Papers and Originals

SPLENECTOMY IN CRYPTOGENETIC SPLENOMEGALY

BY

J. COOK, F.R.C.S.Ed., F.A.C.S.
Former Senior Surgical Specialist

A. J. S. McFADZEAN, M.D., F.R.C.P.
M.R.C.P.Ed.
Professor of Medicine

D. TODD, M.D., M.R.C.P.Ed.
Lecturer in Medicine

The University Department of Medicine and Queen Mary Hospital, Hong Kong

Among the Chinese in Hong Kong there is a syndrome of enlargement of the spleen, commonly massive, associated with varying degrees of liver damage up to an atrophic cirrhosis possessed of the pathological features of post-necrotic scarring. In a proportion scarring may be minimal or absent. In such cases the liver is usually enlarged, and histological examination shows infiltration of the sinusoids and not infrequently of the periportal tissue by round cells dominantly plasma cells and lymphocytes. Commonly there is hyperplasia of the Kupffer cells. In some instances the round-cell infiltration is so pronounced as to be reminiscent of that encountered in chronic lymphatic leukaemia. Histological examination of the spleen and a study of injection corrosion specimens show that the splenomegaly is dominantly due to remarkable hyperplasia of the sinusoids and of the venous channels into which they drain. Fibrosis, both periarterial and trabecular, occurs in all cases, but it varies widely in degree, in some instances being so extensive as to suggest that the spleen, but for the sinusoids, is a useless fibrous organ. Impressive even in the most fibrous spleens is the diminution in size after surgical removal or death.

The spleen may be so large that it fills the greater part of the abdomen, and its size alone constitutes a physical handicap which leads the patient to seek advice. Attacks of pain and tenderness over the spleen are frequent and are presumably due to infarction. Although portal hypertension is encountered in all cases it is greater in those with established cirrhosis of the liver. Ascites and gastrointestinal haemorrhage are often encountered, and the former is commonly resistant to management by salt restriction and diuretics. While in a proportion of patients bleeding from oesophago-gastric varices occurs, in many instances the character of the haemorrhage suggests that varices are not the source. Further, in a number of patients haemorrhage presents as melaena in the absence of haematemesis. Aspiration of the stomach contents in many such cases shows that there is no blood in the stomach. Such non-gastric bleeding may be fatal. Bleeding from the nose and gums is common, and this has been shown (McFadzean and Tsang, 1956a) to be due not to depression of factors involved in clotting but to a vascular fragility which arises as a result of a hyporeactivity of small vessels, probably veins. This fragility is corrected by splenectomy.

There would appear to be an unusually high incidence of thrombosis of the portal vein. Although this complication is much more commonly encountered in those patients with established cirrhosis of the liver it is not restricted to such. The haematological findings are those of hypersplenism, most commonly pancytopenia. It has been shown that the anaemia is partly haemolytic and partly attributable to an expansion of the plasma volume (McFadzean, Todd, and Tsang, 1958a, 1958b). McFadzean and Tsang (1958) reported a high incidence of chronic leg

ulcers and showed that the inflammatory-necrotizing response was significantly increased. If the condition develops in childhood dwarfism or infantilism may occur. Amenorrhoea may be encountered in females.

Frequently there is a previous history of intermittent fever, irregular both in occurrence and in duration. There is no history of alcoholism, nor is there a history suggestive of hepatitis. Theoretically the diet of the large majority is deficient, yet clinical evidence of deficiency states, even in the presence of advanced cirrhosis, is lacking. Extensive investigations, including a series investigated at necropsy, have failed to shed light on the pathogenesis of the condition, and the diagnosis is made by exclusion of other causes of splenomegaly and cirrhosis of the liver. It is possible that we are not dealing with a single entity. The size of the spleen bears no relation either to the liver pathology or to the portal venous pressure. We are satisfied that when extrahepatic obstruction of the portal vein or splenic vein occurs it is a complication and has no role in pathogenesis.

This syndrome has been the subject of numerous communications in the Chinese medical literature and has been reported from North and South China and Formosa. In an excellent review McIntosh (1932) applied the term "cryptogenetic splenomegaly." He considered that it was identical to "tropical febrile splenomegaly" of the Philippines, described originally by Musgrave, Wherry, and Wooley (1906), and to "splénomégalie algérienne" of Goinard (1907). There are many reports of a similar condition from other tropical and subtropical areas, and recently Leather (1961) described an entity in Uganda which is indistinguishable from "cryptogenetic splenomegaly."

Early in our experience it became obvious that treatment of this condition must include removal of the spleen, and it was decided to observe the effect of splenectomy alone. The purpose of this communication is to report those observations.

Material and Methods

Splenectomy was performed upon 175 patients (134 males, 41 females) with cryptogenetic splenomegaly. Their ages ranged from 9 to 56 (mean 31 ± 0.8) years. The spleen was palpable in all, the lower edge being defined from 2 to 23 (mean 11 ± 0.4) cm. below the costal margin in the midclavicular line. This measurement is not an accurate index of the size of the spleen, for it may be small—for example, in the case of a grossly enlarged spleen lying transversely. In 34 patients the spleen was so large that it filled the greater part of the abdomen, and its size alone constituted the physical handicap which resulted in advice being sought. None of the patients had a history suggestive of hepatitis or of an excessive consumption of alcohol; other causes of splenomegaly were excluded. In the case

of patients previously resident in an area where schistosomiasis is endemic this infestation was excluded by repeated examination of the stools, by sigmoidoscopy, including biopsy of rectal mucosa, by the histological examination of a biopsy of the liver taken at operation, and by histological examination of the spleen.

A liver biopsy was performed on all patients either before or during operation. This, coupled with the macroscopic appearances at operation, allowed of the division of the 175 patients into a group of 123 in which scarring was moderate to severe (group 1, post-necrotic cirrhosis) and a group of 52 (group 2) in which scarring was minimal or absent. In 116 (94%) of the patients in group 1 the scarring was severe and the liver was coarsely nodular and reduced in size, whereas in group 2 the liver was enlarged and the surface smooth.

In Table I the cases are dealt with under three heads: (1) *Operative and Hospital Deaths*.—These comprise 14 patients who died within three weeks of operation. (2) *Late*

measures, nor was it affected by blood transfusion. Whole blood obtained by venepuncture seemed to fail to clot, but this was shown by Kwaan, McFadzean, and Cook (1957) to be due to the development in the plasma of fibrinolytic activity of such intensity as to lyse fibrin as rapidly as it was being formed in the process of clotting. They further showed that the abnormality in the plasma was the presence of large amounts of activator which, after clotting, converted plasminogen to plasmin with resulting rapid lysis of the fibrin formed. Five of these patients had ascites and showed a poor response to treatment.

Haemorrhage of this nature occurred in 6 (8%) of the first 77 operations, and was not encountered in the subsequent 98 when human fibrinogen was available and was freely used, 1 or 2 g. being given intravenously immediately any oozing of blood was seen. It would seem reasonable to conclude that by using fibrinogen the haemorrhage can be prevented and the mortality of the operation thereby reduced. This form of haemorrhage is

TABLE I.—*Distribution of Patients According to Sex and to Presence or Absence of Cirrhosis of Liver (Under the Three Heads of Consideration)*

	No. of Patients	Sex		Operative and Hospital Deaths			Late Results						Contact Lost		
							Late Deaths			Present Status Known					
							No.	Sex		No.	Sex		No.	Sex	
		M	F	M	F	M		F	M		F				
Group 1 ..	123	98	25	13	13		25	21	4	65	47	18	20	17	3
„ 2 ..	52	36	16	1		1	1			36	30	6	14	5	9
Total	175	134	41	14	13	1	26	22	4	101	77	24	34	22	12

Results.—These comprise 127 patients who have been under observation since their operation: 26 have died, and the present condition of 101 is known; from these 101 cases the late results of splenectomy have been determined. (3) *Contact Lost*.—In 34 cases contact has been lost. A number of these are known to have returned to China; the others have not been located and all efforts to contact them have failed.

Vascular fragility was determined by the reactive hyperaemia method and graded as described by McFadzean and Tsang (1956a), and the findings before splenectomy are compared with those six months after splenectomy. Standard haematological methods were used and the findings before splenectomy are compared with those recorded at the last attendance at the out-patient clinic. Copper-oxidase activity was determined by the method of Ravin (1956).

Standard statistical methods have been employed and, unless otherwise stated, means are shown with their standard errors.

OPERATIVE AND HOSPITAL DEATHS

Fourteen patients (8%) died in the first three weeks after operation and certain details are set out in Table II.

Six (five males in group 1 and one female in group 2) died within 24 hours from uncontrollable intraperitoneal haemorrhage. This form of bleeding merits description. In each case, when the spleen was removed from the abdomen, blood was oozing from the area of splenic bed denuded of peritoneum and fragments of clot were seen to disappear. There followed bleeding from the visible serosal surface, including areas which, at most, had received minimal trauma, from the abdominal wound, and from recent needle punctures. No discrete bleeding-points could be defined. The haemorrhage progressively became more profuse and was uncontrollable by any local

not peculiar to Hong Kong Chinese. For example, Blakemore (1951) encountered it in 5 out of 102 portacaval shunt operations and speculated on its cause.

The remaining eight deaths were in males in group 1. One was due to hepatic necrosis and seven were due to thrombosis of the portal vein, symptoms of which first appeared 48 to 96 hours after operation. The diagnosis in each case was confirmed at necropsy. The livers in all seven were greatly reduced in size.

In an investigation of the possible causes of this complication we found no correlation between the platelet count and the onset of the thrombosis. When the appearances of specimens of the liver obtained by aspiration needle biopsy at operation and 48 hours thereafter were compared the latter showed intensification of the cellular infiltration in the periportal tissue and especially in the sinusoids, which were distended. There was also irregularly distributed swelling and necrosis of liver cells. The administration of cortisone for 48 hours after splenectomy was found to prevent the development of these changes, which we considered might result in slowing of flow in the portal vein, thereby predisposing to thrombosis. The inhibition of spontaneous fibrinolytic activity of the plasma after operation, described by Kwaan *et al.* (1957), may also have

TABLE II.—*Operative and Hospital Deaths*

No. of Patients (14)		Cause of Death	Time of Death after Operation	Pre-operative History		
				Gastro-intestinal Haemorrhage		Ascites (Response to Treatment)
				Single	Multiple	
5	1	Intraperitoneal haemorrhage due to "fibrinolysis"	<24 hours	2	1	5 (5 poor)
3	1	Thrombosis of portal vein	3rd day	1	1	7 (4 fair, 3 poor)
1	1		7th day			
1	1		10th day			
2		Necrosis of liver	10th day		1	
1				—		—

a part to play. The seven patients in whom this complication developed were among the first 67 patients in group 1. The complication was not encountered in the subsequent 56 members of this group when cortisone was given post-operatively to those with livers significantly reduced in size.

LATE RESULTS

Contact post-operatively with 34 of the 161 survivors has been lost. These are discussed later. Of the remaining 127, 26 (20%) died from 2 months to 8 years (mean 2.1 ± 0.4 years) after operation. The 101 survivors (70 males, 31 females) have been followed up for from 2 to 9 (mean 4.3 ± 0.2) years. Of these, 65 and 36 belonged to groups 1 and 2 respectively.

Deaths

Details of the 26 deaths are set out in Table III. Four of these patients were females and all save one belonged to group 1.

TABLE III.—Late Deaths

Cause of Death	No. of Patients (26)	Time since Splenectomy (Years)
Gastro-intestinal haemorrhage	1	2/12
	1	9/12
	3*	1
	2 (both female)	2
	1†	2½
Hepatic failure	1	3½
	1 (female)	2½
	1	4½
	1	5½
Perforated duodenal ulcer	1	1
	1	3
Hepatocellular carcinoma	1	4
	1	8
Meningitis (pneumococcal)	1	6½
	1	2
Septicaemia (staphylococcal)	1	5
Peritonitis (pneumococcal)	1	2½
Reticulum-cell sarcoma	1	1
Uraemia (nephrolithiasis)	1 (Group 2)	4
Bronchopneumonia	1	1
Typhoid	1 (female)	1

* One associated with a perforated duodenal ulcer.

† Bleeding from artery in base of chronic gastric ulcer.

Of the 25 deaths in group 1, seven were due to rupture of oesophageal varices, five to hepatic failure, and two to hepatocellular carcinoma. These 14 deaths are recognizably linked with the cirrhosis of the liver. Gastric or duodenal ulcers were responsible for four deaths, and here again there is a link with the cirrhosis, for the incidence of ulcers in such patients is undoubtedly high. Koide, Texer, and Borden (1958) reviewed the incidences reported in the literature and found them to range from 3.6 to 24.7%. In the 127 patients followed up after splenectomy ulcers were demonstrated radiologically in 12, including the four who died. All 12 belonged to group 1, an incidence in this group of 13%. Six of the remaining seven deaths in group 1 were due to infection, and, as is discussed later, a proportion of these may be attributable to splenectomy. The remaining death in this group was due to an unrelated disease, as was the single death in group 2.

Jordan and Heck (1956) concluded from observations on "patients with splenomegaly and hypersplenism not treated by splenectomy" that the presence of hepatic disease was the most important factor in prognosis. This is true of the present series both with regard to the immediate outcome of the operation and that subsequent to it.

1. Haemorrhage

(a) Incidence of Gastro-intestinal Haemorrhage

The 26 patients who died and the 101 patients whose present condition is known are divided into a group of 71 with no history of gastro-intestinal bleeding prior to splenectomy, a second group of 23 with a previous history of a single such haemorrhage, and a third group of 33 with a history of two or more.

Of the 71 patients with no history of gastro-intestinal bleeding prior to splenectomy 12 died from causes other than gastro-intestinal haemorrhage in from 3 months to 7 years (mean 2.1 ± 0.6 years) following splenectomy. A patient who survived five years, the only patient to bleed, had four attacks of haematemesis, one, two, three, and five years after splenectomy. He was known to have a large gastric ulcer, and death was due to a staphylococcal septicaemia following portacaval anastomosis performed in another hospital. The remaining 59 patients have been observed from 2 to 9 (mean 4.4 ± 0.2) years. Four have had one haematemesis (two, two, three, and five years after splenectomy, the duration of observation being two, seven, five, and eight years respectively). In one, the first, the haemorrhage proved fatal. The incidence of gastro-intestinal haemorrhage in this group following splenectomy was 7%.

A history of a single gastro-intestinal haemorrhage from 1 to 48 (mean 10.3 ± 0.3) months prior to splenectomy was obtained in 23 patients. Two of these who had no further bleeding died from hepatocarcinoma four and eight years respectively after the operation. The remaining 21 have been observed from 2 to 9 (mean 4.3 ± 0.4) years, and further bleeding has been encountered in six. In one, the only fatal haemorrhage in this group, the bleeding occurred two months after operation. Three bled once (10 months, one year, and five years after splenectomy, the duration of observation being six, four, and seven years respectively). The remaining two bled twice (one in the first and third years of a five-year follow-up, and the other in the eighth month and second year of an eight-year follow-up). The incidence of gastro-intestinal haemorrhage following operation in this group was 26%.

The response of the 33 patients with a history of recurrent bleeding prior to splenectomy is set out in the Chart. It will be seen that 10 died within 2 months to

3½ years (mean 1.6 ± 0.4 years) after splenectomy; seven of these were associated with massive gastro-intestinal haemorrhage. In one of them the source of the final fatal haemorrhage was established at necropsy to be due to erosion of an artery in the base of a chronic gastric ulcer. However, this patient had had two previous haemorrhages the source of which was not determined. In a second patient the bleeding occurred in association with perforation of a chronic duodenal ulcer, but the source of the bleeding could not be demonstrated at necropsy. Only one of the remaining five of the group who died bled once before death, which was due to perforation of a chronic duodenal ulcer. Five of the 23 surviving patients observed for from 2 to 9 (mean 4.1 ± 0.4) years have had one or more gastro-intestinal haemorrhages. The incidence of haemorrhage following splenectomy in this group was 36%.

If the three groups are combined 56 patients (44%) had one or more gastro-intestinal haemorrhages prior to splenectomy, whereas after splenectomy 23 (18%) had one or more such haemorrhages. However, 9 (39%) of these latter haemorrhages, including that from a chronic gastric ulcer, were fatal.

Of the 56 patients who bled prior to splenectomy five were in group 2. Of the 23 patients who bled after splenectomy two only were in this group at operation. Both had bled once prior to operation. They have been followed up for four years and in both the further haemorrhage occurred within the first year.

It is evident that a history of gastro-intestinal haemorrhage before splenectomy is associated with an increased incidence of such haemorrhage following it. Further, a history of multiple gastro-intestinal haemorrhage before operation affects adversely the prognosis after operation, and it does so by an increased liability to the occurrence of fatal haemorrhage. It is also evident that a history of single gastro-intestinal haemorrhage does not affect the prognosis after operation. On the other hand, a history of multiple gastro-intestinal haemorrhages preceding splenectomy is compatible with survival for considerable periods. Of the 65 patients in group 1 surviving for from 2 to 9 (mean 3.9 ± 0.4) years following splenectomy, 23 (35%) had a history of repeated gastro-intestinal haemorrhage, and they had survived for from 2 to 9 (mean 4.1 ± 0.4) years.

(b) Form of Gastro-intestinal Haemorrhage

McFadzean and Tsang (1956a) pointed out that, while in a proportion of patients bleeding from oesophageal varices occurred independent of the severity of the liver changes, in a significant number of instances haemorrhage presented as melaena in the absence of haematemesis. In a number of such cases aspiration of the stomach contents showed an absence of blood. Of the 23 patients with a history of a single gastro-intestinal haemorrhage 12 had a history of melaena alone. The Chart shows that of the 33 patients with a history of two or more gastro-intestinal haemorrhages before splenectomy five had melaena alone and 13 had one or more attacks of melaena in addition to one or more attacks of haematemesis. McFadzean and Tsang (1956a) emphasized that after splenectomy the pattern of bleeding changed and melaena in the absence of haematemesis was not encountered save in the presence of an ulcer of the stomach or duodenum. This was true in the present series. Further, at necropsy on patients dying from gastro-intestinal haemorrhage following splenectomy, with two exceptions, bleeding was shown to be due to

rupture of varices either in the fundus of the stomach or in the oesophagus. In one of the two exceptions the source was an eroded artery in the base of a chronic gastric ulcer, and in the other, in which bleeding was associated with a perforated duodenal ulcer, the source of haemorrhage was not demonstrated.

(c) Bleeding from Other Mucous Membranes

Epistaxis and bleeding from the gums occurred in 59 of the 127 patients before splenectomy. This form of bleeding was not encountered after operation except in the patient ultimately dying of uraemia.

(d) Vascular Fragility

Before splenectomy the vascular fragility was increased in 81% (grade 1, 17%; grade 2, 21%; grade 3, 19%; grade 4, 24%). After splenectomy an increased vascular fragility was encountered in 5 (4%). The fragility in four of these, all with post-necrotic cirrhosis, was grade 1, and in the fifth, the patient ultimately dying of uraemia, prior to death it was grade 4.

It may be stated that splenectomy abolishes bleeding from the nose and gums and that it would appear to alter the form of gastro-intestinal haemorrhage encountered and to effect a significant reduction in its incidence. However, an additional factor must be considered. We are satisfied that gastro-intestinal haemorrhages in a significant number of instances prior to splenectomy are provoked by gastro-intestinal irritants ranging from aspirin to those commonly prescribed by practitioners of traditional Chinese medicine. On discharge from hospital all patients were warned to avoid such substances, and we are not in a position to assess the effect such a warning might have had.

The mechanism whereby splenectomy might influence bleeding from mucous surfaces is complex. It has been shown that the operation almost invariably results in the disappearance of an increased vascular fragility demonstrable in subcutaneous vessels in the majority of patients. It should be noted that a vascular fragility which is abolished by splenectomy can also be demonstrated in the buccal and rectal mucosae and in the peritoneum of patients showing a negative vascular fragility test (McFadzean and Tsang, 1956a). Splenectomy, as is shown later, corrected a thrombocytopenia present in the majority of patients. McFadzean and Tsang (1956a) also found that it resulted in the disappearance of increased fibrinolytic activity of the plasma and in a reduction in the bleeding-time, which showed a minor prolongation to normal. None of the other factors involved in haemostasis were affected by splenectomy. They further showed that neither the thrombocytopenia nor the increased fibrinolytic activity was responsible for the vascular fragility, and they concluded that it resulted from the action upon small vessels of a factor elaborated by the enlarged spleen. It would seem reasonable to conclude that splenectomy influences haemorrhage from mucous surfaces dominantly by removing this factor, thereby correcting the vascular fragility and possibly also by restoring the platelet count to normal.

2. Thrombosis of the Portal Vein

It is difficult to determine the incidence of thrombosis of the portal vein in untreated cryptogenic splenomegaly. At necropsy on a series of patients with post-necrotic cirrhosis of the liver a recent thrombus was found in the portal vein in 18%.

None of the 90 patients in group 1 followed up after splenectomy have at any stage developed the clinical

picture of thrombosis of the portal vein, nor has such a thrombus been found at necropsy on any of the 25 patients in this group who have died.

It may well be that splenectomy prevents the occurrence of thrombosis of the portal vein. Hou and McFadzean (1963) investigated the pathogenesis of such thrombi, and concluded that at least two factors are involved. The first of these is the occurrence of mural haemorrhages in the vein, and the second is the presence in blood from the spleen of anti-activator activity which results in the inhibition of fibrinolysis (Kwaan *et al.*, 1957). They thought that the mural haemorrhages were an expression of the increased vascular fragility encountered in cryptogenetic splenomegaly, and which, as described above, is corrected by splenectomy. At necropsy on splenectomized subjects mural haemorrhages are not encountered in the portal vein and its tributaries.

3. Oesophageal Varices

Radiological evidence of oesophageal varices was present in 85 (70%) of the 123 patients in group 1 and in 20 (38%) of the 52 patients in group 2. Sixty-five patients—45 in group 1 and 20 in group 2—were reinvestigated one year or more after splenectomy. Before splenectomy there was radiological evidence of oesophageal varices in 25 in group 1 and in 7 in group 2. Evidence of varices was found to persist in all 32 after splenectomy and appeared for the first time in 7 of the 33 patients (five in group 1 and two in group 2) with negative findings before splenectomy. Splenectomy therefore does not exert a permanent influence on oesophageal varices. The qualifying adjective is necessary, for we have found that in a number of patients radiologically examined within three months of splenectomy the evidence of varices present prior to operation had disappeared. Such, however, reappeared later.

Pan and Wong (1962) have determined the hepatic-vein wedge pressure and the estimated hepatic blood flow in a series of patients before and after splenectomy. Their findings may be summarized here: splenectomy exerted no significant effect upon the hepatic-vein wedge pressure; it did result, however, in a significant reduction in the hepatic blood flow as estimated by the continuous bromsulphthalein infusion technique.

4. Ascites

At the time of the patients' admission to hospital ascites was present in 78 (61%) of the 127 followed up, and 67 were in group 1. The onset of ascites followed upon gastrointestinal haemorrhage in 27. In 43 of the 78 patients the ascites had been present for from 1 to 24 (mean 7.5 ± 1.4) months and there was no previous history of ascites. In the remaining 35 there was a history of recurrent ascites over periods ranging from 6 months to 5 years (mean 2.4 ± 0.3 years). The response of the ascites to salt restriction and diuretics after admission to hospital was regarded as good in 46 (59%), fair in 15 (19%), and poor in 17 (22%).

In the first two weeks after splenectomy despite salt restriction and diuretics ascites recurred in the majority of patients who had shown good response to treatment before operation and was aggravated in the remaining two groups. Thereafter, in all patients it progressively cleared, the diuretics were withdrawn, and salt restriction was then relaxed.

In the subsequent period of observation ascites recurred in eight patients and occurred for the first time in two. The responses to therapy in the former group prior to

splenectomy were classified as good in four and fair or poor in two each. Haemorrhage anticipated the onset of ascites in three patients, and in another three it was anticipated by diarrhoea, which in two was due to acute shigella dysentery.

Six of the 10 patients died and the ascites was a terminal development. The remaining four are alive, and in two the ascites was a transient incident occurring one and three years after splenectomy in a period of observation of five years in each case. Haemorrhage anticipated the ascites in one case and shigella dysentery in the other. In the remaining two patients, both with a history of ascites showing a fair response to treatment prior to splenectomy, it has recurred repeatedly in a period of observation, in each case of three years. It is readily controlled by salt restriction and intermittent administration of diuretics.

Prior to the inception of this study patients with ascites showing fair or poor response to treatment were not subjected to operation. Their numbers have been augmented by patients with ascites showing similar response who refused operation. All of 31 such patients observed died within two years of the onset of the "resistant" ascites. It seemed possible that the presence of ascites and its response to treatment prior to splenectomy might afford an index of prognosis. This, however, proved not to be so. Of the 25 deaths in patients with post-necrotic cirrhosis (group 1) occurring from 2 months to 8 years (mean 2.1 ± 0.4 years) after splenectomy ascites had been present in 16 (64%) and the response to therapy had been good in 10 (63%), fair in 4 (25%), and poor in 2 (12%). Of the 65 patients in group 1 alive from 2 to 9 (mean 3.9 ± 0.4) years after splenectomy ascites had been present in 51 (80%), and the response to therapy had been good in 27 (53%), fair in 9 (18%), and poor in 15 (29%).

We are at a loss to offer an explanation of the effect of splenectomy upon ascites. Cherrick, Kerr, Read, and Sherlock (1960) pointed out that the only forces known to influence the rate of transfer of fluid between portal capillary and ascitic compartment are the hydrostatic and colloid osmotic pressures of the fluid on either side, the sum-total of which is the net transfer pressure. These observers showed a significant correlation between the height of the net transfer pressure and the presence of ascites. Atkinson and Losowsky (1961) found the threshold level of portal pressure for the formation of ascites to be directly related to the level of the serum albumin. As stated above, splenectomy did not exert a persistent significant effect on hepatic-vein wedge pressures. Further, it has been found that no significant increase in serum albumin occurs after splenectomy, this despite the resolution of the ascitic fluid, which has a significant albumin content, and despite the reduction in plasma volume.

5. Haematological Findings

The findings on examination of the peripheral blood are set out in Table IV. It will be seen that splenectomy was followed by a significant rise in haemoglobin, haema-

TABLE IV.—Haematological Findings Before and After Splenectomy

	Splenectomy	
	Before	After
Haemoglobin (g./100 ml.) ..	5.0-13.2 (9.8 $\pm$ 0.3)	10.1-15.7 (12.3 $\pm$ 0.3)
Haematocrit ..	14-39 (30 $\pm$ 1)	30-43 (39 $\pm$ 1)
W.B.C. (thousands/c.mm.) ..	1.0-7 (3.7 $\pm$ 0.3)	5.7-16 (9.2 $\pm$ 0.6)
Platelets (thousands/c.mm.) ..	18-284 (85 $\pm$ 8)	200-900 (402 $\pm$ 28)
Haemoglobin { Previous history		
(g./100 ml.) { of bleeding ..	7.0-11.7 (9.2 $\pm$ 0.4)	11-15.7 (13.3 $\pm$ 0.4)
{ No previous history of bleeding	5.0-13.2 (10.1 $\pm$ 0.5)	10.1-15.7 (13.1 $\pm$ 0.4)

tocrit, leucocytes, and platelets. The increase in the haemoglobin and in the haematocrit levels cannot be related to the influence of splenectomy upon haemorrhage, for there is no significant difference on comparison of the response to splenectomy of the group with a history of gastro-intestinal haemorrhage with that without such history (Table IV). McFadzean, Todd, and Tsang (1958a, 1958b) investigated this anaemia, having excluded patients with iron-deficiency anaemia following haemorrhage, and concluded that it was partly attributable to excessive haemolysis and partly to an expansion of the plasma volume. They showed that after splenectomy the evidence of excessive haemolysis disappeared and the plasma volume, although still significantly expanded, was reduced. The fall in plasma volume was not entirely due directly to removal of the spleen, since it continued for some months after the operation. More recent investigations employing radioactive isotope techniques have yielded similar results (McFadzean and Todd, 1963).

6. Tests of Liver Function

It has been found difficult to compare the results of tests of liver function before splenectomy with those of tests performed after splenectomy. In certain individual patients improvement was encountered, notably in the flocculation tests and in the plasma albumin levels. However, on further analysis these patients, prior to splenectomy, had a history of recent haemorrhage or had gross ascites, and we doubt whether such improvement could be attributed directly to the splenectomy. Consequently we have elected to review the results as a whole. With the exception of copper oxidase no significant difference emerges on comparison of the results of the various tests of liver function before splenectomy and one year thereafter: the mean copper oxidase activity prior to splenectomy in 35 patients investigated was 12.0 ± 0.3 units, whereas after splenectomy it was 9.6 ± 0.3 units. The fall has been shown to occur immediately after splenectomy and is probably due directly to the removal of the spleen.

7. Hepatic Encephalopathy

If episodes provoked by haemorrhage are excluded, only two patients, both in group 1, had a history of encephalopathy prior to operation. After splenectomy one has had no further attacks in five years whereas the other had repeated attacks in one year prior to death in hepatic failure. Encephalopathy developed for the first time in 28 patients, all save one in group 1, after operation. Thirteen of these have died from 2 months to $5\frac{1}{2}$ years (mean 1.7 ± 0.4 years), and in all of them the encephalopathy arose as a terminal event, being precipitated by gastro-intestinal haemorrhage in seven instances. The remaining 15 patients have been observed for from 2 to 8 (mean 4.2 ± 0.5) years, and the episodes of encephalopathy started from $1\frac{1}{2}$ to 8 (mean 3.8 ± 0.6) years after splenectomy. It may reasonably be concluded that splenectomy did not precipitate the onset of hepatic encephalopathy. If it is assumed that the occurrence of hepatic encephalopathy represents progression of the disease in the liver it would appear that splenectomy does not affect that progression.

8. Leg Ulcers

Active chronic leg ulcers which had persisted for from 6 months to 7 years (mean 3 ± 0.6 years) were present in 18 patients. In five they were bilateral. All ulcers healed within five weeks of splenectomy.

Prior to splenectomy 32% of the patients had a history and typical scars of leg ulcers. None of the splenectomized patients have developed leg ulcers in the period of observation after operation.

It should be noted that McFadzean and Tsang (1958) have shown that the inflammatory necrotizing response to bacterial allergy is intensified in this syndrome and that splenectomy results in the disappearance of the intensified response. They suggested that the intensified response may have a part to play in the pathogenesis of the leg ulcers.

9. Growth and Development

Infantilism.—This was encountered in 11 patients, all save one of whom were males aged 18 to 25 (mean 20 ± 1) years). Six belonged to group 1 and five to group 2. One of these patients died in hepatic failure four months after operation. The remaining 10 have been followed up for from 2 to 8 (mean 3.9 ± 0.5) years. Six have grown and have developed secondary sex characters. The female patient, aged 22, has been delivered of a normal full-term child. Two patients aged 19 and 24 have been observed for three and six years respectively. They have remained dwarfed but normal sexual development has taken place. One other patient, aged 25, has been observed for five years, during which time he has grown but sexual development has not occurred. The last patient, aged 22, observed for $2\frac{1}{2}$ years, has remained infantile.

Dwarfism.—This was present in two male patients aged $9\frac{1}{2}$ and 11, one of whom had post-necrotic cirrhosis. The former died one year after operation, but he had grown in this period. The second has been observed for two years, during which he has grown and sexual development has been normal.

Failure in Development of Secondary Sex Characters.—These had failed to develop in one male and one female patient, aged 18 and 25 years respectively, the former belonging to group 1. They have been observed for three and five years respectively and normal development has occurred.

Amenorrhoea.—Nine females aged from 16 to 35 (mean 27 ± 3) years had amenorrhoea for from 6 months to 7 years (mean 3 ± 0.4 years) before splenectomy. After splenectomy menstruation was re-established in eight and has remained normal for from $1\frac{1}{2}$ to 7 (mean 3.8 ± 0.7) years. The ninth patient, aged 31, has been observed for four years and amenorrhoea has persisted.

We have no knowledge of the mechanism whereby an enlarged spleen exerts such a profound effect upon growth and development. The response to splenectomy can reasonably be called dramatic. It has previously been described. One of the patients with cryptogenetic splenomegaly reported by McIntosh (1932) was dwarfed and growth took place after splenectomy. The occurrence of dwarfism and infantilism in association with schistosomiasis is generally recognized. Huang, Chiang, Lu, Yu, P'an, P'an, and Kuo (1957) found, in an area where over 90% of the population were infested with *Schistosoma japonicum*, that 12.4% of the patients aged 16 to 20 years were infantile. Common to all of the dwarfs they examined was a markedly enlarged spleen.

10. Incidence of Pneumococcal and Streptococcal Infections

Such infections occurred in 24 of the 127 patients followed up. Of the 24, 15 were males and 9 females, and 15 belonged to group 1 and 9 to group 2. Pneumococcal

segmented pneumonia was encountered in 10 patients, and in one it proved fatal. Primary pneumococcal meningitis occurred in five, being fatal in two; and fatal primary pneumococcal peritonitis developed in one. Eight patients suffered from severe streptococcal cellulitis. The fatal pneumonia occurred in a boy aged $9\frac{1}{2}$ years. The ages of the remaining patients ranged from 23 to 41 (mean 31 ± 1) years.

King and Schumacker (1952) thought that splenectomy in infancy might predispose to infection. Since that time many papers on this subject have appeared, notably in the United States, and these have been ably reviewed by Finland (1961), Smith, Erlandson, Stern, and Hilgartner (1962), and Lowdon, Walker, and Walker (1962). The case for an increased incidence of severe infections following splenectomy in infancy is well established. It has become evident also, as first noted by Smith *et al.* (1962), that the risk is not restricted to infancy but may be encountered in children and young adults. The evidence in the present series strongly suggests that there is an increased incidence in adults of infection following splenectomy for cryptogenetic splenomegaly, and, as is the case in infancy and childhood, pneumococcal infections are most common. This may be related to the effect of the operation upon antibody formation. In observations on patients with cryptogenetic splenomegaly McFadzean and Tsang (1956b) found that the response to particulate antigen injected intravenously was greatly reduced after splenectomy. This was in contrast to the response to antigen injected subcutaneously, which in non-splenectomized patients was significantly lower than in healthy subjects, whereas in splenectomized patients the response was not significantly different from that in healthy subjects.

Patients With Whom Contact Has Been Lost

Contact was lost with 34 patients within 1 to 8 (mean 3.1 ± 0.3) months of splenectomy. There were 22 males and 12 females and 20 and 14 belonged to groups 1 and 2 respectively. Five had a history of one gastro-intestinal haemorrhage from one to four months before splenectomy, and six had two or more such haemorrhages within three months to two years before operation. Ascites was present in nine and the response to therapy was classified as good in seven and fair or poor in one each. We have no knowledge of the outcome of splenectomy in this group. Save for an increase in the proportion of patients belonging to group 2 there is no significant difference between these patients and those followed up. It might well be argued that the increased proportion of patients in group 2 may have resulted in a better survival rate.

SUMMARY

An attempt which suffers from the defects of a "before and after" study has been made to determine the effects of splenectomy upon 175 patients with cryptogenetic splenomegaly. In 129 there was post-necrotic cirrhosis (group 1) whereas in the remaining 46 the hepatic condition was of less severe degree (group 2).

Fourteen patients, 13 in group 1, died in the first three weeks after operation, a mortality of 8%. Observations suggest that the mortality can be reduced, for it would appear that the use of human fibrinogen and of cortisone may prevent respectively "fibrinolytic" intraperitoneal bleeding and thrombosis of the portal vein, the two major causes of death.

Contact with 34 of the 161 patients surviving operation was lost within one to eight months. The late effects of splenectomy have been assessed on the remaining 127.

Twenty-six died from 2 months to 8 years (mean 2.1 ± 0.4 years) after operation, and the causes of death are presented. Only one of these deaths, from an unrelated disease, occurred in group 2. Of the remaining 25 deaths all save one were related either directly or indirectly to cirrhosis of the liver or to splenectomy. It is concluded that the presence of established cirrhosis of the liver is the most important factor in prognosis.

The surviving 101 patients have been observed for from 2 to 9 (mean 4.3 ± 0.2) years.

After splenectomy the incidence of gastro-intestinal haemorrhage was reduced and its form altered. Bleeding from other mucous surfaces ceased. Presumably these effects were due to the correction of a vascular fragility which occurs in this condition. It is concluded that it is unlikely that the operation influenced bleeding from oesophago-gastric varices.

Thrombosis of the portal vein, which has a high incidence in this syndrome, was not encountered after splenectomy.

The operation did not result in any permanent effect upon oesophago-gastric varices or upon portal venous pressure. A remarkable beneficial effect was exerted upon ascites, but an explanation of this effect is lacking.

After operation there was a significant elevation of the venous haematocrit, the consequence of correction of excessive haemolysis and of reduction in the previously expanded plasma volume, and leucopenia and thrombocytopenia were also corrected.

The only significant change in tests of liver function was a reduction in the serum copper oxidase activity, and this was a direct consequence of removal of the spleen. Although splenectomy did not precipitate the occurrence of hepatic encephalopathy, this complication developed for the first time in a number of patients during the period of observation after operation.

Chronic ulcers of the leg healed rapidly after operation and no further ulcers developed.

In a majority of instances in which they occurred dwarfism, failure in development of secondary sex characters, and amenorrhoea were corrected.

Evidence is presented indicating that the operation was followed by an increased incidence of pneumococcal and streptococcal infection and this increase was not restricted to the younger age-group.

We would express our thanks to Mr. John Gray and Mr. Timothy Kong, who operated on a number of the patients in this series, and to Dr. Rudy Khoo, who prepared the Chart.

REFERENCES

- Atkinson, M., and Losowsky, M. S. (1961). *Quart. J. Med.*, **30**, 153.
- Blakemore, A. H. (1951). *Bull. N.Y. Acad. Med.*, **27**, 477.
- Cherrick, G. R., Kerr, D. N. S., Read, A. E., and Sherlock, S. (1960). *Clin. Sci.*, **19**, 361.
- Finland, M. (1961). *Pediatrics*, **27**, 689.
- Goinard, P. (1927). *Sur certaines splénomégales algériennes*. Arnette, Paris.
- Hou, P. C., and McFadzean, A. J. S. (1963). To be published.
- Huang, M. H., Chiang, S. C., Lu, C. W., Yu, K. J., P'an, J. P., P'an, J. S., and Kuo, P. F. (1957). *Chin. med. J.*, **75**, 449.
- Jordan, G. L., jun., and Heck, F. J. (1956). *Ann. Surg.*, **143**, 29.
- King, H., and Schumacker, H. B., jun. (1952). *Ibid.*, **136**, 239.
- Koide, S. S., Texter, E. C., and Borden, C. W. (1958). *Amer. J. dig. Dis.*, **3**, 24.
- Kwaan, H. C., McFadzean, A. J. S., and Cook, J. (1957). *Scot. med. J.*, **2**, 137.

- Leather, H. M. (1961). *Brit. med. J.*, **1**, 15.
 Lowdon, A. G. R., Walker, J. H., and Walker, W. (1962). *Lancet*, **1**, 499.
 McFadzean, A. J. S., and Todd, D. (1963). To be published.
 ——— and Tsang, K. C. (1958a). *Blood*, **13**, 513.
 ——— (1958b). *Ibid.*, **13**, 524.
 ——— and Tsang, K. C. (1956a). *Brit. J. Haemat.*, **2**, 355.
 ——— (1956b). *Trans. roy. Soc. trop. Med. Hyg.*, **50**, 433.
 ——— (1958). *Ibid.*, **52**, 354.
 McIntosh, J. F. (1932). *Chin. med. J.*, **46**, 992.
 Musgrave, W. E., Wherry, W. B., and Wooley, P. G. (1906). *Johns Hopk. Hosp. Bull.*, **17**, 28.
 Pan, Y. C., and Wong, C. C. (1962). Unpublished observations.
 Ravin, H. A. (1956). *Lancet*, **1**, 726.
 Smith, C. H., Erlandson, M. E., Stern, G., and Hilgartner, M. W. (1962). *New Engl. J. Med.*, **266**, 737.

ROLE OF HYPOTENSION IN THE GENESIS OF TRANSIENT FOCAL CEREBRAL ISCHAEMIC ATTACKS

BY

R. E. KENDELL, M.B., M.R.C.P.

Academic Registrar

JOHN MARSHALL, M.D., F.R.C.P.Ed., M.R.C.P., D.P.M.

Reader in Clinical Neurology

Institute of Neurology and the National Hospital for Nervous Diseases, London

During the past ten years transient focal cerebral ischaemic attacks have attracted much attention, partly because of their intriguing character and partly because of the possibility of successful treatment before permanent cerebral damage occurs. It is generally assumed that the recurrent loss of local cerebral function that is the basis of the clinical picture is due to intermittent local ischaemic anoxia; but it is not clear how this intermittent local ischaemia is produced. It is known that a high proportion of patients with recurrent ischaemic attacks have atheromatous narrowing of either the intracranial or extracranial arteries supplying the relevant cerebral territory. However, constrictions in the arterial tree cannot by themselves account for a situation in which ischaemia is present only intermittently. Clearly some other factor is operating.

It has often been suggested that systemic hypotension may be this intermittent factor (Denny-Brown 1951, 1960; Rothenberg and Corday, 1957; Alajouanine *et al.*, 1960); and indeed it is easy to visualize how a temporary fall in arterial pressure might produce a crucial fall in blood-flow in a diseased arterial tree—the “haemodynamic crises” of Denny-Brown. In an ingenious series of experiments (Denny-Brown and Meyer, 1957; Denny-Brown, 1960) it was shown that, in monkeys with an artificial occlusion of the internal carotid or middle cerebral artery, a transient hemiplegia could be produced at will by lowering the arterial pressure, although arterial occlusion by itself was ineffective. Attempts to reproduce transient ischaemic attacks in man by inducing hypotension have, on the other hand, been unsuccessful. In most cases hypotension has been induced simply by tilting the patient from the horizontal to the vertical planes on a pivoted table (Victor and Adams, 1953; Fisher, 1958a; Denny-Brown, 1960) and the fall in blood-pressure has been rapid and short-lived. Eastcott, Pickering, and Rob (1954) used a hypotensive drug to produce a drastic fall in blood-pressure in a single case, but no ischaemic attack was produced.

It appeared to us that the evidence in support of the hypothesis that temporary falls in systemic blood-pressure are responsible for spontaneous transient ischaemic attacks in man is slight. The therapeutic implications of the hypothesis—that hypotension should be avoided, if necessary by the use of pressor drugs, and that treatment of hypertension is contraindicated, even if highly desirable on other grounds—have had considerable influence on clinical practice. It therefore seemed important that the role of hypotension in the production of transient ischaemic episodes should be more closely examined. This conviction was strengthened by our experience with one patient.

Case Report

A man aged 55 gave a history of a cardiac infarction in 1955 and a right visual field defect of unknown duration in February, 1960. Six days before he was first seen, in July, 1960, he experienced two transient episodes of weakness of the left arm followed two days later by a severe right-sided weakness which improved after a few days but left some persistent weakness. Aortography did not reveal any lesion of the arch of the aorta nor of the carotid and vertebral arteries. His blood-pressure was 190/120.

In April, 1961, he had an episode of weakness of all four limbs without disturbance of speech or swallowing lasting a few days. In September, 1961, as his blood-pressure remained at levels of 190/120 it was decided to start him on guanethidine. Six weeks later, when the dosage was 30 mg. a day, he began to have episodes of slurred speech, inability to swallow, and incoordination of his upper and lower limbs. Each attack lasted about 5 minutes. He had two or three attacks each day over a period of 10 days before readmission to hospital. It was assumed that these were transient ischaemic attacks due to hypotensive episodes precipitated by guanethidine. However, after admission to hospital he had further episodes in two of which the blood-pressure was recorded. In one it rose from its current level of 200/115 to 220/150, subsiding after the attack; in the second episode it reached 190/165 and again fell subsequently. Hypotensive therapy was therefore reinstated and his blood-pressure was rigorously maintained at 160–180/100–115. The ischaemic episodes ceased and did not recur.

The coincidence of the commencement of hypotensive therapy and the onset of transient ischaemic episodes in the light of the haemodynamic crisis hypothesis might well have resulted in a failure to treat this patient's hypertension. The deleterious effect of hypertension on life expectancy in patients with cerebrovascular disease is well established (Marshall and Kaeser, 1961). The hazard of hypotension, on the other hand, has not been established in man. Indeed, the extensive experience of anaesthetists with “controlled hypotension” during surgery (Hampton and Little, 1953; Enderby, 1961) indicates that the danger of a cerebrovascular incident is negligible. Eckenhoof (1962) kept patients with a head-up tilt of 28 degrees at an arterial pressure of 60 mm. Hg for as long as 70 minutes without untoward effects. Nevertheless it seemed wiser before instituting long-term hypotensive therapy in patients with cerebrovascular disease to test their response by subjecting them to a brief period of severe hypotension under carefully controlled conditions.

Method

The 37 patients (22 men and 15 women) studied were aged 39 to 69, with a mean of 57 years. They were divided