pensive and it is very difficult for most people to find the money for return visits of several months. This is where the government should step in. Arthritis and rheumatic diseases are so prevalent and yet there is no legislation passed to help in the diagnosis and treatment of these cases.

SUMMARY

1. Most cases of early rheumatoid arthritis, under one year's duration can be arrested and apparently cured by proper treatment.

2. In later cases, both moderate and severe, the disease may in many instances be brought to rest: further pain and crippling was stopped and some improvement in deformity noted.

3. Rheumatoid hips are sometimes mistaken for osteoarthritic hips, especially when the diagnosis is made by x-ray film alone.

4. Gold is a useful addition to our equipment for fighting rheumatoid arthritis. Good judgment must be used in its employment because of its toxicity.

5. Gold should be given only while the patient is in bed, preferably in an institution where she can be kept under daily, regular supervision.

6. The outlook for chronic arthritis cases is brighter than for almost any other chronic disease.

7. Legislation should be brought in to assist in the hospitalization of these cases. Rheumatoid arthritis is probably the greatest disabling condition with which we have to contend.

How rapidly flies will multiply when conditions are favourable is shown in a report by Dr. J. A. Charles, medical officer of health, Newcastle-upon-Tyne. Following an air raid on a railway goods yard, water used to extinguish the fire made a compost of flour, sugar, and fat which became widely dispersed in the nooks, crannies, and crevices of the buildings and provided an excellent breeding place for flies. "Within 14 days of the fire the whole of the centre of Newcastle was invaded by hordes of *musca domestica*, which were found at distances of as much as half a mile from the central breeding ground. In some houses the plague was so great and the importunity of the insects so persistent that to drink a cup of tea under reasonably hygienic conditions it was necessary to use a straw under cover, or a saucer as an umbrella."—*J. Roy. Inst. Pub. Health & Hyg.*, November, 1943, 7.

HEREDITARY ACHOLURIC JAUNDICE IN THE RAT

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THERE appears to be no record of hereditary jaundice among animals other than man, except in a new mutant strain of albino rats in which jaundice is evident at birth or shortly afterwards and persists throughout the life of the animal (Gunn[3]). This mutation was observed for the first time in the breeding stock of the rat colony of the Connaught Laboratories in 1934. Three young of a litter of thirteen rats, whose parents were apparently normal albino rats, were found to have a definite yellow tinge. The proportion of the litter affected, together with the normal appearance of the parents, suggested the possibility of this being a recessive mutation from two hybrid parents. This stock of rats is of Wistar origin among which Dr. Helen King has no record of such a mutation (King and Castle[4]).

The chief causes of yellow coloration of mammalian skin are those grouped under blood pigments, bile pigments, carotene, melanin, and lipids.

The yellow pigmentation in mutant rats was found to be inherited as a recessive character similar to carotinæmia in rabbits, and as the body fat of both mutant forms was found to be yellow in colour, specific tests were carried out to differentiate the two mutations. Tests for carotinoid pigment in the rats were entirely negative (Palmer[5]), while the van den Bergh test, which is specific for bilirubin, was found to be consistently positive.

Jaundiced rat serum is golden yellow in colour in contrast with the pale, straw-coloured blood serum of normal rats. Differential tests were carried out to determine whether the jaundice was obstructive, toxic, or hæmolytic in origin.

MANIFESTATIONS OF ACHOLURIC JAUNDICE

1. *Absence of bile in the rat urine* (Table I).—Urine was collected from jaundiced and normal adult male rats which were maintained under identical conditions with respect to housing and diet. Tests for the presence of bile were negative in both control and jaundiced animals. Similarly, the urine of hybrid rats,

presenting a normal appearance, was found to be free of bile.

2. *Bile in the rat blood plasma* (Table II).—Van den Bergh tests performed on blood plasma of the jaundiced rats consistently gave a negative direct immediate test and a positive indirect reaction, as seen in Table II.

TABLE I.
TESTS FOR BILE AND UROBILIN IN RAT URINE

No. Rats	*Phenotype*	*Genotype*	*Age (mos.)*	*Sex*	*Av. Bilirubin (blood)*	*Tests*	*Bile*	*Urobilin*
13	Jaundiced	ww	3-9	♂	9.8	11	–	Trace
13	Normal	WW	6-12	♂	0	13	–	Trace
3	Normal	Ww	4	♂	0	3	–	Trace

A few samples of blood plasma gave a positive delayed direct reaction which, as in the indirect van den Bergh test, is suggestive of a hæmolytic type of icterus. Blood plasma of normal rats gave a negative van den Bergh reaction. The amount of bile in the blood of individual jaundiced rats varied from 5.0 to 12.5 van den Bergh units, with an average of 9.8 units for the group of 20 animals. Obstructive jaundice experimentally induced in two normal rats and in one rat with hereditary jaundice gave immediate direct van den Bergh reactions. Hybrid rats, like the homozygous normal animals, gave completely negative tests for bilirubinæmia. The amount of bile in the blood of the jaundiced rats is probably dependent upon the rate of hæmolysis as against the efficiency of excretion by the liver and kidneys.

3. *Erythrocyte fragility* (Table III).—Table III shows that the fragility of 24 normal animals varied between 0.40 and 0.55, expressed in percentage sodium choride solution. In 6% of the mutant rats there was a decreased fragility while the remaining 52% were within the range found in the control animals. Similarly, 5 of the 11 hybrid animals tested, although they were not jaundiced, showed a marked increased fragility of their erythrocytes.

The hybrid rats, like human carriers of familial acholuric jaundice, may show some abnormalities of the blood picture. The blood smear from one such rat (Fig. 1) shows a definite microcytosis. Anæmia and microcytosis

TABLE II.
VAN DEN BERGH TESTS ON RAT PLASMA

Rat No.	*Phenotype*	*Genotype*	*Sex*	*Direct*		*Indirect test*	*Units of bilirubin*	*Age*
				Immediate	*Delayed*			
17	Jaundiced	ww	♂	–	+	+	10.8	3 months
25	"	"	♂	–	–	+	8.0	9 months
48	"	"	♂	–	–	+	11.4	45 days
50	"	"	♀	–	–	+	10.4	45 days
57	"	"	♀	–	–	+	5.0	44 days
74	"	"	♀	–	+	+	12.5	6 months
No. tested								
20	Jaundiced	ww	♀ and ♂	–	±	+	Av. 9.8	All ages
13	Normals	WW	♀ and ♂	–	–	–	0	All ages
5	Normals	Ww	♀ and ♂	–	–	–	0	All ages
2	Normals (Exp. obs.)	WW	♀ and ♂	+				Adults
1	Jaundiced (Exp. obs.)	ww	?	+				

TABLE III.
FRAGILITY OF RAT ERYTHROCYTES TO NaCl SOLUTION

No. tested	*% of animals tested*	*Phenotype*	*% NaCl Solution*										
			0.3	0.35	0.4	0.45	0.5	0.55	0.6	0.65	0.7	0.75	0.8
24	100	Normal (WW)	h	h	hn	hn	hn	hn	n	n	n	n	n
34	41.1	Jaundiced (ww)	h	h	h	h	h	h	hn	hn	hn	hn	hn
	52.9	"	h	h	hn	hn	hn	hn	n	n	n	n	n
	6.0	"	hn	hn	n	n	n	n	n	n	n	n	n
11	45.0	Normal (Ww)	h	h	h	h	h	h	hn	hn	hn	hn	hn
	55.0	"	h	h	hn	hn	hn	hn	n	n	n	n	n

Key: h—hæmolysis; n—negative hæmolysis; hn—beginning of hæmolysis.

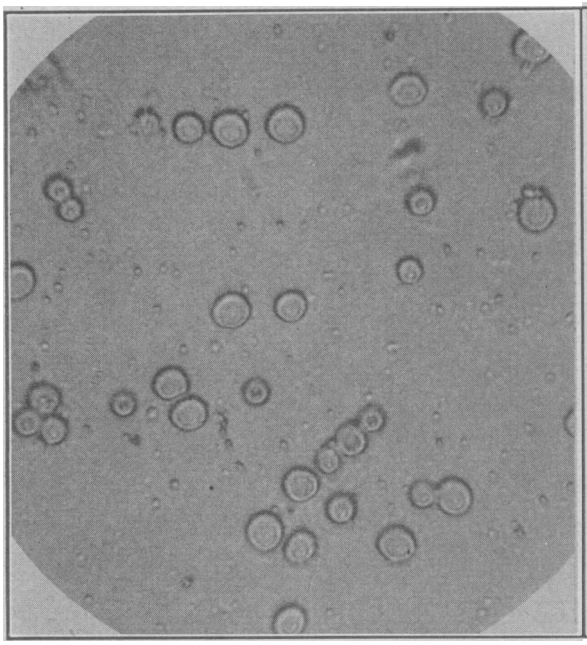


Fig. 1.—Photomicrograph of a blood smear of a hybrid rat showing microcytosis.

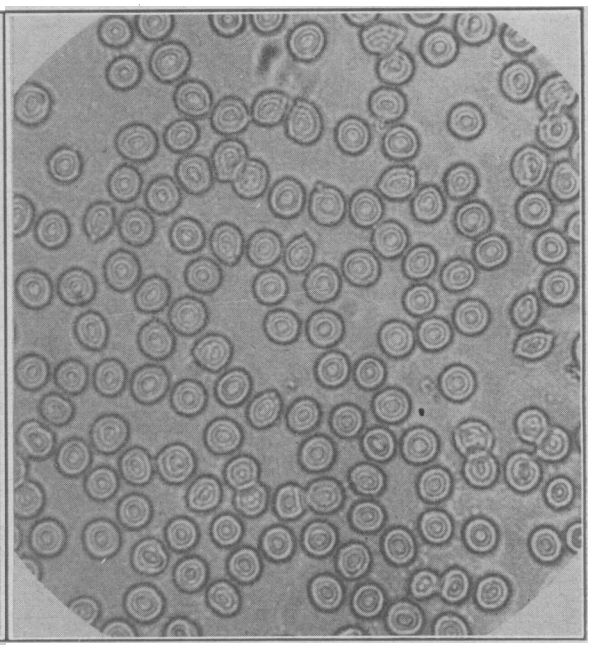


Fig. 2.—Photomicrograph of a blood smear of a normal rat.

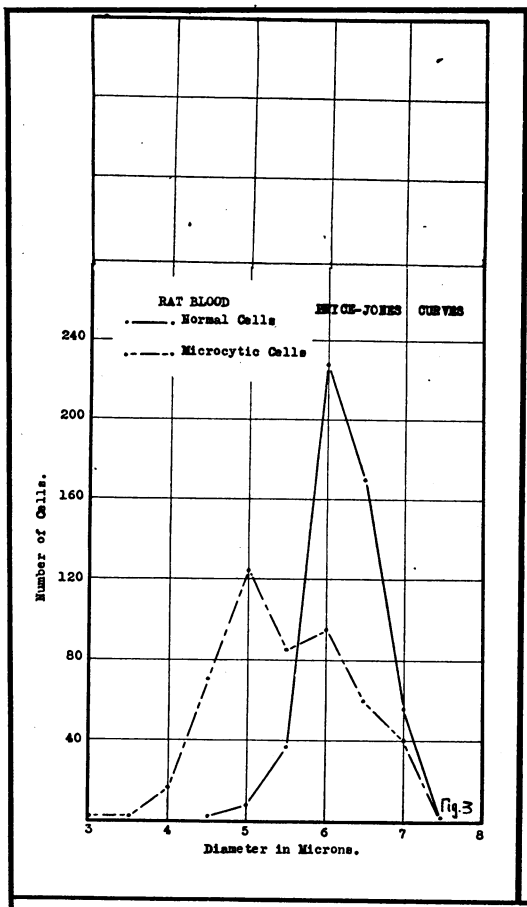
were not frequent findings in the blood picture of adult jaundiced or hybrid rats. When the abnormal blood smear from the hybrid rat is compared with that of a homozygous normal animal (Fig. 2), the uniformity in size of the normal erythrocytes (coefficient of variability of 2.6%) is significantly greater than in the case of the affected rat (coefficient of variability, 14.9%). The Price-Jones frequency curves (Fig. 3), using diameter measurements of 500 erythrocytes from blood of normal and hybrid rats, show the relative distribution of the blood cells of different sizes. The average erythrocyte diameter of the normal rat was 6.2 ± 0.0289 microns, while that of the abnormal animal was 5.0 ± 0.257 microns.

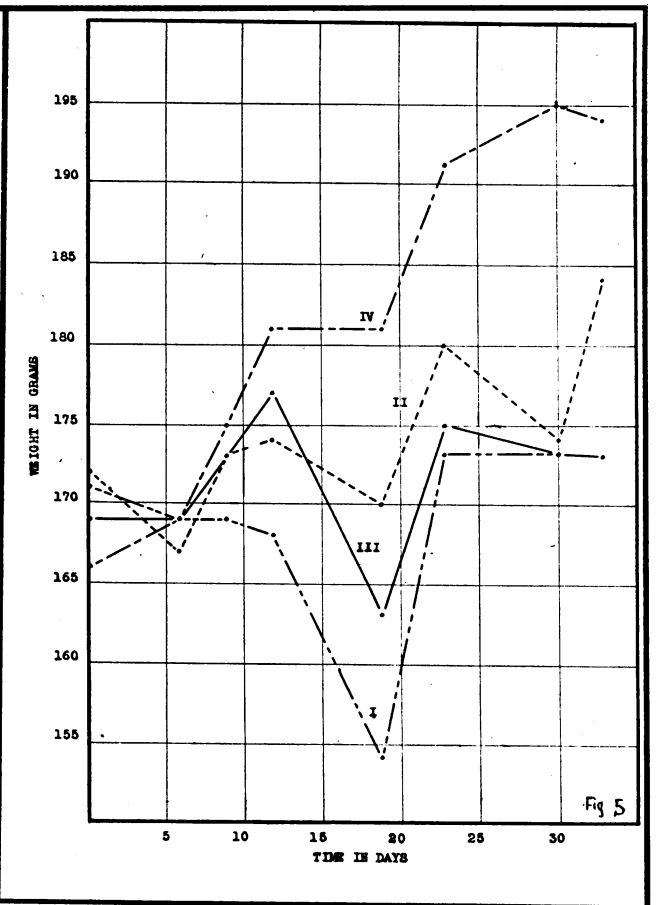
4. *Blood cell counts.*—A study of the blood-cell counts shows certain interesting results, especially in groups of young rats of the same age, sex, and of known genetic constitutions (Table IV). The average erythrocyte count of the normal group was 4.4 million cells, of the

TABLE IV.
RAT BLOOD CELL COUNTS AND HÆMOGLOBIN ESTIMATION

No. Rats	*Sex*	*Phenotype*	*Grams weight*	*Age*	*Red blood cells**	*White blood cells*	*Hæmo-globin*	*Index*	*% Retic.*
							%		
5	♂	Normal (WW)	150	44 days	4,140,000	13,528	85	1.0	3.5
	♂	" "	136	" "	4,690,000	9,432	82	0.9	4.5
	♂	" "	158	" "	3,420,000	11,832	79	1.1	3.0
	♂	" "	156	" "	5,370,000	9,800	86	0.8	2.5
	♂	" "	138	" "	4,280,000	14,132	84	1.0	3.5
5	♂	Jaundiced (ww)	114	" "	4,870,000	13,532	85	0.9	7.0
	♂	" "	141	" "	4,510,000	13,666	81	0.9	18.0
	♂	" "	104	" "	4,100,000	12,666	75	0.9	9.0
	♂	" "	132	45 "	2,840,000	13,200	91	1.6	7.5
	♂	" "	...	" "	3,240,000	12,400	86	1.2	11.0
5	♂	Normal (Ww)	154	" "	3,910,000	10,900	94	1.2	9.5
	♂	" "	136	" "	4,280,000	16,432	93	1.1	11.3
	♂	" "	150	44 "	4,090,000	12,966	77	0.9	11.5
	♂	" "	152	" "	3,750,000	12,332	62	0.8	16.0
	♂	" "	142	" "	4,070,000	12,220	92	1.1	6.5
23	♀ and ♂ 6 17	Normal (WW)	...	Adult	7,170,000	13,920	98	0.7	1.2
14	♀ and ♂ 10 4	Jaundiced (ww)	...	"	7,900,000	12,126	87	0.5	1.7
5	♂	Normal (Ww)	...	"	8,940,000	....	100	0.5	0.65

*Heart blood was used in all estimations.





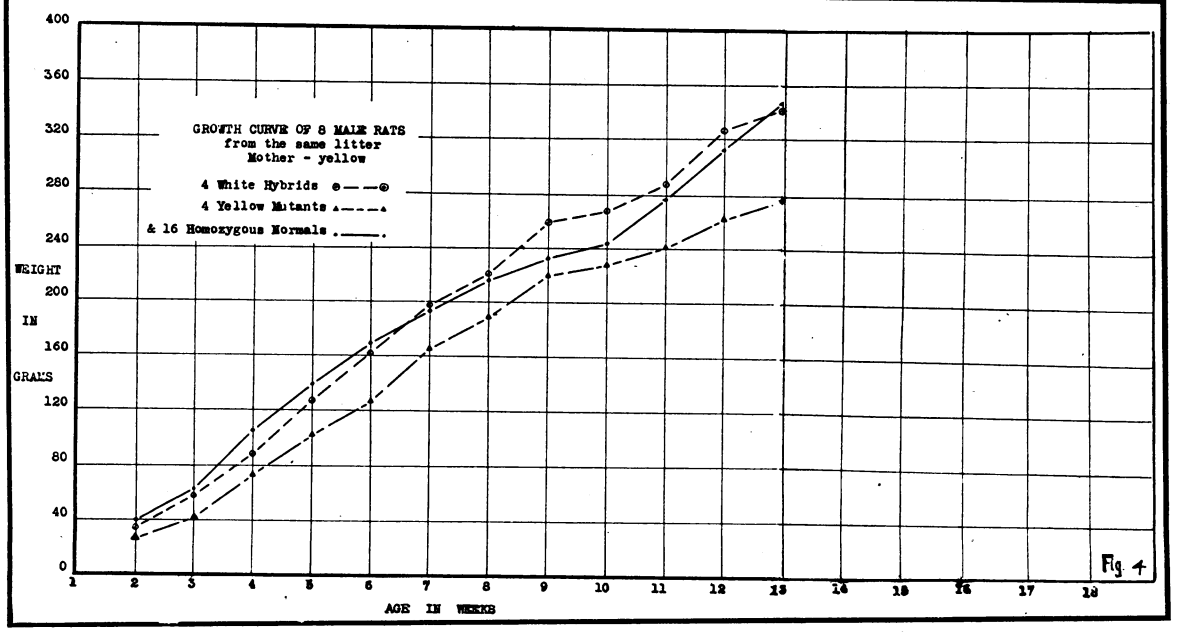


Fig. 3.—Price-Jones curves of normal and microcytic rat erythrocytes. **Fig. 4.**—Growth curves of normal and jaundiced rats. **Fig. 5.**—Carotene as a source of vitamin A in jaundiced and normal rats. Of the jaundiced rats, group I received the basal diet, group II the basal diet plus cod-liver oil and group III the basal diet plus carotene and viosterol. Normal rats (Group IV) received the basal diet plus carotene and viosterol.

jaundiced rats 3.9 and that of the hybrid group 4 million.

Examination of the reticulocyte counts, on the other hand, shows that the average percentage in normal animals is considerably lower than that of the jaundiced and hybrid groups of rats. The average red-cell count of adult hybrid rats slightly exceeds the average count of both normal and jaundiced groups. Coexistent with the high erythrocyte count there is a lower reticulocyte count in the jaundiced group, which probably indicates a more quiescent state of the bone marrow. No significant difference was observed in the white cell counts of the different groups of animals.

In the animals with the higher hæmoglobin indices (1.2 and 1.6) some anæmia appears to be present.

5. *Colour of the fæces.*—The fæces of jaundiced rats were found to be as deeply pigmented as those of normal control animals. There was no evidence of clay-coloured fæces such as occur in obstructive jaundice from faulty absorption of fats. However, the colour of the fæces is not always an accurate indication of the amount of urobilin excreted. In some, but not in all, tests, the amount of urobilin was increased in the excreta of the jaundiced rat over that of normals. Here, probably, as in other symptoms of this disease when remission takes place, the amount of urobilin excreted may also approach that found in normal rats.

6. *Malnutrition of jaundiced rats.*—When the jaundiced rats were being reared it was noticed that they had a slower growth rate than normal litter mates of the same sex suckled by the same dam (Fig. 4). Eight young male animals were selected from a mixed litter of thirteen rats of which the dam was jaundiced and the sire was of normal hybrid constitution. A similar series of weights was recorded for young of the female sex, of which one of the hybrid controls had to be taken from a different litter. In both examples the jaundiced pups showed a definite lag in growth rate (Table V). As a control of possible heterosis in the hybrid male growth curve (Fig. 4), a corresponding curve for 16 homozygous normal males was included. Litters of rats upon which weight tests were carried out were all maintained under similar environmental conditions and fed the same rations in comparable amounts.

Some of the jaundiced rats were very much underweight and resembled animals on a deficient diet. This suggested the idea of determining their ability to utilize carotene as a source of vitamin A, for Greaves and Schmidt[2] have shown that jaundiced rats may not be able to convert carotene into vitamin A. The above investigators used rats in which experimental obstructive jaundice had been induced, but they eliminated the possibility of faulty absorption by injecting the carotene subcutaneously, intravenously, and intraperitoneally, as well as giving it orally.

TABLE V.

Age days	*4 normal hybrids; average weight in grm.*	*4 jaundiced recessives; average weight in grm.*
Birth	6.0	5.5
7	12.0	11.5
10	15.0	13.0
14	22.0	19.0
21	40.0	33.3
28	61.5	51.75
35	88.0	78 5
42	111.75	101.75
49	116.75	112.5
56	133.5	127.5
63	152.25	145.75
70	163.5	150 0
77	176.5	155.5
84	186.5	154.0
91	193.75	171 5
98	203.0	176.5
105	207.0	181.5
112	212.0	186.0

The above weights were obtained from a mixed litter of rats from a cross of a hybrid male with a jaundiced female, of which there were 4 jaundiced and 3 hybrid females in the litter. One hybrid rat of the same age and sex was added to the litter to make up the eight animals. Weighings were made at weekly intervals.

An experiment employing paired feeding was carried out in which 15 jaundiced rats of the same sex and weight were divided into three groups of five. One group was given a Sherman vitamin A deficient diet of:

Casein	18%	
Yeast	8%	
Starch	65%	
Salt mixture	4%	(Cowgill)
Vegetable oil	5%	(corn oil)

The second group was given the same diet and cod-liver oil as the source of vitamin A. The third group was given the basal diet plus carotene, and viosterol was added to supply approximately the same amount of vitamin D as group II received. To make sure that the diet received by group III was adequate, five normal rats (group IV) of the same weight and sex were fed this diet along with the five jaundiced rats.

The results of the experiment as judged by the average weight changes for the different

groups (Fig. 5) suggest that the normal rats did relatively well on the carotene diet, while the jaundiced animals grew poorly and at the termination of the experiment were in a condition comparable to that of the rats in the group not receiving any vitamin A in the diet; however, these rats did not develop carotinæmia. Those which received cod-liver oil, although not so heavy as normal rats, appeared to be in relatively good condition. This was in contrast with the animals of groups I and III which not only lost weight but showed marked nervous symptoms. The method of paired feeding used in the experiment ensured that each group of rats consumed the same quantity of food.

7. *Nervous phenomena of jaundiced rats.*— While the stock of jaundiced rats was being reared on a diet of "Purina Chow", in which the main source of vitamin A is in the form of carotene, some of the rats developed marked nervous symptoms. This condition was noted particularly in animals which were very much underweight. The affected animals appear to have a weakness of the posterior extremities which gives them a wobbly gait. A marked lateral eversion of the hind feet is a characteristic feature in the walking movements of the jaundiced rats. A more detailed comparison of these two male rats, which are from the same litter, is given in Table VI.

These nervous symptoms of the jaundiced rats are remarkably similar to those found in normal rats which have been reared on a vitamin A deficient diet (Aberle[1]). Prolonged feeding of a diet deficient in vitamin A has been shown to give rise to a condition of weakness and paralysis of the hind limbs in normal rats which is accompanied by a characteristic lateral eversion of the hind feet when walking.

Examination of sections of spinal cord and of peripheral nerves from three jaundiced animals in which the nervous symptoms were particularly evident, revealed no gross lesions which might account for the symptoms. The microtechnical procedure consisted of formalin fixation, followed by Weil's method for staining myelin sheaths, Scharlach R, hæmatoxylin and eosin, and Marchi's method.

8. *Hereditary nature of rat jaundice.* — The data from rat-breeding experiments show that the jaundiced condition is inherited as a non-sex-linked recessive character (Gunn[3]).

9. *Polyuria.* — The mutant jaundiced rats showed a marked polyuria. The volume of urine excreted was ten times that of normal control rats in some cases. The results of tests for sugar and ketones were similar to those found in urine of normal rats. Two jaundiced rats were given repeated subcutaneous injections of 0.5 c.c. of posterior pituitary extract in an attempt to stop the polyuria. Negative results were obtained.

The data of Table VII show that there is a real difference in the liver fat (per 100 grams of weight) between the sexes, but not between normal and jaundiced animals.

TABLE VI.

	Normal rat	*Nervous rat (jaundiced)*
Age	21 day	21 days
Sex	Male	Male
Genotype	Hybrid	Recessive (homozygous)
Jaundice	Negative	Positive
Erythrocyte count	4.2 million	3.8 million
Red blood cell fragility	0.45 (normal)	0.75 (increased)
Reticulocytes	9.6 %	39.1% (count of 500 red blood cells)
Hæmoglobin	69	73
Hæmoglobin index	0.8	0.95
Sections of cord and brain	Normal	Normal (Marchi and Weigert-Pal)
Sections of spleen	Normal	Congested with red blood cells
Sections of liver	Normal	Normal (Cinnamon-coloured liver)
Section of kidney	Normal	Normal (Cinnamon-coloured kidney)

TABLE VII.

LIVER FAT

	Mgm. % Liver fat	
Sex	*Normal*	*Jaundiced*
Female	3.71	4.04
Male	6.54 7.29	6.79 6.12

Blood-urea estimations were made upon 6 normal and 6 jaundiced animals of the same sex. The results are expressed in milligrams per 100 c.c. of blood as in Table VIII. Tests were carried out upon 4 normal and 4 jaundiced animals while upon a diet of Purina Chow, and also on animals which had been fasted 24 hours. The data show a marked difference between the blood urea estimations in animals which were fed and those which were deprived of food for 24 hours previous to the tests, but there is no

TABLE VIII.

	Blood urea	
Rat number	*Normal*	*Jaundiced*
	mgm. %	*mgm. %*
1	23.8*	29.2
2	25.4	22.0
3	22.0	24.5
4	24.0*	28.0*
5	15.5†	13.5†
6	13.5†	12.5

*Estimations made on rats on Purina Chow diet.
†Estimations made on rats fasted 24 hours.

significant difference between the quantities of blood urea of jaundiced and normal animals.

Attempted therapeutic measures on jaundiced rats. — Splenectomies were performed on 10 jaundiced rats of about 3 months of age. All survived the operation and were still jaundiced at the end of 6 weeks. The rat condition differs in this respect from human acholuric jaundice. The results of the above experiment suggested the possibility that adequate reticulo-endothelial tissue had not been removed by splenectomy in the case of the rats. Liver lobectomies, therefore, were performed upon 3 jaundiced animals of 200 grams weight which had previously undergone splenectomy. Portions of liver weighing 1.6, 1.4 and 1 gram were removed from three rats of which the average total liver weight was 10 grams. Examination of these animals 30 days later showed that the jaundiced condition was still present. Definitely enlarged spleens were found in approximately 20% of the young jaundiced rats which were examined at autopsy and others in which splenectomies were performed. However, examination of biological sections of 7 spleens taken from jaundiced animals showed no qualitative differences from those of normal animals, except that they were engorged with erythrocytes and the reticulo-endothelial cells were filled with breakdown products of blood.

DISCUSSION

The findings on jaundiced rats can be separated into those which are persistent throughout the life of these animals, and others which are more or less transitory, or more apparent at certain ages than at others.

The more constant findings in the affected rats are: a definite non sex-linked recessive inheritance of the jaundiced condition; an absence of bile in the urine; a persistent bilirubinæmia throughout the life of these animals; a consistently negative immediate direct van den Bergh reaction, and a lag in growth rate.

In 20 litters, comprising 135 rats, resulting from crosses of normal with jaundiced parents, none of the offspring was affected, whereas 86 jaundiced and no normal young were produced from matings in which both parents were mutants. Of 249 jaundiced rats reared none reverted to the normal state. The bilirubinæmia persisted throughout the life of these animals.

Blood plasma of jaundiced rats consistently gave indirect or delayed van den Bergh tests. However, direct immediate tests were obtained by ligating the bile ducts in normal and jaundiced animals.

A definite lag in growth rate was a characteristic finding in the mutant rats. This was evident in both sexes and occurred in young with the jaundiced constitution, whether they were reared by jaundiced or by normal mothers.

Tests for bilirubin and urobilin in the urine of mutant rats gave results similar to those of normal animals. A marked polyuria of unknown etiology was present, however, in the jaundiced rats.

Among the inconstant signs in the mutant rats were: increased fragility of the erthrocytes, microcytosis, reticulocytosis, anæmia, splenomegaly and nervous symptoms.

The abnormal findings in the blood of the jaundiced rats were seen only in young growing animals of 3 to 8 weeks of age. Many of the mutant rats died during this period, but others which survived to the adult state appeared to be healthy, except for a persistent bilirubinæmia. Such adults were usually fertile and raised young.

Definite splenic enlargement was observed in some young mutant rats. Histological sections, however, showed no qualitative differences from those of normal animals, but many erythrocytes were present and the reticulo-endothelial cells were filled with yellow pigment. Splenectomies did not alleviate the jaundiced condition of the mutant rats, thus apparently differentiating this disease from familial acholuric jaundice in man.

Muscular tremors and a wobbly gait were observed in some of the jaundiced rats. These symptoms could be detected in young rats of 3 weeks of age and they usually persisted throughout the life of such animals. However, it was found that the above nervous symptoms could be induced in jaundiced rats by feeding a diet

deficient in vitamin A or one in which carotene was the source of this accessory factor.

The chain of symptoms described in this work may vary widely, and the different symptoms may appear to have no relationship to each other. Nevertheless, by breeding experiments, the fundamental origin of the abnormal constitution of the affected animals can be shown to have its starting point in but one pair of defective hereditary carriers or genes. These were derived from the germ plasm of the original mutant rat.

SUMMARY

1. A new mutant jaundiced rat has been found among the rats of the breeding colony in the Connaught Laboratories.

2. The mutant rats regularly show bilirubinæmia (indirect van den Bergh reaction), jaundice, acholuria, polyuria and subnormal growth rate. They occasionally show changed erythrocyte fragility, microcytosis, reticulocytosis, and nervous symptoms.

3. Splenectomy does not alleviate the jaundiced condition of the mutant rats.

The author wishes to thank the Connaught Laboratories for the plentiful supply of experimental animals, among whose animal colonies the new mutant strain of rats was found, and also for the opportunity to carry out this work in that institution.

He is also greatly indebted to Dr. J. W. MacArthur, under whose supervision the work for the degree of Doctor of Philosophy was done in the field of genetics of which this paper is a part, and to Dr. N. Ford for a moving picture film of the rats.

Appreciation is also expressed to Dr. E. W. McHenry, and especially to Dr. C. H. Best of the Connaught Laboratories, for valuable suggestions on the physiological aspects of the problem and for the many facilities placed at the disposal of the writer.

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"Increased employment and incomes for large sections of the population have resulted in consumption of more of the protective foods by many persons who previously could not afford these foods. One effect of this has been to create shortages, notably of meat and butter. This experience has demonstrated for all time that the supposed surpluses of foods in the years before the war were not surpluses at all, but relative deficits that were masked by inequality of distribution."—Russel M. Wilder, *New Eng. J. Med.*, 1943, **229**: 496.

ANTISYPHILITIC THERAPY WITH CLORARSEN WITH EVALUATION OF TOLERANCE*

By Frederick Kalz, M.D., L. P. Ereaux, M.D., Hope Prichard, and Barbara Dean

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THE mechanism by which the arsphenamines destroy spirochætes has been the subject of considerable controversy. Ehrlich believed that these drugs were directly spirochæticidal, a view which has been modified by later authors, whose investigations have demonstrated that the arsphenamines must first be converted to a partially oxidized product before a spirochæticidal action is noted. Since Eagle's investigations,[1] in which he tested the spirochæticidal action of arsphenamine under anaerobic conditions and found it negligible when dissolved in an atmosphere of nitrogen, this latter view has been generally accepted. Therefore, it seems rational to use such an oxidized product as an antisyphilitic drug.

The term arsenoxide, not scientifically correct, is used in clinical literature to designate a particular oxidation product of the arsphenamines (meta-amino parahydroxyphenylarsine oxide). This compound was first investigated by Ehrlich and Hata,[2] and then, after careful clinical and laboratory research, by Tatum and Cooper,[3] it was introduced for general use under the trade name of mapharsen. It is now generally recognized and is probably the most widely used of all the arsenicals. The advantages of such a drug may be listed as follows: (1) it is a pure and stable chemical substance; (2) it can be chemically standardized without complicated procedures; (3) it requires no special precautions in storage, in preparation or administration. Solutions may be prepared in advance, may be kept without changes for hours and may be injected rapidly. On the other hand, the neoarsphenamines are unstable colloids and different lots may vary considerably in therapeutic effect and toxicity. Both effect and toxicity can only be measured by biological methods, as chemical standardization is impractical and deterioration may occur in the ampoule or in solution without being noticeable. These drugs must not be older than six months, must be kept cool and in a dark place, and in-

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