

Nutrition and animal models of inherited metabolic disease

By G. BULFIELD,* *Institute of Animal Genetics, The University, Edinburgh*

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

*Present address: Department of Genetics, The University, Leicester.

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 & Gowen, 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*

Mutant	Syndrome	References
Microcytic anaemia	deficient red cell iron uptake	Russell <i>et al.</i> 1970 Edwards & Hoke, 1975
Pink eyed sterile	deficient TSH-LH or prolactin	Johnson & Hunt, 1975
Testicular feminisation	deficient androgen carrier protein	Lyon & Hawkes, 1970 Bullock & Bardin, 1975
Beige	Chediak Higashi syndrome	Padgett <i>et al.</i> 1967
Pallid	lysosomal disorder transport of manganese, Dopa and tryptophan	Oliver & Essmer, 1973 Cotzias <i>et al.</i> 1972
Exocrine pancreas insufficiency	cystic fibrosis (?)	Pivetta & Green, 1973
Oedematous	lipid deficiencies, brittle skin, leucocytosis	Schiffman <i>et al.</i> 1975
Lethal milk	—	Dickie, 1969
Foam cell reticulosis	Niemann-Pick disease (?)	Lyon <i>et al.</i> 1965

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 *wabblers-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*

Mutant	Biochemical effect	References
Dilute lethal	brain lipids phenylalanine levels	see text
Wabblers lethal	aromatic amino acid levels	see text
Cribiform degeneration	normocytic anaemia electrolyte disorders	Green <i>et al.</i> , 1972
Quaking	deficient fatty acyl/CoA elongation	Kandutsch & Saucier, 1972 Goldberg <i>et al.</i> , 1973
Jimpy†	deficient sterol synthesis and galactolipid	Nussbaum <i>et al.</i> , 1969
Myelin synthesis deficiency*†	low sterol synthesis	Kandutsch & Saucier, 1972
Ducky*	low liver and kidney esterase	Tsuji & Meier, 1970
Varitint waddler	hyperactive dopaminergic mechanism	Cools, 1972

*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, 1972*a,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% CuCl_2/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*

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

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.

I would like to thank Dr Henrik Kacser for all his help and encouragement. This work was supported by an MRC project grant.

REFERENCES

- Aebi, H., Sutter, H. & Feinstein, R. N. (1968). *Biochem. Genet.* **2**, 245.
 Beloff-Chain, A., Edwardson, J. A. & Hawthorn, J. (1975). *J. Endocrinol.* **65**, 109.
 Bernstein, S. E. (1969). *Genetics in Laboratory Animal Medicine*. p. 9. Washington, DC: National Academy of Science.
 Blake, R. L. (1972). *Biochem. J.* **129**, 987.
 Blake, R. L. & Russell, E. S. (1972). *Science* **176**, 809.
 Blake, R. L. & Russell, E. S. (1973). *Genetics* **74**, 826.
 Blake, R. L., Grillo, R. V. & Russell, E. S. (1974). *Life Sci.* **14**, 1285.
 Bulfield, G. (1972). *Genet. Res.* **20**, 51.
 Bulfield, G. & Kacser, H. (1974). *Arch. Dis. Childh.* **49**, 545.
 Bulfield, G. & Kacser, H. (1975). *J. Neurochem.* **24**, 403.
 Bulfield, G. & Moore, E. A. (1974). *Clinica Chim. Acta* **53**, 265.
 Bullock, L. P. & Bardin, C. W. (1975). *Endocrinology* **97**, 1106.
 Cohen, P. T. W. & Cohen, P. (1973). *FEBS Letters*. **29**, 113.
 Coleman, D. L. (1960). *Archs. Biochem. Biophys.* **91**, 300.
 Coleman, D. L. (1962). *Archs Biochem. Biophys.* **69**, 562.
 Coleman, D. L. (1973). *Diabetologia* **9**, 294.
 Coleman, D. L. & Hummel, K. P. (1973). *Diabetologia* **9**, 287.
 Cools, A. R. (1972). *Psychopharm.* **24**, 384.

- Cornelius, C. E. (1969). *New Engl. J. Med.* **281**, 934.
- Cotzias, G. T., Tang, L. C., Miller, S. T., Sladic-Simic, D. & Hurley, L. S. (1972). *Science* **176**, 410.
- Denniston, J. C. (1963). *Pediatrics* **63**, 461.
- Dickie, M. M. (1969). *Mouse News Lett.* **41**, 30.
- Edwards, J. A. & Hoke, J. E. (1975). *Blood* **46**, 381.
- Eicher, E. V. & Beamer, W. G. (1976). *J. Hered.* **67**, 87.
- Falconer, D. S. (1967). *Ann. Hum. Genet.* **31**, 1.
- Feinstein, R. N. (1970). *Biochem. Genet.* **4**, 135.
- Feinstein, R. N., Seaholm, J. E., Howard, J. B. & Russell, W. L. (1964). *Proc. Natl. Acad. Sci.* **52**, 661.
- Feinstein, R. N., Howard, J. B., Braun, J. T. & Seaholm, J. E. (1966). *Genetics* **53**, 923.
- Feinstein, R. N., Jaroslow, B. N. & Howard, J. B. (1972). *Biochem. Genet.* **6**, 263.
- Goldberg, I., Shechter, I. & Block, K. (1973). *Science*, **182**, 497.
- Green, E. L. (editor) (1966). *Biology of the Laboratory Mouse*. 2nd edn New York and London: McGraw Hill.
- Green, M. C., Sidman, R. L. & Pivetta, O. H. (1972). *Science*. **176**, 800.
- Gross, S. R. & Mayer, S. E. (1974). *J. Biol. Chem.* **249**, 6710.
- Gross, S. R., Longshore, M. A. & Pangburn, S. (1975). *Biochem. Genet.* **13**, 567.
- Harper, P. S. (1975). *Heredity* **34**, 289.
- Huijing, F. (1970). *Biochem. Genet.* **4**, 187.
- Hunt, D. M. (1974). *Nature, Lond.* **249**, 852.
- Hunt, D. M. & Johnson, D. R. (1972a). *Biochem. Genet.* **6**, 31.
- Hunt, D. M. & Johnson, D. R. (1972b). *J. Neurochem.* **19**, 2811.
- Hutton, J. J. & Bernstein, S. E. (1973). *Biochem. Genet.* **10**, 297.
- Hutton, J. J. & Chilcote, R. R. (1974). *J. Pediat.* **85**, 494.
- ILAR News (1976). Washington, DC: Institute of Laboratory Animal Resources, Natl. Res. Comm.
- Johnson, D. R. & Hunt, D. M. (1975). *J. Reprod. Fert.* **42**, 51.
- Kandutsch, A. A. & Saucier, S. E. (1971). *Biochim. biophys. Acta.* **260**, 26.
- Kacser, H., Bulfield, G. & Wallace, M. E. (1973). *Nature, Lond.* **244**, 77.
- Kacser, H., Mya Mya, K., Duncker, M., Wright, A. F., Bulfield, G., McLaren, A. & Lyon, M. F. (1977). *Nature, Lond.* **265**, 262.
- King, J. (1955). *J. Genet.* **53**, 487.
- Lyon, I. C. T., Gardner, R. J. M. & Veale, A. M. O. (1974). *Archs Dis Childh.* **49**, 581.
- Lyon, J. B. (1970). *Biochem. Genet.* **4**, 169.
- Lyon, M. F. & Hawkes, S. G. (1970). *Nature, Lond.* **227**, 1211.
- Lyon, M. F., Hulse, E. V. & Rowe, C. E. (1965). *J. Med. Genet.* **2**, 99.
- Mayer, J. (1960). *Am. J. Clin. Nutr.* **8**, 712.
- McKusick, V. A. (1975). *Mendelian Inheritance in Man* 4th edn. London: Johns Hopkins Univ. Press.
- Nussbaum, J. L., Neskovic, N. & Mandell, P. (1969). *J. Neurochem.* **16**, 927.
- Oliver, C. & Essner, E. (1973). *J. Histochem. Cytochem.* **21**, 218.
- Padgett, G. A., Reiquam, C. W., Gorham, J. R., Henson, J. B. & O'May, C. C. (1967). *Am. J. Path.* **51**, 533.
- Paglia, D. E. & Valentine, W. N. (1974). *Am. J. Clin. Path.* **62**, 740.
- Pivetta, O. H. & Green, E. L. (1973). *J. Hered.* **64**, 301.
- Rauch, H. & Yost, M. T. (1963). *Genetics* **48**, 1487.
- Rugh, R. (1964). *Radiology* **82**, 917.
- Russell, E. S., Nash, D. J., Bernstein, S. E., Kent, E. L., McFarland, E. C., Matthews, S. M. & Norwood, M. S. (1970). *Blood* **35**, 838.
- Schiffman, M. B., Santorineou, M. L., Lewis, S. E., Tunchin, H. A. & Gluecksohn-Waelsch, S. (1975). *Genetics* **81**, 525.
- Schaible, R. H. & Gowen, J. W. (1961). *Genetics* **46**, 896 (Abstr).
- Searle, A. G. (editor) (1976). *Mouse News Lett.* **54**.
- Seller, M. J. (1972). *Clin. Genet.* **3**, 495.
- Shahidi, N. T., Nathan, D. G. & Diamond, L. K. (1964). *J. Clin. Invest.* **43**, 510.
- Sidman, R. L., Green, M. C. & Appel, S. H. (1965). *Catalog of Neurological Mutants of the Mouse*. Harvard University Press.
- Siegal, S. J. & Rauch, H. (1969). *Biochem. Genet.* **2**, 311.

- Staats, J. (1968). *Bibliography of the Obese Mutant in the Mouse*. Bar Harbor, Maine, USA: Jackson Laboratory.
- Staats, J. (1975). *Diabetologia*. **11**, 325.
- Tsuji, S. & Meier, H. (1970). *Biochem. Genet.* **4**, 539.
- Tsuji, S. & Meier, H. (1971). *Experientia*. **27**, 258.
- Winterbourn, C. C., Woolf, L. I. (1971). *J. Neurochem.* **18**, 1077.
- Woolf, L. I., Jakubovic, F., Woolf, F. & Bory, P. (1970). *Biochem. J.* **119**, 895.
- Valentine, W. N. (1968). *Calif. Med.* **108**, 280.
- Zannoni, V. G., Weber, W. W., Van Valen, P., Rubin, A., Bernstein, R. & La Du, B. (1966). *Genetics*. **54**, 1391.

Printed in Great Britain