

# HEREDITARY ACHOLURIC JAUNDICE

## in a New Mutant Strain of Rats

C. H. GUNN\*

*Department of Biology and Connaught Laboratories,  
University of Toronto, Canada*

A NEW mutant strain of rats was discovered in 1934 among the breeding stock of the Connaught Laboratory animals. The mutant appears relatively yellow in color owing to an abnormal amount of bile pigment in its system; or in other words it is jaundiced.

In animals other than man there appears to be no record of hereditary jaundice, save that of the rat, in which the icterus (yellow pigmentation) is evident at birth or shortly afterwards and persists throughout the life of the animals. The first indication of a new mutation relates to the observation of three young of a litter of thirteen which had a definite yellow tinge, while both parents were normal in appearance. The original rat stock is of Wistar origin, among which Dr. Helen Dean King has no record of such a mutation.<sup>5</sup>

### Human Jaundice

In man, acholuric jaundice was first accurately described by Minkowski<sup>6</sup> at the beginning of this century. Little was understood of the disease however, until Chauffard<sup>2,3</sup> made the important observation that the red blood cells showed a markedly diminished resistance to hypotonic salt solution and also observed that reticulocytes were usually present in large numbers. Widal<sup>8</sup> was the first to recognize the fundamental haemolytic nature of acholuric jaundice, i. e., that it was caused by an agency which destroyed large numbers of red blood cells.

The human form of this malady is

sometimes divided into a hereditary and an acquired type, of which the former is more common. The first kind belongs to the inheritable diseases, occurring often in several generations, occasionally in several members of one family without the descendants having the condition,<sup>7</sup> and also in a single member of a family who may be affected from birth. As a result of the precedence of the above findings, the hereditary form in man is often alluded to as the Minkowski-Chauffard type, and the acquired form as that of the Hayman-Widal syndrome.

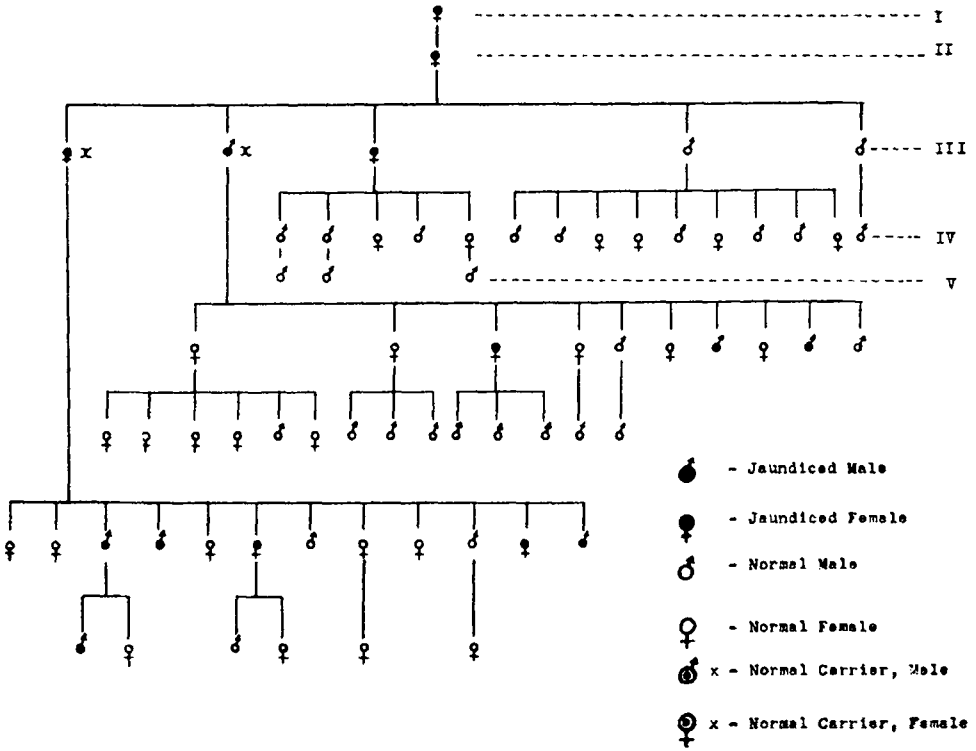
### Definite Inheritance

One of the constant attributes of the rat jaundice is its definite mode of hereditary transmission. Once the jaundiced condition became established, in none of the 249 jaundiced rats which came under observation did any revert to the normal state. An interesting observation however, was that the young with the genetic constitution for jaundice, when born to a normal hybrid mother, were normal at birth and became jaundiced in the course of the next twelve hours or so. Progeny with defective constitutions born to jaundiced dams were yellow at birth.

Reference to data from our rat breeding experiments shows (Table I) that a cross of homozygous normals with jaundiced rats gave rise to hybrid offspring which were definitely normal in appearance. When both parents were jaundiced, however, 100 per cent of the offspring were affected. Normal appear-

---

\*Geneticist at the Dominion Experimental Fox Ranch, Summerside, P.E.I. The author is indebted to Dr. J. W. MacArthur, Professor of Genetics, and to Dr. C. H. Best, Professor of Physiology and Director of the Connaught Laboratories, for aid in the genetical and physiological aspects of the problem.



A PEDIGREE OF JAUNDICE IN MAN

Figure 14

Type of inheritance of jaundice observed in man. Often the defect appears in several consecutive generations, as in dominant inheritance. In other cases several sibs will show the disease, with neither ascendants nor descendants affected, suggesting recessive heredity. After Campbell and Warren.<sup>1</sup>

ing rats (hybrids) mated with jaundiced animals gave rise to mixed litters of normal and jaundiced individuals, in which 113 yellow and 120 normals were produced from 26 litters of such matings, where the expected ratio was 50 per cent normal and 50 per cent jaundiced. Hybrid  $\times$  hybrid matings produced the largest average number per litter, while

the smallest litters resulted from crosses of jaundiced with hybrid animals. Similarly hybrid  $\times$  hybrid matings are significant of a 25 per cent to 75 per cent ratio.\*

**“Carriers” Sub-Normal**

Although the hybrid rats are normal in appearance, 50 per cent of those tested

\*THE CHI-SQUARE TEST FOR GOODNESS OF FIT OF A RATIO

$$\chi^2 = \sum (a - t)^2 / t$$

Theoretical frequency of Hybrid to Hybrid matings, 3 normal : 1 jaundiced.

Normal Appearing Rats	Jaundiced Rats	
132	50	Actual Ratio
136.5	45.5	Theoretical Ratio
- 4.5	+ 4.5	

Then  $\chi^2 = (4.50)^2 / 136.5 + (4.50)^2 / 45.5 = 0.593$

Degrees of freedom for estimating  $\chi^2 = 1$ . For  $\chi^2 = 0.593$ ,  $P = 0.30$  to  $0.50$  and therefore the deviation as observed in the actual ratio would occur in 45 per cent of cases due to chance variation. Thus the actual proportion is a very good fit of a 3 : 1 ratio.

Similarly for a theoretical frequency of normal hybrid rats mated with jaundiced individuals (1 : 1 ratio), for  $\chi^2 = 0.208$ ,  $P = 0.66$  which again is a close fit.

showed an increased fragility of the erythrocytes and a reticulocytosis. These findings parallel those of "human carriers" of acholuric jaundice, who like the normal appearing hybrid rats can transmit the complete syndrome to their progeny. Such a finding indicates the incomplete nature of dominance in human "Familial Acholuric Jaundice."

Campbell and Warner<sup>1</sup> have a record of acholuric jaundice in five generations of a family, in which two latent carriers were included ( $x \times$  Figure 14). The latter, although normal in appearance upon examination were found to have an increased erythrocyte fragility and also to show slight indications of increased blood breakdown beyond that of normal individuals.

Unlike this disease in man the rat jaundice does not respond to splenectomy. Other attempted therapeutic measures were: treatment with liver extract and whole raw liver, injections of hypertonic and anti-haemolysins. While upon other jaundiced rats liver lobectomies were performed subsequent to splenectomy in an attempt to further reduce the reticulo-endothelial tissue beyond that produced by splenectomy.

None of the above measures removed the jaundiced condition of the mutant rats.

A marked lag in growth was found to be a characteristic feature in the majority of mutant rats. Associated with the latter condition was the presence of marked nervous symptoms, such as a "wobbly gait," or partial paralysis, confined chiefly to the hind limbs. This symptom was particularly manifest in jaundiced animals that were markedly underweight. Experimental evidence indicates that the lag in growth and nervous symptoms are associated with an inability on the part of the jaundiced rats to use carotene as a source of vitamin A, and as a result were suffering from

a prolonged vitamin A deficiency.

New evidence was found in this work for the single gene theory of a syndrome. The chain of symptoms constituting the syndrome in the mutant rats, such as fragility of erythrocytes, bilirubinemia, microcytosis, reticulocytosis, splenomegaly, jaundice and anemia, were only pronounced in young growing animals. This chain of symptoms offers opportunity for study of quantitative effect as well as a variety of qualitative variations from the normal state; all of which probably trace back to a fundamental abnormality of the erythrocyte.

Familial acholuric jaundice in man has usually been associated with metabolic derangements such as albinism, pentosuria, glycosuria, etc., of which Gates<sup>4</sup> says, "In all such cases of inborn deranged metabolism the probable cause is the lack of an enzyme in the absence of which a chemical step is missed and some normal metabolic process fails to take place."

### Literature Cited

1. CAMPBELL, J. M. H., and E. C. WARNER. *Quart. Jour. Med.*, 19:333. 1925-26.
2. CHAUFFARD, A. *Semaine Med.*, 27:25. 1907.
3. ————. *Semaine Med.*, 28:49. 1907.
4. GATES, R. R. *Heredity in Man*. Macmillan Co., New York. 1930.
5. KING, H. D., and W. E. CASTLE. *Proc. Nat. Acad. Sci.*, 21:390. 1935.
6. MINKOWSKI, O. *Verhandl. d. deutsh. Kongr. f. inn. Med.*, 18:316. 1900.
7. TILESTON, W. *Medicine* 1:353. Detroit. 1922.
8. WIDAL, F., ABRAMI and M. BRULE. *Presse Med.*, 15:641. 1907.

TABLE 3. MATING OF JAUNDICED RATS

	Genotype		Number		Jaundiced	Normal	Mortality Ratio
	Male	Female	of Litters	of Pups			
1.	nn	nn	0	0	0	0	100%
2.	nn	Nn	14	110	0	113	100%
3.	nn	nn	12	90	80	0	100%
4.	Nn	nn	2	20	13	10	80% - 90%
5.	nn	Nn	23	200	100	100	80% - 90%
6.	Nn	Nn	12	132	80	128	80% - 90%

Nn = Heterozygous Normal Rat, nn = Recessive Rat. (Normal in appearance)  
 80 = Jaundiced Mutant Rat, 0 = Recessive Rat. (Normal in appearance)