handling difficulties, which may be overcome with more experience.

The analysis of five samples of human blood showed that when alcohol is present the plasma contains over 40% more than whole blood (plasma to R.B.C. ratio, 1.43:1; plasma to whole blood ratio, 1.15:1). Thus the alcohol content of a given blood sample will be critically dependent on the separation or otherwise of plasma from red blood cells during handling.

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Addendum

Since this paper was written the Road Safety Act 1967 has been published. In section 7 subsection (4) it is stated that "For the purposes of this Part of this Act 107 milligrammes of alcohol in 100 millilitres of urine shall be treated as equivalent to 80 milligrammes of alcohol in 100 millilitres of blood."

What in effect this means is that it becomes an offence to drive or to be in charge of a motor vehicle when the alcohol content of the urine is 108 mg./100 ml. or more. But of the 35 suspects studied in our series no fewer than 19 would have

had less than 80 mg. of alcohol per 100 ml. in blood when the equivalent urine sample contained 108 mg./100 ml.; indeed subject No. 25, whose urine to blood ratio was 2.44:1, would have a blood level of only 44.3 mg. of alcohol per 100 ml. at this urine level.

Thus the warning given in our paper that the uncritical acceptance of a urine to blood ratio of 1.33:1 will lead to miscarriages of justice when it becomes an offence to drive or to be in charge of a motor vehicle with more than a stipulated amount of alcohol in the blood is entirely justified. In the interests of justice therefore suspected drivers would be well advised to insist on a blood specimen being taken if asked to provide a sample of urine for examination.

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Splenectomy in "Big Spleen Disease"

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Idiopathic or cryptogenic tropical splenomegaly is sometimes treated empirically by splenectomy. Moreover, in areas where this condition is commonly encountered medical facilities are usually not available for the full investigation of such cases before or after splenectomy. Recently, a group of patients suffering from idiopathic tropical splenomegaly were studied in detail in the Mulago Hospital, Kampala, Uganda. All known causes of tropical splenomegaly were excluded in these patients, who on liver biopsy showed varying degrees of lymphocytic infiltration of the liver sinusoids and Kupffer-cell hyperplasia. In addition they all had high fluorescent antibody titres for malaria. This association is known locally as "big spleen disease" (Hamilton *et al.*, 1966) and is referred to by that title in this paper. Williams *et al.* (1966) showed in haemodynamic studies that these patients suffered from considerable portal hypertension, apparently due to increased spleen blood flow.

Richmond *et al.* (1967), reporting the haematological findings on the same group of patients, found that they all had anaemia, sometimes of severe degree, and this appeared to be due to sequestration of a large proportion of the red cell mass in the spleen, expansion of the plasma volume, and reduction of the red cell life-span. Seven of the 15 patients were treated by splenectomy in June-July 1965, the indications for splenectomy being either incapacitating abdominal pain or discomfort or the finding of pronounced hypervolaemia with anaemia. Follow-up studies on these seven patients two months after splenectomy showed satisfactory improvement in the haemoglobin level in six of them and correction of the red cell survival time in the four in whom this was measured.

This paper describes follow-up studies on five of the splenectomized patients 15 months after the operation.

Patients and Methods

Six of the seven patients splenectomized in June-July 1965 were traced to their homes in October 1966 by one of us (V.L.); one patient, who was in good health, could not be traced. Five patients were studied in detail.

All were males aged 20-55 years. Full clinical examination, routine haematological tests (Dacie and Lewis, 1963), standard liver-function tests, and brucella and salmonella serum agglu-

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tination reactions were carried out. Each patient had a liver biopsy by the Menghini technique. The serum fluorescent antibody titre for malaria was measured, *Plasmodium falciparum* being used as antigen (Voller, 1964). Plasma volumes were estimated by ^{131}I -labelled human albumin; the test sample being taken 20 minutes after the injection of albumin.

Results

Subjectively all the patients felt much better after the operation and were particularly relieved of their constant abdominal discomfort. Four patients had put on weight and all had been able to work again. No patient had had a haematemesis or melaena. Immediately after the operation all had been started on antimalarial drugs prophylactically, these being continued for six to eight months; after this interval they all defaulted from further attendance. None of them had taken antimalarial drugs for at least six months previous to this study. They all complained of occasional attacks of fever, but none of them described having had a classical attack of malaria.

On examination they looked well, liver size was not significantly different from that before operation, and there were no other abnormalities.

Haematological Changes.—The haematological findings are given in the Table. There was a marked rise in haemoglobin level and haematocrit values in all cases. Except for one patient (Case 1) who had a reticulocytosis of 6%, the postoperative reticulocyte counts were not significantly different from those before the operation. In all cases the plasma volume dropped—in Cases 3 and 5 by 2 and 4 litres respectively. The volumes in Cases 1, 3, and 4 were within normal limits, while that in Case 5 was just outside the upper limit for Africans in Kampala as reported by Leonard *et al.* (1965). The plasma volume in Case 2 remained rather high, though the haemoglobin rose from 9.5 to 14.6 g./100 ml. and the P.C.V. from 30.5 to 40.0%.

Liver Changes.—The repeat liver biopsy in Case 1 showed immature myeloid cells and occasional megakaryocytes in the hepatic sinusoids consistent with myeloid metaplasia. Difficulty was experienced in withdrawing marrow, which suggested the patient had myelofibrosis. A review of earlier liver biopsies on that patient from 1965 and 1964 showed some immature cells within the hepatic sinusoids which differed from the usual findings in big spleen disease. Re-examination of the splenectomy histology also showed the presence of immature myeloid cells, confirming the diagnosis of myeloid metaplasia. Despite this, both preoperative and postoperative studies showed a very high malarial antibody titre, and it seems possible that there were two factors accounting for the splenomegaly. Whether or not this was so, the haematological and haemodynamic results were exactly comparable to the other four cases, and so the patient has been included in this series. Liver biopsies from the other four cases showed varying degrees of lymphocytic

infiltration of the liver sinusoids with some Kupffer cell hyperplasia; these changes were not significantly different from those found in 1965. Standard liver-function tests were normal before and after splenectomy except for two slightly raised alkaline phosphatase levels in 1966. Total serum proteins have risen in all cases (see Table). In two out of the four cases for which results are available the rise is accounted for by a marked increase in the serum albumin, while in three out of four cases the serum globulin levels are almost unchanged.

Malaria and Other Studies.—No malaria parasites were found in six successive films on three patients and three successive films on two patients. In all cases the malaria antibody titre was equal to or above that found before splenectomy (see Table). Three patients had developed very light hookworm infections and two had high antibody titres to brucella, but no patient had a raised antibody titre for salmonella.

Discussion

The symptomatic and haematological improvements in these patients 15 months after splenectomy are most striking. Richmond *et al.* (1967) concluded that the improvement in the haematocrit two months postoperatively is largely due to the fall in the plasma volume. Our results confirm this and show that there has been a further improvement in the 15 months since the operation. These findings are in keeping with those of McFadzean *et al.* (1958), Cook *et al.* (1963), Weinstein (1964), and Bowdler (1967).

The immediate effect of splenectomy is to remove from the body a certain mass of red cells and plasma, but the mass of plasma contained in the spleen is quantitatively quite insufficient to account for the marked changes in the plasma volume. Neither the mechanics of the preoperative hypervolaemia nor that of the postoperative fall in plasma volume is understood. Weinstein (1964) suggested that changes in the plasma proteins and other macromolecules might be an explanation. This series is too small from which to draw any conclusions about the protein pattern; however, there has been a rise in the total serum proteins in all cases, and in two there was a marked rise in the serum albumin level after surgery. Studies of the macroglobulin pattern in these cases are being undertaken in greater detail and will be reported later.

A number of cases of big spleen disease respond well to treatment with antimalarial drugs and show a marked symptomatic improvement and a reduction in spleen size (Hamilton, unpublished observations). It is not yet clear exactly which cases will respond in this way, but one patient with big spleen disease in the 1965 study has been on continuous antimalarial therapy for 14 months. In this time his spleen has regressed from 17.8 to 8 cm. below the costal margin. He feels better, his plasma volume has fallen from 73.1 to 46.4 ml./kg. (total from 3,380 to 1,940 ml.), and his P.C.V. has risen from 30 to

Clinical, Haematological, and Immunological Data in 5 Patients with Splenomegaly Before Splenectomy and 15 Months after Splenectomy

	Case 1		Case 2		Case 3		Case 4		Case 5	
	Before	After	Before	After	Before	After	Before	After	Before	After
Age (yr.)	52	—	27	—	20	—	55	—	40	—
Wt. (kg.)	50.7	54.5	50	50	45.5	58	57	64.5	63.5	63.6
Hb (g./100 ml.)	10.0	11.8	9.5	14.6	8.2	16.6	12.0	15.3	5.6	13.3
P.C.V. (%)	30	41	30.5	40.0	27	56	38	48	18	41
Retic. (%)	3	6	4	1	3	0.5	1.0	1.0	2	1.0
Platelets ($\times 10^3$ /cu. mm.)	151	291	145	207	177	172	163	203	111	260
W.B.C. (/cu. mm.)	6,400	17,000	3,300	5,800	3,300	6,000	8,100	15,000	9,000	9,000
M.C.H.C. (%)	33	25	32	30	33	30	31	32	32	32
Spleen wt. (g.)	1,438	—	4,200	—	1,930	—	1,032	—	5,050	—
Plasma vol. total (ml.)	3,240	2,560	3,810	3,310	4,690	2,760	3,310	2,540	7,780	3,970
Plasma vol. (ml./kg.)	63.9	46.9	76.2	66.2	95.0	47.5	54.6	39.3	122.5	62.4
Serum albumin (g./100 ml.)	2.5	2.7	2.2	3.1	1.3	3.2	2.7	2.4	Not avail.	5.0
globulin	3.8	4.2	4.4	4.6	5.4	5.3	4.2	5.2	4.9	7.5
Total protein	6.3	6.9	6.6	7.7	6.7	8.5	6.9	7.6	3.200	12,800
Malaria antibody titre	3,200	3,200	3,200	12,800	3,200	6,400	1,600	12,800	<1:50	<1:50
Brucella	<1:50	1:1,600	<1:50	1:1,600	<1:50	<1:50	<1:50	<1:50	<1:50	<1:50
Salmonella	1:50	<1:50	1:50	<1:50	1:50	<1:50	1:50	<1:50	1:50	<1:50

44%. His only treatment has been a 15-day course of primaquine followed by 100 mg. of proguanil daily. This is further evidence for a malarial cause of this syndrome and also for implicating the spleen in the plasma volume changes. The role of the spleen is also shown by a case of Felty's syndrome (Pengelly, 1966), in which a marked reduction in spleen size and plasma volume after corticosteroid therapy was found.

Not all patients with big spleen disease or idiopathic tropical splenomegaly respond to antimalarial therapy, and even for those cases which do respond long-term supervision may be impossible. In those patients with chronic abdominal pain, an enormous spleen, and gross dilution anaemia, splenectomy may be the treatment of choice. M. Paliwoda (personal communication, 1967) carried out 70 splenectomies for cases such as these in Uganda with an operative mortality of only 4.3%, and though the follow-up data are incomplete the patients in general seem to have done well. However, the spleens are large, and good surgical technique with wide exposure is necessary. There is a danger of overtransfusing a hypervolaemic patient and also the added risk in the tropics of patients being particularly prone to infection after splenectomy. Fatalities from *P. falciparum* after splenectomy have occurred in West Africa (Watson-Williams, personal communication). In this series, postoperatively, the patients all registered high antibody levels to malaria and two developed a high brucella antibody titre; however, none seem to have suffered from significant clinical malaria. Against these dangers must be set the marked improvement in the well-being of these patients, who were able to return to doing a normal day's work after splenectomy.

Summary

The clinical and haematological effects of splenectomy on five Ugandan patients with "big spleen disease" were studied

15 months after operation and the results compared with those obtained preoperatively.

All patients were symptomatically much improved and they all showed a marked improvement in their haemoglobin and P.C.V. levels. Before operation the patients had marked hypervolaemia and dilution anaemia, but after splenectomy the plasma volumes had returned to normal in three patients and in two were still slightly raised. One patient had developed evidence of myelofibrosis, but the others showed no marked change in liver biopsy appearances.

There were no untoward effects of splenectomy and no acute attack of malaria was described, though the malaria antibody titre had been maintained or raised.

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Splenectomy in Tropical Splenomegaly

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Massive splenomegaly of uncertain cause is frequent in New Guinea and is particularly prevalent in the Upper Watut Valley, 50 miles (80 km.) south-west of Lae, where over 80% of the inhabitants of some villages have enlarged spleens (Pryor, 1967a). Though idiopathic tropical splenomegaly occurs in areas where malaria is endemic (Hamilton *et al.*, 1965), a causal relationship has not been established. The villages of the Upper Watut are situated at 3,000 to 5,000 ft. (914 to 1,524 m.) above sea level, malaria is endemic, and the incidence of splenomegaly decreases at the highest altitudes. Other causes of tropical splenomegaly such as leishmaniasis, schistosomiasis, haemoglobinopathies, and hepatic cirrhosis can be excluded in these patients. The natural history of the disorder in this area is not known, but though enlargement of the spleen is often very great it appears to be a relatively benign condition causing little disability in the majority of individuals.

Anaemia, leucopenia, and thrombocytopenia are commonly associated findings, but haemoglobin values as low as 5 g./100 ml. may occur without apparent disability. A raised

reticulocyte count is usual, and studies with radiochromium-labelled cells demonstrate a shortened red cell life-span with evidence of excessive red cell destruction in the enlarged spleen (Pryor, 1967b). However, the main cause of the low haemoglobin value is a greatly expanded plasma volume, which may be more than twice the normal value.

A few individuals complain of symptoms of anaemia or pain and discomfort due to the size and weight of the spleen. Splenectomy has been performed in 15 patients who had disabling symptoms, and the results form the basis of this report.

Methods

Selection of Patients.—Twelve of the 15 patients requested splenectomy and the other three were similar patients with disabling symptoms. Twelve patients were from the Watut Valley and the remainder from villages in the Lae medical region. Eleven were males and four were females aged from 10 to 45 years (Table I). In each case the spleen was enlarged to below the umbilicus and in nine cases it extended into the right iliac fossa. All had an enlarged liver with a smooth firm

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