meetings were held in 1915 and 1916, and by the end of the war the financial position of the Association was extremely bad.

The turning-point came at the annual meeting in Halifax in 1921. It was realized then that reorganization was essential. The various provincial organizations had not been brought closely enough into relationship with the Association, and the finances needed immediate attention. A full-time secretary was appointed in the person of Dr. T. C. Routley, a bond issue was raised, and once more the Association began to expand. Within a few years it had paid off the bond issue and was showing the vigour and growth which has brought it to its present stature.

The Association has continued not only to deal with the profession's educational and economic problems, but to concern itself with social and political developments. Post-graduate lectures were first organized in 1925, and were carried on throughout Canada for seven years, with the help of generous grants from the Sun Life Assurance Company. A Department of Hospital Service, also aided by this company, was carried on for 20 years.

Health insurance has probably occupied the attention of the Association more continuously than has any other subject. The principle of insurance against the cost of illness has received the support of the Association, particularly through the medium of prepaid medical care plans.

The first proposals to establish a Royal College of Physicians and Surgeons of Canada were made at the annual meeting in Vancouver in 1920, the primary object being to stimulate study and postgraduate work in medicine and surgery. The idea gradually matured, and the College was finally incorporated by Act of Parliament in 1929. Once launched, the College became an entirely independent organization.

Inspection and accreditation of hospitals is one of the later activities of the Association. This work had previously been done in Canada by the American College of Surgeons, and on their withdrawal from this particular field the Association initiated plans for the necessary machinery to carry it on. To Dr. E. K. Lyon, of Leamington, Ont., is due most of the credit for focusing attention on the importance of this phase of hospital life and of eventually bringing into being the Commission to deal with it. The C.M.A. contributes the major part of the very heavy cost of this work. Formation of a College of General Practice originated within the Association some five years ago, and the College came into being last year, with a full-time secretary. There has been an encouraging response to this movement, but of course it is still at a very early stage of development.

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There is little information on the growth and physical development of Indian children, according to the latest annual report of the Nutrition Research Laboratories at Coonoor. However, a start has been made. Workers at the Coonoor Laboratories first analysed data in the literature on 46,000 boys from various parts of India, and from this prepared growth curves for them. Then a homogeneous group of about 2,000 boys were examined from around Coonoor, and their growth curve was found to correspond closely to that derived for India as a whole. But, what is more interesting, these curves were found to parallel, though at a slightly lower level, recent growth curves for British and American boys. The report poses the question of the influence of nutrition in producing the lower growth progression found in the Indian children.

TREATMENT OF POLYCYTHAEMIA WITH RADIOACTIVE PHOSPHORUS

BY

J. B. HARMAN, F.R.C.P.

Physician

P. L. de V. HART, M.R.C.P.

Formerly Senior Registrar

AND

E. M. LEDLIE, M.B., B.S., D.M.R.

Clinical Research Radiotherapist

The Royal Marsden Hospital

Polycythaemia was first treated by radioactive phosphorus (P^{32}) in 1940 by Lawrence, who has reported 201 cases dealt with since that time (Lawrence *et al.*, 1953). Two reports have already been made in this country, comprising 20 cases (Bodley Scott, 1953) and 27 cases (Abbatt *et al.*, 1954). P^{32} was used in the Royal Marsden Hospital at the end of 1948, and 48 cases have been treated since then. Our purpose is to draw attention to the benefits that may be expected and to comment on certain features of the symptomatology and course.

Radioactive phosphorus is prepared by the irradiation of pure sulphur, and is obtained as a solution of orthophosphoric acid. It has a half-life of 14.3 days, but excretion of part of the administered dose in the urine reduces its effective half-life in the body to about 10 days.

When P^{32} is administered the phosphorus participates in the general biochemical reactions of the body. A large amount is incorporated into those cells in which proliferation is most active, because this is where the turnover of phosphorus is greatest. One of the most active tissues in this respect is the bone marrow, and this activity is increased when there is marrow hyperplasia as in polycythaemia or leukaemia. The injection of radioactive phosphorus therefore provides a method of irradiating the overactive haemopoietic tissues more selectively than can be done with external irradiation.

Dosage

The patient is admitted to hospital. The P^{32} is injected intravenously as a solution of sodium phosphate. There are no side-effects and no irradiation reactions have been observed, even following the administration of the maximum dose. After the P^{32} has been given, the urine is collected and its radioactivity measured. The patient is discharged from hospital when the excretion has reached a safe level (100 mC in 24 hours), which in practice means two to three days after the injection.

Two methods of P^{32} dosage have been employed. At first all patients were treated by a "split" dose—that is, two injections of P^{32} at an interval of about two months. Subsequently it was thought that a single injection would probably be sufficient for some patients, and both methods are now used according to the severity of the disease. The split dosage was used for 28 patients, with an interval of 6–12 weeks between the injections. The dose was usually 5 mC followed by 4 mC. The smallest amount given in the two injections was 6 mC and the largest 12 mC. A single injection was given to 16 patients as the first treatment. The dose varied between 4 and 7 mC, according to the severity of the symptoms and haematological findings. The single dose is more convenient, and, since there is no obvious difference

in the results, it is used whenever possible, and almost always in the treatment of relapse. Further treatments are usually required every one or two years throughout the duration of the polycythaemia. The largest total amount of P³² given to one patient to date is 36 mC.

The inhibition of the bone marrow persists in most cases for a year or more. But the effect on the circulating red-cell mass, and hence on the symptoms, becomes apparent only gradually, in the course of two to three months. If this period of gradual improvement is added to the period of gradual worsening before treatment is again worth while, it may be found that a patient who needs treatment once a year is properly controlled for only two-thirds of the time. In order to shorten the period of improvement we have done a massive venesection at the same time as injecting P³² on 48 occasions when the patient has had a notably high red-cell mass. This is made possible only by a simultaneous infusion of a plasma substitute to prevent shock and heparinization to keep the blood flowing. By this means it is possible to bring the haemoglobin down to a normal figure in one operation. The most that has been removed is 5 litres, replaced by 3.6 litres of dextran: the haemoglobin fell from 155% to 94%. It has been found best to reduce the haemoglobin to slightly below normal, since the excretion of plasma substitute in the next 48 hours usually causes it to rise again by about 10%. The replacement should be a half to one litre less than the quantity withdrawn; a rise of pulse rate shows that insufficient plasma substitute is being replaced. It is advisable to keep the patient in bed for a day and forbid solid food, lest fainting or nausea occur.

Present Series

The distribution by age and sex is shown in Table I. It is very difficult to determine the age at which polycythaemia develops, since for a time there may be no symptoms, and

TABLE I.—Age When First Seen at the Royal Marsden Hospital

Age:	30-39	40-49	50-59	60-69	70-79	80+	Total
Male	3	5	8	5	2	1	24
Female	1	4	3	10	5	1	24
Total	4	9	11	15	7	2	48

even when they occur they are often too mild to send the patient to a doctor. For example, a woman first diagnosed at the age of 39 said she had had symptoms since adolescence, and it was clear that her symptoms were due to polycythaemia. Perusal of the histories suggests that the disease was present for an average of four to five years before it was diagnosed.

The frequency of the various symptoms is shown in Table II.

TABLE II.—Main Symptoms of Above 48 Cases

	Cases	%
High colour	48	100
Haemorrhagic phenomena	27	56
Dyspepsia: all cases	17	35
cases with D.U. on x-ray film	6	12
Splenic pain	14	29
Pruritus	17	35
Thrombosis: venous	8	17
arterial	9	19
Dyspnoea, headache, dizziness, etc.	10	21
Ulceration, chronic sepsis, or gangrene	9	19

The high colour is most evident on the face, but is here an unreliable diagnostic guide. It is best to examine the conjunctivae, tongue, nail-beds, and especially the palms of the hands, in which high colour is at least as reliable a guide as an isolated blood count. A complaint of red eyes was not uncommon, and a few patients had been treated for "conjunctivitis" over many months: but soreness was present in only one case. Telangiectases were common on the cheeks. The heightened colour has a distinct purplish tinge, which is, in fact, the natural colour of concentrated oxyhaemoglobin and is not necessarily due to the presence of reduced haemoglobin.

Thromboses and haemorrhages were both common. Arterial thromboses were found in those sites where their occurrence is most easily detected—that is, in the retina, internal capsule, pons, and the coronary, femoral, and popliteal arteries. Venous thromboses were common in the legs. Haemorrhages occur from the nose, upper and lower gastro-intestinal tract, ruptured varicose veins, gums, and as ecchymoses. Prolonged bleeding is also apt to occur after dental extractions and operations. Both thromboses and haemorrhages might occur at the same time, with a normal or high platelet count and no demonstrable abnormality of coagulation or prothrombin generation. It is probable that the haemorrhages are due to some capillary abnormality.

Dyspepsia had the usual characteristics of peptic ulcer, and a duodenal ulcer was demonstrated in 6 of the 17 dyspeptics. Pruritus was usually generalized and always worse in the palms and soles; it is aggravated by a hot bath. Chilblains, ulceration, sepsis, and partial gangrene of the toes were common and occurred in cases with apparently normal vessels. Other symptoms commonly complained of were dyspnoea, faintness, palpitations, headache, thumping in the head, dizziness, fatigue, lethargy, and a congested feeling in the face and head. Splenic pain was due either to infarction or to the weight of the tumour. The spleen was definitely enlarged in 27 of our cases and was below the umbilicus in 9.

Haematology

The most reliable measures of red-cell concentration both at the Royal Marsden Hospital and elsewhere have been the haemoglobin or packed cell volume. The red blood cell count has commonly been extremely variable and unreliable, which is probably due to the difficulty of homogenizing samples properly. No patients were regarded as polycythaemic unless the readings were well above normal—for example, Hb, 130%; P.C.V., 60%; R.B.C., 7,000,000. As is well known, there is usually an increase of polymorphs, with a few metamyelocytes, and less often of platelets. These associated changes are best seen in marrow puncture or biopsy.

Blood Volume

The ordinary methods of haematology measure the concentration of red cells or haemoglobin, and in polycythaemia the concentration is of course raised. The essential pathological change, however, is an increase in the red cell mass, and this can be deduced from measures of concentration only if it is known that the plasma volume remains constant. It would therefore be desirable to have simple and accurate methods of measuring both the red-cell mass and the plasma volume that could be used in clinical medicine. Unfortunately, the measurement of blood volume is attended by considerable theoretical and practical difficulties. Until recently the usual method was to measure the plasma volume by dye dilution and to deduce the red-cell mass from the haematocrit. Radioactive tagged protein fractions of normal plasma can now be used. The plasma volume, however, is not a constant quantity, because water passes in and out of the capillaries in various states of body activity. The same applies to some extent to any substance used as a marker. Moreover, the venous haematocrit is not an accurate measure of the proportion of cells to fluid in the vascular system as a whole. The ratio of cells to fluid is different in arteries, capillaries, and veins, where the rate of flow is different, and the distribution in these compartments will also vary with differing states of body activity. It is, however, now possible to measure the red-cell mass directly by tagging cells with radioactive iron, phosphorus, or chromium. These measurements are simple and fairly accurate, and so the plasma volume is best deduced from the red-cell mass and haematocrit, using appropriate correction factors.

These observations may be sufficient to show why there is no wide and accurate knowledge of blood-volume changes in polycythaemia. It is generally thought that the plasma

volume tends to be unchanged or even to be diminished as the red-cell mass increases until high haematocrit levels ($55\% \pm$) are reached (Mollison, 1951). Our limited observations show that this is usually true, though patients with high haematocrit levels (over 75%) may also have a low or normal plasma volume. Measures of the red-red concentration, by haematocrit or haemoglobin estimations, are therefore usually proportional to the red-cell mass, but this is not always the case. One of our patients has a greatly increased plasma volume, so that he is plethoric though not polycythaemic as ordinarily defined.

We have found that the chromium method is simple to use and consistent in its results, and we are now defining normality in this way. Patients with normal concentration may still retain a plethoric appearance of the face, eyes, and especially of the palms. This does not indicate a raised total blood volume, but is due to an irreversible dilatation of the skin venules.

Diagnosis

The long time that elapsed before some of our cases were diagnosed suggests that polycythaemia is not always readily detected—which is probably due to its rarity or to unfamiliarity with the symptoms.

Once polycythaemia has been recognized there appears to be little difficulty in distinguishing cases that are secondary to heart or lung disease. Doubts may exist where there is emphysema and no splenomegaly, but they are usually settled by the state of the bone marrow. A mistake was made in a man who had gout, nephritis, and multiple arterial abnormalities. Despite his normal marrow he was eventually treated with P^{32} 3 mC and venesection, which threw him into right heart failure. Cardiac catheterization showed that he had a persistent ductus with flow reversed owing to pulmonary hypertension.

Cases are not accepted for treatment unless they are actually polycythaemic when seen. In some cases the only evidence presented has been a raised red-cell count, which is fallacious. It is also just possible that long remissions may occur naturally or with conventional treatment—one man, a roving Irish labourer, had been treated for 13 years at six different hospitals with venesections and phenylhydrazine, but was quite normal for the year and a half that we observed him. Two other patients who undoubtedly had a marrow dysplasia were diagnosed for many years as cases of polycythaemia, which they may well have had; but they had none with us, and one became leukaemic and the other is probably developing myelofibrosis.

Course and Prognosis

The natural history of polycythaemia is probably not completely known. The disease is not common, its course is very long, and the sufferers have not previously been collected into special clinics. It is usually regarded as a disease of older persons that remains with them till they die or are killed by a stroke, which is the natural termination of the disease. This is true of most cases, but exceptions are common enough to deserve mention. The early age at which it may occur has been noted. The other exceptions are those that develop leukaemia or myelofibrosis.

Transition into myeloid leukaemia is not uncommon; the change from leukaemia to polycythaemia is rare but has occurred in our series. Others become anaemic owing to replacement of the bone marrow with reticulum cells or fibroblasts. Anaemia may also be due to haemolysis, which can be stopped by splenectomy as in leukaemia and lymphadenoma. In some cases the erythropoietic tissue is not confined to the bone marrow, but is found in the liver and spleen, and may even form sizable discrete tumours elsewhere which erode bone. The production of polymorphs and platelets is usually both increased and abnormal, and in

some the platelet level is so high that the diagnosis of essential thrombocythaemia might have been made with equal justification.

Observations of this sort have made it impossible to maintain concepts of polycythaemia, leukaemia, myelofibrosis, and so on as separate diseases, though the terms are retained for convenience. The present tendency is to regard them as possible manifestations or phases of a neoplastic disease that affects primitive mesenchyme cells. Although polycythaemia may be but a phase, it is clearly one that is both stable and benign, so that once patients enter into it they are likely to remain in it for the rest of their lives.

These considerations have some bearing on treatment, especially with radiation. Radiation can play a part in the causation of both leukaemia and marrow aplasia. Can it be held responsible for the leukaemia and myelosclerotic terminations of polycythaemia? Leukaemia is known to supervene without radiation therapy, and it has been estimated that its frequency is no greater after P^{32} (Lawrence *et al.*, 1953; Stroebel, 1954). One of our cases became leukaemic, and another is probably going that way. The evidence for myelosclerosis is less certain because of its rarity. But cases certainly occurred before the advent of P^{32} , and the replacement of erythroid tissue by reticulum and fibrous tissue, such as occurs with myelosclerosis, has not been seen after radiation aplasia. One of our cases developed myelosclerosis and another probably did.

Another point is that though P^{32} is indicated in the polycythaemic phase it may be harmful in another. Leukaemia usually develops quite suddenly, and there is no difficulty in detecting its onset. In contrast, the patients who are developing myelosclerosis appear at first to be in a satisfactory remission lasting a year or so. Eventually the blood count sinks below normal and they die despite transfusions. We have been somewhat uneasy about five of our patients whose remissions have lasted more than two years. But two with the longest remissions, over three and over four years each, have now become polycythaemic again. It appears that a fall below the normal haemoglobin is the ominous feature, not the length of remission.

Effect of Treatment

The objects of treatment are to prevent disastrous vascular accidents in the central nervous system and to relieve the patient of annoying symptoms.

Our own observations are not sufficient to prove that major thromboses have been prevented, though none has occurred since treatment. Stroebel (1954) has shown from a ten-year study of 241 cases that the expectation of life is increased with treatment. Most symptoms are completely relieved when the blood count is controlled. This applies particularly to ulceration and sepsis of the toes, haemorrhagic phenomena, the various "congested" feelings, and splenic pain and enlargement. Pruritus has sometimes proved resistant. Dyspepsia has seemed to be improved, except where ulcers were present. In general all patients are better and most are symptomatically normal. Those who have had other forms of treatment are quite certain that P^{32} is both more effective and much more convenient despite the occasional admission to hospital that is required.

Most symptoms that are continuous, such as facial congestion, headache, dyspnoea, ulceration, and gangrene, are clearly due to the increased blood volume, since they are immediately relieved by an exchange venesection. Pruritus is diminished, but seldom completely, and tends to persist in the palms, especially after a hot bath. It is probably caused in part by the irreversible dilatation of the skin venules. We can draw no conclusions about haemorrhagic episodes, thromboses, and dyspepsia because they are too inconstant. The spleen diminishes slowly only when the P^{32} has had time to act. It became impalpable in 10 of the 27 cases in which it was enlarged.

Commentary on Cases

Group I: Observed for More than One Year.—(A) *Successfully treated* (29 cases). Of these, 17 have had more than one treatment. The average length of remission was nearly two years. The longest was four and a half years and the shortest nine months. Of the 12 cases which have had only one treatment the longest remission is three and a half years. (B) *Inadequately treated* (5 cases). Two of these were young men with severe and resistant polycythaemia. One has received 36 mC of P^{32} in four years and the other 17 mC in four and a half years. Possibly this dosage was unnecessarily cautious. Two were elderly women who had difficulty in attending regularly. The last was a man of 49 in whom remissions have been short and incomplete for over three years. Although his haemoglobin is now normal he still has a large spleen and a raised blood volume.

Group II: Observed for Less than One Year (7 cases).—These cases look like doing well, though it is too soon to be certain.

Group III: Dead (4 cases).—(1) Female aged 63 with over 10 years' history. Between 1949 and 1953 she was given 20 mC of P^{32} in three episodes with good remissions. After the last she gradually became anaemic and died from acute myeloid leukaemia. (2) Male aged 42. Severe polycythaemia was treated with 13 mC of P^{32} . A year later the patient became anaemic and died, according to reports, from

myelosclerosis. (3) Male aged 66. Admitted to hospital with a cerebral thrombosis in 1947. Severe polycythaemia was diagnosed and he was treated by bath irradiation to the trunk (4.2 m.g.r.). In 1948 he was given 4 mC of P^{32} with no effect, and he died elsewhere four years later with polycythaemia. (4) Male aged 77. Diagnosed 1948. Given 7 mC of P^{32} in 1950. Remission for two years was followed by anaemia due to myelofibrosis and haemolysis, of which he died six months later.

Group IV: Insufficiently Followed Up (3 cases).—These patients attended too irregularly for any conclusion to be drawn about the effect of treatment.

Summary

A group of 48 patients treated with radioactive phosphorus is described. In severe cases the blood concentration was brought to normal by a massive venesection and simultaneous infusion of plasma substitute.

The presenting symptoms and general course of the disease are reviewed. Observation over a period of up to six years shows that the blood concentration can be kept at or near normal in most cases. When this is done symptoms are relieved. Relief may last from just under one year to over four years, with an average of just under two.

The haemoglobin chart of four illustrative cases. P means the injection of radiophosphorus and the figure in brackets is the dose in millicuries. V means a venesection; the figure is the amount in litres removed, a smaller amount of dextran being replaced.

Case I.—Good control. A woman now aged 68. She is sensitive to small doses of P^{32} (5 and 4 mC). Note that the fall to normal is quicker with venesection and P^{32} than with P^{32} alone. She was out of control in the winter of 1952-3. This is the only case in which the haemoglobin level fell below 100%.

Case II.—Bad control. A man now aged 38. Note the absence of visible effect of 9 mC of P^{32} in 1950. Haemoglobin brought to normal in 1951 by a large venesection, but continues to range around 130% despite subsequent treatments. Total dose of P^{32} was 36 mC and probably should have been more. Nevertheless he is much better for treatment.

Case III.—Good control. A woman now aged 70. Remission of over four years after 8.4 mC of P^{32} , which is the longest we have seen. Note that the haemoglobin did not fall below normal despite the long effect of P^{32} .

Case IV.—Good control. Man now aged 73. A very severe case, but easily treated. The haemoglobin has been kept normal for nearly six years. Note the sudden relapses in 1951 and 1953. The slow rise of haemoglobin in 1954 is of a different type. The small dose of P^{32} in 1950 was possibly unnecessary.

This treatment is quite the most effective and is the least disturbing to the patient.

We would like to thank Professor D. W. Smithers, of the Radiotherapy Department, and Professor W. V. Mayneord, of the Physics Department, and members of their staffs, for making this work possible. We are also grateful to numerous colleagues in this and other hospitals for referring cases to us, and in particular to Dr. P. E. T. Hancock. The earlier cases in the series were treated by Dr. R. J. Walton, to whom we acknowledge our debt.

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PROTHROMBIN AND THE ONE-STAGE PROTHROMBIN TIME*

BY

ARMAND J. QUICK, Ph.D., M.D.

AND

CLARA V. HUSSEY, M.S.

(From the Department of Biochemistry, Marquette
University School of Medicine, Milwaukee,
Wisconsin)

The discovery that the prolonged prothrombin time of stored human plasma was caused by the disappearance of a clotting factor, hitherto unrecognized (Quick, 1943), made it clear that prothrombin activity depended on more than prothrombin itself and that the one-stage procedure could no longer be regarded unequivocally as a specific test for this constituent. When it was subsequently established that the plasma contained a second prothrombin accessory factor (Alexander *et al.*, 1952), the need for a reinterpretation of the test was further emphasized. It is the purpose of this paper to present pertinent experimental and clinical observations that should be helpful for the re-evaluation of the test, and for furnishing at least a partial answer to several basic questions concerning the prothrombin time.

Methods and Materials

Since the purpose of this study is a critical evaluation of the one-stage prothrombin time, it is necessary to limit discussion to results obtained by the original rigidly standardized method (Quick, 1938). Of particular importance is the source and preparation of the thromboplastic reagent. Rabbit brain carefully cleared of blood and blood vessels and dehydrated with acetone not only has a high and constant activity but is devoid of both stable and labile factors.

In this study blood was collected with a silicone-coated syringe and needle and kept in test-tubes similarly coated. All clotting tests were carried out in uncoated glass test-tubes at 37° C. unless otherwise stated.

Tricalcium-phosphate-treated Plasma.—By means of this adsorbent, prothrombin and stable factor are quantitatively removed, while labile factor and fibrinogen remain unaltered. Since rabbit plasma is exceedingly high in labile factor, it serves as a good source for this agent as well as for fibrinogen. The preparation of the tricalcium phosphate

reagent and the procedure for deprothrombinizing plasma have been described in detail (Quick, 1951). Plasma treated with tricalcium phosphate is designated as " $\text{Ca}_3(\text{PO}_4)_2$ plasma." Stable factor was prepared by the method of Duckert, Koller, and Matter (1953). In many experiments aged serum from normal blood served as the supply of this factor.

Serum Prothrombin Time.—The blood or plasma was clotted in a glass test-tube at 37° C., centrifuged 15 minutes after a solid clot had formed, and reincubated for an additional 45 minutes. The prothrombin time was carried out as follows: 0.1 ml. of fresh rabbit plasma deprothrombinized with $\text{Ca}_3(\text{PO}_4)_2$ was mixed with 0.1 ml. of 0.02 M CaCl_2 and 0.1 ml. of thromboplastin reagent (from rabbit brain). To this mixture 0.1 ml. of the serum was blown in and the clotting-time determined. In this procedure the deprothrombinized rabbit plasma supplies both fibrinogen and stable factor.

Three patients with true congenital hypoprothrombinaemia were available for this study. Two are brothers whose prothrombin times have remained 19 to 26 seconds for the past seven years. The third is a girl whose prothrombin time is 37 seconds. The patients have a normal concentration of labile factor and their prothrombin time is not shortened by stable factor. A patient with pure stable-factor deficiency was also utilized in this investigation. Her prothrombin time varies from 26 to 55 seconds, but is usually about 27 seconds. The addition of stable factor prepared according to Koller completely corrects the prothrombin time. A detailed study of these patients has recently been presented (Quick, Pisciotto, and Hussey, 1955).

For the sake of simplicity the terms "labile" and "stable" (factors) are employed. Labile factor may be considered to be synonymous with factor V or proaccelerin of Owren and ac-globulin of Seegers, while stable factor is probably the same as factor VII of Koller, proconvertin of Owren, S.P.C.A. of Alexander, stable prothrombin conversion factor of Owen, and co-thromboplastin of Mann.

Why is the Prothrombin Time Constant in Fresh Normal Plasma?

Few values of blood are as constant as the prothrombin time. It is consistently 12 seconds in normal subjects, in contrast to the wide variations of prothrombin concentration as measured by the two-stage method, which, according to Mann and his associates (1948), may vary from 244 to 452 units. While it is established that three agents—namely, prothrombin, and stable and labile factors—affect the prothrombin time, it remains to be determined which of these is specifically responsible for the 12-second value of normal blood. A rather convincing answer can be found from the results of Table I. It is to be noted that an excess of neither

TABLE I.—Effect on Prothrombin Time of Adding Excess Labile and Stable Factors to Normal Plasma and Plasma Deficient in These Accessory Agents

	Prothrombin Time (Seconds)		
	Original	With Excess	
		Labile Factor*	Stable Factor†
Normal plasma	12	12	11½
Stored plasma (labile factor deficient)‡	16	12	16
Plasma deficient in prothrombin	21	21	21
Plasma deficient in stable factor	39	40	12

* To 0.1 ml. of plasma, 0.01 ml. of rabbit plasma deprothrombinized with $\text{Ca}_3(\text{PO}_4)_2$ was added.

† To 0.1 ml. of plasma, 0.01 ml. of aged serum prepared from normal blood was added.

‡ Stored in a silicone-coated test-tube for 24 hours at 4° C.

labile nor stable factor significantly shortens the prothrombin time of fresh normal plasma. After storage in a silicone-treated container for 24 hours, the prothrombin time is increased to 16 seconds. The addition of excess

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