Conclusions

The clinical results of ganglionectomy and of pre-ganglionic sympathetic section for Raynaud's disease are the same.

The absence of unpleasant side-effects from pre-ganglionic section makes it preferable to ganglionectomy.

The similarity in results of the two operations suggests that nerve regeneration is not the chief cause of relapse after sympathectomy.

The possible causes of relapse are discussed. The "local fault" postulated by Lewis is thought to be important.

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SEPTIC JAUNDICE

A COMPLICATION OF PERITONITIS FOLLOWING GASTRO-INTESTINAL SURGERY

BY

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The occurrence of jaundice shortly after operation gives rise to anxiety, and the determination of its cause becomes a matter of importance. That jaundice can be caused by sepsis is known, but reports of this type of case are rare. Brown and Counsellor (1932) described two cases of acute appendicitis in which jaundice was present before operation. An appendix abscess was present in one, and in the other the organ was gangrenous

and purulent. With the subsidence of infection after operation the jaundice cleared rapidly. Philipowicz (1934) reported the development of deep jaundice due to an enormously distended and inflamed caecum and appendix in a 73-year-old man, with no obvious liver or gall-bladder disease at operation. The jaundice receded rapidly after operation. Simeone and Stewart (1940) described two cases of peritonitis after appendicectomy in which jaundice developed. In both cases haemorrhagic manifestations and evidence of liver failure occurred and both terminated fatally. Post-mortem examination, allowed in only one case, showed a diffuse central lobular necrosis of the liver. Only in one of many textbooks consulted is jaundice mentioned as a complication of peritonitis. Muir (1941) states that areas of necrosis may occur in the liver in acute peritonitis, but makes no mention of jaundice.

The six cases described below appear to fall into one category, for which the descriptive title of septic jaundice is suggested. The term "infectious" or "infective jaundice" carries the risk of confusion with infective hepatitis of viral origin, and "toxic jaundice" has been applied to jaundice caused by so many diverse agents that it lacks specificity.

Clinical Description

Details of the cases are shown in Tables I to IV. The histological findings in two further fatal cases of peritonitis following gastrectomy are included in Table IV for purposes of comparison. These two cases did not develop jaundice.

It will be seen that in all cases the operation involved the gastro-intestinal tract, and that post-operative complications were severe. Peritonitis, local or general, occurred in every case. Wound breakdown, subphrenic and intra-peritoneal abscesses, metastatic abscesses, faecal fistulae, abdominal wall abscess, and vesico-perineal fistula occurred, necessitating secondary operation in most cases. Unfortun-

TABLE I.—Pathological and Nutritional States

Case	Sex	Age	Pathological State	Nutrition	Diet
1	F	43	Carcinoma of stomach	Fair	Gastric
2	M	44	Gastric ulcer	"	"
3	M	51	Diverticulitis (localized)	Good	Normal
4	M	36	Gastric ulcer	Fair	Gastric
5	M	58	Carcinoma of rectum	Good	Normal
6	F	35	Intestinal obstruction due to multiple adhesions	"	"

TABLE II.—Details of Operations, Complications, and Treatment.

Case	Operation	Septic Complications	Jaundice: Onset and Duration	Transfusions*	Sulphonamides†
1	13/2/50: abdomino-thoracic total gastrectomy	16/2/50: ? peritonitis 22/2/50: drainage of peritonitis and right subphrenic abscess	17/2/50: jaundice till death on 24/2/50	13/2/50 (3) 17/2/50 (3)	23/2/51: sulphadimidine 2 g. I.M.
2	29/10/49: subtotal gastrectomy	2/11/49: Stomal obstruction—moderate 6/11/49: laparotomy—localized peritonitis and leak from suture line 10/11/49: multiple septic pulmonary infarcts 11/11/49: hypopyon	7/11/49: jaundice till death on 14/11/49	6/11/49 (1)	11-14/11/49: sulpha-triad 17 g.
3	17/11/50: partial colectomy, end-to-end anastomosis	26/11/50: faecal fistula in wound 29/11/50: resuture of wound	4/12/50: jaundice till death on 8/12/50	17/11/50 (1)	7-8/12/50: sulphadimidine 6 g.
4	25/10/47 partial gastrectomy	5/12/50: jejunostomy for intestinal obstruction 26/10/47: stomal obstruction—moderate 2/11/47: wound purulent 7/11/47: drainage of pelvic abscess 11/11/47: drainage of perigastric abscess 14/11/47: jejuno-jejunostomy for obstruction 24/11/47: wound fistulae, gastric and faecal 21/12/47: drainage right subphrenic abscess 4/1/48: Division of strangulating band	30/10/47: jaundice, fading after 17/11/47; conjunctival staining until 2/12/47. 26/2/48: jaundice recurred till death on 28/2/48	25/10/47, plasma (2) 30/10/47 (1) 11/11/47 (2), plasma (1) 14/11/47 (1) 4/1/48 (2), plasma (1)	5-7/11/47: sulphadimidine 14 g. 7-13/11/47: soluthiazole I.M. 35 g. 17-22/12/47: sulphadimidine 38 g. 11-16/1/48: sulphadimidine 30 g. 27/4/51-1/5/51: phthalylsulphacetamide 42 g.
5	2/5/51: abdomino-perineal excision of rectum	3/5/51: vesico-perineal fistula 6/5/51: abdominal distension	8/5/51: jaundice till death on 12/5/51	2/5/51 (3)	
6	28/9/50: division of multiple intestinal adhesions	29/9/50: abdominal pain and distension 7/10/50: wound oozing pus 16/10/50: ileostomy for obstruction. Three faecal fistulae developed in wound	3/10/50: jaundice till 29/10/50	16/10/50 (1) 29/10/50 (2)	

* Unless otherwise stated, transfusions were of stored blood; figure following date gives the number of pints.

† Sulphonamide dosage is shown as a total for each course.

TABLE III.—Details of Liver-function Tests

Case	Date	Serum Bilirubin mg./100 ml.			Thymol		S.C.G.	S.A.P.	S. Chol.
		Total	Direct	Indirect	T	F			
1	21/2/50	17.6	13.2	4.4	0	Neg.	Neg.	12	157
3	1/12/50	0.7	0.3	0.4					
4	31/10/47	2.9	1.6	1.3	1	"	"	3	
5	2/11/47	10.0	6.7	3.3	2				
6	8/5/51	2.9	2.0	0.9	1	"	"	5	118
	5/10/50	8.4	5.5	2.9	1	"	"		
	24/10/50				3	1+	1+	8	
	Sept., 1951	0.6	0.0	0.6					

T = turbidity. F = flocculation. S.C.G. = serum colloidal gold. S.A.P. = serum alkaline phosphatase, King-Armstrong units. S. Chol. = serum cholesterol mg. per 100 ml.

TABLE IV.—Histological Findings in Six Cases with Jaundice and in Two Cases in which Death was Due to Peritonitis but which were not Jaundiced

Case	Abdominal Findings	Liver	Histology of the Liver
1	Diffuse peritonitis; localized pus; r. subphrenic abscess. Leak from duodenal stump	Pale, soft, flabby. Wt. 78oz. (2,210 g.)	Bile-staining in centre of lobule. General vacuolation of liver cells, slightly more marked peripherally. Round-cell infiltration of the portal tracts. Subcapsular zones of necrosis and early fibrosis and congestion, with layer of pus on capsule (see illustration)
2	Fibrino-purulent exudate throughout abdomen. L. subphrenic abscess. Jejunal anastomotic leak	Pale, soft. Normal size	No histology
3	Recent peritonitis; pockets of pus. Fistula from anastomosis of colon	Large, pale, soft. Wt. 69oz. (1,956 g.)	No histology
4	No evidence of peritonitis. All stomata healthy and healed	Flabby. Capsule wrinkled. Wt. 50oz. (1,417 g.)	Acute zonal (centrilobular) necrosis, only small groups of surviving cells. Areas of haemorrhagic exudation and little cellular infiltration. Layer of organized pus on capsule
5	Widespread peritonitis. Large abscess in abdominal wall under suture line. Large infected haematoma round colostomy opening	Fatty	Cells mainly normal; some P.M. change; round-cell infiltration of portal tracts. Recent (probably terminal) thrombosis of portal vein. Layer of superficial pus on capsule
7	Extensive localized peritonitis, with subphrenic and r. perinephric abscess		Superficial layer of necrosis and early fibrosis beneath capsule with sinuses intensely congested below that. Brisk leucocytic infiltration round portal tracts. Scattered foci of fatty infiltration with no particular lobular distribution
8	Several pints of faecal fluid in abdominal cavity due to perforation of duodenal stump following internal herniation and obstruction of afferent loop	Fatty degeneration	Diffuse fatty degeneration affecting the whole of the lobule. Slight round-cell infiltration of portal tracts. No superficial pus. No superficial necrosis

Case 1.—Peritoneal exudate, with underlying necrosis of liver cells and fibrosis. (Haematoxylin-eosin. $\times 100$.)

rapidly occurred from homologous serum hepatitis, with recurrence of jaundice. Biliuria accompanied the jaundice in all cases.

All cases were febrile at the onset of jaundice, and in the fatal cases fever persisted till death occurred. In the two cases in which jaundice cleared, the fever settled at the same time, or soon after.

It was difficult, in such ill patients, to assess the part played by the liver in the picture, but there was no obvious sudden worsening of the general condition that could be associated with the development of jaundice. Haemorrhagic phenomena were not noted, and bleeding at further operations was not abnormal. Pruritus and bradycardia did not occur, nor was hyperpyrexia found.

Adequate causes for death, without invoking liver damage, were present in the fatal cases, sepsis being responsible.

All except one patient had received blood transfusions before jaundice appeared, one also having had plasma; no immediate reactions had occurred. Because of the time relationships, these transfusions are not thought to have played any part in causing this type of jaundice. The second and fatal bout of jaundice in Case 4 was almost certainly due to homologous serum hepatitis.

Sulphonamides could not be held responsible, since three patients had them only after jaundice was established, when they gave rise to no apparent adverse effects, one had only a relatively non-absorbable compound, and one did not have sulphonamides at all.

Shock, haemorrhage, or haematoma formation, anaemia, and thrombo-embolism were not thought to have played any part in causing jaundice since they occurred only infrequently.

Table III gives details of the liver function tests carried out. No pre-operative tests were performed. In Case 3 serum bilirubin estimations were carried out three days before jaundice was definitely noted, but unfortunately further estimations were not made. In Case 2 no tests were made, and in Case 5 no tests were made during the second and fatal bout of jaundice.

Apart from Case 3, all the serum bilirubin estimations were raised, with the direct reacting type two to three times as high as the indirect. Flocculation tests were performed four times in three cases (Nos. 1, 4, and 6), and were uniformly negative; the serum alkaline phosphatase was normal in Cases 1 and 6. Flocculation tests carried out a year later in the one surviving case (No. 6) gave abnormal results, although there was no clinical evidence of liver damage, and faecal fistulae were still discharging up to within a short time of the tests.

The post-mortem findings showed peritonitis, mostly widespread, and evidence of leakage from suture lines in all fatal cases except Case 4, in which recovery from sepsis had occurred. In all cases the gall-bladder and bile ducts

ately bacteriological investigations were made in only three cases, negative swabs being obtained from one, and *Staphylococcus aureus* and *Bacillus aerogenes* from the others.

The anaesthetic agents were those in general use, mainly thiopentone for induction and cyclopropane for maintenance. Chloroform was not used.

Of the six cases four became jaundiced on the fourth and fifth post-operative days, one on the ninth day, and one on the seventeenth. In four cases death occurred from four to seven days after the onset of jaundice and from seven to twenty-one days after operation. Two cases recovered: Case 6, in which jaundice appeared on the fifth day, was lessening on the twelfth day, and had cleared by the twenty-sixth; and Case 4, in which jaundice appeared on the fifth day and remained obvious for twenty days, with conjunctival staining for a further fifteen days. Two months later death

were examined, and no evidence of obstruction was found, nor were liver abscesses or pyelephlebitis present. The histological findings of Cases 1 and 5 showed no gross abnormality and no typical changes, and did not differ from the findings in two similar patients dying from peritonitis after gastrectomy who did not develop jaundice (Table IV, Cases 7 and 8). Case 4 showed severe acute zonal necrosis due to homologous serum hepatitis. An interesting histological finding in Case 1 was a zone of subcapsular necrosis and early fibrosis bounded by a zone of intense congestion of the sinuses, with a layer of organized pus on the capsule; this appearance was also seen in one of the non-jaundiced cases. A similar layer of pus on the capsule was seen in Case 5, without any zone of necrosis or congestion, and also in Case 4, in which severe zonal necrosis was present throughout the liver.

Differential Diagnosis

The causes of post-operative jaundice fall into four main groups. A double infection is one of the possible causes, and the chance association of acute infective hepatitis or cholelithiasis with the operative condition must be considered, although any other disease causing jaundice may be responsible.

Misdiagnosis resulting in operation in the pre-icteric phase of acute infective hepatitis can occur, but is usually easily recognized. Other conditions, more rarely causing jaundice, which may be mistaken for abdominal surgical conditions are typhoid fever, lower lobar pneumonia, and malignant tertian malaria. A haemolytic crisis can also cause confusion. Acute massive hepatic necrosis may be mistaken for a liver abscess, with its high fever, rigors, and leucocytosis, the jaundice appearing a few days or even up to two weeks after the onset.

Jaundice due to various forms of therapy includes that caused by haemolysis after transfusion, homologous serum hepatitis, and sulphonamide jaundice. Many other drugs have occasionally caused jaundice, but confusion should not arise if that possibility is considered; and this applies also to industrial compounds to which the patient may have been exposed. Jaundice due to haemolysis after transfusion when due to incompatibility is usually easy to recognize. Another type, due mainly to normal destruction of transfused erythrocytes and partly to impairment of hepatic function following operation and anaesthesia, has been described by Geller and Tagnon (1950). They showed that a significant rise in serum bilirubin occurred in 24 of 33 patients undergoing major abdominal surgery with blood transfusion during operation. Jaundice occurred in six, developing before the fourth day, and clearing in a few days. The amount of blood given bore a direct relationship to the rise in serum bilirubin, but not to the appearance or intensity of the jaundice. Ross *et al.* (1947) stated that up to 30% of the erythrocytes stored in acid citrate-dextrose may be destroyed in the first 24 hours after transfusion, depending on the length of time of storage.

Homologous serum hepatitis, unless due to pre-operative treatment, should not present any difficulty in diagnosis, since the long incubation period of 50 to 150 days ensures that it develops during or after convalescence.

Sulphonamides, especially intraperitoneal sulphanilamide, are known to cause jaundice occasionally, although the newer relatively insoluble preparations have not been incriminated in this respect. Jaundice may be due to a hepatitis or to an acute haemolytic anaemia, and the two types may coexist. The incidence of this complication varies considerably in different reports (Jackson and Coller, 1942; Hudson and Smith, 1942; Mueller and Thompson, 1942). Exfoliative dermatitis may accompany the jaundice (Garvin 1938; Long *et al.*, 1940). Spring and Bernstein (1940) reported two cases with coexistent toxic hepatitis and acute haemolytic anaemia, with renal damage, due to sulphanilamide therapy; and Cline (1938) and Russell (1940) each described a case of massive hepatic necrosis after treat-

ment with the same compound. Lederer and Rosenblatt (1942) reported four deaths during sulphathiazole therapy, none showing clinical jaundice, but all showing areas of focal necrosis in all viscera, except the central nervous system. Merkel and Crawford (1942) reported similar findings. The cause of the hepatitis in these patients is not clear. Previous liver disease does not appear to be a factor. Rammelkamp (1948) stated that sulphonamides can be given with impunity to patients with liver disease and jaundice, provided that the drug is not the cause of the jaundice.

Jaundice due to post-operative complications includes that due to absorbed blood pigments from a large haematoma or pulmonary infarct, haemolysis due to septicæmia, surgical operation on the bile ducts, septic jaundice, and acute massive hepatic necrosis. Rarely, haemolysis due to septicæmia can give rise to jaundice. In such cases the indirect reacting type of bilirubin exceeds the direct type, and biliuria does not occur. An obstructive type of jaundice, in the absence of overlooked gallstones, can be due to division of the duct, or to obstruction by ligature, oedema, adhesions, or scarring around the duct or in the region of the ampulla. Such cases, in the absence of sepsis, are usually in fairly good general condition, with negative flocculation reactions, a raised serum alkaline phosphatase, and a raised serum bilirubin, mainly of the direct type.

Acute massive hepatic necrosis occasionally occurs as a post-operative complication. Much of the clinical evidence is likely to be obscured if the patient should also be suffering from peritonitis, and this applies especially to the diminishing size of the liver, the ascites, and the enlarging spleen. The mental state also may not be dissimilar in the two conditions. Unexplained oedema and oliguria, haemorrhagic phenomena, neurological signs, and amino-acidaemia and tyrosinuria are valuable aids in diagnosis. The jaundice can be very deep, and the blood sugar, cholesterol, and prothrombin levels are all low.

Discussion

Study of these cases suggests that a well-defined type of jaundice occurs as a complication of peritonitis. The age and sex incidence is as yet uncertain. The jaundice was moderate or severe, accompanied by biliuria, developing with or soon after the onset of peritonitis, and clearing when the sepsis was overcome or persisting until death. Fever and toxæmia were present at the onset, and persisted with the jaundice. All of these cases followed gastro-intestinal operations, and intraperitoneal leakage of gut contents seemed to be the commonest cause of the complication. There was no apparent deterioration in these ill patients when jaundice appeared, nor did it give rise to fresh symptoms; and evidence of hepatic parenchymal failure, such as oedema, haemorrhagic manifestations, and mental and neurological disturbances, did not occur. The fever and toxæmia, and the frequent fatal outcome, were adequately accounted for by the severe degree of sepsis present. Liver-function tests showed that most of the serum bilirubin was of the direct reacting type, and that the flocculation tests were uniformly negative. The serum alkaline phosphatase levels were normal. Bacteriological investigation was scanty, and organisms were recovered from only two cases, being *Staphylococcus aureus* and *Bacillus aerogenes*. The macroscopic appearances of the liver at necropsy suggested only fatty change without any evidence of biliary obstruction or gall-bladder disease, or of liver abscess or pyelephlebitis. Histological examination was carried out in only two cases; the appearances were non-specific, being remarkable perhaps only for the paucity of abnormal findings, and did not differ from the findings in cases of peritonitis of similar aetiology in which there was no jaundice.

The importance of this type of jaundice, as indeed of all other types, depends on the cause. It is a physical sign of peritonitis, and occasionally it may be an early sign. Recognition will also prevent needless and useless exploration of the gall-bladder and bile ducts.

The mechanism of the production can at the moment only be surmised. It seems probable that bacterial toxins, or the organisms themselves, are carried by the portal vein to the liver, giving rise to a hepatitis. Ottenberg and Spiegel (1943) stated that jaundice was an occasional symptom in acute septicaemias, and was usually of unfavourable prognostic significance, with the pneumococcus, haemolytic streptococcus, anaerobic staphylococcus, and *Clostridium welchii* as the commoner organisms responsible. Haemolysis and the effect of bacterial toxins were both usually responsible. Those authors thought that the histological changes in the liver bore no relation to the degree of jaundice. On purely physical grounds peritoneal sepsis would be expected to cause jaundice more often than sepsis elsewhere, owing to the direct drainage of the septic area, often of great extent, direct into the liver.

Another possibility is that the associated ileus and circulatory disturbance give rise to abnormal and toxic gut contents able to affect the liver. Other factors which must be considered are a diminished oxygen content in the portal blood due to stasis, because of the associated ileus, anaemia, and shock, all leading to anoxaemia of the liver. Neither anaemia nor shock played any part in these cases.

The incidence of septic jaundice, compared with that of peritonitis, suggests that the resistance of the liver to the effects of sepsis is high. Although in most of the cases in this series the extent of the sepsis was considerable, equally severe cases of similar duration have not developed jaundice. In the absence of proof to the contrary, however, it seems reasonable to assume that, all other factors being equal, the greater the amount of sepsis the more likely is the development of jaundice. The effects of different organisms in causing it remain to be investigated. The duration of sepsis does not seem to be a factor, since most of these cases occurred early in the post-operative period.

The pre-operative state of the liver may be of importance, but in these cases there was no clinical evidence pre-operatively or pathological evidence at necropsy to suggest any predisposing disease.

Summary

Six cases of jaundice occurring after gastro-intestinal operations complicated by peritonitis are described. They form a group for which the name septic jaundice is proposed.

The onset of jaundice was early, usually within the first week of operation, and it persisted until death or until the infection subsided. Signs of hepatic parenchymal failure were not observed. The thymol flocculation and turbidity tests and the serum colloidal gold reaction were consistently negative, and the serum alkaline phosphatase was normal. Treatment and prognosis are those of the peritonitis.

The post-mortem appearances and the liver histology are described; two non-jaundiced cases of fatal peritonitis are included in this section. In some of the cases the liver showed a zone of subcapsular necrosis bounded by a zone of intense congestion of the sinuses, and a layer of pus on the capsule.

The differential diagnosis and the possible factors affecting the liver in this condition are discussed. Severe peritoneal sepsis is thought to be the cause of the condition.

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VITAMIN K IN THE TREATMENT OF ACUTE HEPATITIS

BY

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Since Dam (1935) described vitamin K and Dam and Schönheyder (1936) defined the part it plays in the maintenance of a normal prothrombin level in the blood numerous papers have been published on vitamin K and prothrombin in animals and man. Since 1935 many authors (Hult, 1939–41, among others) have investigated the effect of vitamin K on the prothrombin level in acute and chronic diseases of the liver; and acute hepatitis has also been a subject for research. It was observed that vitamin K administration in these cases exerted a varying influence on the prothrombin level (Butt, Snell, and Osterberg, 1939; Hult, 1940). Begtrup and From Hansen (1942, 1948) found that patients with parenchymal liver damage mostly showed only a slight increase of the prothrombin level after administration of vitamin K. Patients with obstructive jaundice, on the other hand, responded well to the vitamin.

There are several causes of a low prothrombin level. Severe parenchymal liver damage may retard prothrombin formation by the liver, or the absence of bile salts in the intestinal tract in cases with an impeded bile flow may result in a deficient absorption of vitamin K, necessary in some way for the production of prothrombin. The relative extent to which a deficiency in prothrombin formation is due either to liver damage or to defective absorption of vitamin K remains to be determined.

Present Investigation

From January to the beginning of August, 1950, every second case admitted to hospital for suspected hepatitis was on the day after admission put on vitamin K treatment,* one tablet (0.01 g.) three times a day by mouth. The other cases served as controls and were given a placebo.

The material consisted of 247 cases: 178 of acute hepatitis; 5 of subacute hepatitis; 7 of chronic hepatitis or cirrhosis of the liver; 27 of cholecystitis or cholelithiasis (15 stayed two weeks or more in hospital); 13 of carcinoma of the pancreas or the papilla of Vater or neoplasms of the extrahepatic bile ducts; and 17 with various non-hepatic diseases.

The two groups of acute hepatitis consisted of 87 cases in the K (vitamin-K) series and 91 in the C (control) series. The distribution in age groups was practically the same. No attempt was made to divide the material into epidemic and

* "K-vimin" (water-soluble, 2-methyl-1,4-naphthoquinone tetrasodium diphosphate). Astra, Södertälje, Sweden.