Nutrition and animal models of inherited metabolic disease

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A review by Cornelius (1969) lists a large number of potential animal models of human disease: 93 in farm animals, 98 in cats and dogs and 116 in laboratory rodents (mainly in the mouse). This compendium can easily be brought up to date by the 3-monthly listings of the Institute of Laboratory Animal Resources to include many more animal models now used in research (ILAR News, 1976). Unfortunately the inheritance of a large number of these models has not been investigated and few would probably be of interest to nutritionists; nor are they exact homologues of the human disease, or available as laboratory stocks. Most of the approximately 500 mutants of the laboratory mouse are, however, readily available to research workers (Green, 1966; Searle, 1976).

Nearly all the 500 or so mouse mutants were discovered by the presence of visible abnormalities, such as skeletal malformations, coat colour and structure, size and shape, behaviour (circling, head tossing) and anaemia. A few of these syndromes do have metabolic consequences that might be of nutritional interest and they are discussed in the next section. It is of more interest that there have recently been attempts to search for homologues of human inborn errors of metabolism. Some of the syndromes discovered are discussed in the second section. One of these, histidinaemia, on which there has been a limited amount of nutritional investigation, is discussed in the last section.

Metabolic mutants in the mouse with unknown primary lesions

The most widely used mouse mutants having metabolic effects have been obese and diabetes (formerly adipose). They have been considered as models of human obesity and of human maturity-onset diabetes, which has a polygenic basis (Falconer, 1967), but they are probably more strictly models of the Prader–Willi syndrome (McKusick, 1975). Most work on these syndromes so far has been to try to establish the site of the primary lesion and its physiological consequences (reviews by Mayer, 1960; Staats, 1968, 1975; see also Bulfield, 1972; Beloff-Chain, Edwardson & Hawthorn, 1975). These syndromes are not yet fully understood and little progress has been made towards alleviating them nutritionally. It is, however, worth considering an interesting experiment by Coleman (1973). He placed obese and diabetes on identical inbred backgrounds (Coleman & Hummel, 1973) after which the syndromes, although being controlled by different genes on different

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chromosomes, appeared identical. He then linked obese with diabetes in surgical parabiosis, joining them at the abdominal wall so that they had 1% of their blood supply in common. The obese mice lost weight dramatically, became thin and died, whereas diabetes kept on growing. Diabetes had the same effect on normal mice, but when obese and normal mice were in parabiosis, the obese animals lost weight slightly. Coleman interpreted these results to show that obese lacks some circulating satiety factor but has normal receptors, whereas diabetes has damaged receptors resulting in an overproduction of the circulating factor. The results should make it easier to locate the site of the primary lesion in these mutants and in turn should lead to techniques to alleviate them which might prove useful in the similar human conditions.

The technique of parabiosis would be a useful tool to separate the effects of a mutant gene with metabolic consequences into cellular and circulating components. In this context there is another group of six mouse mutants that confer small body size (Green, 1966; Searle, 1976): dwarf, Ames dwarf, pigmy, miniature, diminutive and little. Three of these, dwarf (H. G. Pidduck, personal communication), little (Eicher & Beamer, 1976) and Ames dwarf (Schaible & Gwern, 1961) are known to have low levels of growth hormone and to respond to injections of it. Nothing much is known about the rest except that pigmy is not due to a pituitary deficiency (King, 1955). The biochemical and endocrinological relationships among these six dwarfing genes have never been fully investigated. They might warrant a more thorough investigation in the light of Coleman’s success with parabiosis and the existence of about twenty inherited dwarfing syndromes in man, some of which are growth hormone resistant (McKusick, 1975).

There are about twelve inherited disorders of erythropoiesis in the mouse (Bernstein, 1969). Because many inherited human anaemias are deficiencies in enzymes of erythrocyte glycolysis and pentose phosphate pathways (Valentine, 1968; McKusick, 1975), Hutton & Bernstein (1973) determined the activity of these enzymes in several of the mouse anaemias, but did not find any deficiencies. One mouse anaemia (microcytic anaemia) has been shown to have a general impairment of red cell iron uptake (Russell, Nash, Bernstein, Kent, McFarland, Matthews & Norwood, 1970; Edwards & Hoke, 1975). There is a similar microcytic anaemia with iron deficiency in man (Shahidi, Nathan & Diamond, 1964).

Several other mouse mutants are similar to human syndromes or have physiological characteristics that might be of interest from the nutritional point of view (Table 1). There are also among the fifty or so ‘neurological’ mutants (Sidman, Green & Appel, 1965; Searle, 1976) some which have biochemical correlates that open them to biochemical and perhaps nutritional investigation (Table 2). These include dilute-lethal which at first was thought to be a model of human phenylketonuria; but the plasma levels of phenylalanine were not as high as in phenylketonuria. It is now considered that they are perhaps a secondary effect of starvation after the onset of paralysis in this syndrome (Coleman, 1960; Rauch &
### Table 1. *Mouse mutants of potential biochemical, medical and nutritional interest*

<table>
<thead>
<tr>
<th>Mutant</th>
<th>Syndrome</th>
<th>References</th>
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<tbody>
<tr>
<td>Microcytic anaemia</td>
<td>deficient red cell iron uptake</td>
<td>Russell et al. 1970</td>
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<tr>
<td>Pink eyed sterile</td>
<td>deficient TSH-LH or prolactin protein</td>
<td>Edwards &amp; Hoke, 1975</td>
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<tr>
<td>Testicular feminisation</td>
<td>deficient androgen carrier protein</td>
<td>Johnson &amp; Hunt, 1975</td>
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<tr>
<td>Beige</td>
<td>Chediak Higashi syndrome lysosomal disorder</td>
<td>Lyon &amp; Hawkes, 1970</td>
</tr>
<tr>
<td>Pallid</td>
<td>transport of manganese, Dopa and tryptophan</td>
<td>Bullock &amp; Bardin, 1975</td>
</tr>
<tr>
<td>Exocrine pancreas insufficiency</td>
<td>cystic fibrosis (?)</td>
<td>Padgett et al. 1967</td>
</tr>
<tr>
<td>Oedematous</td>
<td>lipid deficiencies, brittle skin, leucocytosis</td>
<td>Oliver &amp; Essmer, 1973</td>
</tr>
<tr>
<td>Lethal milk</td>
<td>Niemann-Pick disease (?)</td>
<td>Lyon et al. 1965</td>
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<tr>
<td>Foam cell reticulosis</td>
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Yost, 1963; Zannoni, Weber, VanValen, Rubin, Bernstein & LaDu, 1966; Woolf, Jakubovic, Woolfe & Bory, 1970; Winterbourn, Woolf & Woolf, 1971; Seller, 1972. It has been reported (Siegal & Rauch, 1969) that *wabbler-lethal* has elevated plasma amino acid levels. We have not observed these elevated levels in non-paralysed animals (Bulfield & Kacser, unpublished results).

### Table 2. *Mouse neurological mutants with biochemical effects*

<table>
<thead>
<tr>
<th>Mutant</th>
<th>Biochemical effect</th>
<th>References</th>
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</thead>
<tbody>
<tr>
<td>Dilute lethal</td>
<td>brain lipids phenylalanine levels</td>
<td>see text</td>
</tr>
<tr>
<td>Wabbler lethal</td>
<td>brain lipids phenylalanine levels</td>
<td>see text</td>
</tr>
<tr>
<td>Cribiform degeneration</td>
<td>aromatic amino acid levels normocytic anaemia electrolyte disorders</td>
<td>Green et al., 1972</td>
</tr>
<tr>
<td>Quaking</td>
<td>deficient fatty acyl/CoA elongation</td>
<td>Kandutsch &amp; Saucier, 1972</td>
</tr>
<tr>
<td>Jimpy†</td>
<td>deficient sterol synthesis and galactolipid</td>
<td>Goldberg et al., 1973</td>
</tr>
<tr>
<td>Myelin synthesis deficiency*†</td>
<td>low sterol synthesis</td>
<td>Nussbaum et al., 1969</td>
</tr>
<tr>
<td>Ducky*</td>
<td>low liver and kidney esterase</td>
<td>Tsuji &amp; Meier, 1970</td>
</tr>
<tr>
<td>Varitint waddler</td>
<td>hyperactive dopaminergic mechanism</td>
<td>Cools, 1972</td>
</tr>
</tbody>
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*Six other neurological mutants have lower liver esterases: jolting, myelin synthesis deficiency, reeler, shambling, teetering and tottering (Tsuji & Meier, 1971).†May be alleles (Kandutsch & Saucier, 1972).

A disorder of aromatic amino acid metabolism was at first implicated in the *mottled/brindled* syndrome (Hunt & Johnson, 1972a,b). This X-linked locus has five alleles, which all lighten coat colour, and the hemizygotes range in viability from lethality in utero to fully viable and fertile. Hunt (1974) has now shown that the symptoms of the syndrome can be linked to a copper transport deficiency and the syndrome resembles the lethal Menkes kinky hair disease in man (McKusick, 1975). Recently 3–4 d old *brindled* mice have been injected daily for 7–8 d with
0.025 ml 0.2% CuCl₂/g and 58.5% of them have survived whereas they usually die at about 14 d (D. S. Falconer & J. H. Isaacson, personal communication). This syndrome therefore provides a very useful model to gain information that might be of help in treating the human condition.

Table 3. Inborn errors of metabolism in the mouse

<table>
<thead>
<tr>
<th>Mutant</th>
<th>Human reference number (McKusick, 1975)</th>
<th>References</th>
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<tbody>
<tr>
<td>Albino</td>
<td>20310, 20320</td>
<td>Coleman, 1962</td>
</tr>
<tr>
<td>Glycogen storage disease VIII (formerly VIa—phosphorylase deficiency)</td>
<td>30600</td>
<td>Lyon, 1970; Huijing, 1970</td>
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<tr>
<td></td>
<td></td>
<td>Cohen &amp; Cohen, 1973</td>
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<td></td>
<td></td>
<td>Gross &amp; Mayer, 1974</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gross et al., 1975</td>
</tr>
<tr>
<td>Histidinaemia</td>
<td>23580</td>
<td>Kacser et al., 1973</td>
</tr>
<tr>
<td>Hyperprolinaemia type I</td>
<td>23950</td>
<td>Bulfield &amp; Kacser, 1974, 1975</td>
</tr>
<tr>
<td>Acatalasaemia</td>
<td>20020</td>
<td>Blake &amp; Russell, 1972, 1973</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blake, 1972; Blake et al., 1974</td>
</tr>
<tr>
<td>Glucose phosphate isomerase deficiency (anaemia)</td>
<td>17240</td>
<td>Feinstein et al., 1964, 1966</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aebi et al., 1968</td>
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<tr>
<td></td>
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<td>Feinstein, 1970</td>
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<td></td>
<td></td>
<td>Feinstein et al., 1972</td>
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<tr>
<td></td>
<td></td>
<td>Padua, Bulfield &amp; Peters (in preparation)</td>
</tr>
</tbody>
</table>

Inborn errors of metabolism in the mouse

There are a few of the classic inborn errors of metabolism in the mouse (Table 3). Three of these were found by deliberate screening procedures (acatalasaemia, Feinstein, Seaholm, Howard & Russell, 1964; histidinaemia, Kacser, Bulfield & Wallace, 1974; glucosephosphate isomerase deficiency, Bulfield & Moore, 1974). In each case the same enzyme appears to be deficient as in the human condition. Albino, acatalasaemia, phosphorylase kinase deficiency and prolinaemia are almost benign, like their human counterparts. Glucosephosphate isomerase deficiency has an erythrocyte enzyme activity 25–30% of normal (Padua, Bulfield & Peters, in preparation) and human subjects with this level can be anaemic (Paglia & Valentine, 1974; Hutton & Chilcote, 1974). We found no sign of haemolytic anaemia nor a decrease in haematocrit or erythrocyte count in these mice. So far as I am aware no nutritional research has been done with any of these disorders other than that discussed below.

Histidinaemia

This mutant was found as the result of a screening programme designed to discover inborn errors of amino acid metabolism. Biochemically it is the homologue of human histidinaemia having low levels (<5%) of the enzyme histidase resulting in high levels of histidine and its imidazole derivatives in plasma, liver, brain and urine (Kacser et al. 1973; Bulfield & Kacser, 1974, 1975). The histidase levels in histidinaemic mice (<5%) reduce the flux in vivo through the pathway to 40% whereas both proline oxidase and the flux in vivo in prolinaemic mice are reduced.
to 5% (Whitehouse & Bulfield, in preparation). Work with histidinaemic, prolinaemic and double mutant mice has shown that histidine and proline share different reabsorption sites in the kidney (Bulfield, in preparation).

The mice appear healthy and unaffected as are the majority of human histidinaemics (Bulfield & Kacser, 1974). In the mouse there is, however, a maternal effect of histidinaemic females. Histidinaemic mothers produce some balance-defective offspring even if the offspring themselves are heterozygous (Kacser et al. 1973; Bulfield & Kacser, 1974; Kacser, Mya Mya, Duncker, Wright, Bulfield, McLaren & Lyon, 1977). This is of great interest as there is also a maternal effect with human phenylketonuria; phenylketonuric mothers can produce mentally defective offspring (Denniston, 1963). There has recently been a suggestion that a similar if less severe phenomenon exists with human maternal histidinaemia (Lyon, Gardner & Veale, 1974; Harper, 1975). This moves the nutritional problem from the infant to the pregnant mother.

We have investigated this problem in histidinaemic mice (Bulfield & Kacser, 1974; Kacser et al. 1977). By loading non-histidinaemic mice with a high-histidine diet during pregnancy we were able to produce balance-defective offspring. We were also able to reduce dramatically the numbers of balance-defective offspring born to histidinaemic mothers by placing them on a low-histidine diet during pregnancy. These treatments were effective only in the second week of the three-week gestation, which is the same as the critical period for causing similar lesions by X-rays (Rugh, 1964). Further experiments are in progress to determine a diet suitable for dealing with this situation.

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REFERENCES


