. Jevtic, Thorp, and Hruban (1974) thought that hypertrophy and hyperplasia of the juxta-

glomerular apparatus might be a specific diagnostic feature of hereditary tyrosinaemia. Special staining of the juxtaglomerular granules in our case showed no morphological evidence of this. The same authors record a variability in glomerular size and glomerular basement membrane thickening. Glomerular size varied slightly in our patient but was within the normal range and, in our view, was explicable by the different planes of section through the glomerular tufts. No basement membrane thickening was present.

Hepatic enzymes. It was hoped that the study of the hepatic enzymes would throw some light on the basic defect in this disorder. In the general group alanine aminotransferase activity was notably deficient while that of aspartate aminotransferase was within the normal range. The time lag in performing this enzyme estimation was the same as that of the controls, and co-incubation studies failed to detect the presence of a specific diffusible inhibitor to the enzyme. Alanine aminotransferase is 90% cytoplasmic in origin while that of aspartate aminotransferase is 40% mitochondrial and 60% cytoplasmic. However, since both lactate dehydrogenase and isocitrate dehydrogenase are also cytoplasmic in origin and showed normal activity it seems that the marked decrease in alanine aminotransferase was not due solely to cytoplasmic leakage. Decrease in the activity of this enzyme has been reported in different forms of liver dysfunction (McLean, 1966; Sommerville *et al.*, 1960; Zelman, Wang, and Appelhanz, 1959).

In keeping with other reports (La Du and Gjessing, 1972), activity of the cytoplasmic enzyme pHPPA oxidase was decreased in our case, whereas that of tyrosine aminotransferase was within the control range. The activity of this latter enzyme in patients with hereditary tyrosinaemia has variously been reported to be from greatly deficient to normal (Gentz *et al.*, 1965; La Du and Gjessing, 1972). It is present in both cytoplasm and mitochondria. The activity of both the enzymes of the trans-sulphuration pathway was below those of the control range. Diminished activity of the methionine-activating enzyme cystathionine synthase and cystathionase have previously been reported (Gauld *et al.*, 1970; Perry, 1967) in patients with hereditary tyrosinaemia. The reduced activity of the methionine-activating enzyme is thought to account for the high methionine levels. Of the two lysine enzymes studied the activity of lysine oxoglutarate reductase was substantially decreased, while that of saccharopine dehydrogenase was similar to one of the two adult controls. Galactose-

1-P-uridyl transferase activities lay within the normal range, but the activity of both fructose-1-6-diP aldolase and fructose-1-P aldolase was reduced to 25% of the control livers. The determination of the activity of these three enzymes is important in the differential diagnosis of the acute form of tyrosinaemia, and finding reduced activity of fructose aldolase enzymes may make the distinction between fructosaemia and tyrosinaemia even more difficult.

Conclusion

Our findings do little to further knowledge of the basic defect in acute tyrosinaemia of infancy. The most that can be said is that, from whatever cause, the activity of many of the specific hepatic enzymes is reduced, and this supports the hypothesis that the primary defect is of neither tyrosine nor methionine metabolism.

REFERENCES

- Baber, M. D. (1956). A case of congenital cirrhosis of the liver with renal tubular defects akin to those in the Fanconi syndrome. *Archives of Disease in Childhood*, **31**, 335.
- Baerlocher, K., Gitzelmann, R., Nüssli, R., and Dumermuth, G. (1971). Infantile lactic acidosis due to hereditary fructose 1, 6-diphosphatase deficiency. *Helvetica Paediatrica Acta*, **26**, 489.
- Bakker, H. D., DeBree, P. K., Ketting, D., Van Sprang, F. J., and Wadman, S. K. (1974). Fructose-1, 6-diphosphatase deficiency: another enzyme defect which can present itself with the clinical features of 'Tyrosinosis'. *Clinica Chimica Acta*, **25**, 41.
- Bodegard, G., Gentz, J., Lindblad, B., Lindstedt, S., and Zetterström, R. (1969). Hereditary tyrosinemia. III: On the differential diagnosis and the lack of effect of early dietary treatment. *Acta Paediatrica Scandinavica*, **58**, 37.
- Carpenter, G. (1968). Discussion on Tyrosinosis. Biochemical and dietary studies. *Pediatric Research*, **2**, 404.
- Froesch, E. R. (1972). Essential fructosuria and hereditary fructose intolerance. *The Metabolic Basis of Inherited Disease*, 3rd ed., p. 131. Ed. by J. B. Stanbury, J. B. Wyngaarden, and D. S. Frederickson. McGraw-Hill, New York.
- Gauld, G. E., Rassin, D. K., Solomon, G. E., Harris, R. C., and Sturman, J. A. (1970). Biochemical observations on so-called hereditary tyrosinemia. *Pediatric Research*, **4**, 337.
- Gentz, J., Jagenburg, R., and Zetterström, R. (1965). Tyrosinemia. *Journal of Pediatrics*, **66**, 670.
- Halvorsen, S., Pande, H., Løken, A. C., and Gjessing, L. R. (1966). Tyrosinosis: a study of 6 cases. *Archives of Disease in Childhood*, **41**, 238.
- Harries, J. T., Seakins, J. W. T., Ersser, R. S., and Lloyd, J. K. (1969). Recovery after dietary treatment of an infant with features of tyrosinosis. *Archives of Disease in Childhood*, **44**, 258.
- Howell, R. R. (1972). The glycogen storage diseases. *The Metabolic Basis of Inherited Disease*, 3rd ed., p. 149. Ed. by J. B. Stanbury, J. B. Wyngaarden, and D. S. Frederickson. McGraw-Hill, New York.
- Hülsmann, W. C., and Fernandes, J. (1971). A child with lactacidemia and fructose diphosphatase deficiency in the liver. *Pediatric Research*, **5**, 633.
- Jevtic, M. M., Thorp, F. K., and Hruban, Z. (1974). Hereditary tyrosinemia with hyperplasia and hypertrophy of juxtaglomerular apparatus. *American Journal of Clinical Pathology*, **61**, 423.
- La Du, B. N., and Gjessing, L. R. (1972). Tyrosinosis and tyrosinemia. *The Metabolic Basis of Inherited Disease*, 3rd ed., p. 296. Ed. by J. B. Stanbury, J. B. Wyngaarden, and D. S. Frederickson. McGraw-Hill, New York.

- Larochelle, J., Mortezaei, A., Belanger, M., Tremblay, M., Claveau, J. C., and Aubin, G. (1967). Experience with 37 infants with tyrosinemia. *Canadian Medical Association Journal*, **97**, 1051.
- Levine, R. J., and Conn, H. O. (1967). Tyrosine metabolism in patients with liver disease. *Journal of Clinical Investigation*, **46**, 2012.
- McLean, A. E. M. (1966). Enzyme activity in the liver and serum of malnourished children in Jamaica. *Clinical Science*, **30**, 129.
- Odièvre, M., Gautier, M., and Rieu, D. (1969). Intolérance héréditaire au fructose du nourrisson. *Archives Françaises de Pédiatrie*, **26**, 433.
- Perry, T. L. (1967). Tyrosinemia associated with hypermethioninemia and islet cell hyperplasia. *Canadian Medical Association Journal*, **97**, 1067.
- Perry, T. L., Hardwick, D. F., Dickson, G. H., Dolman, C. L., and Hansen, S. (1965). Hypermethioninemia: a metabolic disorder associated with cirrhosis, islet cell hyperplasia and renal tubular degeneration. *Pediatrics*, **36**, 236.
- Pickering, D., and Bower, B. (1972). Temporary tyrosinosis. (Abst.) *Archives of Disease in Childhood*, **47**, 151.
- Sakai, K., and Kitagawa, T. (1957a). An atypical case of tyrosinosis. 1: Clinical and laboratory findings. *Jikeikai Medical Journal*, **4**, 1.
- Sakai, K., and Kitagawa, T. (1957b). An atypical case of tyrosinosis. 2. A research on the metabolic block. *Jikeikai Medical Journal*, **4**, 11.
- Scriver, C. R., and Davies, E. (1965). Endogenous renal clearance rates of free amino acids in pre-pubertal children. *Pediatrics*, **32**, 592.
- Silverberg, M. (1967). Discussion. Conference on Hereditary Tyrosinemia. *Canadian Medical Association Journal*, **97**, 1086.
- Sommerville, R. L., Fleisher, G. A., Dearing, W. H., Hallenbeck, G. A., and Dockerty, M. B. (1960). Transaminases in hepatic tissue and serum in hepatic disease. *Gastroenterology*, **38**, 926.
- Van Sande, M., Mardens, Y., Adriaenssens, K., and Lowenthal, A. (1970). The free amino acids in human cerebrospinal fluids. *Journal of Neurochemistry*, **17**, 125.
- Woolf, L. I. (1966). Tyrosinosis. (Inborn hepato-renal dysfunction.) *Proceedings of the Royal Society of Medicine*, **59**, 814.
- Yu, J. S., Walker-Smith, J. A., and Burnard, E. D. (1971). Neonatal hepatitis in premature infants simulating hereditary tyrosinosis. *Archives of Disease in Childhood*, **46**, 306.
- Zelman, S., Wang, C. C., and Appelhanz, L. (1959). Transaminases in serum and liver correlated with liver cell necrosis in needle aspiration biopsies. *American Journal of the Medical Sciences*, **237**, 323.

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