Section of Therapeutics and Pharmacology

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**DISCUSSION ON VITAMINS AND HÆMORRHAGIC STATES**

Dr. Harold Scarborough: The literature dealing with the relation of the various vitamins to the different parts of the haemostasis mechanism of the body is confusing, not to say contradictory. This unsatisfactory state of affairs is due to the injudicious selection of experimental material and to infrequent examination of the material selected. In order that future results shall be acceptable the following point should constantly be in the minds of those investigating these difficult and important problems: that “chronic” rather than “acute” forms of disorder be selected for investigation; and that “idiopathic” and not “symptomatic” cases be studied; that cases should be under close observation for at least fourteen days (preferably longer) before the effect of any therapeutic procedure is examined; and that all cases should give a history of excessive or abnormal bleeding extending over at least eight weeks, preferably longer; that female cases be excluded; and that observations should be made frequently since alterations of the various functions investigated sometimes occur with great rapidity and may be temporary.

The number of cases in any one centre suitable for investigation by these criteria is not large and my suggestion, therefore, is that comparatively little is likely to be achieved except by concentrated and, especially, co-ordinated attack.

**Vitamin D.** The first known report of fatal bleeding in association with jaundice was apparently made by Wedels in 1683, since when it has been increasingly recognized that a proportion of jaundiced patients exhibit a latent haemorrhagic tendency, which is liable to become manifest especially after operation. The observations on the relation of vitamin D to this condition which were originally made by Ivy and his associates (1935), and which have been confirmed by Boys (1937) and also by Johnston (1937) stand in danger of being swept away in the space of literature on vitamin K.

Ivy developed a new technique for the determination of the bleeding time, the essential point of which is that a venous occlusion of 40 mm. Hg is applied through the cuff of a sphygmomanometer before the test is made. This manoeuvre has certain consequences, viz. it may cause the bleeding time to be prolonged when the more usual technique (Duke) gives normal values, and, as a result, it becomes possible to demonstrate that vitamin D can reduce the bleeding time in patients with jaundice and certain other conditions. It is plain that a number of things may happen following the venous occlusion. One can imagine, for example, the increased intracapillary pressure exerting a greater tension on any clots that may be formed in the ruptured capillaries, a tension sufficient, if the clots be abnormally fragile, to force them from the capillaries and so prolong the bleeding time. On this basis vitamin D might be supposed to influence directly, or indirectly, the mechanism of clot formation. However, this explanation, which is evidently favoured by Ivy himself, raises the whole problem of the relative importance of the various factors taking part in the arrest of hemorrhage from a small injury—a problem which itself awaits a complete answer.

One may recall in this connexion that Macfarlane (1941) has described structural and functional abnormalities in the capillaries in certain of the bleeding diseases, and I have frequently observed that venous occlusion may exert a profound effect on capillary resistance. There thus arises the attractive possibility that vitamin D may be concerned with the functional activity of the capillary walls.

Apart altogether from such considerations vitamin D is capable, in certain circumstances, of increasing the serum Ca, although the mechanism by which this increase is brought about and the fraction or fractions of the serum Ca which are so increased, are still undecided. A part of the serum Ca—and it is not at present clear which part—fulfils an indispensable function in blood coagulation and it may be on this basis that the phenomenon mentioned is to be explained. It is generally held that the non-diffusible Ca fraction consists of Ca bound to protein but it has been suggested (Watchorn and McCance, 1932) that it is to phospholipoid rather than to protein that the Ca is bound and there is experimental support for this view. Since there is evidence that vitamin D can alter the proportion of non-diffusible Ca in serum, then vitamin D might be supposed to influence the amount of Ca bound to phospholipoid. These points may then be considered in the light of the observations of Ferguson (1936, 1937) who believes that
thrombin is a "definite calcium-phospholipoid-prothrombin complex". On the experimental side it has been shown by a number of workers that irradiated ergosterol can shorten the clotting time in rats.

As in certain cases of jaundice, so in thrombocytopenic purpura, the bleeding time is usually prolonged. It is stimulating, therefore, in this connexion to recall the two cases of thrombocytopenic purpura reported by Lowenburg and Ginsburg (1936) to have been cured by means of a parathormone hypercalcæmia. A single similar case has also been reported by Levine and Michelson (1940).

Possibly these observations may be related to the fact reported on at least two occasions that the symptoms of parathyroid tetany are relieved by massive haemorrhage, following which the serum Ca increases (Cruickshank, 1923, Swingle and Wenner, 1925). It is not at present clear how these various points are related.

**Vitamin C.**—Ascorbic acid immediately controls the haemorrhagic manifestations of scurvy which, it may be noted, have been related to certain pathological changes in and around the smaller blood-vessels originally described by Wolbach and Howe (1926). Thrombocytopenic purpura is also characterized by a tendency to bleed and in this condition there is an associated capillary abnormality—a low capillary resistance. It seems not entirely unreasonable, therefore, by analogy to suppose that ascorbic acid might benefit this condition also. Vaughan, in 1937, came to the conclusion that the chances of favourably influencing the course of thrombocytopenic purpura by means of ascorbic acid was about 33%.

Excluding the 21 cases referred to by Vaughan, we have been able to find 10 reports in the literature, 6 being unfavourable and 4 favourable. Further investigation would, therefore, seem to be justified. I have recently had the opportunity of treating 7 cases of thrombocytopenic purpura with massive doses of ascorbic acid without any demonstrable effect on the bleeding time, the thrombocyte count, or the capillary resistance.

It is widely held that a low capillary resistance is found in scurvy and that this is controlled by ascorbic acid. Determinations of the capillary resistance have been, and indeed are, used as a test for so-called sub-clinical scurvy. There is, however, an increasing body of evidence to suggest that the practice is unjustifiable. I have never found ascorbic acid to be capable of increasing capillary resistance except in very special circumstances. It is true that a low capillary resistance is frequently found in scurvy but it does not, therefore, follow that the lowness of capillary resistance is necessarily due to ascorbic acid lack. Scurvy, as met with to-day, is a complex deficiency state. It is also true, on the other hand, that the capillary resistance in scurvy may be found to be high. This is due to the fact that following the extravascular suffusion of blood into the tissues the capillary resistance becomes temporarily markedly increased (Scarborough, 1941a). Thus, if the test be performed shortly after bleeding into the tissues has occurred, a high capillary resistance will be found; if the capillary resistance be determined either before, or at some time after a hemorrhage has developed, then a low result may be found.

**Vitamin P.**—The presence of this vitamin, whose very existence is still regarded by many as resting on the most tenuous evidence, was first announced by Szent-Györgyi and his associates (1936) as the result of observations on certain cases of purpura which were not benefited by administration of ascorbic acid. Although my observations require further independent support, I personally regard it as established that there is a substance or substances present in fruits, their juices and in certain extracts made therefrom which is capable in man of increasing the resistance of capillary walls to the application of pressure (Scarborough, 1939). The substance is not ascorbic acid but, so far as I know, no satisfactory proof exists that it is a flavanone although statements have been made to this effect. Animal experiments have as yet produced no collateral evidence though there is reason to suppose that this may be forthcoming shortly. In two subjects, by means of experimental feeding, evidence has been obtained that a clinical syndrome may be produced as a result of a specific deficiency of vitamin P in man. The major feature of this syndrome is petechial bleeding and an exhaustive haematological investigation of both cases at the time bleeding occurred revealed a remarkably low capillary resistance and a slightly prolonged bleeding time (Scarborough, 1940). These findings also require independent confirmation. It is well known, and I have repeatedly observed, that certain of the bleeding diseases are associated with a low capillary resistance. If it could be shown, therefore, that the development of purpura were dependent in whole or in part on an excessive fragility of the capillary walls, then the administration of a substance capable of controlling this function, viz. vitamin P, might be expected to be of value in their treatment. It has been found difficult to obtain convincing evidence on these points, but the following two cases are suggestive:

**CASE I.**—A female, aged 76, had for some years noted a tendency to bruise very easily and had for two years prior to her admission to hospital, been troubled with intermittent epistaxis. During the last nine months petechiae had frequently appeared,
especially in the arms. There had been no previous or family history of hæmorrhagic disease and the dietary history was not significant. On examination the patient was a fairly well-nourished, healthy woman. Nothing abnormal was detected on examination of the cardiovascular system. The blood-pressure was 140/80. Renal function was satisfactory. Hæmatological examination revealed no cause for the hæmorrhagic tendency. The capillary resistance was found to be low.

A diagnosis of vascular purpura (purpura senilis) was made.

Fig. 1 (Case I) is a record of the capillary resistance of the patient determined in three separate areas of skin by a method I have already outlined (Scarborough, 1941b). The development of petechial bleeding is indicated at the bottom of the chart. The capillary resistance remained low during the preliminary period of twenty-six days, during which time a hæmorrhagic tendency was manifest. Administration of a preparation containing vitamin P coincided with an elevation of the capillary resistance and an absence of the manifest bleeding tendency in spite of the fact that the patient was allowed to get up during this period. With the cessation of vitamin P therapy the capillary resistance fell to its original level and the hæmorrhagic tendency returned.

Case II.—A female, aged 65, for about ten years had complained of a marked tendency to bruising but of no other symptom. There were invariably one or more bruises on each arm and usually several on the legs. Ecchymoses could be readily induced by the "pinch" test. She had never complained of purpura but, on close examination on several occasions before the investigation began, petechiae were noted in both upper and lower limbs. There was no previous or family history of bleeding and the dietary history appeared to be satisfactory. Nothing abnormal was detected during examination of the cardiovascular system. The blood-pressure was 135/64. Renal function was not impaired. Hæmatological examination revealed no cause for the bleeding tendency. The capillary resistance was low. A diagnosis of vascular purpura (purpura senilis) was made.

Table I.—Capillary Resistance. Mm.Hg. Negative Pressure.

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<th>Area</th>
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<td>V</td>
<td>200</td>
<td>450</td>
<td>350</td>
<td>400</td>
<td>200</td>
<td>225</td>
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Bruising

PERMIDIN
3 × 0.25 g.p.d. by mouth for 46 days.

PERMIDIN
3 × 0.25 g.p.d. by mouth for 29 days.
Table I (Case II) summarizes the progress of the case. Capillary resistance was initially low and associated with a tendency to bruise. A similar condition was again present at the end of the investigation which covered a period of seven months. During the periods indicated, a vitamin P preparation (Permidin) was administered. This apparently had the effect of increasing the capillary resistance and of controlling completely the bleeding tendency.

These two cases are merely suggestive and even when taken together certainly do not constitute proof of the value of vitamin P in the treatment of purpura. The present position is, I think, that vitamin P does exist but that it cannot at present be regarded as a potent therapeutic agent in any one of the bleeding diseases: indeed, I would go so far as to say that preparations of vitamin P should not be used for this purpose outside experimental centres. The clinical worker must await the labours of the chemist for the isolation or identification of the materials in fruit juices which possess capillary-resistance-increasing activity. It is, after all, illogical to make statements about the ineffectiveness, or otherwise, of vitamin P in the treatment of various forms of purpura until: (a) We know what vitamin P is; (b) we have preparations of it suitable for administration; and (c) we test their effect on selected cases.

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VITAMIN K, AND THE ESTIMATION OF PROTHROMBIN

DR. R. G. MACFARLANE: The discovery of vitamin K, and the recognition and treatment of conditions in which it is deficient, mark one of the greatest advances in the field of the hemorrhagic states.

Several naturally occurring derivatives of 1: 4-naphthaquinone have vitamin K activity. Vitamin K occurs in many plants and vegetables, particularly alfalfa, spinach and cabbage. A slightly less active analogue, vitamin K occurs in putrefying fish meal presumably as a result of bacterial synthesis. The substance now known as vitamin K was isolated in 1933 by Anderson and Newman from tuberculosis bacilli, though at that time they were unaware of its activity as a vitamin, and named it phthiocol.

Apart from these, some thirty synthetic compounds with similar activity have been reported. The majority are also derivatives of 1: 4-naphthaquinone, of which the 2 methyl-derivative known as vitamin K is the most familiar. The activity of the various synthetic derivatives is greatly influenced by apparently minor alterations in structure.

Vitamin K deficiency in man may be due to deficient diet, absorption, or utilization. Simple dietary deficiency is rare, although a few probable instances have been reported (Kark and Lozner, 1939; Scarborough, 1940). Vitamin K is found in large amounts in the feces, where it is probably derived from bacterial synthesis, and this intrinsic source may well reduce the incidence of clinical manifestations that might otherwise result from deficient intake. Hemorrhagic disease of the newborn has been shown by many workers to respond to treatment with vitamin K, and it has been suggested that there is normally a deficiency of the vitamin during the first few days of life, conditioned by deficient intake and the absence of bacteria from the intestinal tract (Quick and Grossman, 1939). Such
a deficiency accentuated by other factors is probably responsible for the disease. Deficient absorption of the vitamin is a more frequent abnormality and may be due to absence of the bile salts following obstructive jaundice, or to intestinal defects resulting in general malabsorption, such as sprue, steatorrhea, gastro-intestinal fistula, and short-circuiting operations. Deficient utilization is said to follow liver damage and to be unresponsive to treatment. It has even been suggested that the response to vitamin K is an index of liver function as reliable as the excretion of hippuric acid (Wilson, 1939). Recent work, however, suggests that there is actually little correlation between liver damage, evidence of vitamin K deficiency and response to treatment (Lucia and Aggeler, 1941).

The result of extreme vitamin K deficiency in man and in animals is the development of a hemorrhagic diathesis, which responds, except in some cases of liver damage, to adequate treatment with the vitamin. The type of bleeding that occurs is illustrated by hemorrhagic jaundice, and hemorrhagic disease of the newborn. There is a liability to bleed persistently from injuries, from the gastro-intestinal tract, or into the tissues. Coagulation of the blood is delayed, the bleeding time is sometimes prolonged in jaundice and almost invariably prolonged in hemorrhagic disease of the newborn, the platelets and capillary resistance are apparently normal. It is now almost universally accepted that these manifestations are due to a reduction in the amount of plasma prothrombin, in turn dependent on the deficiency of vitamin K. While there can be no doubt that the coagulation of the blood is impaired in these conditions, it is difficult to explain all the manifestations on this basis alone. The prolonged bleeding time is an example. It has been repeatedly shown that the bleeding time is not influenced by coagulation of the blood and I maintain that it is an index of capillary contractility (Macfarlane, 1941). The same remarks apply to the "needle puncture haematoma" regarded by Kark and Souter (1941) as characteristic of hypoprothrombinæmia, and which do not occur in other conditions with defective coagulation, such as hemophilia. Macpherson (1941) has shown that the prolonged bleeding time in hemorrhagic disease of the newborn becomes normal following treatment with vitamin K, suggesting that a capillary defect may accompany the vitamin deficiency.

If the existence of a coagulation defect is established beyond doubt in these conditions, the nature of this defect is not quite so obvious, and it is necessary to examine the methods which claim to estimate prothrombin before the significance of their results can be assessed. These methods fall into two main groups, those using the single stage as introduced by Quick (1935) and modified by a large number of subsequent workers, and the two-stage methods. The latter as devised by Warner, Brinkhous and Smith (1934), and particularly the modification by Herbert (1940) avoid many of the fallacies of the single-stage group, but are so elaborate and introduce so many pitfalls of their own that they are not yet available for the ordinary laboratory practice.

Quick's test, or some modification, has been widely used in the detection of hypoprothrombinæmia, and the assay of human responses to vitamin therapy. The procedure depends upon the dogma that "in the presence of an excess of thromboplastin and a sufficient amount of calcium, the coagulation time of blood or plasma is proportional to the amount of prothrombin it contains". Details of the remaining part of the procedure do not seem to matter so much. The test can be done on whole blood (Ziffren et al., 1939), oxalated blood (Innes and Davidson, 1941), oxalated plasma (Quick, 1935). If recalcification is carried out it can be done with a fixed amount of calcium (Quick, 1935) or a variable optimum amount (Pohle and Stewart, 1939). The term thromboplastin has included rabbit brain, fresh, heated, dried or extracted with acetone; human brain (Owen and Toohey, 1941); dog, horse or ox lung, Russell's viper venom (Fullerton, 1940) or Russell's viper venom and lecithin (Hobson and Witts, 1941). The normal coagulation time by these different methods varies from about 7-35 secs. and it would be proportional to varying prothrombin concentration only if certain assumptions are correct. Some of these are as follows, beginning with the fibrin end of the clotting process:

1. It is assumed that a given amount of thrombin will necessarily clot different samples of blood or plasma in the same time. This may not be the case. Thrombin is rapidly destroyed in normal blood and variations in this antithrombic activity will alter the coagulation time. Moreover, quite large differences in the reactivity of fibrinogen to thrombin have been observed (personal observation, Herbert, 1941) and variations in fibrinogen concentration may be large and will alter the speed of the reaction.

2. It is assumed that the rate of thrombin production and hence the coagulation time depends only upon the concentration of prothrombin in the presence of excess of thromboplastin. This is not the case. The rate of production of thrombin depends also on the reactivity of the prothrombin to the particular thromboplastin used, on calcium and electrolyte concentration, pH, and many other factors often not controlled. The time relations between activation and coagulation are also involved. If we accept Warner,
Brinkhous and Smith's definition of a unit of thrombin as that amount which will clot 1 c.c. of standard fibrinogen solution in fifteen seconds, then normal plasma will produce about 300 units per c.c. Coagulation may occur within a few seconds of the production of a small fraction of the available thrombin, and further thrombin production goes on for several hours after coagulation is complete (Warner et al., 1936). In other words, when Quick's test is all over, anything up to 95% of the prothrombin that was to be estimated remains unconverted. The practical importance of this relationship is that the test is sensitive to slight changes in reactivity of the prothrombin but relatively insensitive to changes in prothrombin concentration. This is illustrated by Quick's own curve (1938) which demonstrates little change in coagulation time between 100% and 40% prothrombin concentration.

(3) It is assumed that equal amounts of any one of the thromboplastic agents already mentioned will clot different samples of blood or plasma in the same time if the prothrombin concentrations are equal. This assumption leads us into very deep water, because so little is known about thromboplastin. The generally accepted view is that thromboplastin is a lipoid substance present in platelets and body tissues, and the older view that thromboplastin was an enzyme—the thrombokinase of Morawitz—has been discounted (Mertz et al., 1939). It has seemed to me for some time, however, that both views might be correct. and that what is known as thromboplastin is in fact two separate substances, one being a water-soluble enzyme, and the other a lipoid substance that is either catalyst or substrate.

In support of this view there is the analogy of the action of Russell's viper venom. The venom is a water-soluble enzyme-like substance, which behaves as an extremely powerful thrombokinase. Trevan and I found that its action could be greatly accelerated by the addition of tissue suspensions, fat fractions, or by crude lecithin (1936). Moreover, we have been able to show that if plasma is defatted by spinning at 25,000 revolutions per minute or by extraction with solvents, Russell's viper venom is incapable of clotting it unless lecithin or tissue fat is added (Macfarlane, Trevan and Attwood, 1941). We have not been able to show as yet that substances analogous to the venom and lecithin are actually required for normal coagulation, but there is some indirect evidence in support of this view. For instance, saliva contains a thrombokinase-like enzyme, and since the venom is a modified saliva, it is not unreasonable to suppose that the action of one may be merely a greatly exaggerated form of the other. Defatted saliva, like venom will not clot defatted plasma until the fat fraction is supplied. A major difference is in the effect of lecithin which will actively potentiate venom but has no effect on ordinary coagulation. Lecithin has, however, occasionally brought about the coagulation of defatted plasma, suggesting that it can activate the normal enzyme in the absence of the normal lipoid.

The provisional hypothesis, therefore, is as follows. Fresh tissues contain a venom-like enzyme, and a lipoid factor. The two factors together constitute what is known as thromboplastin and each is inactive separately. Plasma also contains both factors, the enzyme being in relative excess. Ordinary coagulation is the result of the reaction between these two factors and prothrombin in the presence of calcium. The addition of tissue extracts accelerates the normal reaction, because it increases the concentration of available lipoid. Russell's viper venom and lecithin represent the addition of both factors and result in the most rapid coagulation yet observed.

If this view of thromboplastin is correct, it will be seen that, in the estimation of prothrombin, no attempt to keep the enzyme factor constant is made, except in the methods using venom. Venom alone is liable to give variable results as it is greatly affected by small variations in available lipoid as shown by Crosbie and Scarborough (1941). The addition of a relatively large constant amount of lecithin as used by Hobson and Witts should control this variable.

Whether this view of the composition of thromboplastin is correct or not the procedures in use in the single-stage method are open to many objections. No account is taken of varying antithromboplastic activity either in the blood under test or in the thrombo-

plastin itself. What is probably more important is that no allowance can be made for variations in the individual reactivity between prothrombin and thromboplastin, nor of the species specificity which has been shown by Trevan (unpublished) to be an important factor in the speed of the reaction, and which may vary from one sample of plasma to another.

There are many other theoretical objections to the single-stage method, but what is more significant is that there are serious discrepancies between the results obtained by the probably more reliable two-stage method and those obtained by the single-stage method. For instance, the incidence of hypoprothrombinemia in jaundice as determined by the two-stage method is nearly twice that as determined by Quick's method (Brink-
hous, 1940). By the two-stage method, dogs and men have approximately identical prothrombin values, but by the single-stage method man has only one-fifth of the normal dog value (Quick et al., 1935; Warner et al., 1939). In newborn babies, the two-stage method indicates that prothrombin is reduced to 14-40% of normal, but the single-stage method gives normal values (Brinkhous et al., 1937; Quick and Grossman, 1939).

The most striking anomaly has been provided by the use of the substances responsible for hemorrhagic sweet clover disease in animals, considered to be due to a prothrombin deficiency (Roderick, 1931; Quick, 1937). Link and his associates have discovered that the disease is the result of a toxic agent identified as 3; 3'-methylenbis (4-hydroxycoumarin). The effect of this substance on dogs was studied by Bingham and his co-workers (1941), who found that it produced in addition to hemorrhagic manifestations, liver destruction and changes in the capillaries. The protocols of their observations on the blood reveal the extraordinary fact that whereas the ordinary blood coagulation time was only a few minutes, the so-called prothrombin times on corresponding samples by Quick's method was many hours (Bingham et al., 1941, see Table I, p. 568). In other words, the thromboplastin added inhibited coagulation. Not the least remarkable point is that the authors themselves make no comment on this anomaly and apparently accept the delayed clotting times as an estimate of prothrombin.

Similar results have been obtained by Witts (1942) in the case of a man given the coumarin compound. Again there was inhibition of coagulation by dried rabbit brain since the "prothrombin time" was more than half an hour, as against four minutes if calcium alone were added. Fresh human brain slightly accelerates the clotting time, and if Russell's viper venom were added to the dried brain coagulation occurred in 13½ seconds. We were able to confirm these results.

It is quite clear that Quick's test has broken down completely where the coumarin compound is concerned. Any attempt to explain the results on the facts so far available would be pure speculation but I cannot resist the temptation. It may be that the inhibition by rabbit brain is an exaggeration of the species specificity, already mentioned. A more attractive but less probable explanation is that coumarin reduces the enzyme component of thromboplastin normally present in the plasma. While there remains enough to produce clotting in four minutes on the addition of calcium the addition of a great excess of lipid in the form of dried brain results in inhibition, a phenomenon frequently seen in precipitin and agglutinin reactions if one of the reactants is in great excess. Fresh brain, because it contains some enzyme, does not inhibit the reaction so markedly. Venom and brain produce rapid coagulation, because the venom supplies the required enzyme.

I have tried to show that Quick's test as usually performed may measure prothrombin, but certainly measures many other variables as well. Russell's viper venom and lecithin seem to be a more reliable source of thromboplastin than the various animal tissues, variously treated, that are so widely used. If Quick's test is to be used at all, and it is a simple and in many cases a valuable procedure, it should no longer be called the "prothrombin time" but rather the "accelerated clotting test" as suggested by Professor Witts.

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Lubahn, S. P., and Aggeler, P. M. (1941), Am. J. M. Sc., 201, 326.
Mr. A. L. Bacharach said that recent work had confirmed the claims of Zacho and of Ruszyná and Benko to have produced a lowered capillary resistance in guinea-pigs receiving a scorbutogenic diet together with large daily doses of pure ascorbic acid. This capillary fragility was prevented or reversed by the administration of certain concentrates from citrus fruits and other sources, including the black-currant and rose-hips. Highly purified hesperidin, one of Szent-Györgyi’s original sources of vitamin P activity, was also active, though less so than a more soluble product made from citrus peel by a modification of Szent-Györgyi’s published procedure for preparing “citrics”. The results so far obtained had been made the basis of a quantitative biological assay method, and it was hoped that this would help towards elucidating the distribution and chemical nature of vitamin P, and so indirectly its physiological role and therapeutic use.