female end of one adaptor. The proximal male end of the other adaptor has a similar spring which clips on to the female component of the other vessel cannula.

Connexion to the extracorporeal circuit is shown in Fig. 5. In this instance the junction was situated in the afferent limb close to its emergence from the skin. The outflow and inflow tubes are passing in opposite directions in an endeavour to disturb the shape of the arc as little as possible. Fig. 4 indicates how the arc can be opened up

FIG. 5.—Showing connexion of patient to extracorporeal circuit.

and the adaptors are placed in position. The male Luer-Lok fittings are placed in the distal end of each adaptor.

At the termination of haemodialysis the sphygmomanometer cuff is again inflated, the adaptors are removed and the arterial and venous limbs of the external arc connected to one another.

This shunt has now been used in 20 patients and a total of 52 dialyses have been performed. It has proved eminently satisfactory because of its simplicity, its few parts, and the facility with which it can be tailored to the specific requirements of the individual patient.

Summary

A simplified arteriovenous shunt is described.

No by-pass component is employed and only a single junction is used.

Connexion to the extracorporeal circuit and re-establishment of the arteriovenous shunt is simple and rapid.

I wish to thank Mr. F. H. Caldwell for his invaluable help in the construction and development of this arteriovenous shunt. To Mr. E. Mackay I am indebted for the photographs and my thanks to Mr. G. Hillas for Figures 1 and 3.

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CONTROL OF ANTICOAGULANT THERAPY BY THROMBOTEST METHOD

BY

J. W. KEYSER, M.Sc., Ph.D., F.R.I.C.

Reader in Chemical Pathology in the University of Wales at the Welsh National School of Medicine; Honorary Consultant in Biochemistry, the United Cardiff Hospitals

From the Institute of Pathology, Royal Infirmary, Cardiff

In his original publication on the thrombotest, Owren (1959) gave the therapeutic range of clotting activity in anticoagulant therapy as 10 to 30% of normal. The lower level was determined by the risk of bleeding and the upper level by the risk of inadequate therapy. In the light of further experience the upper limit was subsequently lowered to 25% (Owren, 1961) and still more recently to 20%, a level of 15% being aimed at (Owren, 1962a, 1962b). Loeliger (quoted by Owren, 1962b) aims at 12%, his therapeutic range being 7 to 15%.

According to Poller (1962), in most centres the main danger to patients on anticoagulant treatment is not haemorrhage but rather a recurrence of thrombosis or the development of embolism; and in a review of venous thrombosis in two hospitals in the United States Zollinger *et al.* (1962) found that therapy with prothrombin depressants had been ineffective in at least 60% of the cases, as judged by an analysis of the laboratory results, and in many patients pulmonary embolism occurred, presumably as a result of inadequate dosage.

It is known that a thrombotest level between 10 and 25% of the normal does not represent as marked a depression of coagulation activity as a similar figure obtained by the Quick prothrombin test or one of its modifications (Lempert and Poller, 1960; Vigran, 1961; Poller, 1962; and others). This accounts for the reduc-

tion in dosage of anticoagulant that usually results from a change from the Quick test to the thrombotest.

In view of these considerations it seemed important to compare the thrombotest with the prothrombin technique in use in this laboratory, especially as the existence of numerous modifications of the prothrombin test have led to some uncertainty about the comparability of the results obtained in different centres; for example, it has been shown in this laboratory (Powell, 1957) that prothrombin ratios (see below) obtained by the use of a fresh brain emulsion (Toohey, 1941, 1950; Owen and Toohey, 1941) are considerably higher than those obtained with an extract of acetone-dried brain.

On the assumption that it is desirable to lower the coagulability of the blood as much as possible without undue risk of haemorrhage, the results of this investigation suggest that in the control of anticoagulant therapy with the thrombotest a range of 8 to 15% is preferable to one of 10 to 20%.

Material and Methods

More than 200 specimens of citrated venous blood, mostly from patients with myocardial infarction, were tested. Most of the patients were receiving phenindione (phenylindanedione; "dindevan"), but some were receiving nicoumalone (3-[2-acetyl-1-(4-nitrophenyl)ethyl]-4-

hydroxycoumarin; "sinthrome"). The thrombotest technique was performed as described by Owren (1959), using half the originally proposed quantities of blood and reagent (Owren, 1960). Blood was collected in a plastic syringe and transferred to a polystyrene tube containing citrate. After performance of the thrombotest the specimen was centrifuged and the plasma prothrombin time determined as described by Keyser and Payne (1960). This technique, which employs acetone-dried human brain, gives results in close agreement with that of Biggs (1951). Prothrombin results were expressed as a prothrombin clotting-time ratio (P.C.T.R.)—that is,

$$\frac{\text{patient's clotting-time (sec.)}}{\text{normal control clotting-time (sec.)}}$$

In the course of these comparisons at least four different batches of thrombotest reagent were used. Two batches of dried brain were used, and the accompanying Table shows the good agreement between the results obtained with them.

Agreement of Prothrombin Clotting-time Ratios Obtained with Two Different Brain Preparations

Specimen	1	2	3	4	5	6	7	8	9	10
P.C.T.R. { Brain A*	1.2	2.0	4.0	1.5	1.6	1.2	1.1	2.0	2.3	1.3
Brain B†	1.2	1.9	3.8	1.4	1.6	1.2	1.1	1.8	2.1	1.2

* Acetone-dried in November, 1961. Normal = 11.7 sec.

† Acetone-dried in October, 1962. Normal = 11.6 sec.

All tests performed in October, 1962.

Results

The results are shown in the Chart, and the salient points may be summarized as follows. As the thrombo-

test level fell below about 7% the P.C.T.R. increased rapidly: at a thrombotest level of 6% the P.C.T.R. ranged from 1.7 to 3.1; at a level of 5% the P.C.T.R. was usually in the 1.8–2.3 range but in one case exceeded 4; and at thrombotest levels below 5% the P.C.T.R. can be very high indeed. On the other hand, most patients in the 15 to 20% range—that is, in the upper part of the therapeutic range recommended by Owren—had a P.C.T.R. of less than 1.5.

Discussion

The range of P.C.T.R. at which to aim in anticoagulant therapy is variously given as 1.5 to 2, 1.5 to 2.5, 2 to 2.5, or 2 to 3.

As a result of their comparison of the prothrombin (acetone-dried brain) and thrombotest techniques, Lempert and Poller (1960) recommended that the P.C.T.R. should not be allowed to exceed 2. Quick (1962), however, recommends a range corresponding to a P.C.T.R. of 1.7 to 2.5, as giving maximum reduction of prothrombin concentration consistent with relative safety from haemorrhage. He suggests that the anticoagulant will have no effect if, with a normal prothrombin time of 12 seconds, the patient's prothrombin time is less than 20 seconds.

Sevitt and Gallagher (1959) found that deep-vein thrombosis was effectively prevented in patients at risk when phenindione was given in sufficient dosage to prolong the prothrombin time to between two and three times the normal. Whether an increase in the prothrombin time to between one and a half times and twice the normal is as effective in preventing thrombosis has not yet been shown

Correlation between prothrombin clotting-time ratios and thrombotest results (%) in patients under treatment with anticoagulants. Note: Several values above 100% on the thrombotest scale are omitted, as are two P.C.T.R.s of 5.5 and 8 (thrombotest value in each case less than 5%).

(*Lancet*, 1962). It is also uncertain whether the same intensity of anticoagulant therapy is needed for the prevention of arterial and venous thrombosis.

As mentioned above, the technique employed may influence the P.C.T.R. appreciably. It is probable that when acetone-dried brain is used as the source of thromboplastin, as in the studies quoted above, most centres would consider a P.C.T.R. between 2 and 2.5 to be within the therapeutic range. This has, in general, been the level of depression aimed at in the Cardiff Royal Infirmary; and with P.C.T.R.s not greatly above 2.5 there have, to our knowledge, been very few serious haemorrhages due to anticoagulant treatment, over a period of several years.

Unless the experience gained with the prothrombin test over a long period is to be entirely disregarded, our results suggest that it is desirable to keep the thrombotest level below 15%, since we found that most values in the 15 to 20% range correspond to a P.C.T.R. of less than 1.5. On the other hand, it is wise to avoid allowing the thrombotest level to fall below 7%: in order to provide a margin of safety 8% is suggested as a suitable lower limit. Such a range (8% to 15%) would strike a balance between insufficient and too much anticoagulant.

It should be noted that for a given range of thrombotest values our results appear to indicate a smaller depression of coagulation activity (as shown by the Quick test) than was found by Matthews and Walker (1959). For example, for the thrombotest range of 10 to 20% our P.C.T.R. values ranged from 1.9 to 1.3; for the same range Matthews and Walker found P.C.T.R. values of about 2.5 to 1.7 (calculated from Fig. 3 of their paper). This presumably results from differences between the pro-

thrombin techniques, and in no way invalidates the present recommendations.

Summary

A comparison of the thrombotest technique with the prothrombin-time estimation suggests that in the control of anticoagulant treatment by means of the thrombotest the blood-coagulation activity should be kept within the range of 8 to 15% rather than 10 to 20%. As the thrombotest level falls below about 7% the prothrombin time increases rapidly; above 15% it may be so short as to suggest inadequate dosage of anticoagulant.

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Preliminary Communications

Absorption of Iron in Cirrhosis of Liver

It has been recognized for some time that iron overload occurs in patients suffering from cirrhosis of the liver, particularly in association with alcoholic cirrhosis (Herbut and Tamaki, 1946). The degree of iron overload may be such that it has even been suggested that primary haemochromatosis does not exist as a separate disease entity (MacDonald, 1961). In the past it has not been clear how the haemosiderosis of cirrhosis arises; indeed, the frequent haemorrhages associated with portal hypertension would be thought to favour iron depletion rather than iron overload.

The present report is concerned with studies of absorption of radioactive iron in patients with cirrhosis of the liver and the effect of pancreatin on the iron absorption.

MATERIAL AND METHODS

Seven patients with cirrhosis of the liver were studied (see Table); in two there was a background of alcoholism, in the remainder the aetiology was unknown. The diagnosis was established on clinical grounds, on the presence of abnormal liver-function tests, radiological demonstration of oesophageal varices, and assessment of liver size and surface contour by pneumoperitoneum. Needle biopsy of the liver was taken in two subjects.

One subject (338877) died some time after the present studies and post-mortem histology was obtained. This last patient was on the verge of hepatic coma during

the investigations and had to be maintained on a severely restricted protein intake. The remainder were all reasonably fit and stabilized at the time of the tests. None had evidence of any recent haemorrhage.

A blood count and serum iron were taken before the tests. The latter was estimated by the method of Bothwell and Mallett (1955). Iron absorption was measured after the administration of either ^{55}Fe ferrous sulphate or ^{55}Fe -labelled rabbit haemoglobin, the dose in each case being adjusted to contain 5 mg. of iron (Callender *et al.*, 1957).

Absorption and Utilization of ^{55}Fe Given as $^{55}\text{FeSO}_4$ or Labelled Haemoglobin in Patients with Cirrhosis of the Liver. (For Comparison, Mean Absorption of $^{55}\text{FeSO}_4$: Normals, 30%; Iron Deficiency, 55%. Mean Absorption of $^{55}\text{FeHb}$: Normals, 13%; Iron Deficiency, 25%)

Case No.	Sex and Age	Diagnosis	Hb (g./100 ml.)	Plasma Iron (μ g./100 ml.)	Faecal Fat (g. day)	Percentage Absorption of Oral Iron		Percentage of Iron Appearing in Red Cells	
						Without Pancreatin	With Pancreatin	Without Pancreatin	With Pancreatin
Haemoglobin Iron									
326218	F 49	Crypto- genic cirrhosis	12.3	60	6	64	13.9	18	7.5
291112	F 59	"	14	128	4.6	54	26	12.5	16
210969	F 61	"	10	48	4.4	57	38	7.5	7.5
Inorganic Iron									
338877	M 46	Alcoholic cirrhosis	12.6	200	4.8	34.5	23	—	—
300408	M 54	"	16.6	274	—	78	33.7	30	12.5
321114	F 73	Crypto- genic cirrhosis	13.4	152	2.5	65	25.8	7.2	1.8
343144	M 76	"	17.4	264	20	60.7	30.4	10.9	3.7