DYNAMIC ASPECTS OF PORTAL HYPERTENSION

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by

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INTRODUCTION

CIRRHOSIS OF THE liver and occlusion of the portal vein are the two lesions most commonly associated with hypertension in the human portal system. The development of thought on portal hypertension has led steadily to the concept that the features of the syndrome such as splenomegaly, oesophageal varices and raised portal pressure are all produced by venous obstruction. Both the cirrhotic liver and the occluded portal vein are considered capable of offering a mechanical resistance to the outflow of venous blood from the portal circulation. Each can provide a rigid and irreversible cause for the hypertension which, to the ancients, was aptly known as " obstructio hepatis " (Frerichs, 1858).

The surgery of portal hypertension is largely concerned with the arrest and prevention of haemorrhage from oesophago-gastric varices. Based upon the simple aetiology just outlined, two main procedures have evolved to become current surgical practice. These are the decompression operations such as portacaval anastomosis and the disconnection operations such as oesophageal or gastric transection.

Recently it has become apparent that for the patient with an extrahepatic obstruction and a normal liver, none of the portal-azygos disconnection procedures confers the degree of immunity from recurrent bleeding that it was originally hoped they would be able to do. The patient with cirrhosis of the liver can, however, be protected from recurrent bleeding by a decompression operation such as portacaval anastomosis. But the good results of this operation are dependent upon careful selection of cases, and even in the best of surgical hands a troublesome incidence of post-operative portal-systemic encephalopathy develops.

Whilst these operations are at present the best available, their results are not so satisfactory as to preclude an attempt to devise new therapeutic measures. Based solely upon the idea that mechanical venous obstruction is the cause of portal hypertension, it is difficult, if not impossible, to devise any new procedure which will not be merely a variation upon the old, and which will not be attended by the same complications. It would seem, therefore, that if a new approach to the problem is required and is to be made, then also new thoughts on aetiology are required.

The purpose of this lecture is to present to you the results of some work performed by my colleagues and myself at Bristol on this aspect of portal hypertension, namely the concept of its aetiology. Before presenting

this work, however, it is my intention to review the results we have obtained from the use of conventional therapy in portal hypertension. I do not intend to comment upon the disconnection procedures, for recently two excellent reviews of these have been published (Walker, 1960; Tanner, 1961). Together with Professor R. Milnes Walker and Mr. K. D. J. Vowles, I have recently conducted a survey of the long-term results of portacaval anastomosis as performed in Bristol (Walker *et al.*, 1961), and it is these results that I will now consider.

PART I—RESULTS OF PORTACAVAL ANASTOMOSIS

Clinical material: method of follow-up

One hundred and seventy portacaval anastomoses have so far been performed in this unit. The first 50 of these cases were operated upon more than five years ago and they constitute the group under review. In each instance the technique of operation was that of an end-in-side anastomosis (Walker, 1959). Of the 50 patients, 15 have died since operation. Their mode of death has been ascertained from hospital or practitioner and, in 11 of the 15, post mortem reports were available. Sixteen of the 35 survivors agreed to return to hospital for assessment, conducted over a period of days. The remaining 19 patients were reviewed as outpatients. In each case the general practitioner's opinion on the patient was sought.

Selection of patients for operation

All 50 patients had proven portal hypertension with oesophageal varices. The portal vein was patent in each case and the livers showed varying degrees of structural change ranging from none at all to severe nodularity and fibrosis. All patients had bled from their varices.

In selecting the cases for operation, it has been the aim to choose those whose liver function was not grossly impaired and who did not show evidence of rapidly progressive liver cell failure. In some cases operation was undertaken with reluctance; these showed stigmata of liver failure which was clearly advancing. The risk of a fatal haemorrhage in these patients was so great that the operation was considered justified. Thus the selection employed was not so rigid that border-line cases were excluded from the operation if they seemed likely to die from bleeding. Of all the criteria by which selection for operation has been made, most reliance has been placed on clinical judgment. The patient who looks and feels well, apart from his haemorrhage, usually does well after operation. A serum albumen level of more than 3 g. per cent. is not a rigid criterion of selection. It should be more widely recognized that this level is not governed by liver function alone, and that any single estimation of the serum albumen carries a laboratory as well as a clinical error. In view of the increased risk of venous thrombosis in the elderly, caution was exercised in recommending the operation in patients over the age of 55.

Aetiology of hepatic lesions

In the majority of the cases, no aetiological factors were found (Table I). Five patients had previously had jaundice, suggesting that viral hepatitis was a cause. Unlike many series from the U.S.A., alcoholism is not a feature in this series.

TABLE I

AETIOLOGY OF CIRRHOSIS

Cause	*No. of cases*
Unknown	38
Previous jaundice: viral hepatitis	5
Chronic alcoholism	2
Congenital fibrosis of the liver	1
Hepatolenticular degeneration	1
Haemochromatosis	2
Schistosomiasis	1
TOTAL	50

Age and sex distribution

The age and sex of the patients are shown in Table II. The youngest patient was aged five years and the oldest 57.

TABLE II

SEX AND AGE DISTRIBUTION

Age at operation (year)	*No.*
0–9	1
10–19	7
20–29	15
30–39	15
40–49	9
50–59	3
31 males.	19 females.

Results

Hospital deaths

As shown in Figure 1, three patients died in hospital after operation, giving a mortality of 6 per cent. The cause of death in each case was liver failure.

Subsequent deaths

Twelve patients have died subsequently, four from causes unrelated to their cirrhosis, e.g. carcinoma of the pancreas, ruptured aortic aneurysm. Eight patients eventually succumbed to liver failure. The mean survival time for these eight cases was 2 years 9 months, with a range of 7 months to 4 years 11 months after operation.

Survivors

Thirty-five of the 50 patients—that is, 70 per cent.—have survived more than five years. These 35 have been classified as follows:

Grade I No symptoms, no recurrent bleeding. At full work.

Grade II — No recurrent bleeding. Symptoms minimal and such that the patient does not feel it necessary to consult a doctor repeatedly. At full work.

Grade III — Symptoms troublesome; has consulted doctor repeatedly, may have been admitted to hospital. On and off work.

Grade IV — Symptoms severe and indicative of rapidly advancing liver failure.

The symptoms experienced are those of hepatic failure such as general deterioration of health, anorexia, fatiguability, attacks of hepatic coma, jaundice or ascites and oedema of the ankles.

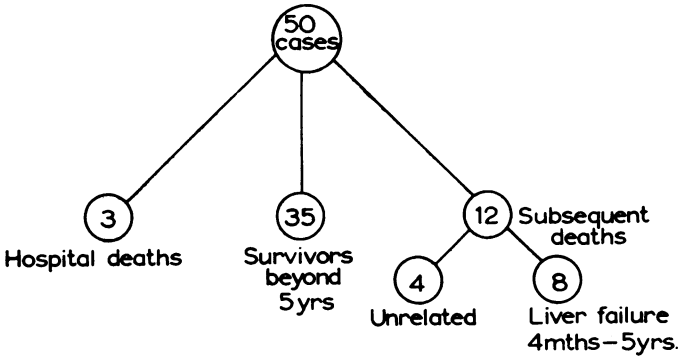


Fig. 1. Fifty portacaval anastomoses. Survivors and deaths.

Table III shows the distribution of patients according to this classification. Twenty-nine of the 35—i.e. 83 per cent.—are at work earning their living or performing their household duties. It will be seen later that liver function in these 29 cases has remained adequate since operation. Their long survival may be attributed, not only to the fact that their cirrhosis is so slowly progressive that it merits the term quiescent, but also to their freedom from recurrent, severe haemorrhage.

TABLE III

DISTRIBUTION OF CASES ACCORDING TO SEVERITY OF POST-OPERATIVE DISORDER

	Years post-operative						*Total*
	6	7	8	9	10	11	
Number of cases in each year	9	8	5	4	8	1	35
Grade:							
I	5	5	1	2	1	1	15
II	2	2	3	1	6	0	14
III	2	1	1	1	1	0	6
IV	0	0	0	0	0	0	0

Recurrent haemorrhage

Six patients have had some recurrence of bleeding after operation—an incidence of 12 per cent. Table IV records these six cases. The first case

bled severely seven months after operation and death followed from liver failure. Despite the recurrence of haemorrhage in this patient, the anastomosis was patent at autopsy. Case 2 had a haematemesis in the first post-operative month but no subsequent bleeding. Cases 3 and 4 had haematemeses during the first pre-operative year, but subsequently have survived without trouble as shown.

TABLE IV

RECURRENT HAEMORRHAGE. SIX CASES, 12 PER CENT.

Case	*Severity*	*Outcome*
1	Major	Died 7 months, liver failure and haemorrhage
2	Minor	Died 2 years, aortic aneurysm
3	Minor	Alive, free from haemorrhage 6 years
4	Minor	Alive, free from haemorrhage 7 years
5*	Minor	Alive, free from haemorrhage 7 years
6*	Minor	Alive, free from haemorrhage 10 years

* Subsequently underwent transection operation.

In Cases 5 and 6, however, a transection operation was performed because, despite the presence of a patent shunt, oesophageal varices persisted. Both patients survive, one to seven and the other to 10 years.

Thrombosis of the shunt

This has been proven in only two cases. In one, the shunt was occluded by a carcinoma of the pancreas; in the other fresh thrombus was removed from the portal vein at operation but recurred and was present at autopsy seven days later. In a third patient, splenomegaly and varices disappeared post-operatively but returned at three years. Since the patient is well and no recurrence of haemorrhage has yet occurred, no further treatment has been undertaken.

In the remaining cases the anastomoses are presumed patent. Evidence that this is so comes from the continued absence of splenomegaly and of varices. In 31 of the 35 survivors, barium swallow shows no varices at five or more years after operation. Four patients still have radiographic evidence of varices which are smaller in size and extent than before operation. Similarly, in 70 per cent. of the cases the spleen shrank after operation to become impalpable. In the remainder the spleen was smaller in size but still palpable. Diminution in size always began in the first post-operative week and often continued for months.

Blood count

The haematological changes of " hypersplenism " persisted after operation. Before shunt, 80 per cent. of patients had a platelet-count of less than 200,000 per c.mm. and in 50 per cent. the count was below 100,000 per c.mm. Five or more years later, the platelet count whenever performed was below 200,000 and in 40 per cent. it was below 100,000 per c.mm. Figure 2 shows the trend of platelet level with passage of time. The white blood count followed a similar course.

However, the only symptom consistently associated with the " hypersplenism " has been epistaxis, which occurred in nine of the 35 survivors. Despite levels as low as 10,000 platelets per c.mm., it has never been felt necessary to perform splenectomy after portacaval anastomosis for " hypersplenism ".

Liver function

Ninety-four per cent. of patients had a serum albumen level of more than 3 g. per 100 ml. at the time of operation. Figure 3 shows the level

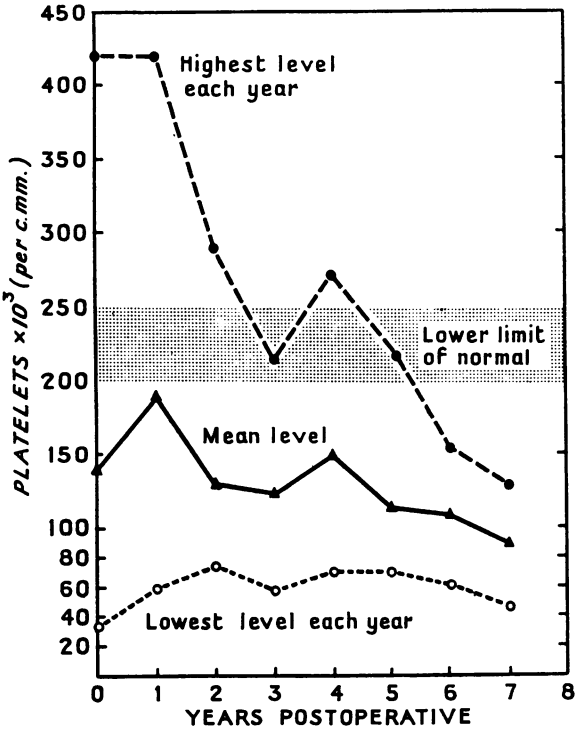


Fig. 2. Platelet counts in each of seven post-operative years.

of serum albumen plotted against time. After five years the mean level is steadily maintained above 3 g. per 100 ml., as those patients with advancing liver failure have died by this time. No deaths have so far occurred after five years and liver function, as judged by the serum albumen, remains at about the same level as before operation.

Portal-systemic encephalopathy (P.S.E.)

This syndrome is now recognized as the major complication of shunt surgery. The manifestations of P.S.E. are extremely varied in nature and severity, in time of onset and duration. Of this series of 50 cases,

evidence of one or more features of the syndrome—e.g. disturbance of conscious level, deterioration of intellect, slowing and slurring of speech—has occurred in 10, that is a rate of 20 per cent. The patients have been classified in the following way:

1. *Patients previously classified in Grade I* (Table III). Only one of these 15 patients developed P.S.E. when drowsiness and tremor occurred three weeks after operation. There has been no subsequent recurrence.

2. *Patients classified in Grade II* (Table III). Two of these 14 developed P.S.E. In one, drowsiness appeared 18 months after operation and occurred periodically for three years. In the other case, P.S.E. began to

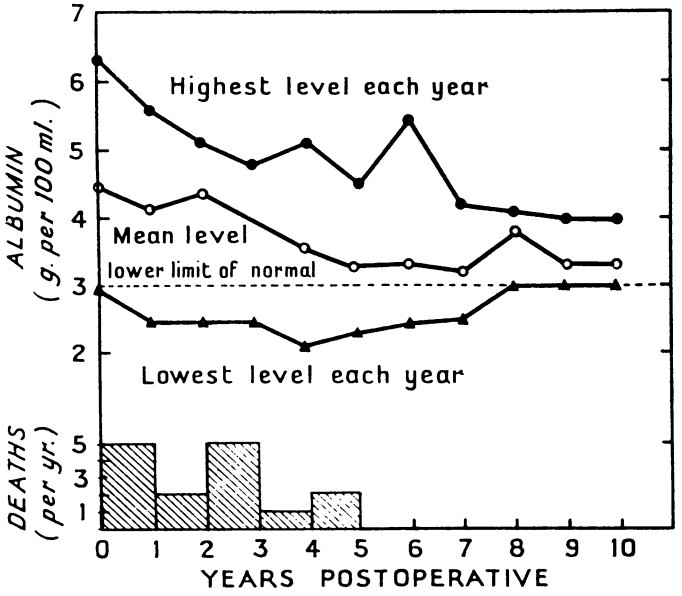


Fig. 3. Serum albumin levels and deaths in each of 10 post-operative years.

appear six-and-a-half years after operation. This man is, however, still able to work.

3. *Patients classified in Grade III* (Table III). In five of these six patients, P.S.E. is recurrent and five are severely incapacitated.

4. *Patients who have died of liver failure.* In two of these 11, recurrent attacks of P.S.E. began before their terminal illness.

Although 10 patients have suffered with P.S.E., in only five is the syndrome incapacitating to a severe extent. Furthermore, only one patient younger than 35 has developed the complication. The chief factor which appears associated with the development of P.S.E. is a period when liver function deteriorates. Constipation and excessive protein intake have also precipitated the syndrome.

Conclusions

These results of portacaval anastomosis show that the operation achieves its aim by drastically reducing the incidence of haematemesis from varices. If liver cell function is adequate, the hospital mortality is low and the time of death thereafter will depend upon the rate at which the cirrhotic process progresses. The chief morbidity lies in the development of P.S.E., but in our experience the incidence of severe incapacitating P.S.E. is low enough to permit of the continued practice of the operation.

Acceptable as these results may be, they still leave room for improvement. They derive from an operation which is based upon the concept of mechanical obstruction as the cause of portal hypertension.

In the second part of this lecture I now hope to show you that this idea is incomplete and that portal hypertension cannot be explained entirely upon the basis of simple organic venous obstruction.

PART II—ADRENALINE AND NORADRENALINE IN PORTAL HYPERTENSION

Introduction

Since 1949, more than 200 patients have been studied and treated at Bristol for portal hypertension. During the course of this study it has been repeatedly observed that the degree of structural change which may be present in an individual liver would seem to bear no strict relationship either to the development of portal hypertension or to the degree which its stigmata may be present. Thus patients have been seen with florid portal hypertension, recurrent haemorrhages, oesophageal varices and splenomegaly, in whom the portal and splenic veins were patent, liver function normal and yet their livers showed little or no abnormality.

There is of course no denying that the majority of patients with portal hypertension do have a mechanical block to the flow of portal blood. What is difficult to explain in the same terms is how the hypertensive state has come about in those cases who have minimal or no organic change demonstrable in their livers. In the last 170 patients who have undergone portacaval anastomosis, 13 examples of portal hypertension have occurred in the presence of normal or near-normal livers. Each of these patients had proven portal hypertension and in each instance the extrahepatic portal system was patent. The livers had a smooth surface and were normal in size. Histology showed either no change at all or very slight fibrosis in the portal tracts together with some lymphocytic infiltration. This observation is not unique to our practice for the literature contains many well documented examples of the occurrence (Hines and Fitzgerald, 1938; Balfour *et al.*, 1954; Tisdale *et al.*, 1959; Aufses, 1960; Oishi *et al.*, 1960; Leather, 1961; Hallenbeck and Adson, 1961).

Experimentally, the production in animals of cirrhosis will cause the development of oesophageal varices and portal hypertension, but only at the stage when gross structural change has occurred in the liver. In the dog, the development of collaterals is then so luxuriant that the hypertensive state tends to fade and tends to become self-curing. In order to maintain the hypertension in this animal, it is necessary to produce, not only severe organic obstruction to the outflow of portal blood, but also an increase in the volume of blood flowing into the portal circulation. This has recently been achieved by construction of a splenic arterio-venous fistula (Tamiya and Thal, 1960). In the dog, then, portal hypertension develops and is maintained only when an increased volume of blood flows into an obstructed portal circulation.

TABLE V

NORMAL CONTROLS: PORTAL VEIN PLASMA ADRENALINE AND NORADRENALINE CONTENT

	Adrenaline		*Noradrenaline*	
Patient	μg./100 *ml.*	±*S.D.*	μg./100 *ml.*	±*S.D.*
1c	<0.10	—	<0.08	—
2c	<0.06	—	<0.09	—
3c	0.26	0.01	<0.06	—
4c	<0.08	—	<0.15	—
5c	0.32	0.03	<0.60	—
6c	0.30	0.03	0.60	0.03
7c	0.18	0.01	<0.15	—
8c	0.53	0.01	<0.23	—
9c	0.33	0.03	<0.42	—
10c	0.13	0.01	<0.16	—
Range	<0.06–0.53		<0.06–0.60	
Mean (μg.)	0.19		0.19	
Log Mean (mμg.)	2.27		2.27	
Log S.D.	±0.94		±0.37	

Patients in chronological order.

All these considerations suggested to us that portal hypertension in man cannot be satisfactorily explained solely upon the basis of mechanical obstruction. It seemed that factors of a dynamic or functional nature would need to be included in a concept of portal hypertension which would explain all the features of the disease at any time in its natural history.

Portal blood flow and pressure can readily be varied by both hormonal and vasomotor influences. The vascular reactivity of the splanchnic circulation, as judged from animal experiments, is of a very high order and its blood vessels are almost completely dominated by the sympathetic nervous system. Furthermore, the portal circulation shows a high degree of reactivity to the administration of adrenaline and noradrenaline which, in addition to being secreted by the adrenal medulla, constitute the sympathetic post-ganglionic neurotransmitter hormones. When a stimulus passes along the post-ganglionic adrenergic fibres of the sympathetic system, noradrenaline and adrenaline are released at the nerve endings. These neurohormones are partly inactivated at their point of release. A

proportion of them, however, will flow over into the blood and will contribute to the circulating levels of noradrenaline and adrenaline. Such levels will normally reflect sympathetic nervous activity in the body.

These considerations suggested that knowledge of the concentration of adrenaline and noradrenaline in the portal vein blood of patients with portal hypertension might help towards our understanding of the aetiology of the condition. For, as already indicated, the splanchnic circulation is vasomotor dominated and activation of the vasomotor nerves to this region or administration of the sympathetic neurohormones, adrenaline and noradrenaline, can produce marked changes in portal pressure. For these reasons our investigations initially turned upon the estimation of the adrenaline and noradrenaline content of portal vein plasma in patients with portal hypertension.

TABLE VI

PORTAL HYPERTENSION AND CIRRHOSIS: PORTAL PLASMA ADRENALINE AND NORADRENALINE CONTENT

	Adrenaline		*Noradrenaline*	
Patient	μg./100 *ml.*	±*S.D.*	μg./100 *ml.*	±*S.D.*
1	2.32	0.04	0.61	0.01
2	1.28	0.07	1.04	0.27
3	4.26	0.28	113.4	8.10
4	0.53	0.03	<0.32	—
5	7.51	0.26	2.50	0.11
6	4.22	0.15	1.44	0.15
7	1.01	0.05	0.26	0.02
8	1.54	0.13	1.12	0.17
9	3.89	0.08	2.32	0.14
10	7.03	0.43	5.02	0.16
11	<0.18	—	<0.22	—
12	0.40	0.01	<0.42	—
13	29.47	0.47	34.00	0.69
14	1.97	0.22	2.94	0.01
15	2.12	0.01	1.05	0.17
16	1.94	0.16	<0.10	—
17	1.17	0.12	0.33	0.02
18	1.43	0.22	1.12	0.02
19	2.68	0.01	1.05	0.17
20	0.24	0.04	0.78	0.04
21	1.24	0.09	25.70	3.27
22	1.38	0.09	0.65	0.02
Range	<0.18–29.47		<0.10–113.4	
Mean (μg.)	1.38		1.41	
Log Mean (mμg.)	3.14		3.15	
Log S.D.	±1.02		±0.94	

Patients in chronological order.

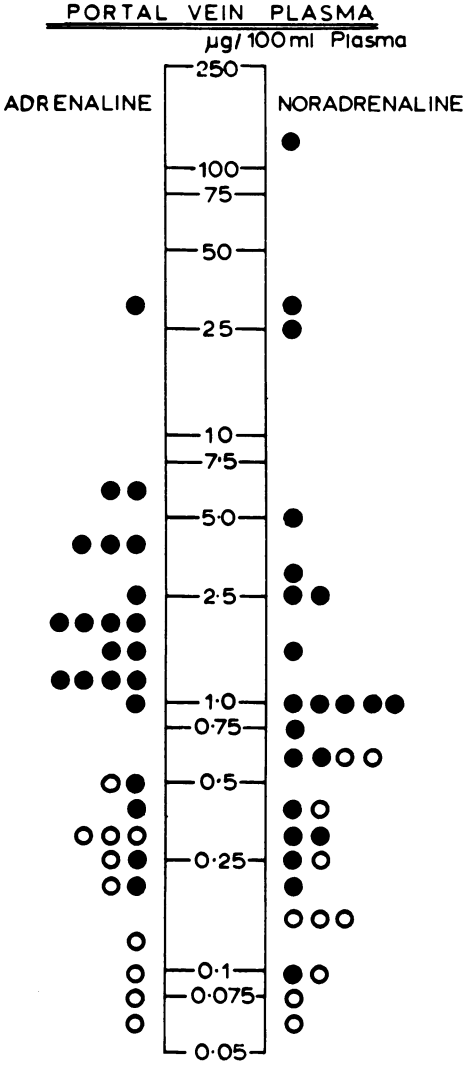
The plasma levels of adrenaline and noradrenaline in portal hypertension and normals

Methods

1. *Patients.*

Portal vein blood was obtained from—

i. Twenty-two patients with proven portal hypertension of the intrahepatic variety who were undergoing portacaval anastomosis. In 21 of



RANGE			
O Normal <0·06–0·53	● Cirrhotic <0·18–29·47	O Normal <0·06–060	● Cirrhotic <0·10–113·4
0·19	1·38 Mean µg	0·19	1·41
2·27	3·14 Log Mean mµg	2·27	3·15
±0·94	±1 02 Log S.D	±0·37	±0·94
<0·01 >0·001	P	<0·02	>0·01

Fig. 4. Adrenaline and noradrenaline content (µg./100 ml.) of portal vein plasma. ●=Cirrhotics. O=Normals. Values plotted on logarithmic scale.

these cases, the liver histology was that of portal cirrhosis. In one patient (Case 15, Table VI) the liver histology was normal.

ii. One patient with cirrhosis and advanced liver failure—jaundice, ascites and portal hypertension—undergoing portacaval anastomosis.

iii. A patient with cholestasis and infective hepatitis undergoing laparotomy.

iv. A control group of 10 patients with normal livers and portal circulations undergoing cholecystectomy or vagotomy.

Regional blood samples were obtained from five of the 22 patients (group i above). In addition to portal vein blood, samples were taken as

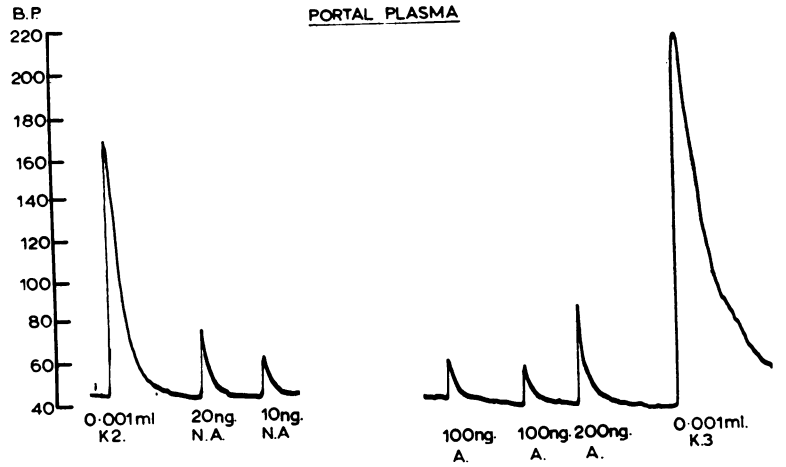


Fig. 5. Assay of adrenaline and noradrenaline from patient with advanced liver failure and portal hypertension. Pithed rate blood pressure preparation. B.P.=blood pressure (mm. Hg.). Noradrenaline (N.A.) and Adrenaline (A). Standards in ng. (mμg.). K_2=Noradrenaline eluate. K_3=Adrenaline eluate. Dose in ml.

near simultaneously as possible from the abdominal aorta, inferior vena cava and a forearm vein.

2. *Blood samples*

These were obtained under direct vision before any clamps were placed on the portal vein. All samples were taken under anaesthesia at operation.

3. *Isolation and assay of adrenaline and noradrenaline*

The adrenaline and noradrenaline were separated by paper chromatography (Crawford and Outschoorn, 1951) and were assayed biologically on the pithed rat blood pressure and rat uterus preparations. Details of the isolation assay and criteria of identity have previously been published (Shaldon *et al.*, 1961; Shaldon, 1962).

Results

Table V gives the levels found in the portal plasma of the normal controls. Many of the noradrenaline estimations are prefixed " less than ". In the majority of these instances some activity was present in the eluates, but the actual amount was below the threshold of the assay. A threshold figure has been quoted on all such occasions. Table VI shows the levels found in the 22 cirrhotic patients, whilst Figure 4 compares the normals with the cirrhotics. It can be seen that there is a significantly greater concentration of adrenaline and noradrenaline in the portal plasma of the cirrhotic patients.

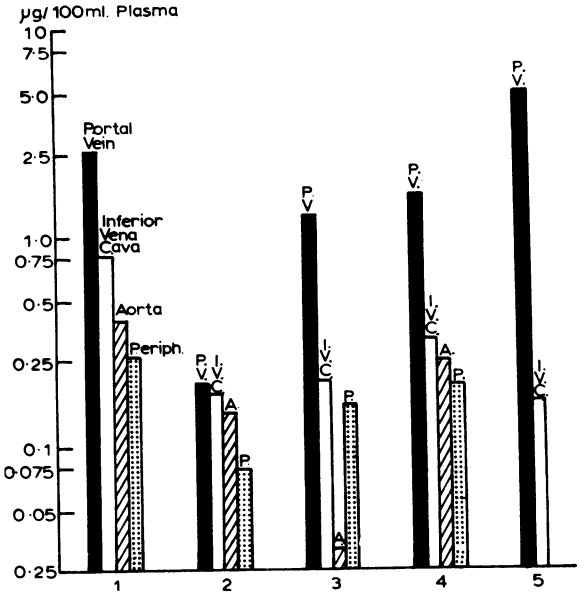


Fig. 6. Regional concentrations of adrenaline in portal hypertension. P.V.= Portal vein. I.V.C.=Inferior vena cava. A=Abdominal aorta. P=Peripheral vein.

In the patient with advanced liver failure, values of 1125.0 µg. adrenaline and 122.5 µg. noradrenaline per 100 ml. plasma were found. These extraordinary results are illustrated in Figure 5. Independent external assay confirmed this result both qualitatively and quantitatively (Shaldon *et al.*, 1961).

During the course of this study we were able to obtain portal blood from a patient with cholestasis due to infective hepatitis. It is well recognized that portal hypertension and oesophageal varices may develop during this condition (Palmer and Brick, 1954; Reichmann and Davis, 1957). It was therefore of considerable interest to find that the portal

plasma of this patient contained raised levels of both adrenaline and noradrenaline—adrenaline 4.1 ±0.42 (normal<0.06–0.53), noradrenaline 10.0 ±0.57 (normal<0.06–0.60) μg. per 100 ml.

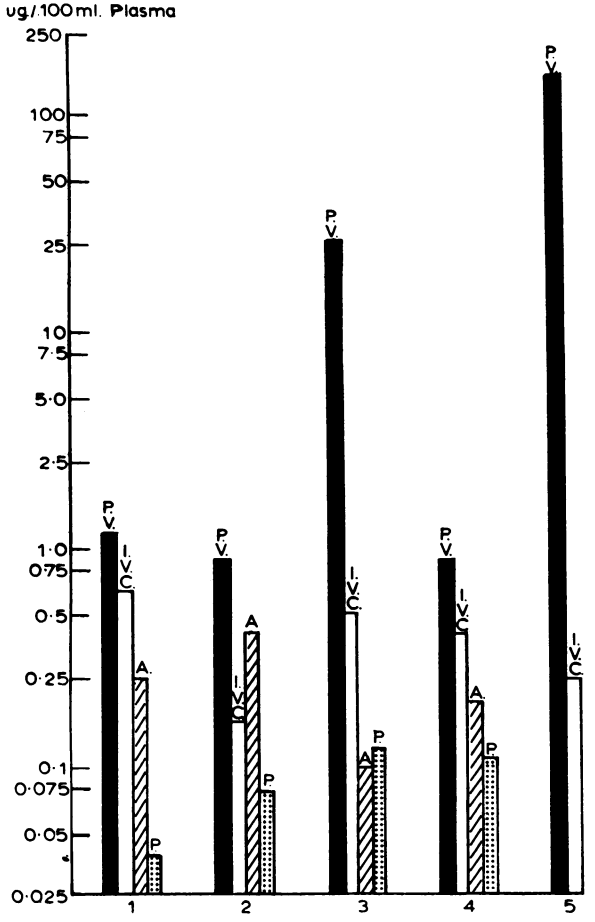


Fig. 7. Regional concentrations of noradrenaline in portal hypertension. Abbreviations as in Figure 6.

Regional samples

In order to determine the site of origin for the excess of portal adrenaline and noradrenaline, regional blood sampling was undertaken. Figures 6 and 7 illustrate these results and show that in each individual case the portal levels are raised above that of the other regions, whilst Figure 8 is an illustrative assay.

Discussion

The results just presented show that patients with portal hypertension and cirrhosis have a concentration of adrenaline and noradrenaline in their portal plasma which is significantly higher than that of normal controls.

If the high levels originated from the adrenal medulla, then regional sampling should have shown an aortic concentration which was above that of the portal vein. In fact this was not the case. For whenever such

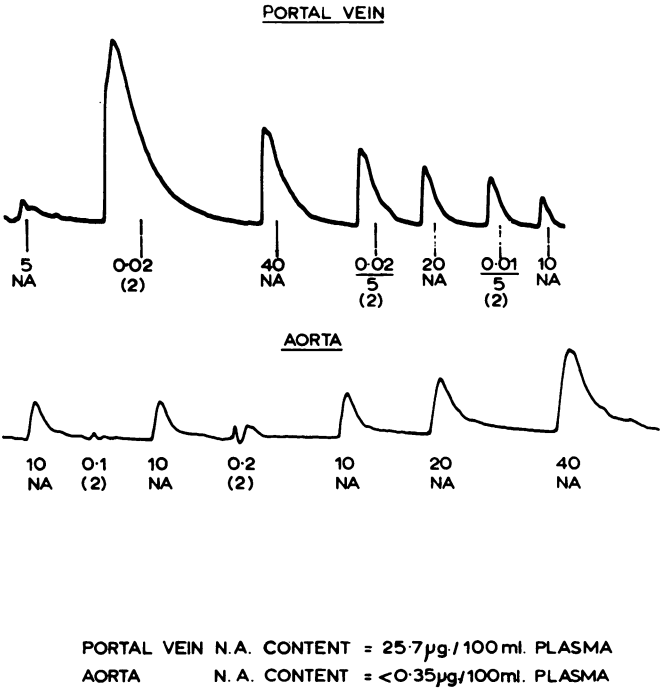


Fig. 8. Assay of noradrenaline in plasma from the portal vein and aorta. Pithed rat blood pressure preparation. Doses of noradrenaline standards (N.A.) in mμg. (2)= Noradrenaline eluates. Dose in ml.

measurements were made, the portal vein concentration was always greater than in any other region. This implies that the site of release of the excess of adrenaline and noradrenaline in the portal plasma lies somewhere between the aorta and portal vein and is not the adrenal medulla. Adrenaline and noradrenaline normally enter the blood as a result of sympathetic nervous activity. The finding of a regional elevation of these substances therefore implies the presence of regional activity in the sympathetic system. Thus it can be said that in the patients with portal hypertension, the increased concentrations of adrenaline and noradrena-

line arose as a result of local, or in this context splanchnic, nervous activity.

It is not known if the enterochromaffin cells which are present in the intestine of man will liberate adrenaline and noradrenaline into the blood when the splanchnic nerves are activated. However, it is known that when the splanchnic nerves are stimulated, neurotransmitter hormone is released into the blood. On this basis, then, it is possible to postulate that the excess of adrenaline and noradrenaline, found in the portal blood, is neurotransmitter hormone being released at the post-ganglionic nerve endings of the splanchnic sympathetic system and that such a finding constitutes evidence of local nervous activity. Now this statement immediately raises questions regarding the identity of the neurotransmitter hormones in man and the factors which control their release, because it is currently considered from animal work that the neurotransmitter hormone is predominantly noradrenaline. But no direct investigation of this has yet been reported in man.

TABLE VII

NORADRENALINE AND ADRENALINE CONTENT OF HUMAN POST-GANGLIONIC SYMPATHETIC NERVES

	Noradrenaline μg/g. *tissue*		*Adrenaline*
Thirteen lumbar sympathetic nerves	0.09–1.20	Range	0.04–0.95
	0.19	Mean	0.15
Hepatic nerves from two patients with portal hypertension	3.40		1.10
	1.10		0.40

What can be released at the post-ganglionic sympathetic nerve endings will largely depend upon the composition of the stores in the nerve. We know from our own investigations at Bristol, that adrenaline as well as noradrenaline is contained in the postganglionic sympathetic nerves of man (Table VII). We also know, from our current investigation into the nature of the neurotransmitter hormone in man, that if the lumbar sympathetic nerves are stimulated during lumbar sympathectomy, then both hormones can be released at the post-ganglionic nerve endings of the skin of the foot and appear in the venous blood.

Under normal circumstances, the neurotransmitter hormones liberated at the sympathetic nerve endings are almost entirely inactivated and taken up by the receptors. The fact, therefore, that we found such large amounts of adrenaline and noradrenaline in the portal blood would indicate that either there is some abnormality present in the systems which inactivate these hormones at the point of release, or that there is some form of blockade at their site of uptake on the receptors. These considerations, however, are still under investigation, and it is not possible to comment upon them further at the moment.

The raised levels of portal adrenaline and noradrenaline have been found in patients with both early and late liver disease, in both adults and in children. We do not, as yet, know whether the raised levels are present in patients with extra-hepatic obstruction of the portal system, for so far we have only been able to estimate the levels in two such cases. We should also like to know whether the raised levels of adrenaline and noradrenaline occur as a primary or secondary event in portal hypertension and whether or not they disappear after the performance of a portacaval anastomosis. When we have the answers to these questions, it may be possible to say why the abnormality in sympathetic nervous activity is present at all in these patients with portal hypertension.

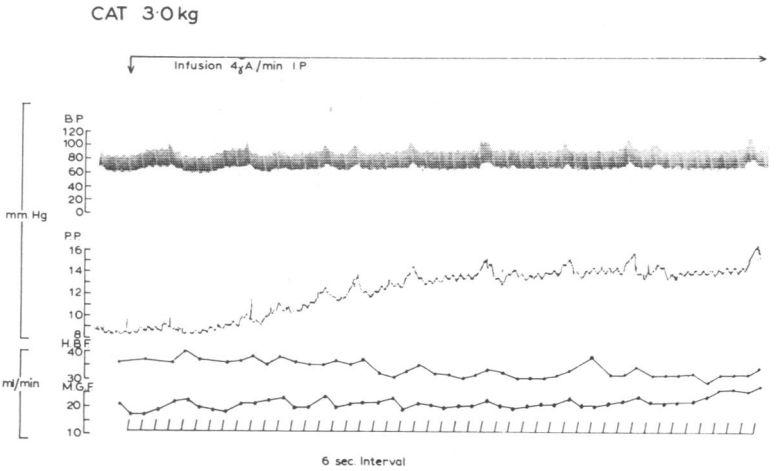


Fig. 9. Cat. Chloralase anaesthesia. Infusion of adrenaline 4 μg./min. into portal system. B.P.=blood pressure. P.P.=portal pressure. H.B.F.=hepatic blood flow. M.G.F.=midgut blood flow. A=Adrenaline. I.P.=intraportal.

Physiological significance

The physiological significance of the findings I have described to you, and hence their contribution to the maintenance of portal hypertension in man, become apparent when one considers the actions that adrenaline and noradrenaline and splanchnic nerve stimulation may have on the portal circulation. We believe from our own researches in man and animals and from the data which are available in the literature, that the high concentrations of portal adrenaline and noradrenaline contribute to the maintenance of portal hypertension in three ways.

The first of these is by the production of functional venous obstruction in the liver. The second is by elevation of the cardiac output and lowering of peripheral resistance. The third is by the opening of arterio-venous anastomoses in the stomach (Walder, 1952) and possibly also the bowel,

Portal venular constriction

When adrenaline or noradrenaline are slowly infused directly into the portal circulation of man or animals, portal pressure rises and liver blood flow is reduced. These effects can be attributed to portal venular constriction and have been demonstrated in animals by McMichael (1932) and by Daniel and Prichard (1951). Provided the rate of infusion is not excessive, there is no detectable change in arterial blood pressure, for the normal liver rapidly inactivates both adrenaline and noradrenaline so that the hepatic vein has the lowest plasma concentration of these substances in the body (Vendsalu, 1960). Figures 9 and 10 illustrate these events. Figure 9 shows the result when 1.1 μg. adrenaline/kg. body weight/minute is infused into a jejunal vein of the cat. Figure 10 shows similar qualitative changes in normal man.

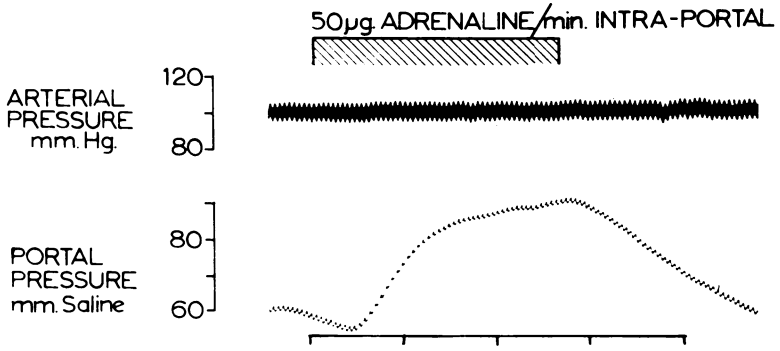


Fig. 10. Normal man. Intraportal infusion of adrenaline at operation for duodenal ulcer. Time in minute intervals.

However, in the presence of portal-systemic collaterals, the actual site of infusion is all important. If the drugs are injected directly into the portal vein, venospasm will occur in the liver. If, however, the site of injection is at a point whence the drugs could be carried, not only to the liver, but also to the collateral channels, then a compound effect will result. When collateral channels are present, an intraportal infusion of adrenaline or noradrenaline can produce not only portal venular spasm but also systemic effects. Figure 11 shows how, in a patient with cirrhosis and patent porta-systemic collaterals, a single rapid injection of 10 μg. adrenaline (0.13 μg./kg. body weight) into an omental vein produced a rise in portal pressure followed by a rise in arterial pressure.

The presence of portal-systemic collaterals has yet another significance. In a normal person, occlusion of the portal vein causes a rise in pressure of 500–600 mm. water. In a patient with portal hypertension, clamping the portal vein produces a smaller rise of the order of 50–150 mm. water. On occasion no rise in pressure occurs. The pressure change which

follows occlusion of the portal vein will depend upon the degree of outflow obstruction already present and also upon the magnitude and efficiency of the draining collaterals. Since total occlusion of the portal vein may result in a small or even no change in portal pressure, it follows that any attempt to demonstrate functional portal venular constriction by the infusion of adrenaline or noradrenaline may be attended by the same results. This explains why we have found that the infusion of 10–50 μg./minute of adrenaline or noradrenaline into the portal circulation of patients with cirrhosis produces variable rises in portal pressure. The rises we have measured have varied between 6 and 32 per cent. of the control level. Because of the presence of collaterals, then, the fact that only a small rise in portal pressure may be produced by the administration of adrenaline and

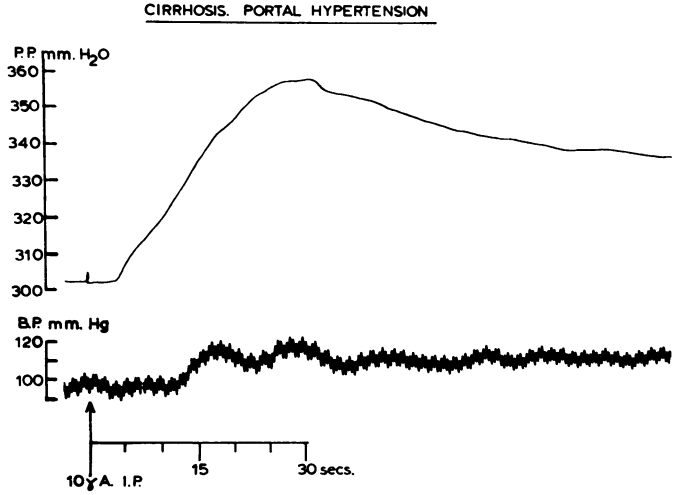


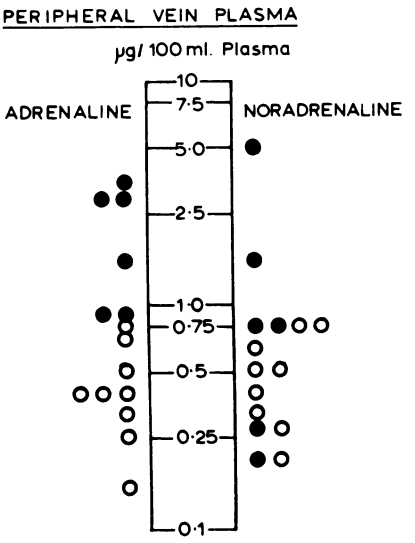
Fig. 11. Intraportal injection of adrenaline (10 μg.) in patient with cirrhosis and portal hypertension. P.P.=portal pressure. B.P.=blood pressure.

noradrenaline does not mean that a marked degree of constriction may not actually be occurring and may not already be present.

These considerations explain the findings of Child (1954), who described an " epinephrine reversal " effect when adrenaline was injected into the superior mesenteric vein of cirrhotic patients. He gave large single injections of 500 μg. and found the portal pressure rose, then fell and then rose again. These effects are explicable on the basis of combined intraportal and systemic vasoconstriction occurring as a result of such large and rapid injections. At any time portal pressure is a mean level compounded from the state of the inflow and outflow tracts of the portal circulation, the level of arterial pressure and the cardiac output. The effects of adrenaline and noradrenaline therefore depend upon the dose given, the rate and site of injection and also the presence or absence of portal-systemic collaterals.

Cardiac output

The second significant action that the raised portal levels of adrenaline and noradrenaline have is the elevation of the cardiac output, and hence the possibility that there is an increase in the volume of blood flowing into the portal circulation. This effect is brought about by the leakage of adrenaline and noradrenaline along the collateral channels and into the systemic circulation. The intravenous infusion of either or both of these



	RANGE		
O Normal 0·15 — 0·89	●Hepatic Coma 0·94 — 3·42	ONormal 0·21 —0·77	●Hepatic Coma 0·20 — 5·31
0·40	1·86 Mean μg	0·47	0·87
2·60	3·27 Log Mean mμg	2·64	2·94
±0·25	±0·25 Log S.D.	±0·17	±0·23
<0·001	P	<0·01 >0·02	

Fig. 12. Adrenaline and noradrenaline content (μg./100 ml.) in peripheral plasma. ●=patients in hepatic coma. O=normals. Values plotted on logarithmic scale.

substances in man, up to a doseleve l of 10 μg./min., is not necessarily accompanied by any significant degree of arterial hypertension (Goldenberg *et al.*, 1948). At this dose level adrenaline may increase the resting cardiac output by as much as 100 per cent., whilst noradrenaline produces either no change in it or a slight decrease.

Two further pieces of work are relevant in this context. First, it has been shown that, in man, the intravenous infusion of adrenaline increases the splanchnic blood flow and reduces splanchnic vascular resistance

(Bearn *et al.*, 1951). Secondly, patients with portal cirrhosis have a significantly greater cardiac output than do normal controls. Their increased cardiac output is related to the magnitude of the portasystemic collateral channels present and to the state of liver function (Kowalski and Abelmann, 1953; Murray *et al.*, 1958). Peripheral blood flow was also increased in these cases. These effects are known to worsen in hepatic failure, and it was therefore of interest to us to find that in six of our patients with hepatic precoma, raised levels of adrenaline and noradrenaline were detected in the peripheral venous blood (Figure 12), thus indicating either a decreased ability of the liver to metabolize these substances in hepatic coma or the presence of an increased collateral blood flow.

On the basis of these considerations it is possible to see how the raised portal concentrations of adrenaline and noradrenaline can contribute significantly to the maintenance of the state of portal hypertension in man.

Therapeutic applications

In recent months we have attempted to assess the therapeutic significance of the work just described to you. This has been done by the administration to patients of drugs which block adrenergic nerve transmission, discharge adrenaline and noradrenaline from the body stores and lower cardiac output.

Obviously in a patient with gross hepatic structural disease, little significant effect on portal pressure might be expected following the administration of these drugs. But in a patient whose liver structure was well preserved a good effect might well occur. It is still too early to assess our results and certainly too early to advocate therapy, but on the occasions it has been used, guanethidine has produced a fall in portal pressure to nearly normal levels without troublesome side effects. The following two examples illustrate this.

1. Female, aged 29. Diagnosis—portal cirrhosis and portal hypertension. Intrasplenic pressure on successive days—330 mm. and 300 mm. saline. Arterial blood pressure 120/85 mm. Hg. (supine). After five days oral guanethidine (10 mg. daily), the intrasplenic pressure (on successive days) was 152 and 99 mm. saline. Arterial blood pressure 100/70 mm. Hg. (supine).

2. Male, aged 48. Diagnosis—portal cirrhosis and portal hypertension. Intrasplenic pressure 430 and 410 mm. saline. Arterial pressure 105/80 mm. Hg. (supine). After oral guanethidine (20 mg. daily for six days), the intrasplenic pressures were 196 and 264 mm. saline—arterial blood pressure 110/60 mm. Hg. (supine).

Both these cases then underwent portacaval anastomosis as it was felt that at present it would be unjustifiable to deny them this operation. These results are as yet completely unassessed in regard to long-term treatment and I would stress that they still constitute an experiment and not a form of proven therapy.

In conclusion, the future this work will have, particularly in regard to treatment, remains to be seen. We believe that the work shows that portal hypertension in man is maintained, not only by gross anatomical change in the liver or portal vein, but also by factors of a dynamic nature, which because of their reversibility offer new potential for understanding and treatment.

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