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LIVER DAMAGE IN THYROTOXICOSIS WITH SPECIAL REFERENCE TO THE RESULTS OF LIVER FUNCTION TESTS IN PATIENTS TREATED WITH THIOURACIL.

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It has been recognised for some considerable time that there is a special tendency for hepatic damage to occur in the course of thyrotoxicosis. Cameron and Karunaratne (1935) in an extensive review of the pathological evidence give pride of place to Paul who, in 1865, reported a case of cirrhosis of the liver in association with exophthalmic goitre. The most outstanding clinical evidence of hepatic damage has been the appearance of jaundice in the course of the disease, this having been recorded by Habersohn (1874), Burton (1888), Sutcliffe (1898) and Eder (1906) amongst others. Lichtman (1941) has emphasized that in patients with hyperthyroidism who show icterus, an unrelated cause should always be excluded. Extensive autopsy studies of the liver in hyperthyroidism have been made over the last twenty years and these have revealed a high incidence of hepatic lesions (Weller, 1930; Beaver & Pemberton, 1933; Foss, Hunt & McMillan, 1939; Schaffer, 1940; Wyndham, 1940; Moschowitz, 1946). Lesions of both acute and chronic type have been described, the former, consisting of fatty changes and of central and focal necrosis of varying degree, the latter, of atrophy and of chronic lesions of the cirrhotic type. In these studies care has been taken to exclude cases in which apparently independent hepatic disease or other anatomic findings might have been considered factors in the production of the hepatic lesions.

Impairment of hepatic function has been noted by several observers using different liver function tests: the phenoltetrachlorophthalein test (Youmans & Warfield, 1926); the cincophen oxidation test (Lichtman, 1932); bromsulphalein dye excretion (Maddock, Coller & Pedersen, 1937); oral galactose tolerance tests (Maclagan & Rundle, 1940), although Althausen, Lockhart and Soley (1940) and Barnes and King (1943) were of the opinion that impairment of galactose tolerance was due mainly to acceleration of absorption of galactose from the bowel; the Takata-Ara

reaction (Ragins, 1935 ; Piper & Poulsen, 1947) ; oral hippuric acid test (Bartels, 1938 ; Boyce & McFetridge, 1938 ; Schmidt, Walsh & Chevsky, 1941 ; Haines, Magath & Power, 1941) ; plasma prothrombin (Lord & Andrus, 1941) ; serum phosphatase (Longo & Lopez, 1945 ; Piper & Poulsen, 1947 ; Goodwin, 1948) ; plasma albumin and Hanger's cephalin cholesterol flocculation test (Longo & Lopez, 1945).

No general agreement has been reached by these various observers regarding the incidence of hepatic impairment in this disease. Bartels (1938) found 85% showing impairment, while Longo and Lopez (1945) found only 36% using oral hippuric acid tests. Piper and Poulsen (1947), as a result of an investigation using liver function tests and aspiration biopsy in fifteen cases, came to the conclusion that in the majority of cases of thyrotoxicosis the functional capacity of the liver is impaired only to a slight extent and that if the liver becomes the site of anatomic changes these are so slight and few that they cannot be detected by aspiration biopsy in spite of the fact that the changes are supposed to be most marked in the subcapsular area from which the biopsy material is obtained. A considerable difference of opinion also exists regarding the relationship which the impairment of function bears to the severity of the disease. Some investigators have noted a general relationship to the basal metabolic rate, others have described a relationship to the loss of weight and still others have failed to demonstrate any relationship to the severity of the disease as judged by any one criterion. In the same way it can be said that no definite relationship between impairment of liver function and age, sex, duration of the diseases or type of thyrotoxicosis has been established. The effect of treatment on the liver function is also in dispute. Some observers have noted improvement on iodine therapy ; others have failed to do so. There is, however, considerable evidence that a return to normal or marked improvement occurs following thyroidectomy, although function is further impaired in the immediate postoperative period.

The mechanism of production of the hepatic damage which occurs in this disease has been the subject of much speculation. Eder (1906) has suggested that jaundice arising in the course of exophthalmic goitre might have arisen from some chronic toxæmia in the intestines and have a cause in common with the goitre. Since Cramer and Krause (1913) demonstrated that if rats were fed on fresh thyroid gland the glycogen content of the liver fell so low that it could not be estimated gravimetrically it has frequently been suggested that the liver damage is related to the low glycogen content of the organ. Opie and Alford (1914) noted that a good glycogen content protected the liver against chloroform and various toxins. However, Davis and Whipple (1919) found that thyroid feeding had no influence on liver injury following chloroform anaesthesia. Goodpasture (1921) confirmed these findings but noted that

there was increased susceptibility to liver damage after thyroid feeding if the chloroform were administered subcutaneously. That infection was of some importance in determining the hepatic lesions was put forward by Haban (cited by McIver, 1942) and experimental evidence of Sealy, (1941, 1942) supports this theory. McIver and Winter (1942) have drawn attention to the importance of anoxia. They subjected hyperthyroid animals to artificial atmospheres of low oxygen content and found that degenerative changes appeared in the liver varying from slight changes when the period of exposure was short to intense degeneration when the anoxia was prolonged. Maddock, Collier and Pedersen (1937) have attributed the further impairment of function found in the immediate postoperative period to an increase in the epinephrine in the blood. Trauma and anaesthetic agents have also been credited as responsible factors. Moschowitz (1946) has described a characteristic type of cirrhosis which he attributed to vascular decompensation which had arisen as a result of difficulty in the equalisation of intravascular pressures within the liver as a consequence of increased blood flow in the organ. He stated that the fibrosis could be traced to the terminal ramifications of the hepatic artery as it passed into the interlobular vascular septa and which commenced as a result of stasis and capillary congestion in these regions. In this conception passive venous congestion was the result of backward failure and the cirrhosis in thyrotoxicosis was the result of forward failure. Himsworth (1947) has suggested that in thyrotoxicosis the increased nutritional requirements consequent on the increased metabolic rate may well contribute to the development of hepatic lesions by leading to a deficiency of protective factors such as cystine, methionine and possibly tocopherol.

The thiouracil group of drugs have also been reported as causing hepatic damage. Sloan and Shorr (1944) observed mild jaundice in a patient after twenty days' treatment with doses of 0.8 g. thiouracil daily. The icteric index returned to normal within ten days of stopping the drug. Jaundice has also been observed in patients under treatment with thiouracil by Kahn and Stock (1944) and Gargill and Lesses (1945) and with propyl thiouracil by Livingstone and Livingstone (1947). On the other hand, Lafrentz and Binimelis (1948) have reported good results using thiouracil in the treatment of hepatic cirrhosis. Goodwin (1948) has recorded the results of serial liver function tests in 81 cases of thyrotoxicosis under treatment with thiouracil. Only 8 had tests carried out before treatment was commenced. Six of these showed abnormalities, and improvement occurred in 5 of them on treatment up to six months' duration, but in 1 further impairment was noted. He found abnormalities in 24 of the remainder and over varying periods of from three to twelve months noted improvement in 14 (58%), deterioration in 6 (25%) and no change in 4 (17%). The most frequent abnormalities were a rise in the serum alkaline phosphatase and a positive Takata-Ara reaction.

The present investigation was commenced with the intention of determining the effect of thiouracil on liver function in patients with hyperthyroidism. Three liver function tests were chosen to assess the impairment of hepatic function. These were the oral hippuric acid test of Quick, the cephalin-cholesterol flocculation test and the serum colloidal gold test. The first was chosen as it had been studied so extensively in previous investigations and would be useful for comparative purposes, the latter two on account of the sensitivity attributed to them, the ease in their performance and the absence of any extensive reports of the results of these tests in this condition. All tests, being of a quantitative or semiquantitative nature, were regarded as being suitable for a serial study. It was thought that the results of the investigation might throw some fresh light on the mechanism of production of liver damage in this disorder.

MATERIAL AND METHODS.

Fifty cases of thyrotoxicosis admitted to the Glasgow Royal Infirmary during the years 1947 and 1948 have been investigated. All cases were regarded as undoubted cases of the disease on clinical grounds, any patient in whom the diagnosis was in doubt being excluded. The basal metabolic rate (B.M.R.) was determined at intervals throughout the course of treatment and the three liver function tests were performed on each patient firstly, within a few days of admission and secondly, when the B.M.R. had been reduced to a normal or near normal figure by the use of the thiouracil group of drugs. The oral hippuric acid test was carried out according to the method described by Quick (1933), the normal value being the excretion of 3.0 g. hippuric acid, calculated as benzoic acid, in the four-hour period immediately following the ingestion of 6 g. sodium benzoate. Hanger's cephalin-cholesterol flocculation test was performed as described by Dick (1945). Care was taken to exclude light from the serum-saline-antigen suspension as recommended by Neeff and Reinhold (1944), who state that this procedure eliminates many false positive reactions. The serum colloidal gold test of Gray was carried out according to the semiquantitative method described by Maclagan (1944). All three tests were performed by the author personally, and throughout the investigation care was taken to employ precisely the same technique in each batch of tests. This was particularly important in reading the results of the serum reactions when every endeavour was made to assess the degree of precipitation or flocculation on the same basis every time a test was performed.

In the analysis of the results which follows, three methods of assessing the degree of impairment of liver function have been used; firstly, the percentage of patients in each group showing positive reactions in one test at least, in two tests at least and in all three tests, the first group including all the patients in the second and third groups and the second group all patients in the third group; secondly, the percentage of patients showing a positive result in each test; thirdly, the average value of each test for the group as a whole. In analysing Hanger's test for average results all one + reactions (although regarded as normal) have been included as the number of such reactions was very much higher in patients with thyrotoxicosis than in groups of controls. The degree of precipitation appearing in the first tube only has been taken into account in calculating the average value of the colloidal gold test. It seemed to be of much more value to use all three methods of assessment as by employing one only discrepancies would be more likely to appear.

RESULTS.

The results of the liver function tests before and after treatment are shown in Tables Ia, Ib and Ic.

Cephalin-cholesterol Flocculation Test. Before treatment, Hanger's test was carried out in 47 cases. Of these, 13 (28%) were positive, ++ values

being obtained in 11 and +++ values in 2. After treatment the test was performed in all 50 and was positive in 6 (12%), ++ values being obtained in 5 and +++ values in 1. The reaction became positive in 3 patients for the first time, and more so in 1 in whom it had been positive before treatment. The average value of the test for the whole group was 1.04+ before, and 0.74+ after treatment.

TABLE 1A.
Cephalin-cholesterol Flocculation Test.

	No.	Degree of flocculation					Positive %	Average Value
		0	+	++	+++	++++		
Before treatment	47	13	21	11	2	0	28	1.04+
After treatment	50	22	22	5	1	0	12	0.74+

TABLE 1B.
Serum Colloidal Gold Test.

	No.	Degree of precipitation (1st tube)						Positive %	Average Value
		0	1	2	3	4	5		
Before treatment	50	20	12	5	11	2	0	60	1.26
After treatment	50	25	13	4	5	3	0	50	0.96

TABLE 1C.
Oral Hippuric Acid Test.

	No.	Positive %	Average Value (g.)
Before treatment	50	72	2.54
After treatment	50	36	3.09

Serum Colloidal Gold Test. The gold test was positive in 30 (60%) of cases before treatment and in 25 (50%) after. The reaction showed improvement in 16 cases, was unchanged in 10, became worse in 4 and became positive for the first time in 2. The average value of the test for the whole group was 1.26 before and 0.96 after treatment.

Oral Hippuric Acid Test. The hippuric acid test was positive in 36 (72%) before treatment and in 18 (36%) after treatment. Two patients showed positive results for the first time after treatment and in 5 in whom the test had given a positive result at the original estimation it became worse. The average value of the test for the whole group was 2.54 g. before and 3.09 g. after treatment. Taking all three tests together, before treatment 88% had one test positive, 54% had two and 16% had three. After treatment the figures were 60%, 34% and 4% respectively.

Relationship between tests. Inspection of results in individual cases revealed that the three liver function tests appeared to bear little or no relationship to one another. A positive result in one test was not necessarily associated with positive results in the other two. Occasionally it was found that in a case where one test was positive and the others negative before treatment, that after treatment the originally positive test had become negative and the originally negative tests had become positive. The following are individual examples of such paradoxical results.

Case No.	Hanger's Test		Gold Test		Hippuric Acid Test	
	Before	After	Before	After	Before	After
29	-	+	000000	100000	2.95 g.	3.64 g.
35	-	++	110000	321000	0.35 g.	3.54 g.

No close relationship appeared to exist between the results of the liver function tests taken separately or together and the commoner features of the disease in individual cases. An attempt was therefore made to divide the patients into suitable groups and compare the results of the liver function tests to see if such analysis could throw any light on the problem by indicating broad trends rather than an absolute relationship. This showed that no definite relationship existed between the impairment of liver function and the B.M.R., the duration of the illness or the type of thyrotoxicosis.

TABLE 2A.

Relation to age. All three tests taken together.

Age	No.	B.M.R.		At least one test positive			At least two tests positive			All three positive		
		1	2	1*	2*	Imp. %	1*	2*	Imp. %	1*	2*	Imp. %
11-20	4	+24	+5	50	25	50	50	25	50	—	—	—
21-30	13	+34	+4	85	46	47	46	23	50	15	0	100
31-40	16	+50	+4	94	63	33	50	38	25	19	0	100
41-50	9	+48	+5	88	66	25	55	44	20	11	11	0
51-60	8	+45	+9	100	88	12	75	38	50	25	13	50

* Expressed as a percentage.

TABLE 2B.

Percentage of patients showing a positive test in each group.

Age	No.	B.M.R.		C.C.			S.C.G.			O.H.A.		
		1	2	1	2	Imp. %	1	2	Imp. %	1	2	Imp. %
11-20	4	+24	+5	—	—	—	50	25	50	50	25	50
21-30	13	+34	+4	33	8	78	39	39	0	69	23	66
31-40	16	+50	+4	32	6	81	63	57	10	69	38	45
41-50	9	+48	+5	22	22	0	66	55	17	66	44	34
51-60	8	+45	+9	25	25	0	75	63	17	100	50	50

TABLE 2c.
Average value of test in each group.

Age	No.	B.M.R.		C.C.			S.C.G.			O.H.A.		
		1	2	1	2	Imp. %	1	2	Imp. %	1	2	Imp. %
11-20	4	+24	+5	0.66+	0.25+	62	0.75	0.75	0	2.90	3.48	20
21-30	13	+34	+4	1.25+	0.46+	63	1.07	0.38	65	2.73	3.37	24
31-40	16	+50	+4	1.13+	0.75+	34	1.44	0.94	35	2.41	2.95	22
41-50	9	+48	+5	0.88+	0.77+	13	1.11	1.66	-50	2.48	2.75	11
51-60	8	+55	+9	0.88+	1.00+	-13	1.50	1.25	17	1.87	2.85	57

1 = Before treatment. 2 = After treatment. Imp. = Improvement.

Age. That there is a general relationship to age can be seen in Tables 2a, 2b and 2c. Taking all three tests together (Table 2a), it is seen that there is a tendency towards an increasing proportion of positive tests as age advances and that the improvement which occurs tends to be of lesser degree in the older than in the younger groups. If the tests are considered individually, Hanger's test shows no relationship between the degree of impairment and age before treatment; but that there is a distinct fall in the amount of improvement which takes place in the test on treatment as age advances. The gold and hippuric acid tests show a tendency to worsen with advance of age, both as regards the percentage of positive tests found in each group and in the average value of the test in the group as a whole. There is, however, no apparent relationship between age and the improvement which occurs in these tests calculated as a percentage of the original value; but it will be noted that in the older groups the average values for the hippuric acid test are still abnormal after treatment and that with the gold test one of the older groups shows further impairment.

Sex. The effect of sex is shown in Tables 3a, 3b and 3c. A lesser degree of impairment of liver function was found in males than in females. No male patient had a positive Hanger's test, none had three tests positive and the average value of the hippuric acid test was within normal limits on admission. The average value of the gold test was essentially the same in both sexes.

TABLE 3a.
All three tests together.

Relation to Sex.

Sex	No.	B.M.R.		At least one test positive			At least two tests positive			All three positive		
		1	2	1*	2*	Imp. %	1*	2*	Imp. %	1*	2*	Imp. %
M.	9	+39	+11	77	44	43	33	22	33	—	—	—
F.	41	+43	+5	90	63	30	61	32	48	20	5	75

* Expressed as a percentage.

TABLE 3B.
Percentage of patients showing a positive test in each group.

Sex	No.	B.M.R.		C.C.			S.C.G.			O.H.A.		
		1	2	1	2	Imp. %	1	2	Imp. %	1	2	Imp. %
M.	9	+39	+11	—	—	—	55	44	20	55	22	60
F.	41	+43	+5	32	15	53	61	57	16	76	39	49

TABLE 3C.
Average value of each test.

Sex	No.	B.M.R.		C.C.			S.C.G.			O.H.A.		
		1	2	1	2	Imp. %	1	2	Imp. %	1	2	Imp. %
M.	9	+39	+11	0.55+	0.33+	40	1.22	0.77	37	3.01	3.19	6
F.	41	+43	+5	1.16+	0.78+	33	1.27	1.00	21	2.43	3.07	22

1 = Before treatment. 2 = After treatment. Imp. = Improvement (as a percentage of the original value).

Weight. Tables 4a, 4b and 4c show the relationship between the impairment of liver function and the actual weight of the patient on admission calculated as a percentage of the Standard Weight for age, sex and height. It was found preferable to use this method of estimating weight loss owing to the difficulty experienced in getting an accurate statement of the amount of weight actually lost from each patient. Very few of the patients had weighed themselves at regular intervals or even had an idea of what their normal weight had been before the onset.

TABLE 4A.
Relation to Weight. All three tests together.

% St. Wt.	No.	B.M.R.		At least one test positive			At least two tests positive			All three positive		
		1	2	1*	2*	Imp. %	1*	2*	Imp. %	1*	2*	Imp. %
100% and over	6	+33	+8	33	16	50	33	16	50	—	—	—
90 - 99%	15	+44	+11	86	53	38	53	26	50	20	0	100
80 - 89%	20	+42	+1	85	60	29	45	35	22	15	5	67
69 - 79%	9	+50	+8	100	88	12	88	55	38	22	11	50

* Expressed as a percentage.

TABLE 4B.
Percentage of patients showing a positive test in each group.

% St. Wt.	No.	B.M.R.		C.C.			S.C.G.			O.H.A.		
		1	2	1	2	Imp. %	1	2	Imp. %	1	2	Imp. %
100% and over	6	+33	+8	—	—	—	66	16	76	50	33	33
90 - 99%	15	+44	+11	26	0	100	59	53	10	67	26	61
80 - 89%	20	+42	+1	30	15	50	50	45	10	65	40	38
69 - 79%	9	+50	+8	33	33	0	78	78	0	100	44	66

TABLE 4C.
Average value of each test.

% St. Wt.	No.	B.M.R.		C.C.			S.C.G.			O.H.A.		
		1	2	1	2	Imp. %	1	2	Imp. %	1	2	Imp. %
100% and over	6	+33	+8	0.60+	0.30+	50	1.16	0.16	76	2.94	3.48	34
90 - 99%	15	+44	+11	1.09+	0.60+	45	1.33	0.93	30	2.54	3.13	23
80 - 89%	20	+42	+1	1.10+	0.65+	50	1.05	0.95	10	2.59	2.99	15
69 - 79%	9	+50	+8	1.11+	1.22+	-10	1.55	1.66	-7	1.89	2.91	54

St. Wt. = Standard weight. 1 = Before treatment. 2 = After treatment. Imp. = Improvement.

It was thought that although such standards cannot apply in individual cases, in a group analysis such as this discrepancies will tend to cancel each other out. Taking all three tests together (Table 4a), it will be seen that there is a distinct tendency to a progressive increase in the percentage of positive tests in each group as the weight falls, with only minor exceptions to this rule. There is also a definite trend shown as far as the degree of improvement is concerned, those patients who have lost most weight improving least. The same broad trends are shown in Tables 4b and 4c with Hanger's and the hippuric acid tests; but not with the colloidal gold reaction. The degree of improvement calculated as a percentage of the original value in the hippuric acid test is an exception to this statement but it will be seen that the average values of this test after treatment show a progressive decrease as the percentage of the Standard Weight diminishes.

The improvement which takes place in patients under treatment as assessed by the reduction in the B.M.R. calculated as a percentage of the original value shows no relationship on group analysis to the improvement in the liver function tests. There is, however, a considerable degree of correlation between the degree of improvement of liver function and the amount of weight gained by the patient under treatment (Tables 5a, 5b and 5c). These show that there is a distinct trend towards greater improvement in liver function in the groups which show the greatest gain in weight. This trend is shown by all methods of assessing impairment with the exception of the hippuric acid test (Table 5c) where the improvement is calculated as a percentage of the original value but if the actual excretion of hippuric acid is taken as an average for the group it is seen that there is a progressive fall in the value obtained as the amount of weight gained decreases.

Infection. During the course of the investigation it was noted that a high proportion (24%) of the patients developed acute sore throat while under observation. Three of them occurred before thiouracil therapy was instituted and the remaining nine while under treatment. If account of the number of days under observation be taken in these patients in

TABLE 5A.

All three tests taken together.

Relationship to variation in weight while under treatment.

Weight increase (lbs.)	No.	Aver. age	B.M.R.		At least one test positive			At least two tests positive			All three positive		
			1	2	1*	2*	Imp. %	1*	2*	Imp. %	1*	2*	Imp. %
+10 or more	10	33	+43	+9	70	40	43	40	0	100	20	0	100
+5 - +9	10	39	+51	+11	100	50	50	70	30	57	30	0	100
+0 - +4	17	35	+35	+2	88	53	28	53	35	34	12	0	100
-5 - +0	12	38	+42	+7	92	77	16	68	51	25	9	17	-100

* Expressed as a percentage.

TABLE 5B.

Percentage of patients showing a positive test in each group.

Weight increase (lbs.)	No.	Aver. age	B.M.R.		C.C.			S.C.G.			O.H.A.		
			1	2	1	2	Imp. %	1	2	Imp. %	1	2	Imp. %
+10 or more	10	33	+43	+9	40	10	75	30	20	33	60	10	80
+5 - +9	10	39	+51	+11	50	10	80	80	60	25	70	30	57
+0 - +4	17	35	+35	+2	20	6	70	60	48	20	72	36	50
-5 - +0	12	38	+42	+7	8	25	-200	100	100	0	91	50	45

TABLE 5C.

Average value of each test.

Weight increase (lbs.)	No.	Aver. age	B.M.R.		C.C.			S.C.G.			O.H.A.		
			1	2	1	2	Imp. %	1	2	Imp. %	1	2	Imp. %
+10 or more	10	33	+43	+9	1.20+	0.60+	50	1.00	0.33	66	2.68	3.36	25
+5 - +9	10	39	+51	+11	1.50+	0.80+	47	1.90	1.40	26	2.46	3.30	34
+0 - +4	17	35	+35	+2	0.80+	0.47+	41	1.24	0.82	34	2.72	3.20	17
-5 - +0	12	38	+42	+7	0.80+	0.90+	-12	1.16	1.41	-22	1.92	2.57	34

1 = Before treatment. 2 = After treatment. Imp. = Improvement.

whom the complication occurred the incidence was one sore throat every 58th day without the drug and one every 49th day while on thiouracil. These results do not appear to be significantly different and do not suggest that thiouracil was responsible for the complication. Only one patient who had a sore throat had granulocytopenia necessitating withdrawal of the drug, and therapy was reinstated without trouble when the throat had settled. The incidence of sore throat in one of the wards over the period during which the investigation was undertaken was calculated with the following result:—

Patients with thyrotoxicosis - one sore throat every 248 days.
 All other patients - - - one sore throat every 515 days.

It would appear from these figures that there is a susceptibility for patients with thyrotoxicosis to develop sore throat and as there is experimental evidence which implicates infection as a factor in the production of hepatic lesions, it seemed desirable to investigate this aspect. The results of the liver function tests have therefore been compared in patients who showed evidence of infection on admission and in those who did not, in Tables 6a, 6b and 6c. The infections which were found

TABLE 6A.

All three tests taken together.

Relation to presence of infection on admission.

Infect.	No.	Aver. age	Aver. % St. Wt.	B.M.R.		At least one test positive			At least two tests positive			All three positive		
				1	2	1*	2*	Imp. %	1*	2*	Imp. %	1*	2*	Imp. %
Yes	19	36	87	+44	+3	95	68	28	68	32	53	26	5	81
No	31	33	89	+41	+8	84	55	35	45	35	22	10	3	70

* Expressed as a percentage.

TABLE 6B.

Percentage of patients showing a positive test in each group.

Infect.	No.	Aver. age	Aver. % St. Wt.	B.M.R.		C.C.			S.C.G.			O.H.A.		
				1	2	1	2	Imp. %	1	2	Imp. %	1	2	Imp. %
Yes	19	36	87	+44	+3	42	10	75	63	58	8	84	62	26
No	31	33	89	+41	+8	16	13	19	58	45	22	65	33	50

TABLE 6C.

Average value of each test.

Infect.	No.	Aver. age	Aver. % St. Wt.	B.M.R.		C.C.			S.C.G.			O.H.A.		
				1	2	1	2	Imp. %	1	2	Imp. %	1	2	Imp. %
Yes	19	36	87	+44	+3	1.15+	0.68+	41	1.63	1.15	29	2.10	3.03	44
No	31	33	89	+41	+8	0.87+	0.71+	18	1.03	0.84	18	2.81	3.13	11

1 = Before treatment. 2 = After treatment. Infect. = Infection. Imp. = Improvement.

were principally of the respiratory type, chronically infected tonsils, and bronchitis, but also included skin infections, gingivitis and leucorrhoea. It will be seen from the tables that whereas the average age, average percentage of Standard Weight and average B.M.R. before and after treatment are all factors which compare almost equally in the two groups, there is a marked difference in the liver function. Those patients who had evidence of infection on admission show a greater degree of impairment

of hepatic function than those without such evidence in all tests and by all methods of assessment. Evidence of infection did not seem to be related to the amount of improvement which took place on treatment. Throat swabs were taken in 5 of the patients who developed sore throat. In two, haemolytic streptococci were grown on culture and the remainder grew mainly *streptococcus viridans*. As it seemed likely that most of the throat infections were due to streptococci it was thought desirable to see if there were any relationship between impairment of liver function and previous streptococcal infection. All patients who gave such a history were therefore compared with those who did not. The following diseases were included for this purpose:—scarlet fever, rheumatic fever, chorea, frequent sore throats, rheumatoid arthritis and growing pains. The results are shown in Tables 7a, 7b and 7c. The two groups are comparable as far as age, percentage of Standard Weight and B.M.R. are concerned.

TABLE 7A.
All three tests taken together.

Relationship to a history of a previous streptococcal or related infection.

History of inf.	No.	Aver. age	Aver. St. Wt.	B.M.R.		At least one test positive			At least two tests positive			All three positive		
				1	2	1*	2*	Imp. %	1*	2*	Imp. %	1*	2*	Imp. %
Yes	27	33	88	+42	+5	89	63	29	59	41	31	26	4	85
No	23	36	89	+46	+8	87	52	40	48	22	54	4	4	0

* Expressed as a percentage.

TABLE 7B.
Percentage of patients in each group showing a positive test.

History of inf.	No.	Aver. age	Aver. % St. Wt.	B.M.R.		C.C.			S.C.G.			O.H.A.		
				1	2	1	2	Imp. %	1	2	Imp. %	1	2	Imp. %
Yes	27	33	88	+42	+5	31	15	50	66	56	15	78	41	47
No	23	36	89	+46	+8	22	11	50	52	43	17	65	25	62

TABLE 7C.
Average value of each test.

History of inf.	No.	Aver. age	Aver. % St. Wt.	B.M.R.		C.C.			S.C.G.			O.H.A.		
				1	2	1	2	Imp. %	1	2	Imp. %	1	2	Imp. %
Yes	27	33	88	+42	+5	1.08+	0.75+	31	1.50	1.04	31	2.28	2.99	27
No	23	36	89	+46	+8	1.00+	0.65+	35	1.00	0.87	13	2.83	3.21	13

Inf. = Infection. 1 = Before treatment. 2 = After treatment. St. Wt. = Standard weight. Imp. = Improvement.

A greater degree of impairment of liver function is indicated by the hippuric acid and colloidal gold tests in the group with a history of previous streptococcal infection but Hanger's test does not show any significant difference. It is noteworthy that 26% of those who gave such a history had all three tests positive but only 4% in the group who did not (Table 7a).

One patient only had digitalis therapy. It was found that improvement occurred in all three liver function tests. This finding is in contradistinction to Bartels (1938) who found that digitalis, given preoperatively, lowered hippuric acid excretion. No other drug which was given, *e.g.*, bromides or barbiturates was found to have any adverse effect on the liver function tests.

Twenty-four of the patients in this series underwent a subtotal thyroidectomy. Of this number only one developed a severe postoperative reaction and liver function tests prior to operation were all normal. No relationship was found to exist between the postoperative course and the results of the liver function tests performed immediately beforehand. There was no postoperative mortality.

DISCUSSION.

This investigation confirms the findings of other workers in this field that in untreated thyrotoxicosis there is impairment of liver function as judged by the results obtained with certain chemical tests. The degree of impairment found over the whole group by the hippuric acid test was slight, and compared with that found by Bartels (1938) was of lesser degree. On the other hand, a greater incidence of impairment was found by this test in this series than was found by Boyce and McFetridge (1938) and Longo and Lopez (1945). The variations found in the incidence of impairment by the several observers may be due to differences in the types of thyrotoxicosis met with in endemic and nonendemic areas or to racial differences as suggested by Boyce and McFetridge (1938). With Hanger's test, an incidence of 26% positive results is somewhat higher than that found by Longo and Lopez (1945) (15.4% of 26 cases). No results are available for comparison with the colloidal gold test. The tests in decreasing order of sensitivity were found to be the oral hippuric acid, serum colloidal gold and Hanger tests. This does not accord with the experience of others. Mateer, Baltz, Steele, Brouwer and Colvert (1947) in a study of miscellaneous hepatic disorders grade Hanger's test as one of the most sensitive of liver function tests, whilst the oral hippuric acid test is graded as being of intermediate sensitivity. The thymol turbidity test (pH 7.8) is also regarded by them as being of intermediate sensitivity and Carter and Maclagan (1948) found this test less sensitive than the colloidal gold reaction in diseases not primarily hepatic. This suggests that some mechanism other than actual hepatic damage may be responsible for the results obtained in this investigation.

That no correlation between the degree of impairment of liver function and the B.M.R. was found to exist may be explained on the grounds that it is well known that the disease is one which undergoes alternating relapses and remissions and that even if liver damage were directly proportional to the severity of the thyrotoxicosis this severity could scarcely be assessed by the reading of the B.M.R. on a particular date. In the same way, a close relationship between the degree of impairment of liver function and the duration of the disease for the same reason could not be expected. The tendency for a greater percentage of positive results to appear in the older age groups is not surprising. It may be due to diminution of functional reserve which one would expect in older tissues; and such diminution may be intensified by the factors causing impairment. The relationship to sex is more difficult to account for especially since Gyorgy (1946) has reported that, under varying dietary conditions, male rats appeared to evince a greater susceptibility to liver injury with carbon tetrachloride than did female rats, especially with a high fat intake. He has also reported that oestrone exerted a small but definite lipotropic effect when fed at a level of $30\mu\text{g./day}$ to intact and castrated female rats on a diet which produced fatty livers.

The fairly close relationship between the degree of impairment of liver function and the percentage relationship which the actual weight of the patient bears to the Standard Weight suggests two things. It has long been accepted that a most useful index of the severity of toxic thyroid disease is the amount of weight which the patient has lost and that the response to treatment can be gauged by the amount of weight which the patient gains. This suggests that the impairment of liver function is related directly to the severity of the thyrotoxicosis as judged by this standard and may be due to the excessive thyroid hormone. On the other hand, it may simply mean that the depressed liver function is caused by the relative malnutrition of which the loss of weight is an excellent index and bears no relationship to the thyrotoxicosis *per se*. The relationship noted between the degree of hepatic dysfunction and the rôle of infection is more difficult to explain. Infection has been known to aggravate the clinical condition of thyrotoxic patients and it has also been found that in such patients liver function is further impaired. My results in Tables 6a, 6b and 6c show that the depression of liver function in such cases can scarcely be accounted for by the aggravation of the thyrotoxicosis and consequent loss of weight. These results show that in spite of there being a close comparison between the degree of thyrotoxicosis as judged by the average B.M.R., and average percentage of Standard Weight, a significant difference exists in the liver function of those who had evidence of an infection on admission and those who had not. This clinical finding supports the evidence of Haban (cited by McIver, 1942), and Sealy (1941, 1942) who regarded infection as an

important factor in producing liver damage in experimental hyperthyroidism. The relationship which appears to exist between impaired hepatic function and a history of previous streptococcal infection is even more difficult to account for. It is possible that hepatic damage may have occurred at the time of the original infection and that such damage is aggravated by the supervening thyrotoxicosis. Infections have been regarded as of etiological importance in the development of hyperthyroidism and it is possible that both the liver damage and the thyrotoxicosis are caused by the same infection. Several patients gave a history of infection at the onset of their disease, usually a sore throat, but in others the infection had occurred many years beforehand. It would seem therefore that in the former patients the infection at the onset of the disease served merely to aggravate a latent thyrotoxic condition and the frequency of a history of infection is due to the susceptibility of these people to infective processes.

Considerable improvement in liver function occurs under treatment with the thiouracil group of drugs and it has been seen that this improvement is most closely correlated with the gain in weight. This confirms the opinions which have already been expressed regarding the relationship to the loss of weight at the original estimation. It appears that the impairment of liver function is in the main reversible and that after treatment normal values may be expected in the majority of cases. There are certain patients in whom further deterioration occurred in spite of a considerable gain in weight without obvious cause. Such cases may be due to the action of thiouracil on the liver as suggested by Goodwin (1948) but on the other hand no other evidence of a toxic effect of the drug could be detected and this therefore seems unlikely although not impossible. It is also possible that an hepatic lesion induced by the thyrotoxicosis may progress in spite of the fact that the hyperthyroidism is controlled. This hypothesis is supported by the results of Lafrentz and Binimelis (1948) in the treatment of cirrhosis of the liver with thiouracil, improvement appearing in some but not in others.

Mechanism of the hepatic damage. The relationships which have been shown to exist between the degree of impairment of liver function and the degree of weight loss in thyrotoxicosis before treatment and the degree of improvement in liver function and the amount of weight gained during treatment are strong supporting evidence for the opinion of Himsworth (1947) who suggested that the liver damage in this disorder was due to a relative deficiency of such factors as cystine, methionine and tocopherol secondary to the increased metabolism. The evidence of Gyorgy and Goldblatt (1945) also supports this view. They placed two groups of rats on a cirrhosis producing diet and added 0.1% thiouracil to one of them. They found that thiouracil exerted a preventive effect

on hepatic necrosis and that this group manifested a milder degree and incidence of cirrhosis, an absence of serious effusions, better survival rates and more satisfactory weight curves. The beneficial action was in accordance with the protective action of sulphanilamide and they suggested that the common denominator was the inhibition of thyroxine secretion. By lowering the metabolic rate a sparing effect on methionine was produced which manifested itself by a lesser incidence not only of trophopathic (purely dietary) but also of toxipathic (postnecrotic) cirrhosis. All the lesions, both acute and chronic with the exception of passive venous congestion, which have been described in this disorder may be satisfactorily explained on this hypothesis. This would bring the condition into line with the hepatic lesions known to occur in other conditions of malnutrition such as kwashiokor, malignant malnutrition and infantile pellagra of tropical countries and occurring in Western civilization only in time of famine. The livers are grossly fatty and may show evidence of diffuse hepatic fibrosis. These changes appear to be due to a deficiency of lipotropic factors and there seems to be a clear relationship between the incidence of this condition and diets which are deficient in protein (Himsworth, 1947). It is obvious that a relative deficiency of such factors is not solely dependent on the increased metabolic rate but will be largely determined by other factors such as the patient's appetite and the economic ability to satisfy it. In this connection the work of Blank (1940) is of interest. He noted four phases of appetite pattern in thyroid fed rabbits ; firstly, depression after the commencement of feeding accompanied by a lowered glycogen content of the liver ; secondly, improvement with a rise in hepatic glycogen if thyroid feeding were continued ; thirdly, the appetite continued improved but the metabolism was augmented and the hepatic glycogen became depleted ; and finally, after a long interval, the appetite gradually declined, then suddenly progressed to complete anorexia which led to a precipitous fall in weight and hepatic glycogen and terminated in death. The case reported by Sutcliffe (1898) also lends support to this view. Jaundice appeared in his patient as a terminal phenomenon in an illness the course of which lasted only three months. Persistent vomiting was a feature of this patient's illness and in the last three weeks only one small cup of milk was taken which was afterwards vomited. That other factors which increase metabolic needs will further contribute to this relative deficiency is exemplified by a case which was associated with pregnancy and showed subacute yellow atrophy at autopsy (Wyndham, 1940). The economic ability of the patient to satisfy the appetite may have a bearing on the variations in incidence of impairment of hepatic function noted by different observers and will depend on the social classes from which their material was drawn. The somewhat higher incidence of impairment of function noted in this investigation compared with the results of most of

the other observers may be related to the rationing system in Great Britain and the difficulty experienced in getting an adequate supply of protein for the increased metabolic needs. It may also account for the paradoxical difference noted in the sexes in this investigation when compared with the results of animal experiments, because in most families in this country the male receives preferential treatment with regard to the amount of protein served at each meal and the female suffers a corresponding lack.

Although hepatic damage in hyperthyroidism would seem to be largely dependent on this relative dietary deficiency it would appear that other factors have to be taken into account. Himsworth (1947) has drawn attention to the production of centrilobular necrosis in hyperthyroid animals occurring, according to some workers, in ordinary air but such lesions undoubtedly appear when the animals are exposed to slightly reduced oxygen tensions. As the oxygen requirements of the liver are increased in hyperthyroidism it is probable that in the central parts of the lobule anoxia occurs, leading to necrosis of liver cells in this situation. Thus anoxia would not account for all the liver lesions which have been described in this condition but it will undoubtedly contribute to hepatic damage. Any factors which will lead to anoxia such as anaemia, respiratory trouble or anaesthetics may thus cause or intensify the liver injury. Infection, too, appears to play some part in the production of hepatic lesions although its rôle is obscure. This may be due to the aggravation of the relative dietary deficiency by aggravation of the hyperthyroidism or to the increased metabolism consequent on pyrexia but in addition there appears to be a more direct effect on the organ which may be brought about by bacterial toxins.

The significance of the liver function tests. It is appropriate to consider the significance of the liver function tests employed in this investigation. Little or no relationship has been noted between the results of liver function tests and the appearance of the liver at biopsy in a variety of hepatic diseases (Sherlock, 1946). Piper and Poulsen (1947) came to a similar conclusion in thyrotoxicosis. It would appear therefore that these tests while indicating impairment of functional capacity need not be indicative of any pathological changes as judged by the usual histological methods.

Quick (1933) in introducing the hippuric acid test was of opinion that diminution of excretion was due mainly to inability of the liver to furnish glycine. Probstein and Londe (1942), as a result of experiments in which they first administered sodium benzoate alone and later gave sodium benzoate and glycine to the same patients and compared the results, concluded that in a certain number there was impairment of the conjugation mechanism as well. That feeding glycine in large doses may

lead to a normal excretion of hippuric acid in thyrotoxicosis has been demonstrated by Bartels (1938). Haines *et al.* (1941), however, had inconsistent results in similar experiments. It is possible that diminished hippuric acid excretion in thyrotoxicosis in many cases, rather than being due to structural change in the liver, might be produced by other factors which would compete with benzoic acid for the available glycine or its precursors. The increase in metabolism may thus deviate glycine or its precursors for metabolic purposes, and these may be used for energy instead of being subject to the process of detoxication. This hypothesis would accord with the observation that there is a general relationship between the amount of weight lost and the excretion of hippuric acid noted in this investigation. It also accords with the observation that excretion of hippuric acid increases as weight increases as at that time more amino acids would be available for detoxicating purposes and competing factors would be reduced. Sloan and Shorr (1944) support this theory with the observation that under treatment with thiouracil the nitrogen balance in hyperthyroidism becomes increasingly more positive. That actual hepatic damage may be produced by extending these principles to other amino acids has already been discussed.

Maclagan (1948) in a recent review of the flocculation tests lists the following fractions of the plasma proteins as acting as precipitating or inhibitory agents in the tests employed thus:—

Test	Protein Fractions Active		Correlation with Total Globulin
	Precipitating	Inhibiting	
Colloidal gold	<i>gamma</i> -globulin	albumin <i>alpha</i> and <i>beta</i> globulin	Slight
Cephalin-cholesterol	<i>gamma</i> -globulin <i>alpha</i> - <i>beta</i> - ,,	albumin	Slight

The principal result of the work reviewed indicates that positive results are due to relative excess of *gamma*-globulin. Various changes have been described in the plasma proteins which might lead to positive results in these tests in hyperthyroidism. Longo and Lopez (1945) record diminution of serum albumin in thyrotoxicosis and attributed it to impairment of liver function. McCullagh (1946) noted as a physiological effect of thiouracil an increase in the *beta*-globulin fraction of the plasma proteins, a similar change occurring after thyroidectomy. Lowering of *beta*-globulin in thyrotoxicosis would thus tend to increase the sensitivity of the colloidal gold test while it would diminish that of Hanger's tests as in the latter the *beta*-globulin acts as a precipitating agent and in the former as an inhibiting agent. This may account for the lack of correlation noted in this investigation in the two tests. Leathem (1945) has stated that hypophysectomy in the rat leads to a rise in serum globulin and a

decrease in serum albumin. Thyroidectomy causes a rise in serum globulin while the albumin remains unchanged. If thyroxine be given to hypophysectomized animals the rise in serum globulin is prevented without preventing the decrease in albumin. He investigated the effect of thiouracil in rats and found that the concentration of serum globulin was increased while the albumin was unaffected. Williams, Bissell, Jandorf and Peters (1944) found no change in total protein in thiouracil treated patients. This does not preclude the possibility that changes do occur which would be detected by the more sensitive flocculation tests. As thyrotoxicosis leads in many cases to a state of malnutrition it is interesting to note that Bieler, Ecker and Spies (1947) as a result of electrophoretic studies in the hypoproteinaemia of malnutrition found a general decrease in all plasma proteins with a relative deficiency of serum albumin. Increases in *gamma*-globulin are not confined to primary liver diseases but have also been found in other conditions the most notable of which are infections. Dole, Watson and Rothland (1945) have reported this finding in scarlet and rheumatic fever, in both conditions being associated with a rise in *alpha*-globulin and depression of albumin. It has also been noted in bacterial endocarditis, chronic malaria and lymphogranuloma. Enders (1946) states that this probably reflects an increase in the amount of circulating antibody. Positive results in the flocculation tests have also been noted in malaria, glandular fever, subacute bacterial endocarditis and rheumatoid arthritis (Carter & Maclagan, 1946).

It is thus apparent that changes in the plasma proteins may occur in hyperthyroidism which would affect the flocculation tests. These changes might appear as the result of increase in thyroid hormone, a condition of malnutrition or as a result of an increase in circulating antibody due to the susceptibility of these patients to infection. It is not clear how these changes in the plasma proteins are produced as all three factors may be associated with liver damage. As far as the rôle of infection is concerned it is interesting to note that in this investigation similar differences occurred in the hippuric acid test in the group which showed evidence of infection on admission, and it is difficult to see why infection should so affect this test as well as the flocculation tests unless it be through the common factor of hepatic injury. It is also interesting to note that qualitative differences in the plasma protein fractions in hepatitis are of importance in determining precipitation in the flocculation tests (Maclagan & Bunn, 1947). This finding supports the hypothesis that hepatic injury is the common factor; but no definite opinion can be reached until the results of more detailed electrophoretic studies of the plasma proteins in these conditions and the effects of such fractions on the suspensions used in the flocculation tests are available.

No particular clinical value appears to be attached to one or all of the tests employed in this investigation. As far as the preparation of the

patient for operation is concerned, if adequate thiouracil therapy be employed to reduce the metabolic rate to normal or near normal limits and the patient is showing a satisfactory gain in weight, postoperative complications are unlikely to develop even in the presence of poor liver function tests.

SUMMARY.

The literature regarding the relationship of thyrotoxicosis to hepatic damage is reviewed.

The results of certain liver function tests in fifty cases of thyrotoxicosis, before and after treatment with thiouracil, are reported.

Evidence is produced which shows a relationship between the impairment of liver function and age, sex, loss of weight and infection.

The mechanism of the hepatic injury is discussed in the light of these findings. The significance and value of the liver function tests employed has been considered.

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