ANOMALOUS FINDINGS IN DIFFERENTIAL DIAGNOSIS OF JAUNDICE BY BIOCHEMICAL TESTS

BY

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In most cases of jaundice it is not possible to make a diagnosis by a single biochemical test, and it has sometimes been said that the so-called liver-function tests give little assistance in the diagnosis of that condition. Maclagan (1947) considered that in routine hospital work it was not practicable to carry out the full battery of tests recommended by some American authorities, and showed that by combining the estimation of serum alkaline phosphatase with his thymol turbidity test it was usually possible to make a diagnosis. Maclagan's scheme is particularly well adapted to the limited time and facilities available in a general clinical laboratory, and the present report illustrates its application in a series of cases of jaundice at Townleys Hospital, Bolton.

Although in a series of 200 cases Maclagan found no exception to the diagnostic criteria put forward, he gives a warning that occasional exceptions to them may be encountered. In the present series there are four cases in which the phosphatase and thymol turbidity findings are anomalous. These cases are given special consideration, because when using this scheme it is important that the possibility of an occasional misleading result should be fully appreciated. Reasons are given for thinking that exceptions are more likely to occur to the criteria for the diagnosis of obstructive jaundice than to those given for non-obstructive cases.

Without greatly adding to the work done it was found possible to include in the routine qualitative tests for urine urobilinogen and the estimation of serum albumin and globulin. The possibility that these further tests will sometimes provide the additional evidence required in difficult cases is discussed.

Methods Used

Colorimetric measurements were made on a Spekker absorptiometer.

Van den Bergh test: K. A. Evelyn and H. T. Malloy, *J. biol. Chem.*, 1937, 119, 481.

Alkaline phosphatase: E. J. King, *Micro-analysis in Medical Biochemistry*, 1947, p. 56. Churchill, London.

Thymol turbidity: N. F. Maclagan, *Brit. J. exp. Path.*, 1944, 25, 234.

Urobilinogen: Both Schlesinger's and Ehrlich's tests were used. G. A. Harrison, *Chemical Methods in Clinical Medicine*, 1947, p. 38. Churchill, London. *Recent Advances in Clinical Pathology*, edited by S. C. Dyke, 1947, p. 154. Churchill, London.

Serum protein (biuret method): G. A. Harrison, *Chemical Methods in Clinical Medicine*, 1947, p. 382. The method was modified by estimating the blue colour in the Spekker, using a curve drawn from a serum of known protein content estimated by the micro-Kjeldahl method.

The Present Series

Seventy consecutive cases of jaundice were investigated and tests were directed to establish a differential diagnosis between cases which were non-obstructive and those in which there was extrahepatic obstruction of the biliary tract. There were 46 cases of non-obstructive jaundice and 24 cases of obstructive jaundice (Table I). The ultimate diagnosis in each case was made on clinical grounds or on the findings at operation or necropsy. Most of the cases were seen at Townleys Hospital, Bolton, but a few were investigated at the Central Clinical Laboratory, Middlesbrough.

Meaning of the Table

The van den Bergh test was carried out to determine the degree of jaundice. It was not expected to assist in the differential diagnosis between obstructive and non-obstructive cases (Gray, 1947). The single case of haemolytic jaundice was, however, distinguished by being the only case in which the direct reaction was negative.

The results of the other tests are given in Table I, which shows only one set of tests for each case, though in a number of cases several sets were carried out. An exception, however, is made in a few cases in which a positive result was obtained to a particular test on one occasion and a negative result on another occasion. When this happened both results are tabulated.

Some explanation of the arrangement of the table is called for. The serum alkaline phosphatase values and the results of the thymol turbidity tests are tabulated according to the diagnostic criteria of Maclagan. According to these criteria a low alkaline phosphatase (less than 15 units) or a strongly positive thymol turbidity reaction (greater

TABLE I.—Results of Tests

	No. of Cases	Alkaline Phosphatase				Thymol Turbidity			Excess Urobilinogen		Derangement of Serum Protein	
		Low Units 5-14	Intermediate		High Units >35	Neg. Units 1-4	Weak Pos. Units 5-8	Strong Pos. Units >8	Neg.	Pos.	Neg.	Pos.
			Units 15-20	Units 21-35								
Obstructive jaundice:												
Carcinoma ..	18	Nil	1	2	15	18	Nil	Nil	12	Nil	7	Nil
Stone	6	Nil	Nil	3	3	6	Nil	Nil	6	Nil	3	Nil
Total ..	24	Nil	1	5	18	24	Nil	Nil	18	Nil	10	Nil
Non-obstructive cases:												
Acute hepatitis ..	32	11	7	8	3	14	5	14	15	15	19	6
Chronic hepatitis ..	5	1	1	Nil	3	Nil	1	4	Nil	5	Nil	5
Cirrhosis ..	6	1	Nil	3	1	2	Nil	4	1	5	3	2
Acute infection ..	2	2	Nil	Nil	Nil	1	1	Nil	1	1	2	Nil
Haemolytic ..	1	1	Nil	Nil	Nil	1	Nil	Nil	1	Nil	Nil	Nil
Total ..	46	16	8	11	7	18	7	22	18	26	24	13

Note.—Tests for derangement of serum protein and for urobilinogen were not carried out in the earlier cases of the series. In four cases the serum alkaline phosphatase was not estimated. One case had a negative thymol turbidity on one occasion and a strongly positive on another; both results are included. Similarly, in two cases urobilinogen was positive on one occasion and negative on another; both results are included.

than 8 units), or both, indicate that the jaundice is non-obstructive, whereas a high alkaline phosphatase (greater than 35 units) combined with a negative (1-4 units) or weakly positive (5-8 units) thymol turbidity indicates obstruction. Other combinations should be regarded as equivocal.

Tests for excess urobilinogen in the urine are recorded as positive or negative. For a positive result only Ehrlich's and Schlesinger's tests showing large amounts were accepted, small amounts being recorded as negative. The significance of excess urobilinogen is discussed by Pollak (1947). In the present series a strongly positive reaction in the absence of acute infection was considered to be evidence that jaundice was due to disease of the liver parenchyma and not to extrahepatic obstruction. Negative results were regarded as providing no evidence either way.

The type of change in the serum albumin and globulin found in some cases of hepatitis and cirrhosis is described by Higgins *et al.* (1944) and Sherlock (1946). In Table I a serum is described as showing derangement of the proteins if there is reversal of the albumin-globulin ratio with a globulin above 3.1 g.%, together with either an albumin below 3 g.% or a globulin above 3.5 g.%. Such a derangement was considered to be evidence of parenchymal liver disease. Again, negative findings were regarded as of no significance.

Analysis of the Results

It is not possible to show in the table how the results of the various tests combine in the individual case. Applying MacLagan's criteria to the phosphatase and thymol turbidity results, it was found that the correct diagnosis was made in 51 out of 70 cases (33 out of 46 non-obstructive cases and 18 out of 24 cases of obstruction). This compares with MacLagan's figure of 68% for a larger series. On the other hand, while 15 cases were classified as equivocal, three cases of hepatitis and one of cirrhosis were wrongly classified as obstructive jaundice by the occurrence of negative (three cases) or weakly positive (one case) thymol turbidity reactions combined with high alkaline phosphatase.

The number of cases of hepatitis or cirrhosis in which a diagnosis could be made by means of positive tests for urobilinogen or derangement of the serum protein can be seen in Table I. In no case did these tests lead to a misclassification. In many cases the urobilinogen and protein confirmed a diagnosis already made, but in others additional evidence was provided. The evidence of urobilinogen or protein enabled a firm diagnosis to be made in 3 of the 15 equivocal cases referred to above and also gave an indication of the correct diagnosis in the four cases wrongly classified.

Anomalous Thymol and Phosphatase Results

The four cases in which these findings were anomalous may be examined further. The biochemical results are set out in Table II. The clinical details were as follows.

Case 1: Subacute Hepatitis.—The onset of jaundice in a male diabetic aged 55 occurred three weeks before admission. On admission he was deeply jaundiced, wasted, and ill. The liver and spleen were enlarged. He developed ascites, which had to be tapped. After a long illness he made an apparently complete recovery. When seen 18 months later there were no signs or symptoms of liver disease.

Case 2: Subacute Hepatitis.—Four days before the birth of her first child a woman aged 28 was admitted to the maternity block with a history of mild jaundice and bile in the urine

TABLE II.—*Biochemical Results in Four Cases with Anomalous Findings*

Case	Day of Disease	Serum Bilirubin mg./100 ml.	Alkaline Phosphatase Units	Thymol Turbidity Units	Excess of Urobilinogen	Serum Protein g. %		
						Total	Alb.	Glob.
1	21	23	25	2	Nil	6.0	2.7	3.3
	28	15	41	3	—	7.6	3.0	4.6
	53	12	55	2	+++	5.6	2.3	3.3
	18 mths.	<0.5	10	1		7.0	3.8	3.2
2	28	0.5	37	1	Trace	9.6	3.5	6.1
	35	<0.5	41	1	Nil	9.6	3.7	5.9
	42	<0.5	25	1	Nil	9.7	4.9	4.8
	11 mths.	<0.5	10	2		6.8	3.6	3.2
3	14	7.5	61	8		6.8	4.7	2.1
	28		67	6	++	6.8	3.8	3.0
4	35	5.0	72	7	++			
	2 mths.?	6.0	50	4	+++	7.1	4.7	2.4

during the last few weeks of her pregnancy. When first seen 14 days after the birth of the child the jaundice was disappearing and the patient did not look ill, but the liver was enlarged to the umbilicus. At first she seemed to recover, but during the next 14 months she was never really well. There was developing mental slowness, with weakness and loss of weight. She suddenly became acutely ill and died in a few days. Necropsy revealed a terminal bronchopneumonia. The liver showed the picture of a healed hepatitis, with disorganization of the lobules by bands of fibrous tissue which contained islands of regenerated liver cells. There was also necrosis of the anterior lobe of the pituitary, which was thought to be the cause of death.

Case 3: Acute Hepatitis.—This patient, a hemiplegic woman aged 50, was a clinically typical case of infective hepatitis. She recovered after two months, and never appeared very ill.

Case 4: Cirrhosis of the Liver.—A woman aged 50 was admitted with an enlarged liver and ascites. Necropsy revealed a multilobular cirrhosis of the liver.

Discussion

Consideration of Table I shows that in liver disease all four tests used can give results over a wide range. Gray (1949) describes the changes which occur in the various liver-function tests during the course of liver disease. He thinks that insufficient attention has been paid to the stage at which these tests have been carried out, and shows that different tests reveal maximum changes at different times during the course of the disease. A series of tests related to progress might have shown a more orderly pattern of result than is seen in Table I. MacLagan's scheme for the use of liver-function tests is directed to the single purpose of making a differential diagnosis. His series of cases, and the present smaller series, show that, in spite of wide variations in the results obtained, tests applied at an arbitrary time can give the correct diagnosis in most cases.

In 4 out of 70 cases in the present series MacLagan's diagnostic criteria gave misleading results, and in all four cases it was the criteria given for the diagnosis of obstruction which were at fault. A study of other papers suggests that the criteria for the diagnosis of obstruction might be found to be less reliable than those for the diagnosis of non-obstructive jaundice.

The results of large numbers of estimations of serum alkaline phosphatase and thymol turbidity tests are given in papers by Higgins *et al.* (1944), MacLagan (1944, 1947), Sherlock (1946), Maizels (1946), and Mawson (1948). While the papers do not describe the combined findings of high phosphatase and negative or weakly positive thymol turbidity, given as characteristic of obstructive jaundice, as occurring in cases of parenchymal liver disease, they contain a number of examples of both findings separately. Mawson describes a case of hepatitis in which the phosphatase was 33 units and the thymol turbidity 1 unit.

None of the results recorded in these papers would have led to a misclassification of obstructive jaundice as non-obstructive. Maclagan refers to the tendency towards positive flocculation reactions in cases of rheumatoid arthritis and heart failure even in the absence of jaundice, and states that the possibility that these diseases may be complications in cases of jaundice should be borne in mind. It would seem possible that an alkaline phosphatase of below 15 units might be found early in a case of minimal jaundice due to stone, but the chance of mistaking surgical obstruction for liver disease seems to be slight.

The present series is too small for any final conclusions to be drawn on whether the routine inclusion of tests for urobilinogen and derangement of the serum protein would make for a significant improvement in diagnostic precision. These tests pointed to the correct diagnosis in the four cases in which phosphatase and thymol findings were anomalous, but this might not occur again. No misleading results were obtained from these tests, but a larger series might not show the same freedom from fallacy. In the present series one case of carcinoma of the pancreas showed amounts of urobilinogen which, while not sufficient to be classified as strongly positive, caused serious consideration to be given to a diagnosis of chronic hepatitis in spite of a high phosphatase and negative thymol. Acute cholecystitis complicating obstruction due to stone could clearly give rise to large quantities of urobilinogen. A normal or slightly raised globulin with a low albumin can occur in cases of obstruction (Sherlock, 1946). These are changes in the same direction, but not to the same degree as the changes observed in hepatitis and cirrhosis.

Summary

The use of the diagnostic criteria of Maclagan is illustrated in a series of 70 cases of jaundice.

Four cases gave anomalous results, and these are discussed.

The use of routine tests for urobilinogen and for derangement of the serum proteins to give increased diagnostic precision is considered.

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The July number of *Marriage Guidance*, the monthly bulletin of the National Marriage Guidance Council, contains a brief report on the work done in 1949. For the first time all affiliated marriage-guidance councils were asked to submit returns of their year's work, and 67 replied. They showed a total of 6,540 married couples helped, and 1,076 engaged couples prepared for marriage. Forty-five of the councils attempted to classify their remedial work, and reported 1,096 successful cases, 679 unsuccessful, and 1,327 unknown, doubtful, or pending, though accurate classification is at present very difficult or impossible. There were 249 counsellors, 50 of whom have passed the national selection procedure and completed their training.

ACUTE IDIOPATHIC PORPHYRIA REPORT OF TWO CASES

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Porphyria may occur as a congenital condition, with red urine, pink teeth, and hydroa aestivale, or as an acute disease, either idiopathic or toxic, or it may be produced by drugs such as sulphonal, methylsulphonol, and others. We are concerned here with the acute idiopathic variety. We have recently encountered three examples, and two of them are recorded. Had Case 1 been admitted during the later stages of her paralysis the diagnosis would probably not have been made, as the urine had then lost its colour. Case 2 came under her doctor's care for hallucinatory psychosis, porphyria being diagnosed only on her death-bed some weeks later, and in this patient previous bouts of "gastric ulcer" may well have been episodes of relapsing porphyria. The testing of urine for porphyrins with ultra-violet light is simple, and porphyria may explain puzzling cases of polyneuritis, Landry's ascending paralysis, psychosis, and acute abdominal pain.

Acute porphyria with nervous complications was first described by Ranking and Pardington (1890). Günther (1911) recorded 14 cases, and Waldenström (1937) 103 Swedish cases. The biochemistry has been defined by Fischer and Zerweck (1924), Rimington (1939), Dobriner and Rhoads (1940), Turner (1937), and others, and the pathology has been reviewed by Denny-Brown and Sciarra (1945).

Case 1

A woman aged 51 was seen in consultation with Dr. W. A. Whitehouse Parkes, of Sutton Coldfield, on April 7, 1948, and was at once admitted to hospital. For six weeks she had been complaining of sharp central abdominal pain, passing through to the back, associated with aching in her limbs, fatigue, and intractable insomnia. Three weeks before admission her urine had become dark red in colour and nephritis had been suspected; a week later she had a slight transient sore throat. There was no significant previous history, nor was there any exposure to lead, sulphonal, or antipyretics.

On examination she was seen to be very ill, drowsy, disorientated, and confused, and had difficulty in answering questions. The skin had a brownish pigmentation and the conjunctivae were injected. The tongue was dry and coated. There was no tenderness in the abdomen,

FIG. 1.—Case 1. Showing myasthenic appearance of the facies due to bilateral facial palsy. The patient was instructed to close her eyes. This appearance is also present during sleep.