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Early jaundice after open-heart surgery

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Two hundred and thirty-two patients subjected to open-heart surgery have been analysed regarding early post-operative jaundice. The overall incidence of jaundice was 13%, being 55% where the mitral valve and 5% where the aortic valve was predominantly involved. Only one out of 59 patients in whom a congenital lesion was repaired became jaundiced. Hyperbilirubinaemia without jaundice was common. The biochemical pattern of the jaundice was singularly constant, the most striking feature being the rise in serum bilirubin level. The highest value occurred between the second and tenth post-operative days. At total levels less than about 4 mg./100 ml. the unconjugated fraction usually equalled or exceeded the conjugated. The alkaline phosphatase was normal in the first post-operative week but was sometimes slightly raised in the second, when the bilirubin levels were usually falling. The S.G.P.T. was normal or very slightly raised. Bilirubinuria was present. Centrilobular congestion with no evidence of extrahepatic biliary obstruction was found at post-mortem examination, and liver biopsy in three very severely jaundiced patients revealed only intrahepatic cholestasis. Pre-operative evidence of liver dysfunction was found in 13 patients who subsequently became jaundiced. Twelve had lesions predominantly affecting the mitral valve. Haemolysis, heart failure, and infection probably all played a part, and the effect of operation *per se* on liver function has been discussed. Drugs and viral hepatitis do not seem implicated in our patients. Maintenance of lower venous pressures in the post-operative period and the use of less blood reduced both the incidence and severity of jaundice.

The occurrence of jaundice in patients with both acute and chronic heart failure has been noted for many years (Jolliffe, 1930; Kugel and Lichtman, 1933; Felder, Mund, and Parker, 1950; Sherlock, 1951; Evans, Zimmerman, Wilmer, Thomas, and Ethridge, 1952; White, Leevy, Brusca, and Gnassi, 1955; Richman, Delman, and Grob, 1961). Jaundice following non-cardiac surgery and injury has also been reported (Geller and Tagnon, 1950; Sevitt, 1958; Pichlmayr and Stich, 1962; Schmid, Hefti, Gattiker, Kistler, and Senning, 1965). Losowsky, Ikram, Snow, Hargreave, and Nixon (1965) have repeatedly observed evidence of unexpected liver failure after operations for advanced heart disease, but give no details of their patients. We also have observed jaundice following closely upon heart surgery.

In this retrospective survey we consider only jaundice starting in the first few days after open-heart surgery. We discuss the factors which may play a part in its causation and suggest ways of reducing the incidence.

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MATERIAL

Two hundred and thirty-two patients who had open-heart operations at the National Heart Hospital have been studied. Table I shows the general distribution of these patients according to lesion, age, and sex.

TABLE I

PATIENTS SURVEYED (232)

Heart Lesion	Male	Female	Age (mean)	Valve Replacement
Congenital ..	32	27	3–56 (20)	0
Acquired:				
Mainly aortic	95	38	15–63 (44)	113
Mainly mitral	15	16	13–59 (41)	25
Multiple valve	2	7	28–49 (39)	9
Total	144	88		147

METHODS

BYPASS TECHNIQUE In the majority of patients a haemodilute, normal temperature bypass technique with disc oxygenation was used (for details see Lockey, Longmore, Ross, and Sturridge, 1966).

BLOOD TRANSFUSION All patients were screened pre-operatively for the presence of antibodies to the ABO, Rhesus, MNS, P, Lutheran, Lewis, Kell, and Duffy blood group antigens. Blood was cross-matched using saline and albumin techniques at 12° C., room temperature, and 37° C. The indirect Coombs' test was also performed. Pump blood was used to transfuse most patients for the first 12 hours or so after operation.

BIOCHEMICAL METHODS Serum bilirubin was measured by the method of Malloy and Evelyn (1937); alkaline phosphatase by a modification of the method of King and Armstrong (1934); S.G.O.T. and S.G.P.T. colorimetrically using Sigma reagents.

RESULTS

GENERAL INCIDENCE OF POST-OPERATIVE JAUNDICE Thirty patients (13%) were definitely jaundiced after operation. Eighteen of them died in hospital, but in none was death ascribable primarily to liver failure. Jaundice was always manifest by the fourth post-operative day. In 19 patients the highest total serum bilirubin value occurred between the second and tenth post-operative day; in nine, the level was still rising at death but all died before the tenth post-operative day. In one patient the highest value was recorded on the first day and in another the jaundice fluctuated. The incidence of jaundice was markedly higher in patients in whom the mitral valve was primarily involved (17 of 31 patients), was relatively uncommon when the lesion primarily affected the aortic valve (7 of 133 patients), and was rare when the lesion was congenital (1 of 59 patients). The incidence of severe jaundice was also highest in the mitral group. Table II illustrates these facts.

Hyperbilirubinaemia without jaundice was common after surgery. We measured the serum bilirubin levels for several days after operation in 105 of the remaining 202 patients in whom jaundice was either not suspected or was clinically doubtful. In 37 of them the highest recorded value was less than 0·8 mg./100 ml.; in 50, the values were between 0·8 and 2·0 mg./100 ml.; in four, levels up to 3·0 mg./100 ml. were recorded on the first post-operative day but had dropped below 1·2 mg./100 ml. by the second; in nine, slightly raised levels around 2·0–2·5 mg./100 ml. were maintained for up to a week after operation; five patients died within four days of operation, the bilirubin levels being minimally raised at death.

TABLE II

INCIDENCE OF EARLY POST-OPERATIVE JAUNDICE IN 232 PATIENTS SUBJECTED TO OPEN-HEART SURGERY

Lesion	Total No. of Patients	No. of Patients with Maximum Total Serum Bilirubin (mg./100 ml.)		Jaundiced (%)
		3·0–11·5 (mean = 6·5)	12·0–28·5 (mean = 19·5)	
Congenital ..	59	1	0	2
Mainly aortic valve disease	133	5	2	5
Mainly mitral valve disease	31	12	5	55
Multiple valve replacements	9	4	1	Insufficient

INCIDENCE OF POST-OPERATIVE JAUNDICE RELATED TO AFTER-CARE OF PATIENTS In the first 126 patients the venous pressure (measured from the right atrium) was maintained at or above 15 cm. of water by means of blood or plasma transfusion. The average amount of blood used at operation and in the subsequent 48 hours was 8 litres. In the last 106 patients, post-operative venous pressures were maintained around 5 cm. of water. Every effort was made to reduce the amount of blood used both during and after operation, and the average decreased to 4·5 litres.

Since the incidence of jaundice proved disproportionately high in patients with mitral valve disease, the 38 patients who had either operations on the mitral valve only, or had multiple valve replacement including the mitral valve and who survived for at least three days post-operatively, are compared in Table III. In the first series (higher post-operative venous pressures, higher blood usage) there are 17 patients, one of whom had a multiple valve operation. In the second series (lower post-operative venous pressures, lower blood usage) there are 21 patients, seven of whom had multiple valve replacements.

TABLE III

INCIDENCE AND SEVERITY OF JAUNDICE RELATED TO POST-OPERATIVE VENOUS PRESSURE AND VOLUME OF BLOOD TRANSFUSED IN 38 PATIENTS WITH PREDOMINANTLY MITRAL VALVE DISEASE

Series	Venous Pressure Measured from Right Atrium (cm. H_2O)	Blood Used (litres) (mean)	Serum Bilirubin (mg./100 ml.)		
			0·5–3·5	4·0–11·5 (mean = 7·0)	14·0–28·5 (mean = 1·80)
First[1] (17 patients)	15 or higher	5½–11 (8)	7		
		8½–17 (12)		5	5
Second[2] (21 patients)	Around 5	1–7½ (4)	13		
		3–8½ (6)		7	1

[1]First series = Higher post-operative venous pressures and higher blood usage.
[2]Second series = Lower post-operative venous pressures and lower blood usage.

The incidence of severe jaundice (serum bilirubin more than 11·5 mg./100 ml.) decreased from 29% in the first series to 5% in the second. Conversely, the percentage of patients who were not jaundiced or only slightly so (serum bilirubin less than 3·5 mg./100 ml.) increased from 41% in the first series to 62% in the second.

POST-OPERATIVE BIOCHEMICAL FINDINGS The biochemical pattern in these jaundiced patients, although not characteristic of any well recognized form of liver disturbance, was remarkably constant.

A rise in total serum bilirubin level with little or no change in other indices of liver function was the most striking feature, and at levels between 1 mg./100 ml. and 4 mg./100 ml. the unconjugated fraction usually equalled or exceeded the conjugated. Bilirubinuria was also present.

The serum alkaline phosphatase was notably normal. It was measured in 20 of the 30 jaundiced patients. In the first post-operative week the values ranged from 5 to 14 K.A. units (average 8 K.A. units). Nine of these patients had total serum bilirubin levels greater than 8·5 mg./100 ml., and in six the level was between 14·0 and 28·4 mg./100 ml. In seven patients the serum alkaline phosphatase showed a distinct rise in the second post-operative week, the highest recorded value being 23 K.A. units; at this time the total serum bilirubin level had fallen to normal in five patients, in none of whom had it in fact ever been higher than 5·0 mg./100 ml. In two patients the serum bilirubin level was still rising.

S.G.O.T. and S.G.P.T. levels greater than 200 units/ml. may occur immediately after open-heart surgery and persist for several days. These tests, therefore, are of limited value in the differential diagnosis of jaundice. Five of the jaundiced patients showed this gross elevation of enzyme values. In another five, S.G.P.T. values around 75 units/ml. were recorded in the presence of higher S.G.O.T. values, and in nine, S.G.P.T. levels higher than 50 units/ml. were never recorded.

No change in the flocculation tests was noted in the first four weeks after operation.

POST-OPERATIVE MORBID ANATOMY OF THE LIVER Post-mortem examinations were made in 17 jaundiced patients. In all, macroscopic examination of the liver revealed only centrilobular congestion producing a 'nutmeg' pattern. The extrahepatic biliary tree showed no evidence of obstruction. Two patients had small pulmonary infarcts. In one, the infarct was old; in the other, it was recent and about 1 cm. in diameter.

Percutaneous liver biopsy was performed in three severely jaundiced patients immediately after death. All showed evidence of intrahepatic cholestasis. Liver cell necrosis was either very slight or absent.

DISCUSSION

Many factors are probably concerned in the production of jaundice after open-heart surgery. Liver dysfunction may be present before operation. Surgery itself constitutes a gross insult to a sick body, and haemolysis, heart failure, infection, and drugs may all play a part afterwards.

PRE-OPERATIVE EVIDENCE OF LIVER DYSFUNCTION Pre-operative liver function tests had been done in 24 of the 30 patients who subsequently became jaundiced; 13 showed abnormalities and all but one had disease predominantly affecting the mitral valve. In 10 patients the serum bilirubin levels were between 1·2 and 2·4 mg./100 ml. before operation (average = 1·4 mg./100 ml.). Six patients had serum alkaline phosphatase values greater than 13 K.A. units, two were prothrombin-deficient, and two had grossly abnormal flocculation tests.

A certain incidence of jaundice, particularly after mitral valve surgery, might therefore be expected.

OPERATIVE PROCEDURES It has been recognized for many years that surgical operations of many kinds may be followed by jaundice with no obvious cause. Boyce and McFetridge (1938), using Quick's hippuric acid test, concluded that there was a marked decrease in hepatic function after operation, and Tagnon, Robbins, and Nichols (1948) and Geller and Tagnon (1950) showed that bromsulphalein excretion was impaired post-operatively. Zamcheck, Chalmers, and Davidson (1949) found liver biopsy evidence of acute inflammation of the liver at the end of operation in six patients, which was not present when the abdomen was opened. Shock itself has been shown to produce congestion and centrilobular liver cell necrosis (Ellenberg and Osserman, 1951). Shackman, Graber, and Melrose (1952) deduced that splanchnic blood flow could be reduced by about 30% in some patients under general anaesthesia.

Pichlmayr and Stich (1962) and Schmid *et al.* (1965) are among those who have reported overt jaundice after surgery and blood transfusion. The clinical and biochemical picture of the jaundice in their series, apart from a greater incidence of raised serum alkaline phosphatase values in the patients observed by Schmid and his colleagues, is similar to that seen by us. Schmid *et al.* (1965) noted that liver biopsy revealed only evidence of intrahepatic cholestasis, which we also observed in the three patients in our series investigated in this way.

HAEMOLYSIS The bilirubin level may be raised as a result of the destruction of non-viable red cells. The destruction of increasing quantities of red cells does not normally produce a proportional rise in serum bilirubin, because the rate of clearance of bilirubin varies approximately with the square of serum bilirubin level (Weech, Vann, and Grillo, 1941). It should also be noted that a preponderance of the conjugated bilirubin fraction is

not necessarily evidence against a haemolytic process, since Tisdale, Klatskin, and Kinsella (1959) and Schalm and Weber (1964) have shown that excess of unconjugated bilirubin may so overload the excretory capacity of the liver, particularly if it is damaged, that regurgitation of conjugated bilirubin into the blood stream occurs, resulting in high levels compared with those of the unconjugated pigment.

Mollison and Young (1942) showed that stored blood contains a proportion of non-viable red cells, this proportion increasing with storage time. Such cells are removed from the circulation within a few hours of transfusion and resultant elevations in serum bilirubin level return to normal within 24 hours. It is also probable that the passage of red cells through the heart–lung machine reduces their life span. Anderson, Gabrieli, and Zizzi (1965) studied two patients subjected to open-heart surgery and noted that haemolysis which occurred during perfusion cleared the circulating plasma of free haptoglobins for 12 to 24 hours after perfusion. They also noted that the plasma haemoglobin level was raised in both patients during the first few post-operative days. We have noted this elevation of plasma haemoglobin in two jaundiced patients.

The presence of mechanical prostheses may also decrease the survival time of red cells. Anderson *et al.* (1965) considered this to be so particularly in patients with aortic prostheses, but Brodeur, Sutherland, Koler, Kimsey, and Griswold (1964) found shortened red cell survival times in patients with aortic valve disease before surgery. In our series, 53 patients had caged-ball valves inserted. In 21 patients the aortic valve was replaced ; only two became jaundiced (9·5%), but as one of them had a rapidly rising serum bilirubin level before operation, the true incidence is probably 5%, the same as for homograft replacement of the aortic valve. Thirty-two patients had caged-ball mitral valves inserted and 20 became jaundiced (62·5%). The presence of a mechanical valve *per se* is not therefore a consistent cause of jaundice.

A drop in haemoglobin level in the week following perfusion was usual in our patients, about half showing a fall of at least 10% during this period. It seems possible, therefore, that a continuing destruction of red cells occurs in patients subjected to open-heart surgery and that a prolonged slight elevation of serum bilirubin levels may be due to this cause. It is unlikely, however, that haemolysis alone could explain the development of severe jaundice.

HEART FAILURE The presence of a raised unconjugated fraction does not exclude heart disease as the prime cause of jaundice. Levine and Klatskin (1964) found heart disease with or without congestive failure to be the commonest association in a large series of patients with unconjugated hyperbilirubinaemia but without evidence of haemolysis. Usually the conjugated fraction is higher in patients with heart disease and particularly in patients with marked congestive failure. Sherlock (1951) pointed out that overt jaundice was less common than a slight elevation of serum bilirubin levels in such patients and was usually confined to patients with mitral stenosis and tricuspid regurgitation ; patients with deep jaundice tended to have very high right atrial pressures. She reported a patient with aortic and tricuspid incompetence and mitral stenosis with a total serum bilirubin level of 25 mg./100 ml. ; Gadeholt and Haugen (1964) ascribed a level of 26·5 mg./100 ml. to congestive failure in a patient with aortic stenosis and regurgitation and mitral stenosis. Losowsky *et al.* (1965) investigated 14 patients thought to have chronic venous congestion of the liver but with no clinical or radiological evidence of pulmonary embolism. They found that the standard bromsulphalein retention test was abnormal in all and closely paralleled the right atrial pressure. A improvement in liver function occurred after medical and surgical treatment. These findings suggested to them that congestion itself was the basic cause of the hepatic dysfunction. It is of interest, in view of our findings, that Sherlock (1951) noted that the alkaline phosphatase was usually normal in patients with heart failure and that some of the patients with deepest jaundice had the lowest alkaline phosphatase values. She also noted that the mean serum bilirubin level was usually higher in patients with severe grades of hepatic cell necrosis and with pulmonary infarction. The three liver biopsy specimens in our series were all obtained from severely jaundiced patients but showed little or no evidence of cell necrosis. Only two of our patients were known to have macroscopic evidence of pulmonary infarction, but as all patients after open-heart surgery must have a certain amount of extravasated blood in the tissues, an increased load of unconjugated bilirubin would come from this source. It may be of importance to note here that, whereas a midline sternotomy was invariably used for operations on the aortic valve, a lateral thoracotomy involving muscle splitting was the usual approach for the mitral valve. This latter incision could be expected to entrap much more spilt blood than the former

and might in part explain the greater incidence of jaundice in patients who had had mitral surgery.

Despite the relationship between heart failure and jaundice noted above, it is unlikely to be the complete explanation in our series. Thus, although 18 of the 30 jaundiced patients were in severe heart failure after operation and all but one died, nine who had no post-operative heart failure became jaundiced.

INFECTION A biochemical and histological pattern similar to that seen after operative procedures has been described in patients with jaundice associated with bacterial infection by Fahrländer, Huber, and Gloor (1964) and Eley, Hargreaves, and Lambert (1965). Intrahepatic cholestasis only was found on liver biopsy. Two of our jaundiced patients had severe bacterial infections, *Pseudomonas pyocyanea* empyema in one and bilateral lung abscesses due to *Escherichia coli* in the other.

Viral hepatitis, although one of the commonest forms of jaundice, is unlikely to be the cause in our patients. The time interval from the operation is too short and a much more severe course, with hepatic coma, would have been anticipated if such major surgery had been performed on patients incubating the disease. Furthermore, biopsy in three cases showed none of the typical changes of viral hepatitis.

DRUGS Although a cholestatic histological pattern is seen in patients with steroid jaundice, none of our patients was given oral anabolic steroids. Halothane anaesthesia was used in some patients, but none received monoamine oxidase inhibitors. All had penicillin of some type; some had chloramphenicol or streptomycin in addition. A few received chlorpromazine. Many of the patients with mitral valve disease had received phenindione for varying periods of time before operation. Hargreaves and Howell (1965) have described three cases of jaundice of a hypersensitivity type due to phenindione, noting that only 12 previous cases have been reported. They also found that it interfered with the conjugation of bilirubin *in vitro*. However, in our series there was no greater incidence of jaundice in the mitral valve disease and multiple valve replacement patients who had previously received anticoagulant therapy than in those who had not.

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