volved are the bones (ribs and vertebræ), lungs, kidneys, liver and pleuræ, in that order. In the case reported here no metastases were found.

On account of the varied histological characters many terms have been applied to these sarcomata of the prostate, *e.g.*, spindle-cell, round-cell, mixed-cell, myxosarcoma, rhabdomyosarcoma, etc. This is partly due, as in the above case, to the very complex cell-picture present, the histology varying in sections from different parts of the tumour. In the present instance myxomatous change predominated in some sections, in others spindle-cells, and in still others marked pleomorphism of the cells. It was only by a close study of many sections that the true diagnosis was reached. It is thus essential that a number of blocks be examined from different parts of the tumour. The presence of large bundles of cells with strongly eosinophilic, rather elongated, cytoplasm is suggestive of a rhabdomyosarcoma, but for a definite diagnosis to be made cross striations must be demonstrated. This is especially difficult in undifferentiated tumours, such as the one reported, where the striated myoblasts were seen in only one of the many sections examined.

TREATMENT

Because of the very malignant nature of these neoplasms the clinician rarely sees the patient sufficiently early for radical surgery, *i.e.*, total prostatectomy, to be of benefit, although surgical intervention is indicated in the treatment of the urinary obstruction and its complications, so often present. Gilbert, who reviewed the literature to determine the value of radiation methods in treating this disease, states that the use of vigorous radium and deep x-ray therapy gives a slight degree of clinical control in some cases; several have been reported living from two to six years following this type of treatment in patients over 40 years of age. The majority, however, merely show a temporary improvement.

My thanks are due to Mr. G. Stevenson for permission to use his clinical records, and to Professor J. W. S. Blacklock for his kindness in helping me with the preparation of the paper.

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HEREDITARY JAUNDICE IN THE RAT

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THE jaundiced rats described in this paper first occurred as a mutation in the stock of Wistar albino rats in the Connaught Laboratories in Toronto. Gunn,[1] who discovered them, showed the subsequent inheritance of the jaundice to be of Mendelian recessive character. The jaundice occurs in the expected ratio in a significant number of mixed matings, and when both parents are jaundiced all the offspring are jaundiced. Because of the hereditary nature of the disease and the fact that the bilirubin in the serum is invariably of the indirect type, Gunn suggested an analogy with hereditary hæmolytic jaundice in the human subject. This was further supported by his finding of an increased fragility of the red cells in hypotonic saline. This observation we were unable to confirm and the investigation outlined in this paper finally resolved itself into an attempt to discover the cause of the jaundice. With this end in view the possibilities of the jaundice being caused by an excessive destruction of red cells or by an impairment of bilirubin excretion were investigated in order.

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RESULTS

Blood picture.—Table I shows the blood picture of 20 normal and 20 jaundiced rats weighing between 200 and 250 grams, fed on a diet of purina biscuits, supplemented once weekly with lettuce and carrots. To save space, only the mean of the normals is shown. The rats

were free from infection, and had not been bled for other purposes for at least a month previously. Under these conditions the hæmoglobin level, red cell counts, and hæmatocrit readings on the normal control rats are about 10 per cent lower than those reported by Higgins and Stasney[2] for normal rats. All but four of the jaundiced rats show an anæmia and an accompanying reticulocytosis when compared with the normal controls.

TABLE I.

HÆMOGRAMS OF JAUNDICED RATS AND NORMAL CONTROLS

Hgb.	*R.B.C.*	*C.I.*	*Retic.*	*Ht.*	*M.C.V.*	*W.B.C.*	*Bili-rubin*
gm. %	10^3/mm.^{3}		%	%			mg.%
			NORMAL RATS				
16.0	8,200	62	3	45	55	15,000	0
			JAUNDICED RATS				
15.1	8,400	58	6	48	57	15,500	4.5
14.1	7,650	59	9	47	61	17,000	5.0
16.5	9,240	57	2	47	51	13,200	5.0
15.3	8,600	57	8	46	56	12,800	6.2
15.6	8,550	58	6	48	54	16,000	7.0
14.5	7,270	64	11	41	56	11,430	6.3
14.8	6,100	78	13	38	62	16,800	6.1
15.4	7,530	65	10	45	59	8,800	5.9
14.2	5,750	78	17	40	69	10,000	7.0
15.4	6,890	70	9	45	65	15,200	5.3
14.2	8,260	55	12	39	47	12,300	6.2
14.2	7,720	59	10	39	51	11,780	7.5
14.0	7,870	57	15	43	54	17,900	6.2
14.0	6,665	67	11	38	55	11,000	7.2
15.6	8,200	64	6	46	56	17,000	7.1
16.0	8,200	62	4	45	55	13,340	4.8
15.6	8,550	59	3	48	56	12,900	6.2
13.8	5,890	75	14	40	68	16,200	6.7
15.8	8,000	63	2	46	57	14,000	5.9
16.0	8,400	61	3	48	57	15,500	6.1

Hgb.; hæmoglobin, determined by the method of Evelyn.[6] R.B.C., red blood cells. C.I., colour index. Retic., percentage of reticulocytes in 500 red blood cells, by brilliant cres 1 blue, dry mount technique. Ht., hæmatocrit. M.C.V., mean corpuscular volume. W.B.C., white blood cells. Bilirubin, determined by a micro modification of the method of Malloy and Evelyn.[7]

The lowest recorded hæmoglobin level is 13.8 grams per cent and the highest reticulocyte count is 17 per cent. On the whole, it can be seen that the degree of reticulocytosis bears a fairly close relationship to the degree of anæmia. No significant deviation from normal is seen in the colour-index, the mean corpuscular volume, or in the number of white cells. Bilirubin levels of 4.5 to 7.5 mg. per 100 c.c. of plasma are observed but no obvious correlation can be seen between the degree of anæmia and the degree of bilirubinæmia. The bilirubin is invariably indirect in type.

Measurement of the diameter of the red cells revealed no significant difference between the normal and the jaundiced rats.

Red cell hæmolysis. — No difference in the fragility of the red cells in hypotonic saline was detected between the normal and the jaundiced rats. When the cells were suspended in hypertonic saline followed by dilution in water, according to the method of Murray,[3] the cells from normal and jaundiced rats again behaved in an identical manner. No difference in the rate of hæmolysis with staphylococcus toxins α and β could be detected.

Curves A and B, Chart 1, show the increased resistance of washed red cells of jaundiced rats towards hæmolysis by saponin when compared with the washed red cells of normal rats. Curves C and E show the protective action which normal rats' serum exerts in saponin hæmolysis and curves D and F show the even greater protection afforded by jaundiced rats' serum.

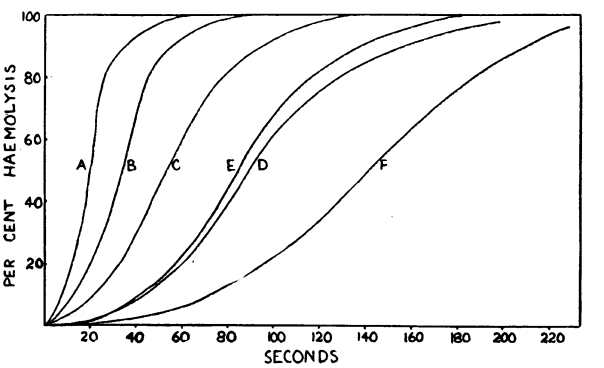

Chart 1.—Hæmolysis with saponin. A saponin concentration of 1/10,000 was used in each experiment. The rate of hæmolysis was determined on the Evelyn photoelectric colorimeter with filter 660, at which wavelength hæmoglobin does not interfere. A, normal red cells. B, jaundiced red cells. C, normal red cells with normal serum. D, normal red cells with jaundiced serum. E, jaundiced red cells with normal serum. F, jaundiced red cells with jaundiced serum.

Splenectomy.—Gunn[1, 4] reported that splenectomy performed on bartonella-free jaundiced rats did not cure the jaundice. Our attempt to confirm his observation on eight jaundiced rats resulted invariably in the death of the animal from bartonella infection within four or five days after the operation.

Post-mortem examination. — Autopsies performed on the jaundiced rats revealed a marked yellow tint of the skin and connective tissue. The muscles, lymph nodes, stomach, intestine, pancreas, heart and lungs, and the adrenal, parathyroid and pituitary glands were normal in appearance, except for a slight icteroid tint,

much less marked than in the skin. The liver and kidneys were dark in colour but otherwise appeared normal. The spleen was also dark and distinctly smaller than normal. Marked deposition of an almost black pigment was seen in the thyroid and in Harder's gland. The distribution of the bone-marrow was normal, being present in all the long bones except the radius and ulna. The bone-marrow was of ordinary greyish-red colour, not fatty, and not obviously hyperplastic. On microscopic examination no divergence from the normal was detected in the liver, spleen, or bone marrow, either in fixed preparations stained with hæmatoxylin and eosin or in the fresh tissue stained supravitally.

Since no direct evidence emerged from the above observations which pointed to a hæmolytic process being responsible for the jaundice, attention was directed to the ability of the rats to excrete bilirubin.

Bilirubin injection.—Chart 2 shows the result of injecting 1 mg. of bilirubin into normal and jaundiced rats. It can be seen that the jaundiced rats are unable to excrete bilirubin at the normal rate. In fact the curves of bilirubin retention in the jaundiced rats bear a close resemblance to those obtained from rats in which excretion had been made impossible by tying the bile duct or removing the liver just prior to injection. This result provides the first real clue to the cause of jaundice in the jaundiced rat.

In experimental bilirubin retention in the normal rat, produced by tying the bile duct, part of the injected bilirubin appears as direct bilirubin in the serum, shown in heavy shading in Chart 2. This does not occur in the hepatectomized rat nor in the jaundiced rat, which leads to the conclusion that some abnormality of the liver of the jaundiced rat prevents direct bilirubin formation. This is suggestive as a second possible clue to the cause of jaundice in the jaundiced rats. Since only direct bilirubin is found in urine and in fresh bile it seems logical to assume that its adequate formation is an essential precursor to bilirubin excretion. Hence its inadequate formation by the liver of the jaundiced rat may be the cause of bilirubin retention in these animals.

Bile duct occlusion.—The experiment shown in Chart 3 was designed as a further test of the ability of the jaundiced rats to make direct bilirubin. By tying the bile ducts a true obstructive jaundice was produced in normal and in jaundiced rats. In the normal rats the picture is one of classical obstructive jaundice in which the accumulation of direct bilirubin predominates

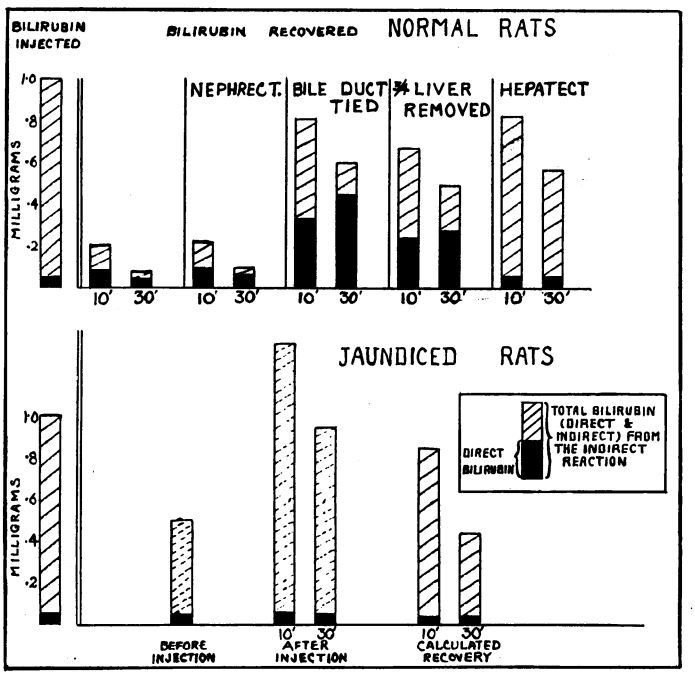

Chart 2

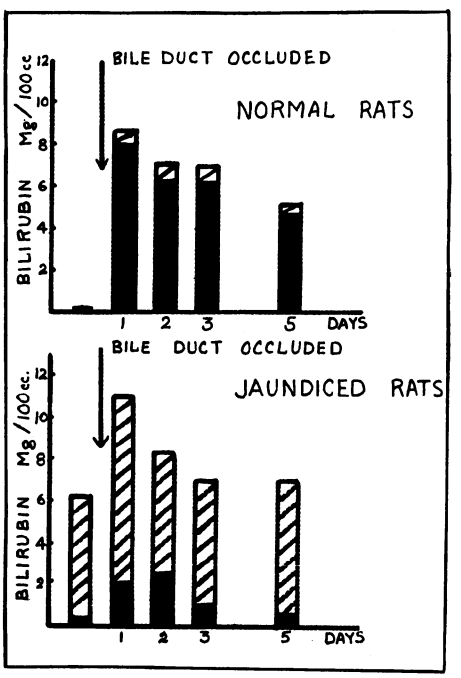

Chart 3

Chart 2.—Recovery of injected bilirubin. Bilirubin determinations (7) were done on plasma drawn in 10 and 30 minutes after injection. The total recovery was calculated from the plasma volume, assuming a 200 gram rat to have a plasma volume of 10 c.c. The operations on the normal rats were performed immediately preceding the injection. Light ether anæsthesia was used throughout. **Chart 3.**—Bile-duct occlusion.

over indirect bilirubin. In the jaundiced rats much less direct bilirubin is formed and the blood bilirubin picture remains largely indirect in type. Some direct bilirubin is however formed, showing that the jaundiced rats are not entirely deficient in their ability to make direct bilirubin. These experiments thus provide supporting evidence for the cause of jaundice in the rats suggested by the results of the bilirubin injection experiment.

The experiments are of further interest in that they demonstrate the failure of the bilirubin reaction as an aid to clinical diagnosis in the special case of the jaundiced rats. Even when the bile duct is tied the serum bilirubin remains largely indirect in type.

Bile pigment excretion. — Investigation of existing methods for urobilinogen and urobilin has revealed that they are even more unreliable than has been previously considered, and for this reason the actual figures obtained have not been considered sufficiently accurate to report. Qualitatively, whether the stool urobilin was measured as urobilin or as urobilinogen, the results would indicate that less appears in the stool of the jaundiced rats than in the stool of the normal rats. It does not appear to be entirely absent in the stool of the jaundiced rats.

Liver function tests.—The abnormal findings in the bilirubin liver function test have already been reported. The plasma prothrombin level was normal in the jaundiced rats, both normal and jaundiced rats' plasma clotting in an average of 14 seconds when tested by the method of Quick.[5] The Takata-Ara test was negative. Brom-sulphonphthalein excretion was normal, the injection of 5 mg. resulting in the retention of 5 to 10 per cent of the dye in 10 minutes and less than 2 per cent in 30 minutes in both normal and jaundiced rats.

SUMMARY

1. The problem of hereditary jaundice in the rat was investigated by searching for evidence of a possible hæmolytic process or of a possible impairment of bilirubin excretion.

2. Indirect evidence of a hæmolytic process was the fact that the bilirubin in the serum is invariably indirect in type. From the blood picture, red-cell fragility determinations, and post-mortem examinations no direct evidence of a hæmolytic process sufficient to explain the jaundice was obtained. An unexplained slight anæmia is usually present which is not directly related to the amount of bilirubin in the serum. The fragility of the red cells in hypo- and hypertonic saline is normal, and in saponin the red cells show increased resistance. The serum of jaundiced rats was more protective towards saponin hæmolysis than normal rats' serum. No evidence of marked bone-marrow or splenic hyperactivity was found. The spleen is smaller than normal.

3. Intravenous injection of bilirubin revealed a marked impairment of bilirubin excretion. In experimental bilirubin retention in normal rats, direct bilirubin was formed from the injected bilirubin. This did not occur in hepatectomized rats nor in the jaundiced rats.

4. Tying the bile ducts of the jaundiced rats further revealed the abnormality in direct bilirubin formation. The serum bilirubin remained largely indirect in type in spite of the imposed acute obstruction.

5. Urobilin excretion in the stool was less than normal but not entirely absent.

6. Brom-sulphonphthalein and Takata-Ara liver function tests were normal. Plasma prothrombin was normal.

7. It is concluded that the jaundiced rats have a retention jaundice which the evidence would suggest is caused by an inability of the liver to make direct bilirubin at a rate sufficient for normal excretion.

8. Attention is directed to the failure of the bilirubin reaction as an aid to clinical diagnosis in the special case of the jaundiced rats.

9. It is suggested that the jaundiced rats present a close resemblance to the cases of familial jaundice in human beings found by Damashek.[8]

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