HYPERGLYCAEMIA AS A MENDELIAN RECESSIVE CHARACTER IN MICE.

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In the course of an investigation into the factors controlling the sugar content of the blood in mammals, commenced some years ago, we found that if the effects of fright and shock were guarded against by using only animals accustomed to being handled, the percentage after a twelve to twenty-four hours fast rarely varied more than about 5 mg. from a mean average of 85 mg. per 100 c.c. when self-coloured or piebald animals were considered, but that albinos and animals which were uniformly black frequently gave results differing by 25 mg. or more from this average, the former showing high and the latter low figures. These exceptional levels for the fasting blood sugar were so regularly encountered that it was evident they were not merely the result of accident, and it seemed probable there was some hitherto unrecognised relation between the factors determining colour and those controlling the sugar content of the blood. As our records showed that albinos did not invariably possess high fasting blood sugars, and that in black animals the percentage of sugar in the fasting blood was not always below the average, it was clear that the colour factors and the sugar factors were not identical, although the frequent association of abnormalities of colour with pronounced deviations from the mean average of sugar in the blood suggested some connection. In order to discover, if possible, the law underlying this apparent relation we commenced a series of breeding experiments, using mice for the purpose. These animals were selected because they multiply rapidly, occupy little space, and a large volume of work has already been published concerning colour transmission in them. They present the disadvantage, however, that, owing to their small size, it is necessary to kill the animal to obtain sufficient material for a reliable determination of the percentage of sugar in the blood, so that if death occurs naturally or by accident before a breeding experiment is completed a series of observations may be nullified. This happened in several of our series, but a sufficient

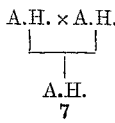
number of completed observations have been made to warrant conclusions being drawn regarding the relation between albinism and hyperglycaemia, and for the present we shall confine ourselves to that aspect of the question.

As will presently appear, the experiments showed no genetical connection between albinism and high sugar percentage, and the association first observed must consequently be regarded as fortuitous.

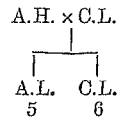
In all cases the blood required for the sugar estimations was obtained by decapitating the animal and the determinations were carried out by a modification of the Folin and Wu process, employing 0·2 c.c. of blood, which we have described elsewhere[1].

First Generation.

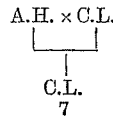
Family A. A mating between two albino mice, both possessing high fasting blood sugars of 116 mg. and 120 mg. respectively, yielded a family of seven, all albinos with high blood sugars ranging from 114 to 124 mg. per 100 c.c.



Family B. By mating ♂ albino having a high blood sugar, 120 mg., with ♀ black and white piebald having a low blood sugar, 80 mg., we obtained a second family consisting of five albinos showing low blood sugars, 76 to 84 mg., and six black and white piebalds also showing low blood sugars, 76 to 80 mg.



Family C. A third family consisting of seven chocolate coloured animals, all with low blood sugars ranging from 78 to 86 mg., resulted from the crossing of ♂ albino having a high blood sugar, 118 mg., with ♀ chocolate having a low blood sugar, 76 mg.



[1] *New Views on Diabetes*, Oxford Med. Publications, p. 5, 1923.

[2] A., albino; C., coloured; H., high; L., low.

Family D. By crossing ♀ albino having a high blood sugar, 118 mg., with ♂ piebald chocolate and white having a low blood sugar, 84 mg., we obtained a fourth family of nine, all piebalds, showing low blood sugars ranging from 76 to 84 mg.

C.L. × A.H.
|
C.L.
9

These initial results indicated that a high blood sugar behaves as a recessive to a normal blood sugar in the same way as albinism behaves to colour. In the families *A*, *C* and *D* both parents were obviously homozygous for colour and for sugar, but in family *B* the coloured partner was apparently heterozygous for colour, although homozygous for sugar, thus explaining the appearance in their progeny of approximately equal numbers of albinos and coloured animals, all with low blood sugars.

Second Generation.

Family E. On mating ♂ albino having a high blood sugar, 120 mg., from family *A*, with ♀ albino having a low blood sugar, 80 mg., from family *B*, we obtained 35 individuals, 18 of which were albinos with high blood sugars, 114 to 124 mg., and 17 were albinos with low blood sugars, 76 to 84 mg.

A.H. × A.H. A.H. × C.L.
| |
A.H. ♂ × A.L. ♀ .....F_1
|
A.H. A.L. .....F_2
18 17

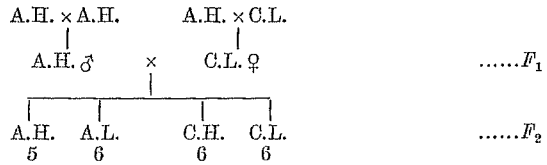
Expectation : Equality.

Family F. A cross between one of the ♂ high blood sugar albinos, 116 mg., of family *A* with a ♀ low blood sugar piebald, 80 mg., from family *B*, gave 23 mice consisting of 8 albinos with high blood sugars, 116 to 122 mg., 8 albinos with low blood sugars, 76 to 85 mg., 7 piebalds with high blood sugars, 116 to 120 mg., and 8 piebalds with low blood sugars, 80 to 84 mg.

A.H. × A.H. A.H. × C.L.
| |
A.H. ♂ × C.L. ♀ .....F_1
|
A.H. A.L. C.H. C.L. .....F_2
8 8 7 8

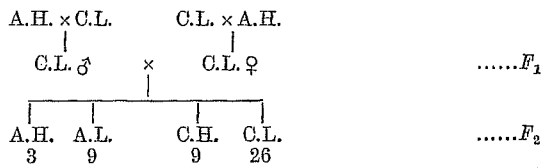
Expectation : Equality.

Family G. A high blood sugar albino, 114 mg., from family *A* on being mated with a low blood sugar black and white piebald, 78 mg., from family *B* gave a family of 23, 5 albinos having high blood sugars, 114 to 120 mg., 6 albinos having low blood sugars, 76 to 84 mg., 6 piebalds having high blood sugars, 116 to 122 mg., and 6 piebalds having low blood sugars, 80 to 84 mg.

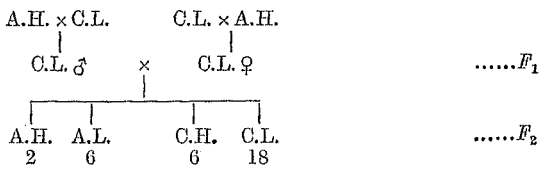


Expectation : Equality.

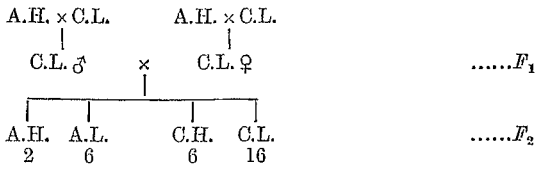
Family H. The crossing of a chocolate coloured mouse possessing a low blood sugar, 78 mg., from family *C* with a piebald chocolate and white, also having a low blood sugar, 80 mg., from family *D* gave a second generation of 47, constituted of 3 albinos with high blood sugars, 118 to 120 mg., 9 albinos with low blood sugars, 78 to 84 mg., 9 coloured animals with high blood sugars, 116 to 120 mg., and 26 coloured with low blood sugars, 74 to 88 mg.



Family J. The mating of two other mice from the same families, *C* and *D*, one a chocolate having a low blood sugar, 82 mg., and the other a chocolate and brown piebald also with a low blood sugar, 80 mg., resulted in a family of 32. Classified according to colour and the sugar content of the fasting blood, these showed 2 albinos with high blood sugars, 116 to 120 mg., 6 albinos with low blood sugars, 78 to 84 mg., 6 coloured with high blood sugars, 113 to 120 mg., and 18 coloured with low blood sugars, 76 to 84 mg.



Family K. In a third experiment with members of families *C* and *D*, a chocolate coloured mouse possessing a low fasting blood sugar, 80 mg., was crossed with a piebald chocolate and white, also showing a low fasting blood sugar, 82 mg., and a second generation of 30 resulted. Two of these were albinos with high blood sugars, 118 to 120 mg., 6 were albinos with low blood sugars, 78 to 84 mg., 6 were coloured and had high blood sugars, 116 to 120 mg., while 16 were coloured but showed low blood sugars, 78 to 88 mg.



Families *H*, *J*, *K* added together give:

	A.H.	A.L.	C.H.	C.L.
	7	21	21	60
where	*6·8*	*20·4*	*20·4*	*61·2*

is the expectation.

The findings obtained with the second generation confirmed the conclusion that hyperglycaemia, like albinism, is a recessive character, for examination of the figures showed that they were in close accord with those required for such a condition by the Mendelian theory. They further demonstrated quite distinctly that, although both hyperglycaemia and albinism are recessive characters, they are genetically independent, as the one is not necessarily associated with the other. It would therefore seem that the factors giving rise to albinism do not include those leading to an abnormally high blood sugar as our original observations suggested might possibly be the case. The numbers moreover dispose of any idea of linkage between the two factors. The association originally noticed must therefore have been an accidental feature of the strains used. It is clearly a matter of considerable interest and importance, however, that a definite chemical abnormality, such as hyperglycaemia, should have been proved experimentally to be transmitted in accordance with Mendel's theory of heredity. Evidence suggesting that certain other abnormalities of metabolism may be transmitted according to Mendel's laws has been collected and published by several observers, but as their investigations have been confined to a study of the family histories of cases presenting such chemical defects the data have necessarily been incomplete.

Bateson[1] and Punnett[2] have pointed out that the incidence of alcaptonuria in human beings suggests that it is a recessive character in the Mendelian sense, and Garrod[3] has collected histories of cases indicating that congenital steatorrhoea, congenital haematoporphyria, pentosuria and cystinuria may be of a similar type.

We wish to acknowledge our indebtedness to Sir F. W. Andrewes for permission to carry out the experimental part of this work in the Pathological Department of St Bartholomew's Hospital, and also to thank Professor Bateson for very kindly revising the proofs of this paper.

[1] *Report of the Evolution Committee of the Royal Society*, 1902, No. 1, p. 133 note.
[2] *Proc. of the Royal Soc. of Med.* 1908, I. Epidem. Sect., p. 148.
[3] *Inborn Errors of Metabolism*, Oxford Med. Publications, 1923.

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