Liver Function in Thyrotoxicosis with Special Reference to the Results of Liver Function Tests in Patients under Treatment with Thiouracil.

By

ANDREW ALLISON, Jr.,

B.Sc., M.B.Ch.B.,F.R.F.P.S.G.,M.R.C.P.(Lond.)

INTRODUCTION.

That an association between thyrotoxicosis and hepatic damage exists has long been postulated. The evidence for this has been forthcoming on clinical, pathological, experimental and biochemical grounds. No general agreement has been reached as to how or why such damage does occur in this condition although numerous theories have been advanced to account for it. Several writers have especially attempted to link the hepatic disorder with the occurrence of thyroid crisis or 'storm'. Lahey (1935) has gone so far as to state that in his opinion the majority of deaths associated with hyperthyroidism are liver deaths. Other studies have failed to show any consistent evidence of a direct relationship between the severity of the liver damage and the severity of the hyperthyroid state. Reports on the effect of iodine therapy have likewise been inconsistent but there is abundant evidence that thyroidectomy is followed by a marked improvement in cases in which the hyperthyroidism is successfully controlled. Until recently no reports had been published on the results of liver function tests in patients with toxic thyroid disease under treatment with thiouracil compounds but Goodwin (1948) has published a report of such an investigation since this study was commenced. It appeared therefore that with the advent of such potent drugs for controlling this disease the results of liver function tests might throw some further light on the problem of hepatic damage and that the subject was deserving of further study.

SOME HISTORICAL ASPECTS of the RELATIONSHIP between THYROID and HEPATIC DISEASE.

Clinical.

From the clinical side the most outstanding evidence has come from the presence of jaundice in cases of toxic goitre. Habersohn (1874) recorded the case of a patient, a female, aged 20, who noticed that her eyes became prominent 4 years after a doubtful attack of rheumatic fever. Three months later she developed jaundice which deepened until death 10 days after its appearance. At autopsy there was marked exophthalmus, the thyroid was not grossly enlarged, the heart weighed 14 oz., showed evidence of pericarditis and there were recent granulations on the aortic and mitral valves with signs of old disease of the mitral valve. The liver weighed 74 oz., was bright yellow in colour, anaemic and in no way nutmegged. Burton (1886) addressing the Cambridge Medical Society referred to the prevalence of exophthalmic goitre in that part of the country and attributed it to the high incidence of anaemia and rheumatic fever which he thought to predispose to it. He described the case of a male, aged 34, with exophthalmic goitre who had slight jaundice and bile-stained urine for three days. In 1898, Sutcliffe reported under the title 'An Extraordinarily Acute Case of Graves Disease' the terminal appearance of jaundice in a patient in whom the whole course of the disease lasted only 3 months. Persistent vomiting was a feature of her illness and in the last three weeks she took only

one/

one small cup of milk which she vomited afterwards. Eder (1906) discussed the presence of jaundice in 3 cases of exophthalmic goitre. One patient passed gallstones in her stool and the jaundice subsided. The two remaining had transient jaundice of from 4 to 6 weeks duration and were at first regarded as being catarrhal in nature. He expressed the opinion that the jaundice in these cases might have arisen from some chronic toxaemia in the intestines and might have a cause in common with the exophthalmic goitre. Icterus was noted in 23 of 107 cases of exophthalmic goitre coming to post-mortem by Beaver and Pemberton (1933). Schaffer (1940) noted its presence under similar circumstances in 5 out of 24, being well-marked in 3 but only in the sclerae in 2. In 1940 Wyndham reported 2 cases which had been jaundiced before death and which at autopsy proved to have acute and subacute yellow atrophy. Lichtman (1941) has emphasized that in patients who show icterus, an unrelated cause should always be excluded.

Jaundice has also been noted in patients under treatment with thiouracil. Sloan and Shorr (1944) observed mild jaundice with an icteric index of 23 after 20 days treatment with 0.8gm. daily. There was no evidence of haemolysis or hepatic damage at the time and subsequent gallbladder X-rays and liver function tests were normal. The icteric index returned to normal within 10 days of stopping the drug. Kahn and Stock (1944) reported a fatal case of agranulocytosis in a patient who had received 30.8gm. thiouracil/

thiouracil over a period of 54 days. Jaundice appeared as a terminal phenomenon. At post-mortem examination the liver was smaller and softer than normal, dark brown in colour and the lobules were indistinct. Microscopically distension of the sinusoids was present. They concluded that the thiouracil was responsible for both the agranulocytosis and the toxic hepatitis. Gargill and Lesses (1945) observed jaundice in two patients undergoing thiouracil therapy. Liver biopsy in the first of these showed dilatation of the central vein, normal parenchyma, empty sinusoids and periportal infiltration. The icterus cleared 100 days after omission of the drug. In the second patient it cleared within a few weeks when the drug was omitted. Jaundice has also been reported in a patient with thyrotoxicosis and auricular fibrillation who was being treated with propylthiouracil (Livingstone and Livingstone 1947). Agranulocytosis developed at the same time and the patient responded to treatment with streptomycin, penicillin, blood transfusion, Amigen, vitamin K, vitamin B complex, liver extract, protein hydrolysate and choline. They attributed both conditions to the toxic effect of propylthiouracil.

Pathological.

In a historical review of the anatomic changes in the liver in hyperthyroidism Cameron and Karunaratne (1935) give pride of place to Paul who reported a case of cirrhosis of the liver in association with exophthalmic goitre in 1865. Several observers have/

have since reported similar instances but within the past 20 years exhaustive investigations into the pathological picture have been made and reported from various sources. Weller (1930) selected 44 cases of thyrotoxicosis coming to autopsy for investigation. All had to be proved cases both clinically and histologically and all who had cholelithiasis, cholecystitis, syphilis or other condition which would cause changes in the islands of Glisson were excluded. Of the 44 cases 6 showed no evidence of hepatitis, 22 well-marked hepatitis and 16 slight or moderate hepatitis. Hepatitis was characterised by lymphocytic infiltration, bile duct proliferation and increased stroma in the islands of Glisson. A pathological study of 107 cases of exophthalmic goitre was carried out by Beaver and Pemberton. All cases in which apparently independant hepatic disease or in which other anatomic findings might be considered factors were excluded. They recognised two types of hepatic damage, acute and chronic, and give the following percentage incidence:-

Acute lesions were present in 91.5% and consisted of

Fatty changes.....87.8%

Central necrosis.....50.4%

Focal necrosis.....7.0%

The fatty changes were usually centrilobular but were sometimes peripheral. In the areas of necrosis hyaline thrombosis of the hepatic sinusoids was sometimes seen. The necrosis in 5 cases was of such degree as to pass for the changes of a moderately acute yellow/

yellow atrophy. Passive venous congestion was seen in 13 instances. Of the chronic changes atrophy, meaning loss of weight, of the organ was the most conspicuous. The average weight of the liver was 1316gm. Chronic hepatic lesions of the cirrhotic type were found in 59.81%. These were divided into 4 grades. Grade 1 showed changes of slight degree which could hardly be classified as a cirrhosis. Grades 2,3, and 4 represented a moderately severe to a well-advanced cirrhosis. They found the histological picture agreed well with Weller's description - interlobular parenchymatous hepatitis. Cameron and Karunaratne investigated 30 patients who came to autopsy. Ten showed passive venous congestion, 5 fatty change with or without necrosis, 5 atrophy and nodule formation and 10 cirrhosis. They grouped the latter into three grades:- A. Insular showing lymphocytic infiltration and prominence of the portal canals but no alteration of the lobular structure. B. Interinsular in which widened portal canals become connected by narrow bands of connective tissue; there may or may not be considerable alteration of lobular structure. C. Annular - the completed picture of cirrhosis. They recognised three types of change associated with exophthalmic goitre:- 1. Cases of acute liver damage - marked fatty change or acute hepatic necrosis. 2. Cases with evidence of progressive damage (various stages of cirrhosis). 3. Arrested cases (nodule formation and atrophy). In an investigation into the cause of death in patients with thyrotoxicosis with particular reference to thyroid crisis Foss et al. (1939)/

(1939), found that of 29 cases in 9 the cause could be attributed to some other condition recognised before death e.g. cerebral haemorrhage. In the remaining 20 the cause was clinically crisis but in 9 of these there was overwhelming infection antedating the symptoms of crisis. In the remaining 11 they concluded that true crisis had occurred and they found the following changes in the livers. One was normal. The other 10 showed varying degrees of necrosis in the centres of the lobules. In 8 fatty degeneration was a prominent feature. Cellular infiltration was present in 3 and congestion in one (the heart showing a healed mitral endocarditis in the latter). Schaffer examined the livers of 24 cases of thyrotoxicosis dying at the Cincinnati General Hospital having excluded all cases in which independent anatomic change might have produced hepatic lesions and found atrophy (the average weight of the livers was 1275gm.), fatty infiltration in all but 2 of the 24, low grade inflammatory change at the periphery of the lobules associated with a patchy increase in the fibrous connective tissue and with lymphocytic infiltration in 83%. The sole criterion for the latter diagnosis was lymphocytic infiltration in the periportal spaces. No attempt was made to estimate changes in the fibrous tissue except where marked periportal fibrosis or cirrhosis was evident. Comparative studies in patients dying from accidental causes and from rheumatic heart disease were 22% and 26% respectively. Cirrhosis was found in 6 cases, the criteria for diagnosis being degenerative changes leading to disappearance of hepatic cells, a chronic/

chronic inflammatory reaction at the periphery of the lobules and regenerative changes of an imperfect type. It was found in only 2% of cases of accidental death and in none with rheumatic heart disease. Lesions secondary to chronic hepatic congestion were found in 9 - dilatation of venous sinusoids, atrophy of liver cords and varying degrees of necrosis of the central zones. Chronic venous congestion was found in 85% of cases of rheumatic heart disease and hepatic fibrosis was found in 9 of them but in all cases it originated in the centres of the lobules instead of the peripheral position and was most marked in the subcapsular lobules. There was no evidence of chronic interstitial hepatitis. He compared the incidence of these charges with similar changes in 33 patients dying with vitamin B or C deficiency thus:-

	Total	Fatty Infiltration	Chronic interstitial hepatitis	Cirrhosis
Vitamin B or C. deficiency	33	33	21	0
Thyrotoxicosis	24	22	20	6

and concluded that vitamin B or C deficiency was not a factor in the production of the hepatic lesions. Wyndham examined autopsy material from 43 patients dying with thyrotoxicosis. In 6 a macroscopic examination only was made. His findings were similar to those of Cameron and Karunaratne. Passive congestion in 13 cases, fatty change without liver atrophy in 10, early cirrhosis in 6, fatty change with atrophy in 8. In two of the latter the atrophy was/

was of severe degree. One a female who showed subacute yellow atrophy was pregnant on admission. Labour commenced at 7½ months, the child being delivered under light ether anaesthesia. On the evening of the day of delivery she became very ill and obviously jaundiced. The second was a female aged 20 who had had Graves' disease for 2 years and had been trated with iodine - the liver showed the changes of acute yellow atrophy. Moschowitz (1946) investigated the liversof 31 cases of diffuse toxic goitre dying in the Mt. Sinai Hospital between the years 1930 and 1944. Cirrhosis was found in 11 (35.5%) and chronic venous congestion in 13. In 3 the venous congestion was associated with cirrhosis and in the remaining 8 of cirrhosis no venous congestion was present. The chronic venous congestion in the other 10 cases was unassociated with any other lesion. He described a pathognomic type of cirrhosis occurring in the interlobular septa and often encroaching on the lobule. In the early stages the areas of fibrosis could be traced to the terminal ramifications of the hepatic artery as it passed into the interlobular vascular septa. He expressed the opinion that this artery represented a significant factor in the equalization of intravascular pressures between the hepatic artery and the portal vein within the liver. He believes that the lesion is the consequence of the increased blood flow which is almost peculiar to this disease in its early stages. The increased velocity is associated with increased blood volume and increased blood flow. These altered circulatory dynamics result in/

in difficulty in the maintenance of the normal pressure relationships between the hepatic artery and the portal vein within the liver. Eventually decompensation arises with resulting stasis in these areas and the lesion begins as a capillary congestion. In time, just as in chronic venous congestion of central origin, capillary sclerosis results with eventual fibrosis. In this conception the cirrhosis of the liver of diffuse toxic goitre is the consequence of forward failure, while that of chronic venous congestion is the result of backward failure. The cirrhosis is distinguished by the fact that it is most marked in the subcapsular zone of the liver. Evidence is submitted that as in chronic venous congestion of the ordinary type this is due to the resistance of the capsule of the liver. The cirrhosis also possesses the peculiar quality that it arises only from the smaller divisions of the portal spaces. This is because the interlobular branches of the hepatic artery arise only from such spaces. The cirrhosis bears a definite but not absolute relation to the duration of the malady which is what one might expect from the pathogenesis. Nevertheless this is sometimes absent in persons who submit a history of apparently long duration of the disease. This may be accounted for by the observation that chronic venous congestion is an exceedingly common consequence of longstanding diffuse toxic goitre, even in patients without cirrhosis and that this venous congestion neutralizes the increased velocity of blood flow.

EXPERIMENTAL/

EXPERIMENTAL.

Since Farrant (1913) noted fatty degeneration principally of centrilobular distribution in thyroid fed cats and rabbits, hepatic lesions under similar circumstances have been reported from several sources. Hashimoto (1921) reported similar lesions with acute necrosis in albino rats and Gerlei (1933) cited by Cameron and Karuntaratne found centrilobular necrosis in rabbits after 57 days with doses (4mg.) of thyroxine subcutaneously. Youmans and Warfield (1926) failed to produce liver lesions in dogs with large amounts of thyroid extract and the phenoltetrachlorphthalein test was normal. Hoskins (1916) reported that the livers of albino rats fed on thyroid were larger than in controls and Hewitt (1920) reported to the same effect. In a study of the livers of dogs in normal, starving and hyperthyroid animals Simonds and Brandes (1930) found that in starvation the liver lost in greater proportion to the body weight than it did in hyperthyroid animals. They attributed this relative, if not absolute, hypertrophy to increased and augmented blood flow to the organ. Higgins (1933) confirmed the increase in size of the liver in rats which had been fed on thyroid and further showed that when subtotal removal of the liver was carried out regeneration of liver tissue occurred more rapidly than in control animals.

It was demonstrated by Cramer and Krause (1913) that if rats were kept on a high carbohydrate diet and fed relatively small doses/

doses of fresh thyroid gland the glycogen content falls so low that it cannot be estimated gravimetrically. This finding was confirmed in cats and they attributed it to inhibition of the glycogenic function of the liver rather than to increase utilisation of carbohydrate. Confirmation has also come from Kuriyama (1917,1918) and Coggleshall and Green (1933) the latter further reporting that when desiccated thyroid and thyroxine were administered in equi-iodine dosage the latter lowered the liver glycogen to a greater extent than the former. Blank (1940)investigated thyroid fed rabbits and noted four phases of appetite pattern. Firstly, depression after the commencement of feeding accompanied by a lowered glycogen content of the liver, secondly improvement in appetite if thyroid feeding were continued with a rise in hepatic glycogen, thirdly, the appetite continued improved but the metabolism was augmented and the hepatic glycogen became depleted. Finally, after a long interval, the appetite declined gradually, then suddenly progressed to complete anorexia which led to a precipitous fall in weight and hepatic glycogen and terminated in death. It has also been noted that a good glycogen content protects the liver against chloroform and various/

various toxins (Opie and Alford, 1914; Davis and Whipple, 1919,1921) and the depletion of liver glycogen has been held to explain the liability of the liver to damage in thyrotoxicosis. However contradictory evidence exists as to the susceptibility of the organ to the effects of toxins in hyperthyroid animals. Davis and Whipple (1919) found that thyroid feeding had no influence on liver injury following chloroform anaesthesia in dogs. Goodpasture (1921) confirmed this finding but noted that if the chloroform were given subcutaneously in doses of C.2c.c. per kilo in an equal amount of olive oil death occurred within 24 hours with extreme central necrosis of the liver. McIver (1940) had similar results in albino rats. Chloroform in doses of 0.4 - 1.5cc. per kilo was administered to 15 animals which had been given thyroxine over a period of one or two weeks. Eleven died and four recovered. Twenty control animals all survived and were killed at the end of 48 hours showing no symptoms of chloroform poisoning. McIver and Winter (1943) followed up this work and found that it could not be attributed to depletion of liver glycogen by thyroxine and showed that a high protein diet did not protect the liver of hyperthyroid rats from injury following chloroform injection. Cameron and Karunaratne found no difference in the minimal toxic dose of carbon tetrachloride in albino rats fed on thyroid and in control animals from the same litters. That thyroid feeding may not be the sole factor determining liver lesions is/

is suggested by evidence from Haban, 1935 (cited by McIver 1942) who fed rabbits on desiccated thyroid and thyroxine and found central necrosis in 4 out of 7 animals. All 4 had intercurrent infection and he concluded that infection was necessary to cause liver necrosis. Schultz (cited by Sealy, 1941) came to a similar conclusion using thyroxine and thyroid and chronic streptococcal infection. Sealy in an investigation of experimental hyperthyroidism in rabbits having sloughing infected skin tumours (Shope papillomata) found widespread central necrosis in these animals but none in controls without papillomata or with papillomata but given no thyroid. He also reports the production of liver necrosis in hyperthyroid rabbits given injections of haemolytic staphylococcus aureus but none in controls (Sealy, 1942). McIver and Winter drew 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 lesions when the period of exposure was short to intense degeneration when the anoxia was prolonged. The livers of normal animals similarily exposed showed no lesions. The mortality was high in hyperthyroid animals but was absent in controls.

BIOCHEMICAL.

Liver function tests of many types have been used by different observers in an attempt to estimate the degree of liver damage present in toxic thyroid disease. There has been little consistency in the various results reported. Youmans and Warfield in 1926 compared the results obtained with the glucose tolerance test and liver function tests in 27 consecutive cases of thyrotoxicosis and performed the latter in a further 21 patients. They excluded from their investigation with one or two exceptions, patients presenting features of cardiac failure until compensation had been established. They found evidence of impairment of liver function in 22 of 44 patients studied using Rosenthal's modification of the phenoltetrachlorphthalein test, in 3 of 7 cases with the laevulose tolerance test, in 7 out of 9 where the icterus index was employed (icterus index over 6 being regarded as abnormal) and Widal's haemoclastic crisis test was positive in 3 out of 8. The glucose tolerance index was used to aid analysis, their results being graded as follows -

Markedly abnormal(over 20).....4
Moderately abnormal (14 to 20) 9
Slightly abnormal (10 or over).....8

No clear relationship was established between the evidence of liver damage as judged by the results of the liver function tests and the glucose tolerance tests. No relationship was noted between the degree of functional impairment of the liver and the basal metabolic/

metabolic rate. Some slight correlation was found between the degree of impairment of liver function and the degree of loss of weight. No correlation was found between the liver injury and the clinical type of disease age, sex, or the usual laboratory tests except that frank jaundice or a subicteric tint occurred in 7 patients and in all but one they showed the most severe degrees of liver damage. Lichtman (1932) used as a measure of hepatic function a test based on the excretion of oxycincophen in the urine. In normal persons less than 100mg. (21%) of a test dose of cincophen is excreted in this form; with disturbance of hepatic function larger amounts are excreted. His method included the estimation of the icterus index, of urobilinuria by the zinc acetate method, of urobilinogenuria using Ehrlich's aldehyde reagent and the galactose tolerance by Bauer's method. In 20 cases of hyperthyroidism he found the icterus index increased in 3 but failed to demonstrate any increase in serum bilirubin by Van den Bergh's method. Galactosuria was noted in 3 patients out of 16 but in only one, a diabetic, was it excreted in abnormal amount. Increased excretion of urobilin was found in 3 cases one of whom had a high icterus index and a pleural effusion, another had auricular fibrillation. With the cincophen oxidation test abnormal amounts were excreted in 16 out of 20 cases. He showed that in 9 out of 15 cases the test carried out before treatment was the highest, and in 5 in whom the basal metabolic rate was reduced to normal by rest, iodine, or subtotal thyroidectomy the excretion of oxycincophen/

oxycincophen was also reduced to normal. In 4 of 7 cases in which treatment failed to reduce the basal metabolic rate the excretion of oxycincophen remained high. In 2 in whom the basal metabolism remained high the excretion of oxycincophen became normal. He also noted that in one patient who developed acute thyrotoxicosis leading to a fatal result two tests prior to the attack were normal. No relationship was found between the degree of impairment of liver function and the basal metabolic rate, the known duration of the disease, or the percentage of weight lost; in individual cases there appeared to be a tendency to improve as the basal metabolic rate became normal. Maddock, Coller and Pedersen (1937) used three procedures to test liver function - the blood bilirubin, bromsulphalein dye excretion and the estimation of the blood amino acid nitrogen. Of 13 patients 8 (61%) showed evidence of liver damage preoperatively. They found essentially normal results with the blood amino acid nitrogen. Considerable correlation was found to exist between the severity of the thyrotoxicosis as judged by the basal metabolic rate and the impairment of liver function. They also noted that further impairment of liver function occurred on the first post-operative day and that improvement occurred on succeeding days, a variable time being required for it to return to normal. No relationship existed between the degree of impairment of liver function and the postoperative reaction as judged by the rise in pulse rate or in temperature. They concluded that the impairment of liver function found was not the cause of post-

operative/

operative hyperthyroid reactions and produced evidence to show that a relationship existed between the postoperative reaction and the level of epinephrine in the blood. That a relationship might exist between liver damage and epinephrine they offered in explanation the evidence of Perozzo that in dogs the administration of epinephrine intravenously causes well marked fatty changes in the liver.

Althausen and Wever (1937) discuss the galactose tolerance test. 40 gm. galactose dissolved in 400cc. of water were given orally to the fasting subject (14 hours). Blood was withdrawn after 5,15, and 30 minutes and the dextrose and galactose fractions estimated separately. In normal patients little or no galactose was found in the 5 minute specimen and the blood galactose rose to 15mg. at 30 minutes. In hyperthyroidism (26 cases) galactose was present in the blood of most patients at 5 minutes and in all but two had risen to 30mg. or over at 30 minutes. Following thyroidectomy a marked increase in galactose tolerance was observed. In 14 diabetics only two showed abnormal curves. Five patients with miscellaneous hepatic disease showed diminished tolerance. They offered two explanations, firstly acceleration of absorption explaining the appearance of the galactose in the blood in the 5 minute specimen and secondly hepatic injury. They pointed out that the low glycogen content of the liver could not account for the diminished galactose tolerance in view of the results obtained in almost/

almost all diabetics. The diagnostic significance of the test was illustrated by one patient who was suspected of having hyperthyroidism in whom the basal metabolic rate was +26% and +28% on two occasions but in whom the galactose tolerance test was normal. The patient was eventually shown to have rheumatic heart disease. In a further communication Althausen et al.(1940) report on the galactose tolerance test in 130 cases of hyperthyroidism, 121 patients with normal thyroids and seven with myxoedoema. In the thyrotoxic patients they found the blood galactose to average 68mg. in the 60 minute specimen. High peaks were also found in patients with hepatic disease and Paget's disease. The rates of disappearance of galactose (40gm.) given intravenously were compared in 10 normal persons, 10 with hyperthyroidism and 11 with parenchymatous disease of the liver. By this method it was shown that the utilisation of galactose was normal in thyrotoxicosis. With the oral test, out of 130 patients 124 showed positive results, 5 were doubtful and one was negative. No correlation was found to exist between the basal metabolic rate and the galactose tolerance curve. They considered that the impairment of galactose tolerance found in the oral test indicated acceleration of absorption and that the test was of greater diagnostic value than the basal metabolic rate. Subtotal thyroidectomy restored the curves to normal but occasionally failed when the basal metabolism remained high. Maclagan and Rundle (1940) investigated the galactose tolerance in hyperthyroid patients and found it impaired but noted no significant alteration after 14 days rest/

rest and iodine therapy although the basal metabolic rate was lowered. Thyroidectomy produced a striking drop in both the basal metabolism and the galactose index. They noted that individual variations in age and in the duration of the thyrotoxic condition seemed to be of importance in isolated cases. The impairment of galactose tolerance was attributed by them to hepatic dysfunction and they found in one patient coming to autopsy who had had a galactose index of 448, periportal and focal necrosis and generalized liver atrophy. Lichtman (1941) using a modified technique for performing the galactose tolerance test based on the differentiation of galactose and glucose in the urine by means of yeast fermentation, found 6 patients abnormal out of 13 with hyperthyroidism. There was a tendency to improvement shown with iodine therapy and decrease in the basal metabolic rate. The patients with normal values averaged a decade younger than those with abnormal and the weight loss averaged 6 lb. less in the former group. He thought that there was greater correlation between the clinical severity of the disease and his test than had been shown with others. He further noted that it was a common clinical observation that hyperthyroid patients tolerated upper respiratory infection poorly and that the galactose tolerance indicated that such infection further compromises liver function even in the absence of fever. He comments that the mechanism of the functional derangement is not established and suggests that glycogen exhaustion and protein depletion deprive the liver of its prime protective/

protective agents against poisons. The unprotected liver cells then may become vulnerable to circulating thyroxine, the products of endogenous metabolism or bacterial toxins from the intestinal tract or other source in the body and suggest that the anatomic changes are produced by these toxic elements. Smith et al.(1942) discussing the significance of the galactose tolerance test found little correlation between it and the basal metabolic rate and confirmed its value in diagnosis in cases where the basal metabolism was low. Barnes and King (1943) produced experimental evidence to show that intravenous galactose tolerance tests are normal in most cases of thyrotoxicosis except the most severe and came to the conclusion that the high galactose index in these cases was due to increased absorption from the intestine. This confirmed the opinion of Althausen; and Rosenkrantz, Burger and Lockhart (1942) came to similar conclusions.

Ragins (1936) employed the Takata-Ara reaction in 14 cases of hyperthyroidism and obtained positive results in 6.

Kugelmann (cited by Lichtman) found evidence of hepatic dysfunction in 10 cases studied by the laevulose tolerance test.

The Quick hippuric acid test has been extensively studied in thyrotoxicosis. Bartels (1938) investigated 148 cases all of whom came to operation. Determinations were made on the day of admission, on the day prior to operation after 8 to 14 days pre-operative treatment and on the 6th or 7th day postoperatively. Of 78 cases of primary hyperthyroidism whose condition was of sufficient mildness/

mildness to permit a subtotal thyroidectomy the average hippuric acid excretion was 2.30 gm. and the average basal metabolic rate was + 36%. Of the group only 15% had determinations above the accepted normal of 3 gm. Eight of this number had had iodine before admission or had not suffered weight loss and these factors were considered the basis for the normal values obtained. After the usual preoperative period the average hippuric acid excretion had risen to 2.55 gm. and the basal metabolic rate was + 22%. Post-operatively the average excretion was 2.39 gm. and at a check up three months postoperatively was 3.34 gm. (This latter figure excluded two cases who had myxoedoema and one with a recurrence of hyperthyroidism). Of 39 cases of primary hyperthyroidism having the disease with sufficient clinical severity to require a two-stage operation the average hippuric acid excretion was found to be 1.88 gm. on admission and the average basal metabolic rate was + 54%. On the 6th day of preoperative treatment the average basal metabolic rate was + 36% and the average hippuric acid excretion 2.33 gm. The average value fell in the immediate postoperative period to 2.27 gm. with an average basal metabolic rate of + 23%, but when the time for the second stage had come, had risen to 2.51gm. and the basal metabolic rate was + 21%. Postoperatively in the second stage the average findings were 2.66 gm. with an average basal metabolic rate of + 7% and at the three month check up was 3.12gm. and minus 7% respectively. Of 31 cases of adenomatous goitre with hyperthyroidism the average hippuric acid excretion on admission was 2.27 gm. and the B.M.R. plus 36%. On the 6th day the figures were/

were 2.33 gm. and + 24% respectively, in the postoperative period 2.36 gm., and + 20% and at the three months check up 3.34 gm. and minus 6%. He showed that there was a relationship between the height of the B.M.R. and the average hippuric acid excretion and that the trend of the latter was upwards in the preoperative period followed by a slight drop in the immediate postoperative period in patients with primary hyperthyroidism. In patients with adenomatous goitre a more constant excretion was noted but in all groups a return to normal figures was found at the three months check up. No correlation was found to exist between the quantity of hippuric acid excreted and the duration of the disease. Patients with acute hyperthyroidism were found to develop degrees of liver impairment in a few months whilst patients with milder types had little change after several years. There was likewise no correlation between the degree of liver impairment and the post-operative rise of temperature or pulse rate. Digitalis appeared to have a toxic effect on the liver in hyperthyroidism as it lowered the hippuric acid excretion if given preoperatively and abnormally low values were found for the degree of thyrotoxicosis in patients who had had the drug before admission. Seventeen cases whose average hippuric acid excretion was 1.77 gm. on admission were given high carbohydrate and low fat diets and after 10 days treatment the average excretion had risen to 2.4 gm. Thirteen of these cases showed striking increases in output. Glycine was given orally in doses/

doses of 15 gm. daily to three patients whose average excretion on admission had been 0.92 gm. hippuric acid. The hippuric acid excretion returned to normal.

Boyce and McFetridge (1938) report their results in 108 cases of surgical thyroid disease using the Quick test. Pre-operatively normal values were found in 58% of cases with toxic diffuse goitre and in 57.7% of cases with toxic nodular goitre. The results in cases of non-toxic diffuse and non-toxic nodular goitre were 83% and 78.8% respectively. In 100 controls all were normal. They attribute the results in non-toxic goitre to latent toxicity. A marked fall in the immediate postoperative period was found in all groups including the controls, (a group composed of young normal persons submitted to elective appendectomy or hernioplasty). In contrast to Bartels they found a greater response to preoperative treatment in patients with toxic nodular goitre than in those with the toxic diffuse type and suggested that the difference might be accounted for by the varieties of thyroid disease in endemic and non-endemic areas. It may also have been due to the fact that their preparation was more intensive in the toxic nodular group which was composed largely of older negroes with whom they had learned to fear trouble. It was also noted that in negroes invariably lower figures were found than in white patients of the same group except in toxic diffuse goitre. They were inclined to think that the negro exhibits a low toxicity and as a consequence is inclined to ignore his symptoms. Another factor is that negro girls/

girls between 10 and 15 exhibit both a relatively and absolutely lower function regardless of the nature of the disease, thyroid or non-thyroid, than do white girls of the same age. In occasional cases they noted normal hepatic function in the face of clinical evidence of severe hyperthyroidism and offer in explanation that liver dysfunction is not present in all cases of the disease or it may be due to excessive carbohydrates or pure dextrose immediately before the test was performed. It may also be as Chiray (cited by Youmans and Warfield) has suggested that the first response of the liver to injury may be an increase in functional efficiency and states that this holds true for hepatic cirrhosis and other hepatic states and may be true here also. They regard the use of dextrose preoperatively and postoperatively as being of the greatest value in reducing the preoperative mortality in thyroid disease at the Charity Hospital and recommend its free use. They also suggest the post-operative use of oxygen and cite Judd who showed that the oxygen saturation of the blood in patients with hepatic disease is decreased.

Schmidt et al. (1941), using the oral hippuric acid test with a normal standard of excretion of 3.4 gm. benzoic acid in the four hour period as 100% and regarding 90% (3.06 gm). as the lower limit of normal, found the following values in cases of goitre:- The incidence of hepatic insufficiency in all types was 55% In diffuse hyperplastic goitre mild impairment was found in 80% and marked impairment in 40%. In toxic nodular goitre 29% showed mild impairment, 21% significant impairment, and 12% marked impairment. Much lesser degrees of insufficiency were found in diffuse/

diffuse colloid goitre and foetal adenoma. They noted no relationship to the B.M.R. and failed to produce a significant degree of improvement by the use of iodine and the bromides or barbiturates. If, however, they gave in addition intravenous glucose, insulin, bile salts, liver concentrate and glycine in doses of 6 drachms per day, improvement in liver function was produced. A drop of 10 to 20% in the hippuric acid excretion was noted on the second postoperative day and this had returned to the preoperative level by the end of a week in most cases. Such a drop was not shown in patients subjected to surgery other than thyroidectomy.

Lord and Andrus (1941) studied the plasma prothrombin levels in 36 cases of hyperthyroidism and in a series of controls (10 with non-toxic goitre, 10 who had undergone hernioplasty, 9 subjected to a major abdominal operation and 5 who had brain operations). They did not attempt apparently to test the response of the plasma prothrombin to the injection of 2-methyl-1,4-naphthoquinone. Their results showed that the level of plasma prothrombin preoperatively in hyperthyroidism bore no direct relationship with the severity of the disease, the duration of illness, the age or sex of the patient or with the type of goitre. Postoperatively a significant fall occurred in 29 out of 36 cases - the degree of fall being closely correlated with the severity of the postoperative course as evidenced by the rise in temperature, pulse rate and clinical appearance. In non-toxic goitre no significant fall occurred but there was a postoperative rise towards normal from the slightly reduced preoperative level (92%). In toxic goitre slight/

slight improvement from 87% to 92% occurred in the average prothrombin figures with preoperative treatment but after operation a precipitous fall occurred to 77% within 24 hours with a return towards the normal level at the end of 7 days. (93%). In 9 major abdominal operations no postoperative fall occurred. In 5 patients with brain operations the average postoperative fall was 6%. In these there was a moderately prolonged hyperpyrexia and they concluded that the fever alone could not account for the fall noted in toxic goitre. In 9 out of 10 hernioplasties no postoperative fall was noted. In the tenth, who developed shock, the plasma prothrombin fell to 50% two hours after operation but had returned to 90% by the 24th hour, and 100% by the 48th hour. They concluded that their evidence suggested an intimate relationship between the functional or even morphological changes in the liver and severe postoperative reaction and suggested that preoperative treatment by a high calorie, high carbohydrate, high protein and low fat diet supplemented with liberal amount of vitamin B complex was indicated.

Haines et al (1941) investigated 17 cases of adenomatous goitre and 61 cases of exophthalmic goitre. In 9 of the first group and 42 of the second the oral hippuric acid test was employed. In the remainder the intravenous test was used and in cases tested by both methods comparable results were obtained. In 22 cases the bromsulphalein retention test was also carried out and they found that a low hippuric acid output occurred in the absence of bromsulphalein retention but in all cases with dye retention/

retention greater than grade 1 there was some reduction of hippuric acid excretion. In patients with a B.M.R. of less than + 40% the average hippuric acid excretion was 3.42 gm. while in those over + 40% the average was 2.85 gm. Many with slight elevation of the B.M.R. had a low output. They found a general relationship between severity and output but there was no correlation with the amount of weight lost or with the duration of the disease. They noted improvement in the hippuric acid excretion in the preoperative period during the administration of Lugol's iodine but no significant increase in output occurred in patients who were given 9.9 mg. of thiamine chloride daily. In 8 patients who were given glycine in doses of 4 to 8 gm. thrice daily for two to three days between tests, no consistent results were obtained. The output failed to increase in two and there was only a slight increase in two others. In one patient the hippuric acid excretion remained constant throughout on a course of prolonged preoperative therapy. Postoperatively a severe reaction developed leading to a fatal result within 48 hours, and at autopsy marked hepatic changes were found. They concluded that the test was not of any great value in hyperthyroidism.

Longo and Moyano Lopez (1945) report on a variety of liver function tests carried out on 70 patients with thyrotoxicosis who came to operation. They found values of less than 3 gm. in 36% of cases using the hippuric acid test but the curve formed by all the results stayed about 3 gm. which though not fully normal showed that the insufficiency was slight. The combined hippuric acid/

acid and glycocoll test was used in 13 cases and improved the excretion of hippuric acid, hepatic insufficiency being demonstrated in only 26% of cases by this method. Bauer's galactose test as modified by Fiessinger and Thiebaut was used in 30 patients. The results led to the conclusion that there is an evident disturbance of carbohydrate metabolism probably not due to the toxic action of thyroxine on the liver but to the changes which the thyroid hormone produces on the carbohydrate metabolism. It could be affirmed that the mechanism by which the alteration is produced is not clear. The blood proteins were estimated in 13 patients by the Kjeldahl method. The total protein values were not proportional to the basal metabolism but a fall in plasma albumin was detected in 23% of patients. The blood bilirubin was determined in 17 patients and was found to be above normal in 3 (17%). The blood phosphatase in 5 cases out of 17 showed values above 4 Bodansky units but the values supposed to indicate biliary obstruction were not reached. Hanger's test was positive in 4 (15.4%) out of 26. A fall in the blood prothrombin content occurred in the postoperative period which was most marked in those with deficient prothrombin levels before operation. The original level was attained within 72 hours of operation. They noted that the results of duodenal intubation were of no practical value. They concluded that the liver was affected in a certain percentage of cases of thyrotoxicosis and that this affection is increased by surgical trauma and may then reach unsuspected levels, and therefore recommend that therapeutic steps/

steps be taken in the preoperative stage to counteract this tendency.

Piper & Poulsen (1947) investigated 30 patients with thyrotoxicosis by liver function tests and carried out liver biopsy in 15. Although the group was small it compared very closely on the average as far as duration of disease, increase in metabolism, loss of weight and age distribution with a series of 417 cases reported previously by Poulsen. They found the Takata-Ara reaction positive in 20%. The serum phosphatase in 28 cases showed a doubtful increase in 14 (8 to 10 Buch units) and an unquestionable increase in 9 (11 Buch units or more). The Formol-gel test was negative in 24 patients examined. The prothrombin time was normal in all 19 patients tested. The plasma colour was normal (less than 7) in 26 while one showed a value of 8. The platelet count was 150,000 per c.mm. or over in 24 cases, and in 3 was between 100,000 and 140,000. The urobilin in the urine diluted 1:10 was negative in 26 cases and positive in 3. No relationship could be detected between the positive results and the increase in metabolism. The results of liver biopsy are as follows:-

Glycogen content.....	Normal in 8 cases, slightly reduced in 5, markedly reduced in 2.
Normal liver tissue.....	5 cases.
Slight steatosis.....	3 cases.
Delicate dark streaks of cells as in chronic irritation.....	5 cases.
Slight round cell infiltration.....	2 cases.
Commencing cirrhosis (?) (Hyalinized connective tissue).....	1 case.

They concluded that in the majority of cases of thyrotoxicosis the functional capacity of the liver is affected only to a slight extent and that if the liver becomes the site of anatomic changes they are so slight and few that at any rate their presence 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. Liver biopsy can be of no value when it comes to estimate the state and operability of the thyrotoxic patient but on the other hand they believe that in the absence of definite signs of liver damage - Icterus or urobilinuria - there is no particular reason to hesitate with operative treatment under a general anaesthetic. If a patient with thyrotoxicosis shows signs of damage to the liver it may very well be mere coincidence.

Goodwin (1948) reports the results of serial liver function tests carried out in patients with thyrotoxicosis undergoing treatment with thiouracil. 81 patients in all were tested and had been undergoing therapy with thiouracil compounds for varying periods. Only 8 patients were tested before therapy was started and 6 of these showed abnormalities, the alkaline phosphatase being abnormal in 5 and the Takata-Ara reaction in one. In 5 cases improvement occurred on treatment up to six months duration, but in one, further impairment was noted. (The alkaline phosphatase rose from 18 to 24 King-Armstrong units). Five months later after stopping treatment the Takata-Ara reaction

was/

was positive and the alkaline phosphatase was 18 King-Armstrong units. The remaining 73 patients had all been under treatment before the tests were performed for the first time and 24 of them showed abnormality. The results of further treatment with thiouracil compounds for periods varying from 3 to 12 months were assessed. Liver function improved in 14 (58%), deteriorated in 6 (25%) and was unchanged in 4 (17%). The most frequent abnormalities found were a rise in the serum alkaline phosphatase and a positive Takata-Ara reaction. In only 8 cases were abnormalities shown in two or more tests. Two of these patients were jaundiced, one died of hepatic cirrhosis which appeared to be related to the disease rather than the therapy and the other improved with further thiouracil treatment. He concluded that in many cases thiouracil drugs improve or do not affect liver function but that in some deterioration may occur under treatment. This should not constitute a contraindication to thiouracil therapy since such deterioration may be due to the disease rather than to the thiouracil.

Lafrentz and Binimelis (1948) used thiouracil in 11 cases of hepatic cirrhosis in doses of 0.6 gm. per day to a total dosage which fluctuated between 3.6 gm. and 20.4 gm. The results were compared with the effect of therapy in two control groups, one group having a hydrocarbonate diet, glucose, serum and paracentesis; a second with a hyperprotein diet and vitamin B complex; the patients getting thiouracil also getting the second diet. Greater improvement was noted in the group on thiouracil than in the others, seven patients/

patients (63.6%) improved, one (9%) was unchanged and 3 (27%) got worse. The corresponding figures in the two control groups were 1 (11%), 4 (44.5%) and 4 (44.5%) in the first and 7 (41%), 4 (24%) and 6 (35%) in the second.

Present Investigation.

Objects.

This investigation was commenced with the object of determining the effect of thiouracil compounds on liver function in hyperthyroidism. Three liver function tests were chosen to assess the impairment of hepatic function. These were the Oral Hippuric Acid test (Quick-1933) since it had been used so extensively in previous studies before the introduction of thiouracil and two of the more recent empirical tests - Hanger's Cephalin-cholesterol Flocculation test and the Serum Colloidal Gold test. The latter tests were chosen on account of the sensitivity attributed to them, the ease in their performance and the absence of any extensive reports on the results of these tests in this condition. Both tests are semi-quantitative and were therefore regarded as 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.

Materials and Methods.

Fifty cases of thyrotoxicosis admitted to the Glasgow Royal Infirmary during the years 1947 and 1948 have been investigated. All/

All cases were regarded as being undoubted cases of the disease on clinical grounds, any patient in whom the diagnosis was questionable being excluded. The basal metabolic rate was determined at intervals throughout the course of treatment and 3 liver function tests were performed on them, 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 thiouracil drugs. The following were the liver function tests employed:-

1. The Oral Hippuric Acid (O.H.A.) test as described by Quick (1933). The normal value being the excretion of 3.0gm. hippuric acid calculated as benzoic acid in the four hour period immediately following the ingestion of 6gm. sodium benzoate.
2. Hanger's Cephalin-cholesterol Flocculation test (C.C.) as described by Dick (1945). In performing this test readings were made after 24 hours and care was taken to exclude light from the serumsaline-antigen suspension as recommended by Neefe and Reinhold (1944). The latter showed that such suspensions were markedly influenced by the amount of light to which they were exposed and many false positive reactions eliminated by observing this precaution. Normal values are designated 0 or +, abnormal values, ++,+++, and ++++.
3. The serum colloidal gold (S.C.G.) test of Gray as modified by Maclagan (1944). The semi-quantitative method described by the latter was used. No precipitation occurs with normal serum and is recorded as 0. Varying degrees of precipitation are recorded/

recorded as 1,2,3,4 up to 5 in which it is complete and the supernatant fluid is quite clear.

All three tests were carried out personally and throughout the investigation care was taken to employ precisely the same technique each time a test was performed. This was particularly important in reading the results of the serum reactions as no standards are available for comparison. Every endeavour was made to assess the degree of precipitation or flocculation on the same basis in each batch of tests.

In the analysis of results which follows three methods have been used; firstly, the number or percentage of positive results appearing in each group; secondly, the number or percentage of patients in each group showing positive reactions in one test at least, in two tests at least and in all three tests; thirdly the average result for the group as a whole. In analysing the C.C. test for average results all one + reactions although regarded as normal have been counted, as the number of such reactions appearing was very much higher in the group tested than in groups of normals. Mateer et al. (1947) found only 10% of one + reactions and 2½% of two + reactions in a group of 40 controls. In this series 42% showed one + reactions before treatment. The degree of precipitation appearing in the first tube only has been taken into account in the S.C.G. test in calculating the average result. It seemed to be of much more value to use all three methods of analysis 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 Table 1. The main features of the disease in each patient are also tabulated. Before treatment the C.C. test was carried out on 47 cases. Of these 13 (28%) were positive, ++ values being obtained in 11 and +++ values in 2. After treatment the test was done 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 of greater degree in one in whom it had been positive before treatment. The average value of the test for the group as a whole was 1.04 + before and 0.74+ after treatment.

The S.C.G. reaction was positive in 30 (60%) of cases the following values being found:-

Table 1a.

Serum Colloidal Gold Test - Distribution of Positive Results.

Degree of Precipitation	1	2	3	4	5
On admission	12	5	11	2	-
After treatment	13	4	5	3	-

It became positive for the first time in 2 patients, became worse in 4, was unchanged in 10, and improved in 8. In 7 patients it became normal. The average value of the test for the group as a whole was 1.26 before treatment and 0.96 after treatment.

The/

CASE NO.	AGE	SEX	TYPE OF DISEASE.	DURATION.	PERCENTAGE OF STANDARD WEIGHT	B.M.R.		SERUM CHOLESTEROL MG. Per 100 c.c		C.C.		S. C. G.		O. H. A. (GRAMMES).		PERCENTAGE FALL IN B.M.R.	WEIGHT DURING TREATMENT (Lbs).	INFECTION PRESENT ON ADMISSION	PREVIOUS STREPTOCOCCAL OR RELATED INFECTION	AMOUNT OF THIOURACIL (GRAMMES).
						1	2	1	2	1	2	1	2	1	2					
1	17	F	P	6mos.	104	+10	-11	217	160	-	0	211000	000000	2.50	4.55	19	+1	-*	-	7.2
2	15	F	P	6 "	97	+12	+3	95	200	+	+	110000	321000	2.43	2.95	8	+1	-	-	6.3
3+	34	F	P	3 "	85	+16	+0	133	190	+	+	000000	000000	2.06	3.52	14	+4.5	-	+	10.8
4+	23	F	P	4yrs.	92	+18	-20	214	150	-	0	100000	100000	2.64	3.63	32	-2	+*	+	12.9
5	22	F	P	11"	88	+18	+6	147	277	+	0	000000	000000	2.48	3.36	10	+1	-	-	7.7
6+	28	F	P	4mos	107	+18	-1	200	227	0	0	310000	110000	2.08	2.97	16	+1	+	+	13.6
7	25	F	P	9 "	89	+19	-7	170	217	+	+	000000	000000	3.62	3.68	14	+2	-	-	10.2
8+	25	F	P	9 "	83	+24	-6	133	227	0	0	000000	000000	2.72	2.95	15	+4	-	+	9.6
9	55	M	P	5yrs	91	+25	+14	188	-	+	+	300000	210000	2.63	3.80	9	+5	-	-	12.3
10	57	F	P A.F	9mos	85	+26	+5	143	153	+	+	210000	100000	1.46	2.25	17	-1	+	+	11.4
11	40	M	P	4 "	90	+26	+14	111	100	+	+	321000	100000	3.38	3.28	10	+4	-	-	18.6
12	23	F	P	9mos.	93	+27	+13	155	100	++	0	000000	000000	1.70	4.07	11	+9	+	-	P.T. 12.0
13	57	F	P	5yrs.	85	+29	-3	70	250	++	0	110000	000000	1.43	2.47	25	+0.5	-	+	13.2
14	16	M	P	1yr.	86	+31	+12	67	133	+	0	000000	000000	3.49	3.35	15	+10	-	+	16.2
15	36	F	P	1yr.	85	+31	-12	111	119	+	0	000000	000000	1.99	1.13	33	-1	+*	+	2.7
16	47	F	P	1yr.	102	+33	-4	130	180	+	+	000000	000000	2.80	1.97	28	+15	+	-	18.6
17	39	F	P	6mos	69	+33	-3	200	208	+	+	110000	1100000	1.52	1.48	27	-1	-*	-	15.6
18	33	F	P	6mos	74	+33	+20	118	154	++	0	431000	200000	1.97	3.37	10	+11	+*	+	14.1
19+	37	M	P	6mos	82	+36	+ 7	188	250	0	0	000000	000000	3.65	3.76	21	+1	-*	+	16.8
20	26	F	P	3mos	80	+37	-30	167	250	+++	+	332000	000000	2.37	3.15	49	+10	+	+	M.T. 28.8
21	45	F	P	4mos	83	+38	+3	125	180	+	++	100000	443100	0.99	1.63	25	=2	+	+	14.0
22	21	F	P	1½yrs	101	+38	+48	118	133	0	0	000000	000000	3.03	3.95	+7	-2	-	-	P.T. 20.4 225
23+	34	M	P	3mos	98	+39	+13	250	105	0	0	000000	000000	1.54	3.02	19	-5	+*	+	16.8
24+	47	M	P	4yrs	82	+39	+9	125	100	0	0	320000	320000	2.89	2.85	22	+1.5	-	+	11.4
25	30	M	P	9mos	107	+40	+3	111	129	+	0	100000	000000	3.76	3.36	26	+ 5	-	-	11.6
26	21	F	P	1yr.	97	+41	+13	100	200	+	+	000000	000000	2.86	3.23	20	+17	-	-	18.0
27+	52	F	S	8mos	75	+43	+0	250	-	0	++	100000	430000	2.55	1.69	30	-2	-	-	15.0
28+	31	F	P	2yrs	99	+44	+17	161	144	-	+	100000	000000	1.49	3.20	19	-3.5	-	+	15.6
29+	27	F	P	3mos	89	+44	-5	80	164	+	++	000000	100000	2.95	3.64	34	-1.5	-	+	12.0
30	16	F	P	1yr.	92	+44	+16	68	105	0	0	000000	000000	3.18	3.07	19	+11	+*	+	14.4
31+	40	F	P	1yr.	77	+46	+17	125	250	++	+	000000	000000	2.20	4.26	20	+18	+	-	18.6
32+	49	F	P	1yr.	99	+46	+20	125	167	0	0	000000	000000	3.01	3.69	18	+15	-	-	P.T. 3.6 6.0
33+	50	F	P	1yr.	89	+49	+15	139	250	+	0	100000	000000	3.17	3.13	23	+0	-	+	14.4
34+	51	F	P	2yr.	76	+50	+14	118	182	0	++	000000	000000	1.54	3.83	24	+11	-	-	P.T. 6.4 5.4
35	43	F	P	1½yr.	79	+50	-6	99	143	++	+++	110000	321000	0.35	3.54	37	+9	+	+	M.T. 22.0
36	47	M	P	1yr.	90	+50	+9	154	266	0	0	000000	000000	2.86	3.17	27	+9	-	+	19.8
37	42	F	P	4mos.	75	+53	+16	200	148	+	0	321000	321000	2.76	2.79	24	+8	-	-	15.4
38+	29	F	P	3yrs.	96	+54	+20	117	125	+++	+	320000	100000	1.81	2.25	23	+6.5	-*	+	22.8
39+	39	F	P	1yr.	88	+54	+1	79	143	++	++	000000	100000	2.52	3.07	34	+4	-	+	17.8
40+	34	F	P	5mos.	105	+56	+12	74	180	+	+	221000	000000	3.47	4.06	29	+7	-	+	18.6
41	40	F	P	1yr.	96	+57	+9	154	266	++	+	321000	100000	2.86	3.17	31	+4.5	+*	+	M.T. 21.4
42+	54	F	S A.F	7yrs.	82	+61	-10	118	166	0	0	000000	000000	2.35	3.67	44	+0	+	-	14.4
43+	36	M	P	2yr.	78	+65	+4	70	83	+	+	100000	100000	2.89	2.14	37	+1.25	-	-	14.4
44+	26	F	P	6wks.	82	+65	+13	147	154	++	0	321000	100000	3.40	3.66	32	+12	+	-	P.T. 14.4 5.0
45+	36	F	P	6mos.	87	+66	+7	143	133	0	+	321000	321000	3.19	2.60	36	+2.5	+*	+	13.8
46+	55	F	P	3yrs.	75	+74	+12	113	200	+	+	321000	100000	1.25	3.13	37	-1	+	+	23.8
47	45	F	P	1½yr.	82	+74	-12	118	200	++	+	210000	210000	3.50	3.96	49	+8	-	-	26.0
48+	36	F	P	1yr.	92	+78	+25	148	100	++	+	431000	421000	1.70	2.33	30	-4.5	+*	+	21.8
49	53	F	S	3mos.	89	+78	+36	140	-	++	+	210000	210000	1.73	1.97	24	+5	-	-	19.2
50	36	F	P	6mos.	90	+99	+1	131	181	+	+	100000	100000	4.06	2.80	49	-	-	-	10.4
Avge.	34.4				88	+42	+7			104+	0.74+	1.26	0.96	2.54	3.09					

1 = Before Treatment
2 = After "
+ = Subtotal thyroidectomy (Col.1).

P = Primary hyperthyroidism
S = Secondary hyperthyroidism
A.F.= Auricular Fibrillation.

* = Acute sore throat whilst under treatment.
M.T.= Methyl thiouracil
P.T.= Protyl thiouracil.

TABLE I.

The O.H.A. test was positive in 36 (72%) before treatment and in 18 (36%) after. 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 group as a whole was 2.54gm. before and 3.09 gm. after treatment.

Taking all three liver function tests together before treatment 88% had one test positive, 54% had two, and 16% had three. After treatment the figures are 60%, 34% and 4% respectively.

It is seen from inspection of Table 1 that the three liver function tests appear to bear little or no relationship to one another. One finds that in some cases one test may be positive while the others are negative and yet after treatment the originally positive test becomes negative and the originally negative test becomes positive. This is exemplified in cases 29 and 35.

No close correlation appears 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 has therefore been made to divide the patients into suitable groups and compare the results of the liver function tests in these groups to see if such analysis can throw any light on the problem by indicating broad trends rather than an absolute relationship. The results of this analysis follow.

Tables 2a,2b and 2c show the findings with the B.M.R. on admission.

Relation of liver function tests to the original B.M.R.

Table 2a.

All three tests together.

B.M.R.	No.	At least one test positive			At least two tests positive.			All three positive.		
		1	2	Impr.%	1	2	Impr.%	1	2	Impr.
0 - +20	7	86%	43%	50	57%	29%	50	-	-	-
+21 - +40	17	84%	66%	21	60%	24%	60	18%	6%	57%
+41 - +60	17	90%	48%	46	48%	30%	38	18%	6%	67%
+61 - +100	9	100%	88%	12	66%	44%	33	22%	0%	100%

Table 2b. Percentage of patients showing a positive test in each group.

B.M.R.	No.	C. C.			S.C.G.			O. H. A.		
		1	2	Impr.	1	2	Impr.	1	2	Impr.
0 - +20	7	-	-	-	57%	43%	23%	84%	28%	66%
+21-+40	17	24%	6%	75%	54%	42%	22%	78%	48%	38%
+41-+60	17	30%	30%	0%	54%	42%	22%	72%	18%	75%
+61-+100	9	44%	0%	100%	88%	88%	0%	55%	55%	0%

Table 2c. Average value of each test.

B.M.R.	No.	C. C.			S.C.G.			O. H. A.		
		1	2	Impr.	1	2	Impr.	1	2	Impr.
0-+20	7	0.8+	0.43+	46%	0.85	0.57	33%	2.75	3.23	17%
+21-+40	17	1.0+	0.47+	53%	1.23	0.80	33%	2.33	2.84	18%
+41-+60	17	1.06+	1.0+	5.7%	0.76	0.76	0%	2.46	3.24	32%
+61-+100	9	1.22+	0.78+	36%	2.12	1.89	11%	2.66	2.92	11%

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

No relationship exists between the degree of impairment of liver function and the height of the B.M.R. nor does the B.M.R. have any bearing on the degree of improvement which occurs in the tests on treatment. This is particularly well seen in Table 2b in which the C.C. tests shows increasing impairment with rise in B.M.R. while the O.H.A. test shows progressive diminution. In the highest group 100% improvement occurs in the C.C. test but none whatsoever in the O.H.A. test.

Tables 3a, 3b, and 3c, show that there is no relation between the duration of the disease and the degree of impairment of liver function. They further show that the duration has no bearing on the degree of improvement in the tests which takes place under treatment.

Tables 4a, 4b and 4c show the correlation with age. Taking all three tests together (Table 4a) 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 the younger groups. If the tests are considered individually the C.C. test shows no relation 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 with increase in age. The S.C.G. and O.H.A. 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/

Relation to Duration of Disease.

Table 3a. All three tests together.

Duration	No.	Av.B.M.R.		At least one test positive			At least two tests positive			All three positive.		
		1	2	1	2	Impr.	1	2	Impr.	1	2	Impr.
0-6 mos.	18	+42	+6	94%	60%	28%	55%	50%	9%	17%	6%	68%
6mo-1yr.	18	+41	+7	77%	44%	43%	39%	22%	44%	11%	6%	50%
1-3yrs.	8	+56	+12	100%	75%	25%	88%	38%	57%	25%	0%	100%
Over 3 yrs.	6	+32	-1	100%	67%	33%	67%	17%	75%	17%	0%	100%

Table 3b. Percentage of patients showing a positive test in each group.

Duration	No.	Av.B.M.R.		C.C.			S.C.G.			C.H.A.		
		1	2	1	2	Impr.	1	2	Impr.	1	2	Impr.
0-6mos	18	+42	+6	24%	11%	54%	78%	67%	14%	67%	44%	34%
6mos-1yr.	18	+41	+7	28%	11%	61%	33%	11%	67%	67%	33%	50%
1-3yrs.	8	+56	+12	43%	25%	42%	75%	50%	33%	75%	25%	67%
Over 3yrs.	6	+32	-1	20%	0%	100%	50%	50%	0%	100%	33%	67%

Table 3c. Average value of test in each group.

Duration	No.	Av.B.M.R.		C.C.			S.C.G.			O.H.A.		
		1	2	1	2	Impr.	1	2	Impr.	1	2	Impr.
0-6mos.	18	+42	+6	1.0+	0.72+	28%	1.77	1.35	24%	2.56	3.07	20%
6mo-1yr.	18	+41	+7	1.0+	0.61+	39%	0.66	0.61	8%	2.69	2.98	10%
1-3yrs.	8	+56	+12	1.28+	1.25+	2%	1.37	1.00	27%	1.98	3.25	65%
Over 3yrs.	6	+32	-1	0.8+	0.16+	80%	1.00	1.00	0%	2.40	3.29	37%

1 = Before Treatment.
2 = After Treatment.
Impr.= Improvement.

Relation to Age.

Table 4a. 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%

Table 4b. 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 4c. 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.

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 O.H.A. are still abnormal after treatment and that with the S.C.G. test one of the older age groups shows further impairment.

The effect of sex is shown in Tables 5a, 5b and 5c. A lesser degree of impairment of liver function was found in males than in females. There were however only nine males in the series. No male patient had a positive C.C. reaction, none showed three tests positive and the average value of the O.H.A. test was within normal limits, on admission. The average value of the S.C.G. was essentially the same in the two sexes. Sex did not appear to be related to the degree of improvement which took place under treatment.

Tables 6a and 6b compare the results in primary and secondary hyperthyroidism. A rather higher percentage of positive results was found in the secondary group (Table 6a) than in the primary but the difference does not appear to be of any significance. Table 6b shows a lesser degree of impairment in the secondary group as far as the serum reactions are concerned but both become considerably worse after treatment.

In tables 7a,7b and 7c is shown the correlation between the impairment of liver function and the actual weight of the patient on admission calculated as a percentage of the Standard Weight/

Relation to Sex.

Table 5a. All three tests together.

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%

Table 5b. 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	+29	+11	-	-	-	55%	44%	20%	55%	22%	60%
F.	41	+43	+ 5	32%	15%	53%	61%	57%	16%	76%	39%	49%

Table 5c. 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	0.32	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)

Relation to type of thyrotoxicosis.

Table 6a. Percentage of patients showing a positive test in each group.

Type of disease	No.	Age (Aver.)	B. M. R.		C.C.			S.C.G.			O.H.A.		
			1	2	1	2	Imp.	1	2	Imp.	1	2	Imp.
Primary	47	33	+41	+6	23%	11%	52%	60%	49%	18%	70%	34%	51%
Secondary	3	53	+60	+8	33%	33%	0%	66%	66%	0%	100%	66%	33%

Table 6b. Average value of each test.

Type of disease	No.	Age (Aver.)	B. M. R.		C.C.			S.C.G.			O.H.A.		
			1	2	1	2	Imp.	1	2	Imp.	1	2	Imp.
Primary	47	33	+41	+6	1.07+	0.70‡	35%	1.28	0.90	30%	2.58	3.14	21%
Secondary	3	53	+60	+8	0.66+	1.00+	-50%	1.00	2.00	-100%	2.21	2.44	10%

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. It is 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 7a) 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 7b and 7c with the C.C. and O.H.A. tests but not with the S.C.G. reaction. The degree of improvement calculated as a percentage in the O.H.A. test is an exception to this rule but it will be seen that the average values of this test after treatment show progressive diminution as the percentage of the Standard Weight decreases.

The improvement which took place in the B.M.R. under treatment has been calculated as a percentage of the original value and the series divided into five suitable groups. The results of the liver function tests before and after treatment are compared in these groups in Tables 8a,8b and 8c. No relationship appears to exist/

Relation to Weight (percentage which actual weight bears to Standard weight).

Table 7a. All three tests taken 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% & 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%

Table 7b. 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 7c. 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%

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

Comparison of improvement in B.M.R. with improvement in liver function.

Table 8a. All three tests taken together.

Imp.in B.M.R.	Imp.in Wt (lbs)	No.	At least one test positive			At least two tests positive			All three positive.		
			1	2	Imp.	1	2	Imp.	1	2	Imp.
41-50%	+6	4	100%	50%	50%	50%	25%	50%	25%	0%	100%
31-40%	+2	12	100%	100%	0%	85%	60%	29%	25%	9%	64%
21-30%	+6	16	94%	56%	40%	50%	31%	38%	19%	6%	66%
11-20%	+4	15	73%	33%	55%	40%	13%	68%	7%	0%	100%
1-10%	+1	3	67%	67%	0%	67%	33%	50%	-	-	-

Table 8b. Percentage of patients showing a positive test in each group.

Imp. in B.M.R.	Imp.in Wt (lbs).	No.	C.C.			S.C.G.			O.H.A.		
			1	2	Imp.	1	2	Imp.	1	2	Imp.
41-50%	+6	4	50%	0%	100%	75%	50%	33%	50%	25%	50%
31-40%	+2	12	55%	25%	54%	75%	91%	-21%	83%	42%	50%
21-30%	+6	16	25%	13%	50%	56%	38%	34%	75%	50%	33%
11-20%	+4	15	15%	0%	100%	40%	26%	36%	67%	20%	70%
1-10%	+1	3	-	-	-	67%	33%	50%	67%	33%	50%

Table 8c. Average value of each test.

Imp.in B.M.R.	Imp.in Wt (lbs).	No.	C.C.			S.C.G.			O. H. A.		
			1	2	Imp.	1	2	Imp.	1	2	Imp.
41-50%	+6	4	1.50+	0.75+	50%	1.50	0.75	50%	3.07	3.22	7%
81-40%	+2	12	1.07+	1.00+	7%	1.66	1.75	-5%	2.36	2.81	19%
21-30%	+6	16	1.06+	0.70+	34%	1.06	0.87	18%	2.46	2.88	17%
11-20%	+4	15	0.75+	0.33+	55%	1.00	0.33	67%	2.44	3.55	45%
1-10%	+1	3	0.66+	0.66+	0%	1.33	1.66	-25%	2.73	3.56	30%

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

exist between the two factors either when the tests are taken together or individually. The progress of the patients under treatment has also been assessed according to the amount of weight gained or lost and this has been correlated with the results of the liver function tests in Tables 9a, 9b, and 9c. They show that there is a very apparent relationship between the amount of weight gained or lost and the improvement or worsening which occurs in the liver function tests. This trend is seen by all methods of analysis except with the O.H.A. test(Table 9c) when the improvement which occurs is calculated as a percentage of the original value but if the actual excretion of hippuric acid is taken as an average for each group it is seen that there is a progressive fall in the value obtained after treatment as the amount of weight gained diminishes.

It was noted during the course of the investigation that a high proportion of the patients developed acute sore throat whilst under observation. In all 12 out of 50 had this complication. Three of them occurred before thiouracil therapy was commenced and the remaining nine while under treatment. If account of the number of days under observation be taken in these patients in whom the complication occurred the incidence was one sore throat every 58th day without the drug and one sore throat 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 developed granulocytopenia/

Comparison of results of liver function tests with variation in weight, while under treatment.

Table 9a. All three tests taken together.

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%
+ 5-9.9	10	39	+51	+11	100%	50%	50%	70%	30%	57%	30%	0%	100%
+ 0-4.9	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%

Table 9b. 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%
+5-9.9	10	39	+51	+11	50%	10%	80%	80%	60%	25%	70%	30%	57%
0-+4.9	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 9c. 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%
+5-9.9	10	39	+51	+11	1.50+	0.80+	47%	1.90	1.40	26%	2.46	3.30	34%
0-+4.9	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.

granulocytopenia necessitating withdrawal of the drug and therapy was reinstituted without trouble when the throat had settled. The incidence of sore throat in one of the wards was calculated over the period whilst the investigation was being undertaken with the following results:-

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 throats 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 10a, 10b, and 10c. The infections which were found on admission were principally of the respiratory type - chronically infected tonsils, and bronchitis but also included skin infection, 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 analysis. No constant difference/

Relation to presence of infection on admission.

Table 10a. All three tests taken together.

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%

Table 10b. 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 10c. 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.

difference is noted in the two groups as regards the amount of improvement which takes place under treatment.

Throat swabs in five of the patients who had sore throat were taken. In two haemolytic streptococci were grown on culture and the remainder grew mainly Streptococcus viridans. As it is most likely that all the throat infections were due to streptococci it was thought desirable to see if there were any relationship between impaired liver function and previous streptococcal infection. All patients who gave a history of a previous streptococcal infection 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 11a, 11b and 11c. The two groups are comparable as far as age, percentage of Standard Weight and B.M.R. are concerned. A greater degree of impairment of liver function is indicated by the O.H.A. and S.C.G. tests in the group with a history of previous streptococcal infection than in those without. The C.C. test does not appear to show any significant difference in the two groups. It is noteworthy (Table 11a) that 26% of those who gave a history of such infection had all three tests positive but only 4% in the group without such a history.

One patient only had digitalis during treatment (No.10). It will be seen from Table 1 that improvement occurred in all three liver/

Correlation with history of a previous streptococcal or related infection.

Table 11a. All three tests taken together.

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%

Table 11b. Percentage of patients showing a positive test in each group.

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 11c. 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%

liver function tests. This finding is in contradistinction to Bartels who found that digitalis given preoperatively lowered hippuric acid excretion. No other drug which was given during treatment e.g. bromide or phenobarbitone was found to have any adverse effect on the results of the liver function tests.

Twenty-four of the patients in this series underwent a subtotal thyroidectomy. Of this number only one (No.23) developed a severe post-operative 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.

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 with the O.H.A. test was slightly less than that found by Bartels in 78 cases of primary hyperthyroidism whose condition was of sufficient mildness to permit a subtotal thyroidectomy. It was considerably less than in 39 of his patients whose condition would only permit a two stage operation. On the other hand, a greater incidence of impairment was found by this test in this series than was found by Boyce and McFetridge and by Longo and Lopez. The variations found by the several observers may be due to differences in the type of thyrotoxicosis met with in endemic and non-endemic areas or to racial differences as suggested by Boyce and McFetridge. It may also be that differences in the severity of the disease in the separate series account for the differences. For example the average B.M.R. in Bartels cases who had a one stage operation was plus 36 and in those requiring a two stage operation was plus 54 whereas in the present series the average B.M.R. on admission was plus 42. With the C.C. test an incidence of 26% of positive results is slightly higher than that found by Longo and Lopez (15.4% in 26 cases). No results are available for comparison with the S.C.G. reaction. The tests in order of decreasing sensitivity were found to be the O.H.A., S.C.G. and/

and C.C. This is not in accordance with the experience of others. Mateer et al. (1947) in a study of miscellaneous hepatic disorders grade the C.C. test one of the most sensitive of liver function tests whilst the O.H.A. test is graded as being of intermediate sensitivity. The thymol turbidity test (pH 7.8) is also regarded by him as of intermediate sensitivity and Carter and Maclagan (1946) found this test less sensitive than the S.C.G. in diseases not primarily hepatic. It would appear therefore that some mechanism other than actual hepatic damage may be responsible for the inconsistent results which are found in thyrotoxicosis. That no correlation between the degree of liver impairment and the B.M.R. has been found to exist may be explained on the ground 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 it would not be expected to find a close relationship between the degree of impairment of liver function and the duration of the disease for the same reason. That there is a tendency for a greater percentage of positive results to appear in the older age groups is a matter which does not occasion surprise. It is possible that this tendency is accounted for by the diminution in functional reserve which one would expect in older tissues although such diminution may be intensified by the factors causing impairment. The relationship/

relationship to sex is more difficult to account for except by the old tradition that females are the weaker. The small number of males examined tends to discount the results obtained and renders them less significant. Paradoxically Gyorgy (1946) reporting the results obtained with carbon tetrachloride in rats kept under varying dietary conditions found that male rats appeared to evince a greater susceptibility to liver injury with this substance than females, especially with a high fat intake. He further reports that oestrone exerts a small but definite lipotropic effect when fed at a level of 30 micrograms per day to intact and castrated female rats on a diet which produces fatty livers.

The finding that a fairly close relationship exists between the degree of impairment of liver function and the percentage which the actual weight of the patients 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 thyrotoxicosis. On the other hand, it may simply mean that the depressed liver function is caused by the relative malnutrition of which loss of weight is an excellent index and bears no relationship to the thyrotoxic condition per se. The relationship of the liver function tests to the role of infection is

more/

more difficult to explain. Infection has been shown to aggravate the clinical condition of thyrotoxic patients and it has also been found that in such patients liver function is further impaired. 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 is shown by my results in Tables 10a, 10b, and 10c. These 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 evidence supports the finding of Haban and of Schultz and Sealy who regarded infection as an important factor in producing liver damage in experimental hyperthyroidism. The relationship which appears to exist between a history of previous streptococcal infection and impaired liver function 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. On the other hand, it suggests that streptococcal infection may be responsible for the development of thyrotoxicosis. This seems unlikely as one would expect to find that the hyperthyroid state supervened much earlier and that there would not be such a long latent period. Several patients gave a history of infection, usually a sore throat, at the onset of their disease but it appears more likely that in view of the known aggravation of thyrotoxicosis by an infective process and of the known/

known susceptibility of such patients to infection that the infection merely served to uncover a latent hyperthyroid state.

Considerable improvement in liver function occurs under treatment with thiouracil and it has been seen that this improvement is more closely correlated to the gain in weight than it does to the fall in B.M.R. That the former is more valuable gauge of the degree of improvement has already been discussed and as the relationship to liver damage is open to the same arguments as have been expressed earlier none but confirmatory significance can be attached to the observation. 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 some patients in whom the expected improvement does not take place and in whom further deterioration occurs (Patients 16,34 and 35) in spite of a considerable gain in weight without there being any obvious causal factor. Such cases may be due to the action of thiouracil on the liver but 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 in these cases that a hepatic lesion induced by the thyrotoxicosis may progress in spite of the fact that the hyperthyroidism is controlled. There is some evidence to support this hypothesis (see the results obtained in the treatment of hepatic cirrhosis with thiouracil by Lafrentz and Binimelis, quoted above).

Himsworth (1947) reviewing the pathogenesis of hepatic disease attributes the production of massive hepatic necrosis in experimental animals to deficiency of cystine and possibly tocopherol and the production of fatty infiltration to the deficiency of methionine. The sequelae of these lesions he terms postnecrotic scarring and diffuse hepatic fibrosis respectively. Although two well defined forms of liver injury could be produced by carefully controlled experimental diets, in nature a diet deficient in one factor is likely to be deficient in others and so mixed lesions are commonly found. Malnutrition is common in the tropics and is known variously as Kwashiokor, malignant malnutrition and infantile pellagra. It is much commoner in children especially after weaning when the child is getting adjusted to the coarse deficient diets of his elders. It occurs only in native races and then only in the poorer classes. In Western civilization it attacks previously healthy children only in 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. He expresses the opinion that in thyrotoxicosis the increased nutritional requirements consequent on the increased metabolic rate may well contribute to the development of hepatic lesions. The relationship, noted in this investigation between the loss of weight and impairment of liver function is evidence which strongly supports this view. It is probable/

probable that in thyrotoxicosis liver injury is determined to a great extent by a dietary deficiency of protein which is not absolute but relative and is due to the increased metabolism, rather than a specific toxic effect of thyroxine. That all the lesions which have been described at autopsy may be produced solely in this way is quite possible but other factors may have to be taken into account. Himsworth further refers 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, and although the lesions found in toxic goitre cannot be wholly accounted for on this hypothesis it will undoubtedly contribute towards them.

The Significance of the Liver Function Tests.

It is appropriate to consider the significance of the tests of liver function which have been employed in this investigation. Little or no relationship has been found to exist between the results of such tests and the appearance of the liver as judged by the results of aspiration biopsy. Sherlock (1946) carried out a comparative investigation in cases of acute hepatitis, active and inactive cirrhosis and obstructive jaundice. She noted no relationship between the appearances of the liver and the results of intravenous hippuric acid tests in acute hepatitis or in cirrhosis. Of the liver function tests used the closest correlation appeared to be with the Galactose Time. The work of Piper and Poulsen suggests that in the average case of thyrotoxicosis the changes in the liver are so slight as to be insignificant. However the results of biopsy are open to the criticism that the appearances of a small piece of tissue removed in such a manner need not reflect the changes present in the organ as a whole.

Regarding the hippuric acid test Quick (1933) found that the excretion of hippuric acid remained relatively constant irrespective of the amount of benzoic acid administered. He also noted that in patients showing impairment marked improvement occurred when the patients were fed glycine and came to the conclusion that this indicated a definite capacity for the organism to synthesize glycine. As it was commonly accepted that glycine was formed in the liver it seemed probable that certain types of liver damage/

damage would impair this synthesis and so result in a diminished output of hippuric acid. Probstein and Londe (1942) carried out a series of experiments in which they first administered sodium benzoate alone and later gave sodium benzoate and glycine and compared the excretion of hippuric acid found on each occasion. Out of 30 patients, in 6 no increase in hippuric acid excretion occurred when the mixture was given and in them they concluded that there was a definite impairment of the conjugation mechanism. The remaining 24 responded with a rise in rate of hippuric acid synthesis in the first two hours and they concluded that in them the decreased elimination of hippuric acid in the four hour test was mainly due to the diminished ability of the liver to furnish aminoacetic acid. That feeding glycine in large doses may lead to normal excretion of hippuric acid in patients with thyrotoxicosis has been demonstrated by Bartels. Haines, Magath and Power however had inconsistent results in similar experiments failing to increase the output in 2 out of 8 cases and producing only slight improvement in 2 others. It would thus appear possible that instead of being dependent on structural damage in the liver the decreased hippuric acid excretion may be due to other factors which would compete with the benzoic acid for the available glycine. In hyperthyroidism where metabolism is increased such glycine as is available or formed may be seized on for metabolic purposes and burned for the purpose of providing energy. This hypothesis accords with the observation that there is a general relationship between the amount of weight lost and the excretion of hippuric/

hippuric acid in this disease. It also accounts for the improvement in excretion which occurs in patients when the weight increases for at that time more amino acids will have become available for detoxicating purposes and such competing factors will be considerably reduced. Sloan and Shorr (1944) support this theory with evidence to show that under treatment with thiouracil the nitrogen balance becomes increasingly more positive in hyperthyroidism. That it requires merely an extension of these principles to account for the production of actual hepatic damage has already been discussed. Gyorgy and Goldblatt (1945) 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 serous 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 is produced which manifests itself by a a lesser incidence not only of trophopathic (purely dietary) but also of toxipathic(postnecrotic) cirrhosis.

Maclagan (1948) in a recent discussion on the significance of the flocculation tests lists the following fractions of the plasma proteins as acting as inhibiting or precipitating factors in the tests employed thus:-

Test/

Test	Protein Fractions Active		Correlation with total globulin.
	Precipitating	Inhibiting.	
Colloidal gold	gamma-globulin	Albumin alpha and beta-globulin	Slight
Cephalin cholesterol			
	gamma-globulin		Slight.
	alpha		
	beta "	Albumin	

That little correlation existed between the two flocculation tests in this investigation is not surprising as in one (S.C.G) alpha and beta-globulin act as inhibiting agents but in the other (C.C.) as precipitating agents. McCullagh (1946) notes as a physiological effect of thiouracil an increase of 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 senitivity of the S.C.G. test while it would diminish that of the C.C. The principal result of the work reviewed by Maclagan and referred to above is that all flocculation tests depend on relative gamma-globulin excess. However it has been shown by Maclagan and Bunn (1947) that only the gamma-globulin from hepatitis serum produces flocculation in the thymol test whereas normal gamma-globulin produces no flocculation but only turbidity. Similarily in this work it has been shown that only the hepatitis (alpha and beta) fractions precipitated the cephalin cholesterol and Takata-Ara reagents while normal alpha and beta fractions did not. Differences in the albumin fractions have also been noted, normal albumin inhibiting the thymol turbidity test while hepatitis albumin does not. Similar differences in/

in the inhibitory power of the albumin fractions have been observed by Guttman et al. (1946) and Moore et al. (1945) in studies of the cephalin cholesterol reaction. It would therefore appear that qualitative changes in these fractions are important. Electrophoretic studies of the plasma proteins by Gray and Barron (1942) have shown that in infective hepatitis beta and gamma-globulins are increased while albumin is diminished. In cirrhosis similar changes were found, the increase in globulin affecting particularly the gamma fraction but also the beta and alpha fractions in some cases. These changes are capable of accounting for the positive results found in the flocculation tests in these diseases. In endocrine disturbances alterations in the plasma proteins have also been described. Leathem (1945) states that in rats hypophysectomy 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 thiourea on the plasma proteins of rats and found that the concentration of serum globulin was increased while serum albumin remained unchanged. Williams et al. (1944), cited by Leathem,found no change in the total protein in thiouracil treated patients. This does not preclude the possibility of such changes occurring which might be detected by the more sensitive flocculation tests. Although the rats in Leathem's experiments lost weight he was of opinion that the fall in the blood proteins did/

did not simulate the changes found in partial starvation. In the latter a decrease in serum albumin in addition to an increase of globulin is observed and the latter is of less degree than that seen in thiourea fed animals. Bieler et al. (1947) state that in the hypoproteinaemia of malnutrition the plasma proteins differ from normal only in a slight relative decrease in serum albumin. There is a general decrease in all proteins so that there is not such a marked alteration in the albumin-globulin ratio as in diseases which affect the specialized globulins. The patients in whom their study was carried out were all free from infection and had been subsisting on low protein diets. Krebs (1946) studied the plasma proteins electrophoretically in one patient with nutritional oedoema and found lowering of globulin as well as albumin. The most striking drop being in the gammaglobulin although both alpha and beta fractions were also lowered. Recovery to normal values occurred under treatment.

Increase in the gamma-globulin fraction are not confined to liver diseases but have also been observed in other conditions the most notable of which are infections. Dole et al. (1945) have reported this finding in scarlet and rheumatic fever, in both conditions being associated with a rise in globulin and depression of albumin. It has also been found in bacterial endocarditis, chronic malaria and lymphogranuloma. Enders (1944) states that this probably reflects an increase in the amount of circulating antibody and in studies of Fraction 2 (99% gamma-globulin) of pooled plasma has/

has demonstrated a higher concentration of streptococcus erythrogenic antibody than in the serum of convalescents. Positive results in the flocculation tests have also been noted in malaria, glandular fever, subacute bacterial endocarditis, and rheumatoid arthritis (Carter and Maclagan, 1946) and these may be due to an increase in circulating antibody in the gamma-globulin rather than to actual hepatic change.

It is thus apparent that changes in the plasma proteins may occur in thyrotoxicosis which would affect the flocculation tests without necessarily reflecting any histological change in the liver. Such changes may be due to the effect of certain hormones - pituitary or thyroid, a condition of partial starvation or increase in circulating antibody due to the susceptibility of these patients to infection. Although the role of infection may be responsible for the changes which occur in the flocculation tests it is interesting to note that similar differences occur 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 liver damage.

Conclusions and Summary.

That in cases of thyrotoxicosis which come to autopsy there is an unusually high percentage which show evidence of liver damage is undoubted from the numerous reviews of the subject already quoted. In the average case of thyrotoxicosis met with clinically evidence of hepatic damage may be found in a high proportion by means of liver function tests. The degree of impairment is on the average only slight and in the great majority of cases responds rapidly to the control of the disease with thiouracil. Certain patients however show further impairment of liver function under treatment and the possible reasons for this have been considered.

There has been difficulty in correlating the results of liver function tests with the appearances of the organ found at aspiration biopsy and the significance of the positive results of the tests used in this investigation have been discussed from this viewpoint. It would appear that positive results may be obtained in hyperthyroidism not only as a result of actual liver damage but also from a number of associated factors. The oral hippuric acid test may be impaired on account of competition for glycine for metabolic needs. The flocculation reactions may be complicated by changes occurring in the plasma proteins as a result of the toxic action of thyroid hormone, a condition of partial starvation or infective processes. The precise part which each of these factors may play will have to await the results of more detailed analysis of the factors/

factors causing precipitation and the precise significance of such changes in the conditions in which they have been noted.

Supporting evidence has been produced to show that as had been suggested when liver damage does occur it is probably due to a relative nutritional deficiency of such substances as cystine, methionine and tocopherol which has arisen as the result of the increased metabolism. This being largely a question of balance will be influenced by such factors as the patients appetite and his economic position to satisfy it. The rather higher incidence noted in this series than by certain American writers may be due to the system of food rationing in this country and the inability of the patient to secure an adequate amount of food, particularly protein to satisfy his needs. In individual cases liver damage may be aggravated by anaemia, anoxaemia, chronic venous congestion or the action of drugs such as anaesthetics used at operation.

No particular clinical value appears to be attached to one or all of the tests employed in this investigation. As far as preparation of the patient for operation is concerned, if adequate thiouracil therapy be employed to reduce the metabolic rate to 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.

BIBLIOGRAPHY.

Althausen, T.L., Lockhart, J.C. and Soley,M.H. (1940) Am.J.Med.Sci., 199,342.

Althausen, T.L., and Wever, G.K. (1937) J.Clin.Invest.,16,257.

Barnes, C.G. and King, E.J. (1943) Quart.J.Med.,12,129.

Bartels, E.C. (1938) Ann.Int.Med. 12,652.

Beaver, D.C. and Pemberton, J de J, (1933) Ann.Int.Med.,14,1199.

Bieler, M.M., Ecker,E.E. and Spies,T.D.,J.Lab.and Clin.Med.,32,130.

Blank, E.E. (1940) Surg.Gyn.Obstr. 71,156.

Boyce, F.H. and McFetridge, E.M. (1938) Arch.Surg. 37,427.

Burton, F.W. (1888) Lancet, 2,573.

Cameron, G.R. and Karunaratne, W.A.E. (1935) J.Path.Bact.,41,267.

Carter, A.B. and Maclagan, N.F. (1948) British Medical Journal, 2,80.

Davis and Whipple (1919). Arch. Int. Med., 612 and 711.

Davis and Whipple (1921). Arch. Int. Med., 27,679.

Dick, A. (1945). British Medical Journal, 1, 182.

Drill, V.A. (1937) J. Nutrition, 14,355.

Dole, V.P., Watson, R.F., Rothland, S, with technical assistance of Braun, E. and Winfield, K. (1945) J.Clin.Invest. 24,648.

Eder, M.D. (1906). Lancet, 1, 1758.

Enders, J.F. (1944). J. Clin. Invest., 23,510.

Farrant, R. (1913). British Medical Journal, 2,1363.

Foss, H.L. et al. (1939) J. Amer.med.Ass., 113,1090.

Gargill, S.L. and Lesses, M.F. (1945). Ibid., 127,890.

Goodpasture, E.W. (1921) J. Exper.Med., 34,407.

Goodwin, J. (1948). British Medical Journal, 2,401.

McCullagh, E.P. (1946). Cleveland Clin. Quart., 13, 56.

McIver, M.A. (1940). Proc. Soc. Exper. Biol. and Med., 45, 201.

McIver, M.A. (1942). Surgery, 12, 654.

McIver, M.A. and Winter, F.A. (1942). J. Clin.Invest., 21, 191.

Maclagan, N.F. and Rundle, F.F. (1940) Quart.J.Med., 9, 215.

Maclagan, N.F. (1944). Brit. J. Exp. Path., 25, 15.

Maclagan, N.F. and Bunn, D. (1947). Biochem.J., 41, 580.

Maclagan, N.F. (1948). British Medical Journal, 2, 892.

Maddock, W.G. et al., (1937). J. Amer. med. Ass., 109, 2130.

Mateer, J.G. et al., (1947)a. Gastroenterology, 8, 52.

Mateer, J.G. et al., (1947)b. J. Amer. med. Ass., 133, 909.

Moore, D.B. et al., (1945). J. Clin. Invest., 24, 292.

Moschowitz, E. (1946). Arch. Int. Med., 78, 497.

Neefe, J.R. and Reinhold, J.G. (1944). Science, 100, 83.

Opie and Alford, (1914). J. Amer. med. Ass., 62, 595.

Piper, J. and Poulsen, E. (1947). Acta Med. Scand., 127, 439.

Probstein, J.G. and Londe, S. (1942). Arch. Surg. 45, 523.

Quick, A.J. (1933). Amer. J. Med. Sci., 185, 630.

Ragins, A.B. (1935). J.Lab. and Clin.Med., 20, 902.

Schaffer, J.M. (1940). Arch. Path., 29, 20.

Schmidt, C.R., Walsh, W.S. and Chevsky, V.E. (1941). Surg.Gyn. and Obstr., 73, 502.

Sealy, W.C. (1941) Ann. Surg., 113, 572.

Sealy, W.C. (1942) Ann. Surg., 116, 851.

Sherlock, S.P.V. (1946). J. Path. Bact., 58, 523.

Simmonds, J.P. and Brandes, W.W. (1930). Arch. Path.,16, 226.

Gray, S.J. and Barron, E.S.G. (1942). J.Clin.Invest., 22,191.

Guttman, S.H. et al. (1946). Ibid., 24,296.

Gyorgy, P. (1946). Conference on Liver Injury. Transactions of the Fifth Meeting. New York, N.Y.

Gyorgy, P. and Goldblatt, H. (1945). Science, 102,451.

Habersohn, W. (1874) Lancet, 1,510.

Haines, S.F., Magath, T.B. and Power, M.H. (1941). Ann.Int.Med.14,1225.

Hashimoto, H. (1921) Endocrinol., 5,579.

Hewitt, J.A. (1920). Quart.J.Exper.Physiol., 12,347.

Higgins, G.M. (1933). Arch.Path., 16,226.

Himsworth, H.P. (1947). Lectures on the Liver and its Diseases. Blackwell Scientific Publications, Oxford.

Hoskins, E.R. (1916). J. Exper. Zool., 21,295.

Kahn,J. and Stock, R.P.1944. J.Amer.med.Ass., 126, 358.

Krebs, E.G. (1946). J.Lab. and Clin.Med., 31,85.

Kuriyama,S. (1917). Am. J. Physiol, 43,481.

Kuriyama, S. (1918). J. Biol.Chem., 33,193.

Lafrentz, C.S. and Binimelis, D.V. (1948). British Medical Journal, 1,182.

Lahey,F.H. (1935). New Engl.J. Med. 213, 475.

Leathem, J.H. (1945). Endocrinol., 36, 98.

Lichtman, S.S. (1932). Arch.Int.Med., 50, 721.

Lichtman, S.S. (1941). Ann. Int. Med., 14, 1199.

Livingstone, H.J. and Livingstone, S.F. (1947). J.Amer.med.Ass., 135, 422.

Longo, O.F. and Moyana Lopez,L. (1945). Prensa med. Argent., 32, 943.

Lord, J.W.Jr. and Andrus,W.de W. (1941) Arch.Surg., 42, 643.

McCullagh, E.P. (1946). Cleveland Clin. Quart., 13, 56.

McIver, M.A. (1940). Proc. Soc. Exper. Biol. and Med., 45, 201.

McIver, M.A. (1942). Surgery, 12, 654.

McIver, M.A. and Winter, F.A. (1942). J. Clin.Invest., 21, 191.

Maclagan, N.F. and Rundle, F.F. (1940) Quart.J.Med., 9, 215.

Maclagan, N.F. (1944). Brit. J. Exp. Path., 25, 15.

Maclagan, N.F. and Bunn, D. (1947). Biochem.J., 41, 580.

Maclagan, N.F. (1948). British Medical Journal, 2, 892.

Maddock, W.G. et al., (1937). J. Amer. med. Ass., 109, 2130.

Mateer, J.G. et al., (1947)a. Gastroenterology, 8, 52.

Mateer, J.G. et al., (1947)b. J. Amer. med. Ass., 133, 909.

Moore, D.B. et al., (1945). J. Clin. Invest., 24, 292.

Moschowitz, E. (1946). Arch. Int. Med., 78, 497.

Neefe, J.R. and Reinhold, J.G. (1944). Science, 100, 83.

Opie and Alford, (1914). J. Amer. med. Ass., 62, 595.

Piper, J. and Poulsen, E. (1947). Acta Med. Scand., 127, 439.

Probstein, J.G. and Londe, S. (1942). Arch. Surg. 45, 523.

Quick, A.J. (1933). Amer. J. Med. Sci., 185, 630.

Ragins, A.B. (1935). J.Lab. and Clin.Med., 20, 902.

Schaffer, J.M. (1940). Arch. Path., 29, 20.

Schmidt, C.R., Walsh, W.S. and Chevsky, V.E. (1941). Surg.Gyn. and Obstr., 73, 502.

Sealy, W.C. (1941) Ann. Surg., 113, 572.

Sealy, W.C. (1942) Ann. Surg., 116, 851.

Sherlock, S.P.V. (1946). J. Path. Bact., 58, 523.

Simmonds, J.P. and Brandes, W.W. (1930). Arch. Path.,16, 226.

Sloan, M.H. and Shorr, E. (1944). Science, 99, 305.

Smith, M.C., Johndal, W. and Oschner, (1942), Surg. Gyn. and Obstr., 74, 1083.

Sutcliff, E.H. (1898). Lancet, 1, 717.

Weller, C.V. (1930). Trans. Ass. Amer. Phys., 45, 71.

White, W.H. (1886). British Medical Journal, 2, 151.

Wyndham, N. (1940). Aust. N. Z. J. Surg., 9, 385.

Youmans, J.B. and Warfield, L.M. (1926). Arch. Int. Med., 37, 1.