HIGHLY RAISED SERUM VITAMIN B_{12} LEVELS IN "OBSTRUCTIVE HEPATIC NECROSIS"

BY

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Vitamin B_{12} exists in serum both in a "free" state and "bound" to the alpha-globulin fraction (Pitney *et al.*, 1954). Jones and Mills (1955) reported elevated levels of both free and bound vitamin B_{12} in viral hepatitis and in Laennec's cirrhosis, whereas values were normal in biliary cirrhosis. Rachmilewitz *et al.* (1956) confirmed these observations and also found an increase in the maximal vitamin-B_{12}-binding capacity of the serum in liver injury, but were not able to correlate high vitamin B_{12} levels with changes in any particular serum globulin component; they also found normal levels in jaundice due to extrahepatic biliary obstruction.

We record the finding of extremely high levels of bound serum vitamin B_{12} in a patient with obstructive jaundice and diffuse hepatic necrosis, with return to normal values in the recovery phase. This case represents an example of acute hepatocellular failure with liver coma which may complicate biliary obstruction, particularly in the elderly; we have termed this condition "obstructive hepatic necrosis."

Materials and Methods.—Serial estimations were made of the levels of serum bilirubin, albumin, total globulin, gamma-globulin, and alkaline phosphatase (King–Armstrong units). Cephalin flocculation was read after 24 hours and expressed semiquantitatively as − to +++. Biochemical methods and biopsy techniques have been previously described (Saint *et al.*, 1953). Serum vitamin B_{12} levels were estimated by microbiological assay with *Euglena gracilis* as described by Hutner *et al.* (1956). The normal ranges for total and free vitamin B_{12} are respectively 100–720 $\mu\mu$g. and 40–160 $\mu\mu$g. per ml. of serum (Mollin and Ross, 1952).

Case Report

A retired man aged 71 was seen on November 3, 1956, with a week's history of pain under the right costal margin, deepening jaundice, and stupor. His previous health had been good apart from two episodes of endogenous depression in 1949 and 1954, and one week of right upper abdominal pain in 1954. Relatives gave the following history. He had suffered from slight indigestion and anorexia for three months; eight days previously he had developed a "squirmy" feeling in the abdomen after eating a pie, followed by bouts of right upper abdominal pain, vomiting, and jaundice. The pain had persisted, the jaundice had deepened, and he had taken no food. He had complained of cold shivers two days before admission, and next day had become mentally confused.

On examination he was deeply jaundiced and stuporous. The liver was slightly enlarged; the gall bladder and spleen were not palpable. Movements of the limbs were uncoordinated, and there was a coarse tremor of the hands. The haemoglobin value was normal; the white-cell count was 30,000 per c.mm. The results of serial liver-function tests, serum vitamin B_{12} levels, and other laboratory findings are shown in the Table. It will be noted that initially the usual obstructive pattern of a negative cephalin flocculation associated with an elevated serum alkaline phosphatase is replaced by a pattern suggestive of hepatic necrosis.

Biochemical Data and Vitamin B_{12} Levels in Serum

Date	Leucocyte Count (per c.mm.)	E.S.R. (mm./hour, Westergren)	Serum Bilirubin (mg./100 ml.)	Serum Albumin (g./100 ml.)	Serum Globulin (g./100 ml.)	Serum Gamma-globulin (g./100 ml.)	Cephalin Flocculation	Serum Alkaline Phosphatase (K.-A. units)	Serum Vitamin B_{12} ($\mu\mu$g./ml.)	
									Total	Free
5/11/56	30,000		17·2	3·2	2·3	0·9	+++	18	7,040	452
12/11/56			8·8	2·7	3·0	1·6	+++	25		
19/11/56			6·4	3·0	3·1	2·0	+++	23		
23/11/56	11,000	133							1,276	250
26/11/56			3·2	3·3	2·9	1·9	++	25		
3/12/56			2·0	2·1	3·1	1·7	—	41	820	400
17/12/56	8,000	111	0·4	2·9	2·9	1·8	—	23	404	<40
21/1/57		56	0·4	4·0	2·7	1·5	—	18	288	<40

The provisional diagnosis was gall-stone obstruction of the common bile duct and cholangitis. In spite of antibiotic and intravenous infusion therapy, his condition deteriorated over the next 24 hours, and laparotomy was undertaken to procure drainage of the biliary system. The common bile duct was completely obstructed by a large gall-stone impacted at the ampulla of Vater. The stone was removed, the common duct was drained, and the patient made a protracted but complete recovery. A biopsy of the liver taken at operation showed the following histological appearances (Fig. 1). A lobular structure was preserved, but there were striking changes in the staining character of the liver cells throughout, involving entire lobules in some areas. The changes varied from cloudy swelling to frank eosinophilic necrosis, particularly in the subcapsular zone. Many areas showed focal polymorph infiltrations and occlusion of portal venules by thrombus. A percutaneous aspiration biopsy of the liver six weeks later merely showed a slight increase in fibrous tissue and lymphocytic infiltration in the portal area. Almost complete repair had taken place (Fig. 2).

Discussion

Raised serum vitamin B_{12} levels may occur in two disease states. High bound levels are found in chronic myeloid leukaemia (Beard *et al.*, 1954); secondly, data from Lear *et al.* (1954), Jones and Mills (1955), Rachmilewitz *et al.* (1956), and from this unit (unpublished) have shown elevations in acute viral hepatitis and hepatic cirrhosis, and also

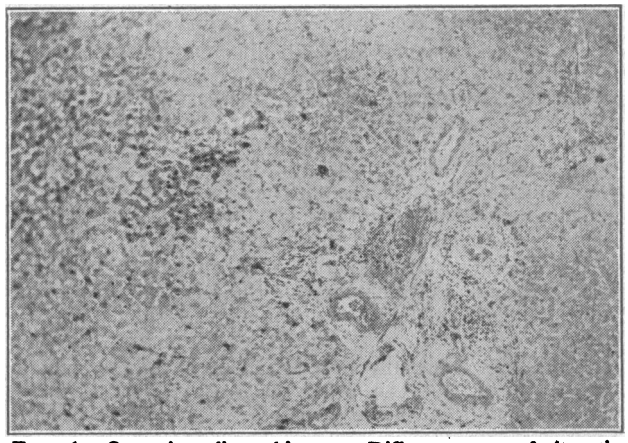

FIG. 1.—Operation liver biopsy. Diffuse areas of hepatic necrosis; the surviving cells are staining darkly. (H. and E. ×72.)

*Working with the aid of a grant from the National Health and Medical Research Council of Australia.

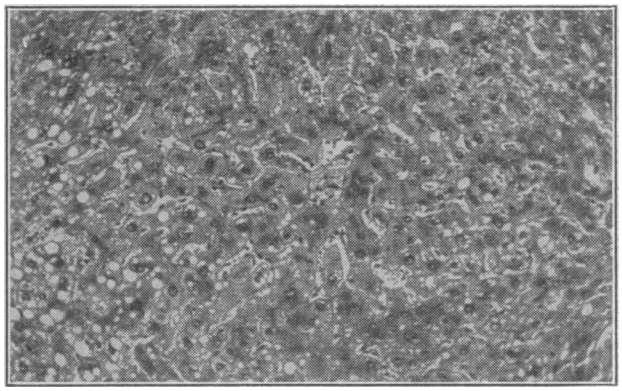

FIG. 2.—Percutaneous aspiration biopsy of liver. Regeneration and restitution of hepatic architecture has occurred. (H. and E. ×168.)

an increased urinary excretion of what is apparently free vitamin B_{12}. Rachmilewitz *et al.* (1956) accounted for elevated serum and urine vitamin B_{12} levels by postulating release from injured liver cells of stored vitamin B_{12}, part presumably becoming bound to alpha-globulin, the remainder being excreted in the urine. A comparable release of enzymes such as oxalacetic glutamic transaminase has been used as an index of hepatic damage (Wroblewski and La Due, 1955); at present serum vitamin B_{12} assay is too protracted for this purpose. The diffuse hepatic necrosis in the present case would favour this hypothesis, and the gradual fall in serum vitamin B_{12} level corresponds well to the clinical and biochemical evidence of recovery of the liver.

Release of vitamin B_{12} as such, however, does not adequately account for serum levels such as 7,040 $\mu\mu$g. per ml. which characterized this case. The vitamin-B_{12}-binding capacity of serum, limited to about 1,000 $\mu\mu$g. per ml. in normals (Pitney *et al.*, 1954), is considerably raised in hepatitis and cirrhosis (Rachmilewitz *et al.*, 1956).

Thus it seems likely that necrosis results in excessive release from the liver of a binding protein with a high avidity for vitamin B_{12}, which would "mop up" any available vitamin B_{12} and hold it in the blood stream. The high serum vitamin B_{12} levels in chronic myeloid leukaemia are similarly accounted for by postulating increased amounts of binding protein, conceivably released from excessive breakdown of granulocytes (Mollin and Ross, 1955); the initial granulocytosis in this case is not considered sufficient to cause these highly elevated levels of vitamin B_{12}. It may be calculated that 7,040 $\mu\mu$g. of vitamin B_{12} per ml. of serum represents a total circulating amount of some 20 μg. Urinary levels were not obtained in this case, but there is no evidence of renal retention of vitamin B_{12} in liver disease (Rachmilewitz *et al.*, 1956). Whilst it seems more likely that this amount of vitamin B_{12} is yielded up by the liver, another possible explanation is that conditions favour uptake from the intestine, where normally a "barrier" exists to absorption to excess vitamin B_{12} (Baker and Mollin, 1955). Circumstances did not permit the testing of this hypothesis by radioactive vitamin-B_{12}-uptake techniques.

The onset of acute liver necrosis and hepatocellular failure in this patient is noteworthy, for it is rarely acknowledged to be an accompaniment of gall-stone obstruction of the common bile duct. Sherlock (1955) advises that hepatic failure should be diagnosed "rarely, and with caution," in a patient suffering from acute biliary obstruction. Other texts make little or no reference to acute biliary obstruction as a cause of hepatic failure, and undoubtedly some cases have remained unrecognized. A possible example was recently reported (Massachusetts General Hospital, 1956). An elderly man with deep jaundice died after a short illness. Necropsy revealed diffuse hepatic necrosis associated with gall-stone obstruction of the common bile duct. The final diagnosis was "acute fulminant hepatitis with atrophy, probably viral, ? toxic," but the clinical findings and histological appearance of the liver bore a close resemblance to this present case of "obstructive necrosis."

The diagnosis is an important one to make, for the condition represents a remediable form of hepatic failure, and prompt surgical intervention, as in our case, may be life-saving; reliance must be placed on the clinical data alone, for routine liver-function tests may be misleading in the presence of liver necrosis. The high serum vitamin B_{12} levels in this case are of particular interest in corroborating the clinical and biopsy impression of hepatic failure due to acute widespread liver-cell necrosis.

Summary

Extremely high serum vitamin B_{12} levels (7,040 $\mu\mu$g. per ml.) were obtained in a patient with acute diffuse liver necrosis and hepatic coma. The liver failure was the result of complete obstruction of the common bile duct by a calculus, the condition being termed "obstructive hepatic necrosis." Prompt biliary drainage initiated eventual complete recovery, with return of vitamin B_{12} levels to normal values.

The interpretation of the extremely high level of circulating vitamin B_{12} in this case is uncertain. It is known that on occasion excessive amounts of a vitamin-B_{12}-binding protein are released from a damaged liver, and we are inclined to regard this as the most important factor in the present case. The bound vitamin B_{12} may have been derived in part from the liver and other tissue depots, but an abnormal uptake from the gut is also a possibility.

Dr. W. R. Pitney kindly reviewed this manuscript. We are grateful to Dr. Leon Taft for histological interpretations, and to Dr. Sara Weiden for biochemical analyses. We thank Mr. George Westlake and Dr. E. N. O'Brien for assistance in the management of this patient.

REFERENCES

Baker, S. J., and Mollin, D. L. (1955). *Brit. J. Haemat.*, 1, 46.
Beard, M. F., Pitney, W. R., and Sanneman, E. H. (1954). *Blood*, 9, 789.
Hutner, S. H., Bach, M. K., and Ross, G. I. M. (1956). *J. Protozool.*, 3, 101.
Jones, P. N., and Mills, E. H. (1955). *J. Lab. clin. Med.*, 46, 927.
Lear, A. A., Harris, J. W., Castle, W. B., and Fleming, E. M. (1954). Ibid., 44, 715.
Massachusetts General Hospital (Case 42322) (1956). *New Engl. J. Med.*, 255, 297.
Mollin, D. L., and Ross, G. I. M. (1952). *J. clin. Path.*, 5, 129.
—— —— (1955). *Brit. J. Haemat.*, 1, 155.
Pitney, W. R., Beard, M. F., and Van Loon, E. J. (1954). *J. biol. Chem.*, 207, 143.
Rachmilewitz, M., Aronovitch, J., and Grossowicz, N. (1956). *J. Lab. clin. Med.*, 48, 339.
Saint, E. G., King, W. E., Joske, R. A., and Finckh, E. S. (1953). *Aust. Ann. Med.*, 2, 113.
Sherlock, S. (1955). *Diseases of the Liver and Biliary System*, p. 92. Blackwell Sci. Publ., Oxford.
Wroblewski, F., and La Due, J. S. (1955). *Ann. intern. Med.*, 43, 345.

The National Association for Mental Health has produced a booklet containing 50 questions and answers on mental health. This booklet, written mainly for non-medical readers, was produced as a result of two B.B.C. programmes: a television programme "The Hurt Mind," and a radio programme "To Comfort Always." In both these programmes questions on mental health were discussed by a panel of experts. Arising from the broadcasts over 25,000 letters were received from listeners, many enclosing further queries. This booklet is an attempt to answer some of these questions. Included in the booklet is a glossary of some of the terms commonly used in connexion with mental illness. As the number of questions dealt with is small, and the answers brief, a book list is appended as a guide to further reading. The booklet, price 1s. net, is obtainable from the National Association for Mental Health, 39, Queen Anne Street, London, W.1.