

# STUDIES ON THE METABOLISM AND NUTRITIONAL THERAPY OF THE GALACTOSAEMIC INFANT AND CHILD

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The various features of the nutrition of preschool and school children in South Africa have involved a study of large numbers, in many instances on a national level. These include aspects of kwashiorkor, vitamin deficiencies, calcium and iodine deficiencies,<sup>1-4</sup> and the physique and body build of school children.<sup>5</sup>

This paper is concerned with the problems of, to date, 7 children and their families. In these children, owing to an inherited defect, there was an inability to metabolize milk sugar (lactose) from birth. As a result, breast or cow's milk or any milk product could have been fatal, or, at least, the cause of severe physical and mental disability.

## CLINICAL FEATURES OF GALACTOSAEMIA

*Acute.* Within a short period after the ingestion of milk, the newborn galactosaemic develops vomiting, diarrhoea, dehydration, a general failure to thrive, liver enlargement and jaundice, with galactosuria and aminoaciduria.

All 7 cases, which consisted of 4 White and 3 Bantu children, exhibited these typical features in varying degree. 'Failure to thrive' was a notable symptom in 5 cases, vomiting and diarrhoea being marked in 3 subjects. Hepatic enlargement and jaundice were prominent presenting features in 5 cases. The establishment of the diagnosis after clinical and laboratory studies took a few

days to several weeks after birth. In severe cases, or if untreated, termination from infection or liver failure often occurs.

*Chronic.* Survivors (or chronic cases) are dwarfed, poorly nourished, often with cataracts, liver cirrhosis and mental retardation. The 7 cases are now between 3 and 9 years old, and 6 are males. At each age period they have been somewhat underweight and shorter in stature than normal children. All have had liver enlargement, and this is still present in some of the cases. Three subjects have had cataracts, and in 2 this regressed after treatment on a lactose-free diet. The mental development and IQ in the White children indicate some degree of mental retardation, and the elder children are 1-2 grades behind normal children for their age. The Bantu children have not, as yet, been tested.

## METABOLIC DEFECT

Why is the presence of galactose in quantity in the urine of a newborn or an infant so lethal a sign, so productive of liver and brain damage? It arises from the nature of the inherited metabolic defect in galactosaemia. Metabolism of milk sugar (lactose) yields glucose and galactose. Galactose, after combining with phosphate, eventually becomes converted to phosphorylated glucose through a

transferase enzyme system, viz. galactose-1-phosphate uridylyl transferase; the transferase system is also the pathway for the formation of brain galactolipids that are essential for cerebral function. This metabolic sequence is the major mechanism of metabolism of galactose.

The metabolism of milk sugar (lactose) and the nature of the inherited defect and therapy in galactosaemia, can be summarized as follows:

1. Lactose  $\xrightarrow{\hspace{2cm}}$  glucose + galactose  
transferase
2. Galactose, on phosphorylation  $\xrightarrow{\hspace{2cm}}$  phosphorylated glucose. Absent liver transferase (foetus to adult) causes galactosaemia
3. Metabolic bypass, weak in neonate, develops in childhood
4. Hence importance of early diagnosis. Low-galactose diet.

The transferase enzyme is absent from the liver and other tissues in cases of galactosaemia. The accumulation of galactose phosphate in tissues is inhibitory to key enzymes involved in glycolysis. This is the basis of the toxicity of galactose phosphate, and while it affects all tissues, the effects are most readily apparent in the lens, kidney, liver, and especially the brain, which is the fastest growing tissue immediately after birth.

There is a minor metabolic path that is poorly developed in the neonate; this shows enhanced activity from childhood onwards. Thus, the severity of symptoms is dependent on the extent of the enzyme deficiency and the amount of milk in the diet in early life.

#### BIOCHEMICAL DIAGNOSIS

Early diagnosis is of paramount importance, since the provision of a galactose-free diet usually produces dramatic improvement, while the penalty to the child for delay may be serious in terms of irrevocable physical and mental damage.

The nature of the sugar in the urine of an infant or newborn must be precisely identified. With regard to urine tests, the specific tests for galactose will depend on finding a positive reducing reaction, a negative test for glucose by the glucose oxidase method, and a positive test for galactose by the galactose oxidase test and other methods of identification. A test strip using the galactose oxidase technique has been prepared in the Electrolyte and Metabolic Research Unit, and used to test the urines of suspected galactosaemics and a number of cases of mental defectives.<sup>9</sup> Further identification of the presence of galactose in the urine can be conveniently carried out by paper chromatography.<sup>7</sup>

The following blood tests may be performed:

1. Blood galactose and galactose-loading test.<sup>8</sup> The oral galactose-tolerance test has certain distinct dangers when carried out on the galactosaemic, owing to the tendency for the blood glucose to fall precipitously as the blood galactose rises and so to cause episodes of convulsions. It should therefore be employed with considerable care, and, since there are other tests available, is probably unwarranted in any known case of galactosaemia.

2. Galactose-1-phosphate in the red cells.<sup>9</sup> This test is of considerable value in following the efficacy of therapy, and was used periodically in 3 cases.

3. Assay of the specific transferase enzyme, which is most conveniently carried out in tests on red cells. This is a direct test for the condition and is of considerable value in the detection of carriers. In the Unit, several types of tests based on the assay of this enzyme are in use, and the results of one type of test have been in all cases confirmed by the other tests.<sup>10</sup>

The provision of a low-galactose diet and the degree of strictness to which it is adhered to, will tend to prevent the ill-effects or to arrest and reverse those that have occurred. Such a diet has to be continued for the first 3-5 years of life, and many galactosaemics will then develop normally as milk comes to occupy a progressively smaller proportion of

food intake, and the metabolic bypass can now adequately cope with small amounts of galactose in the diet.

#### GALACTOSE CONTENT OF FOODS

Exclusion of dietary galactose was the only treatment that met with any success. Free galactose is uncommon in naturally occurring foodstuffs, and milk, with 4.5% and 7% lactose for cow's and human milk respectively, is virtually the only major source of galactose. However, galactose in a combined form may be associated with other oligosaccharides, such as raffinose and stachyose. Raffinose is as widely distributed in the plant world (e.g. yeast, sugar beets) as sucrose, but complete acid hydrolysis is required to release galactose from the raffinose molecule. Stachyose is present in lentils and soya beans (refer to section on nutritional therapy). Polysaccharides, such as agar and various plant gums, yield galactose on hydrolysis, while animal polysaccharides, found in beef lung, brain and spleen, are also a source of galactose. Other sources of combined galactose are present in the galactolipids of the brain and spleen and the mucoid group of glycoproteins. Thus, apart from milk sugar (lactose), other sources of galactose in the diet of a baby or infant are minimal.

Various synthetic milk-free diets have been tested for their galactose content, and the method is presented here briefly. An aliquot of the food was weighed, extracted with alcohol-acetone, and the water-soluble fraction treated with an ion-exchange resin to remove electrolytes, and then with acid to hydrolyse the sugars. Glucose oxidase was then added to remove the glucose formed from the hydrolysis of lactose. By paper chromatography the galactose area was located by spraying an area, with elution of a separate spot for estimation of the galactose quantitatively with galactose oxidase.<sup>11</sup>

#### NUTRITIONAL THERAPY

##### Casein as Main Staple

*Synthetic milk.* This can be prepared from casein, coconut and arachis oil, sucrose, vitamins, mineral salts, and water. Casein, by ordinary precipitation, was found to contain 1% lactose, equivalent to 0.5% galactose (Table I), due to residual lactose adsorbed onto the casein. Each

TABLE I. GALACTOSE CONTENT OF FOODS

Foodstuff	No. of samples assayed	Galactose (mg./100 G food)
Nutrine	1	280
Pronutro	2	320
Nutramigen	5	135-190
Galactomin	3	80-120
Low lactose	2	70-140
Egg	6	85
Casein	3	500
Casein, washed	2	300

ounce of such a preparation would have the equivalent of 12 mg. lactose, that is, 6 mg. galactose. By washing the casein, the lactose content can be reduced to 0.6%, equivalent to 0.3% galactose (Table I). Such a synthetic 'milk' has about 3-4 mg. available galactose per oz.

Galactomin is a commercial product prepared on this basis, and was found to contain 80-120 mg. % galactose.

**Nutramigen.** This is formulated of dextrimaltose and arrowroot starch, giving 59% carbohydrate; hydrolysate of casein, giving 15% protein; corn-oil, 18% fat; mineral salts; and vitamins, principally the vitamin B group. Nutramigen was reported in 1954 to contain 0.7% lactose,<sup>12</sup> that is, 350 mg. galactose per 100 G Nutramigen. The formula for a newborn calls for 40 G Nutramigen, i.e. 280 mg. lactose or 140 mg. galactose. More recently, Schwarz and Simpson<sup>13</sup> have reported that Nutramigen contained 200 mg. galactose per 100 G Nutramigen, while Mead Johnson have indicated that the preparation does not contain more than 230 mg./100 G, equivalent to 70 mg. galactose per 8 oz. feed. Assays of 5 samples by the method described above yielded values of 135-190 mg. galactose %, values that are greater than those for Galactomin<sup>13</sup> (Table I). Nonetheless, Nutramigen appears to be better tolerated and is a more complete food. It has been widely used in the United States of America. All 7 cases had Nutramigen as their staple diet in their infancy and early childhood.

A low lactose preparation is prepared from milk by Cow & Gate, and was reported to contain 50 mg. galactose per 100 G of the dry preparation.<sup>13</sup> Assays by the method described on a series of samples gave results ranging from 70 to 140 mg. galactose %.

#### *Soya Bean Preparations*

Commercial preparations that are based on soya bean flour include Sobee, Mul-Soy, and Wanderlac. Soya bean flour contains the galactoside sugars, stachyose and raffinose. While the human intestinal tract is said not to have enzymes that would release galactose from the sugars, incubation of soya bean flour with 0.1 N hydrochloric acid or 0.1 N sodium hydroxide liberates some free galactose, so that the possibility arises that this can obtain in the human intestinal tract.

#### *Meat Preparations*

A meat base preparation has seldom been used during infancy for the treatment of galactosaemia; this is somewhat remarkable since all the major preparations of foods for galactosaemics are based on materials which could give rise to free galactose, and meat is a staple article of diet which essentially would be free of this sugar.

#### *Cereal Preparations*

These are in general satisfactory, since maize, wheat, oats and rice contain small amounts of galactose only. It should be noted that cereal preparations for babies are often reinforced with milk powder.

#### *General*

Additional minerals and vitamins must always be added to the diet. A recent report, describing a deficiency state in infants on synthetic foods, is especially pertinent in this regard.<sup>14</sup> The vitamin B group is especially called for, since lactose stimulates the growth of intestinal lactobacilli, which synthesize some of the vitamin B group. In their absence, pathogenic *E. coli* tend to appear.

Lactose is used extensively as a tablet base, e.g. in vitamin tablets, etc., and thus may be given unintentionally.

#### EFFECTS OF NUTRITIONAL THERAPY

In all 7 cases, the subjects were seriously ill before the diagnosis was made. The effect of feeding Nutramigen was dramatic: increase of weight, decrease in liver enlargement and disappearance of jaundice, cessation of diarrhoea and vomiting, and decrease in apathy and lethargy. The main persisting defects were liver damage, as evidenced by clinical enlargement and abnormal liver-function tests, and damage to the brain during early development.

The dietary control involved the use of Nutramigen, with tea and/or sweetened with sugar, with the avoidance of liquid milk and all milk-containing foods (all types of confectionery, some breads, puddings, butter, ice-cream, etc.). Water may be substituted for milk in recipes for puddings and porridges. Meat, vegetables, fruit in various forms, including fruit-juice suckers and jams, should be introduced to supplement the basic use of Nutramigen. Eggs should be used sparingly, since they contain mucoids that may liberate galactose. The response in the 7 subjects has varied from excellent to moderately good. *The degree of attention paid to the diet is a major factor in determining the degree of mental retardation.*

The milk-free diet has to be continued for the first 3-5 years of life, and, at the end of this period, a trial test with small and increasing amounts of milk may be attempted. Urinary tests for galactose are performed at intervals, and blood taken for the estimation of blood galactose and the presence of galactose-1-phosphate in the red cells. This latter test is the best indicator of the efficiency of treatment and the ability of the child to handle galactose. Any increase of urinary galactose or elevation of the galactose in blood and red cells requires a further period on a milk-free diet.

#### INTERACTION BETWEEN INHERITANCE AND ENVIRONMENT

Galactosaemia is a classic example of the interaction between inheritance and environment—between the DNA and the diet. The full deleterious effect of the gene is dependent on the environment, and the following examples are illustrative in this connection:

In the first example, the mother died shortly after the birth of her fourth child, all the previous children being in good health and of normal physique, etc. The newborn child was discharged on the tenth day in the care of his aunt, and started vomiting on a cow's-milk formula. By the 14th day there was enlargement of the liver with the presence of eye cataracts. Galactose was then identified in the urine and a diagnosis of galactosaemia was made. Nutramigen was provided as the sole dietary staple. In the first year of life, there was considerable reaction to A.P. Dover powder. This was eventually traced to the lactose in the powder. Lactose is largely used as a sweetener in powders and as a sweetener and binder in pills. It is to be noted that, owing to his mother's death, the newborn did not receive any breast milk with its high lactose content. This contributed possibly to the result that mental and physical damage in this child (now 9 years old) is slight.

In the second case, the third boy (2 previous boys in good health) showed an excess loss of weight after birth, with no diarrhoea or vomiting, but liver enlargement on the fifth day. The urine of the fifth day was shown to

contain galactose. Nutramigen was given from the eighth day, but, despite this early diagnosis, a stormy passage followed, with irregular bouts of diarrhoea and miscellaneous infections. It is probable that, owing to the withdrawal of lactose from the diet, lactobacilli in the intestinal flora did not appear, and pathogens occurred in the absence of these bacteria. At the age of 5 years this galactosaemic was underweight and short for his age with an IQ of 60; now, at the age of 8 years, he is in grade 1.

Finally, where a newborn occurs in a family with a known case of galactosaemia, the plan of treatment is clear-cut. The mother should have a low-milk diet early in pregnancy, and no milk during the later stages of pregnancy. While normally maternal blood does not have galactose after passage through the maternal liver, the low liver transferase in the pregnant carrier may be insufficient to cope with the amount of galactose absorbed from the gastro-intestinal tract. On the birth of the newborn, the cord blood and a subsequent blood sample should be tested to determine whether the case is galactosaemic. Such positives, if treated immediately, are virtually normal in most respects. There is on record a galactosaemic, who was first discovered when he was 45 years old.

#### CONCLUSIONS

A particular genetic constitution may involve the necessity to take certain foodstuffs and to avoid others. Every one of us suffers from the heritable disorder of an inability to synthesize vitamin C, but in general terms, this inherited defect is not of serious import, since one and all are in the 'same boat' and the remedy is readily available. On the other hand, a very small number (probably 1:200,000) suffer from the absence of the enzyme vital for the metabolism of milk sugar (lactose); galactosaemia is a serious affliction, with severe and possibly disastrous results from a universal article of diet. The provision of the special diet (lactose-free) is costly, but early treatment and diagnosis is imperative to avoid mental retardation.

Apart from galactosaemia, other inborn errors of metabolism may be successfully treated in early infancy by appropriate nutritional measures, e.g. diet low in phenylalanine for phenylketonuria,<sup>12</sup> and diet low in branched

amino acids for maple syrup urine disease, which has hitherto proved to be fatal within a few months.<sup>13</sup>

Control of infectious and parasitic diseases and surgical advances have significantly reduced morbidity and mortality, and the recent delineation of the genetic code has resulted in new and intensive research in genetics, clinical and biochemical. Inherited defects have implied for many an irreversible state, and a defeatist attitude with regard to treatment. On the contrary, developments in medical genetics have resulted in the fact that, far from being a matter for despair, there are possibilities for therapeutic attack in terms of cytogenetics, protein abnormalities and enzyme defects.

Congenital defects constitute a formidable challenge to doctors and society in general, since 1 out of every 50 children born has an inherited defect with some degree of disability.

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