patients than in a sample of the controls. In a few of them there was also a significant fall in the level of fibrinogen.

The fibrinolytic agent did not produce any febrile reactions, but it may occasionally have caused hypotension.

The numbers included in this pilot study were too small for differences in mortality to be significant. There were no definite differences in the clinical response of the two groups, nor in the evolution of the electrocardiographic changes.

Detailed transaminase curves have been prepared and appear to differ significantly in one respect—namely, the peak area ratio, which is greater in the treated group. The implication of this is discussed.

A more extended trial is in progress.

Our thanks are due to colleagues at the Royal Victoria Infirmary and many practitioners who referred cases to us; to the following house-physicians—Drs. Ansah, Burdus, Campbell, Kinlen, Sanderson, Todd, Varde, and Waring, who gave a great deal of medical care; to the matron, Miss F. Shaw, and her staff for devoted nursing care; to Dr. A. L. Latner and his staff for biochemical facilities; to Drs. A. Todd and P. Stephenson for help with fibrinolysis; to Professor J. B. Duguid and Dr. P. A. Ellis for necropsy examinations; and to Mr. D. J. Newell for statistical assistance. Finally, we are indebted to Messrs. Merck Sharp and Dohme for generous supplies of thrombolytin.

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Reporting that more teachers are flying from England to New Zealand, *The Times* (August 31) records the following comment by one of them: "The pay here is not high enough to compensate for this land's stinking, dying attitude. My wife and I are escaping from the typical overcrowded and lethargic existence of this welfare state. We and many other teachers here are sick to death of this country. Lack of pay is certainly an important factor, but it is only one of the criticisms we can justifiably level against England to-day."

LIVER FUNCTION IN ACUTE MYOCARDIAL INFARCTION

A STUDY USING BROMSULPHTHALEIN TEST

BY

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The bromsulphthalein (B.S.P.) test is regarded as one of the most sensitive biochemical tests of liver function (Rosenthal and White, 1925; Sherlock, 1955). It is well known that disturbances of liver function occur commonly in cardiac disease. They range from transient abnormalities of liver function, such as occur in reversible congestive cardiac failure (Evans *et al.*, 1952b), to a true cardiac cirrhosis. In states of acute cardiac damage, such as myocardial infarction, jaundice may appear, and excess urobilinogen has been noted in the urine for several days after an attack (Evans *et al.*, 1952a; Koskelo, 1956).

It was therefore decided to investigate liver function by the B.S.P. test in an unselected group of cases of acute myocardial infarction. These results were compared with those of other methods of detecting liver dysfunction.

Material and Methods

A group of 20 patients (15 men and 5 women) aged from 40 to 72 years was studied. Each was admitted with acute myocardial infarction and was examined by me within a few hours of admission. Clinical shock was diagnosed by the following criteria: cold, pale skin, sweating, cyanosis, thready pulse, and hypotension. Blood was taken for the estimation of haemoglobin, serum bilirubin, thymol turbidity, zinc sulphate turbidity, alkaline phosphatase, and blood urea. The B.S.P. test was performed by injecting 5 mg. of B.S.P. per kg. body weight, and specimens were taken after 5 and 45 minutes. The results reported are the percentage retention of B.S.P. in the blood after 45 minutes, the normal being less than 6%. The sample was compared with a standard solution of B.S.P. at a concentration of 10 mg./100 ml., which is theoretically the level of B.S.P. equilibrated throughout the serum in the dose administered.

Results

Clinical details and results of the B.S.P. tests are shown in the Table. Fifteen patients (75%) had abnormal B.S.P. retention within a few hours of myocardial infarction. Of these, three died within three weeks. In eight patients the B.S.P. test was repeated 7–10 days after admission, and was still abnormal in four cases. One year later, B.S.P. retention in three of these patients was 3%, 10%, and 12%. In five patients (25%) it was normal at the time of admission. Shock was diagnosed in two of these patients, one of whom died a few months later. Abnormal B.S.P. retention was more marked in patients who were shocked ($26\% \pm 18.2\%$) than in those who were not ($14.9\% \pm 13.3\%$), but the differences do not reach statistical significance because of the large variance. There was no correlation between abnormality of the B.S.P. test and elevation of the blood urea, the latter being a reflection of reduced renal blood flow.

Discussion

The study reported here was carried out on patients with no previous hepatic dysfunction, and in whom other tests of liver function were in general normal. In the 24 hours after acute myocardial infarction 75% had abnormal B.S.P. retention. These findings contrast with those of Evans *et al.* (1952a), who found normal B.S.P. retention in all those cases of their series in which this test was performed. They do not state, however, how long after the infarct they carried out the test.

There are two possible explanations for abnormal B.S.P. retention in the circulation. Either impairment of intrinsic hepatic-cell function may reduce the uptake of B.S.P. by the liver from the plasma, or reduction or diversion of hepatic blood flow diminishes the amount of B.S.P. presented to liver cells, and results in increased retention in the plasma.

Centrilobular necrosis in cases of fatal myocardial infarction was described by Clarke (1950). This change occurs particularly when shock and hypotension have been present for more than 24 hours (Ellenberg and Osserman, 1951). The present study shows that the results of B.S.P. tests tended to be abnormal more often in patients who were shocked, and that when this was severe initially B.S.P. retention remained abnormally high after 7-10 days. As there was no clinical evidence of systemic venous congestion in any case on admission to hospital, hepatic changes could not be attributed to this cause.

On the other hand, the mechanism of uptake of B.S.P. by the liver may partly account for these results. Normally, when B.S.P. is injected intravenously it is rapidly bound to plasma protein, and is cleared from the circulation, mainly by the liver, if there is normal biliary secretion (Ingelfinger *et al.*, 1948). An important factor in this selective capacity of clearance of B.S.P.

from the plasma is the anatomical circulatory arrangement of the liver (Brauer and Pessotti, 1949). Depression of this circulation may therefore reduce the amount of B.S.P. which comes in contact with the hepatic cells in a given time, and also impair the functional capacity of the cells to remove it from the plasma. Hence the rate of disappearance of B.S.P. from the plasma would be diminished. In shock, not only is the blood flow to the liver reduced, but there is also experimental evidence of an arterial shunt which by-passes the liver (W. H. H. Andrews, 1959, personal communication). Increased retention of B.S.P. in the circulation in cases of myocardial infarction may thus be partly due to alteration in the blood supply to the liver. When systemic shock is present, hepatic blood flow in these cases would tend to be reduced. This may account for the finding that 9 out of 11 patients in this series who were clinically shocked on admission had abnormal B.S.P. retention.

It is well known that in shock renal blood flow is reduced, with a consequent rise in the blood-urea concentration. The results in the Table do not show any consistent relationship between increased B.S.P. retention and rise of blood urea. This may be explained by the different degrees of alteration of blood flow to the liver and the kidney in these cases, possibly due to the differing modes of oxygen utilization by these organs.

Summary

In a series of 20 patients with acute myocardial infarction studied within the first 24 hours of the onset of pain, abnormal B.S.P. retention was found in 15. This was more marked in the presence of shock. There was no significant correlation between abnormal B.S.P. retention and elevated blood urea. Other liver-function tests were normal.

The mechanism of B.S.P. uptake by the liver is discussed, and it is suggested that reduction in blood

Clinical Features and Liver-function Tests

Case	Sex and Age	History and Clinical Features	B.P. on Admission	Blood Urea mg./100 ml.	Liver-function Tests	B.S.P. at 45 Minutes	
						On Admission	7 to 10 Days Later
1	F 71	12 hours' pain. Shocked. Died 3 weeks later from progressive heart failure	140/100	81	Normal	64%	40%
2	F 61	6 hours' pain. Shocked. Increased jugular venous pressure	105/70 Later 75/50	46	"	41%	22%
3	F 50	4 hours' pain. Mild shock and cyanosis	115/80	26	"	35%	3%
4	F 54	Hypertensive diabetic. 6 hours' pain. No shock	200/130	41	"	8%	—
5	F 51	6 hours' pain. Pericardial rub. No shock	115/70	31	"	26%	5%
6	M 62	6 hours' pain. Shocked. Increased jugular venous pressure	90/65	64	Serum bilirubin 1-3 mg./100 ml. Serum bilirubin 1 mg./100 ml.	17%	12%
7	M 63	Less than 4 hours' pain. Not severely shocked, but increased jugular venous pressure	110/85	44	Normal	34%	7%
8	M 58	9 hours' pain. Severe. Died 10 days later from peripheral circulatory failure	110/85	39	"	34%	—
9	M 51	12 hours' pain. Severe shock. Died 7 days later from peripheral circulatory failure	85/75	91	"	13%	—
10	M 54	2 hours' pain. Not shocked	110/85	40	"	34%	5%
11	M 47	3 hours' pain. Not shocked	100/65	—	"	9%	—
12	M 66	6 hours' pain. Not shocked	115/70	35	"	7%	—
13	M 49	Intermittent pain for 1 week	105/70	32	*Alkaline phosphatase 26.3 units	43%	—
14	M 57	12 hours' pain. Shocked. Large doses of morphine given. Required hydrocortisone and mephentermine	90/70	41	Normal	17%	6%
15	M 59	6 hours' pain. Not shocked, but moderate rise in jugular venous pressure	110/80	61	"	12%	3%
16	M 72	6 hours' pain. Mild shock. Given I.V. hydrocortisone. Died a few months later	100/60	46	"	0%	—
17	M 55	3 hours' pain. Moderate rise of jugular venous pressure and minimal shock	95/70	28	"	5%	5%
18	M 45	4 hours' pain on previous day. Not shocked	160/80	52	"	4%	—
19	M 45	3 hours intermittent pain. Not shocked	170/90	26	"	4%	—
20	M 40	1 hour's pain and residual ache. Minimal cyanosis. Not shocked	135/95	20	"	3%	—

Cases 1-15 showed abnormal B.S.P. on admission to hospital; Cases 16-20 showed normal B.S.P. tests. In cases marked with —, B.S.P. tests were not repeated 7-10 days after admission. *Clinically well 1 year later. Alkaline phosphatase 8.6 units; B.S.P. 11%.

flow to the liver is an important factor causing alteration in the B.S.P. test in cases of acute myocardial infarction.

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A SYNDROME DUE TO THE BACTERIAL COLONIZATION OF SPITZ-HOLTER VALVES

A REVIEW OF FIVE CASES

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The treatment of hydrocephalus has been advanced by the introduction of non-return valves that shunt the cerebrospinal fluid (C.S.F.) from the lateral ventricle of the brain to the superior vena cava. At this hospital the Spitz-Holter valve has been used, details of which are shown in Fig. 1. The complications of thrombosis and sepsis are each recognized to occur in approximately 10% of cases. Over 120 cases have been treated at this hospital (Cohen, 1961, unpublished), and in the group complicated by sepsis we have differentiated a new syndrome—persistent bacteraemia—which is characterized by persistent pyrexia, progressive anaemia, splenomegaly, and positive blood cultures. Previously these cases have been included with the septicaemias, and the attempted eradication of the infection by the use of systemic and intraventricular methicillin has been reported (Callaghan *et al.*, 1961). Five case histories of this syndrome and one of septicaemia are recorded.

Case 1

A male infant born on January 1, 1959, had an occipital encephalocele excised on February 24 and subsequently developed progressive hydrocephalus. A Spitz-Holter valve was inserted on April 4, but needed two revision operations before effective shunting was obtained. (The last operation was on August 2.)

In October the infant began to run a continuous temperature—range 99–102° F. (37.2–38.9° C.)—and on investigation was found to have a urinary infection due to *Proteus vulgaris*. This partially responded to sulphadiazine and

chloramphenicol (125 mg. q.d.s.), but during the next three months the infant became anaemic (Hb 47%) and needed two blood transfusions to correct this anaemia. As the symptoms persisted further investigations were carried out and *Pr. vulgaris* was then cultured from the blood. At this stage there was no evidence of infection around the valve. On December 12 the infant was put on kanamycin (100 mg. b.d.), which temporarily reduced the pyrexia, but still *Pr. vulgaris* was repeatedly cultured from the blood (Fig. 2). The C.S.F. obtained by direct ventricular puncture was sterile on two occasions. On January 7, 1960, the catheter was removed from the internal jugular vein and the C.S.F. allowed to drain externally into a container. This C.S.F. was found to be clear and colourless, contained 3 leucocytes per c.mm., yet culture produced a profuse growth of *Pr. vulgaris*. After diverting this infected C.S.F. from the blood-stream the temperature returned to normal and urine and blood cultures remained sterile from then on (Fig. 2). Thus it appeared that bacteraemia had been controlled.

On February 2 (almost one year after its insertion) the valve was removed and *Pr. vulgaris* isolated from all the component parts, indicating colonization of the valve by this organism. As the hydrocephalus was still progressive, ventricular drainage was instituted and C.S.F. draining externally by this method was sterile, confirming that it was the removed colonized valve that had been the source of the bacteraemia. A second valve was inserted on March 31, and this functioned satisfactorily. The child was discharged, but on June 13 he died because of an episode of raised intracranial pressure (16 months after the original operation).

At necropsy there was no evidence of infection, thrombosis, or embolism, but an enlarged spleen was found. This weighed 100 g. and showed marked lymphoid hyperplasia.

Case 2

A male infant born on March 8, 1960, had haemorrhagic disease of the newborn complicated by intraventricular haemorrhage. This led to progressive hydrocephalus and ventriculography demonstrated a basal cistern block. A Spitz-Holter valve was inserted on May 19.

Post-operatively his temperature slowly rose to 101° F. (38.3° C.) and then fluctuated between 97 and 99.5° F. (36.1 and 37.5° C.). On the tenth post-operative day the spleen became palpable and during the next three months enlarged to 2 in. (5 cm.) below the costal margin. Anaemia then slowly developed (Hb 55%) over the next six months, necessitating one blood transfusion. Coagulase-negative staphylococci were cultured from the blood on 15 occasions during the nine months that the bacteraemia was in existence. During this same period coagulase-positive staphylococci were isolated on three occasions, but this was not the organism primarily isolated (see Table).

FIG. 1.—Component parts of the Spitz-Holter valve: a proximal ventricular catheter (A); the valve (X) that shunts the C.S.F. from the lateral ventricle of the brain to the superior vena cava or right atrium via the internal jugular catheter (B). These parts are held together and in position by the black silk sutures (1 and 2).