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Rutin and its use in hemorrhage into the retina

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In Hemorrhage into the Retina

By

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The purpose of this paper is to outline the worthiness of the use of rutin in cases of hemorrhage into the retina due to hypertension and diabetes mellitus. It is an attempt to justify its use even though quantitative experimental data is lacking on the physiological reactions it exerts in the human. I wish also to point out the problems encountered and the current research work which may allow more complete evaluation of this drug. Furthermore, I wish to stress and make distinctions between the terms capillary fragility and permeability which will be encountered often in this study; i. e. the terms are in general too loosely interchanged. I believe it is best to state now that abnormality of capillary walls may be manifested in either or both of the following ways: 1- increased capillary fragility which means there is a weak portion in the capillary which may rupture to form a petechia from extravasation of blood cells into the tissues; and 2- increased capillary permeability which represents an increase of permeation of fluid from the capillary into inter-cellular spaces.

It may be of interest to the reader to review the history of rutin. Lebreton [28], in 1828, isolated the glucoside hesperidin in various citrus fruits. The flavone glucoside rutin

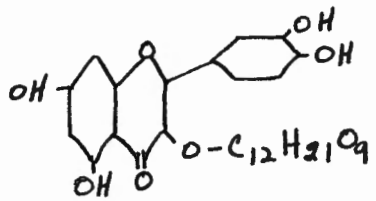
was isolated by Schunck [29] in 1860. Little interest was taken in these discoveries until in 1936 when Szert-Gyorgyi and associates [2] first postulated the existence of a substance called "vitamin P" (permeability vitamin). It was so named because an extract of lemon peel seemed to exert a specific capillary resistance effect in cases of idiopathic or non-thrombocytopenic purpura. This "vitamin P" extract also was soon to be known as "citrin." It was suggested that a deficiency of this substance was pesponsible for purpuric manifestations.

Subsequent chemical studies of the properties and composition of citrin have shown it to be an impure mixture of hesperidin, and eriodictyol, both of which are flavone glucosides [25]. It is of note that many related flavone glucosides occur naturally in plant life and are used abundantly at present date for dyes in silk, wool and cotton. A few of the more common ones are quercitrin, morin, myricetin, galangin, chrysin, apigenin, luteolin and campherol.

Mager [30] in 1942 isolated eriodictyol rhamnoside from citrin and Higby [26] from his studies in 1943 of the crude flavone preparations, concluded that the eriodictyol glucosides were not the source of vitamin P activity. Higby further found that pure hesperidin, pure limonin, or pure eriodictyol had no effect, but a substance isolated from crude orange hesperidin, identified as hesperidin methyl chalcone, was found to be active.

It was left to Couch [27] to note the similarity of structure of rutin to that of hesperidin.

Rutin is a rhamnoglucoside of the flavonol quercetin, having a chemical structure similar to quercitrin [31]; for as a flavonol glycoside it undergoes hydrolysis with acid to yield quercetin, dextrose, and rhamnose. Rutin is found in a variety of plants including tobacco, garden rue, forsythia, elder flowers, violets, buckwheat [3,4,5], and green asparagus [51]. Couch and associates obtained a yield of 2.98% from buckwheat plants 3 weeks old and it now serves as the principle source of supply. Its structural formula, established by Attree and Perkins [1] in 1927, is the following:



The first physiological activity observed of a limited few of such flavones as quercetrin, quercitrin, rutin, myricetrin, and myricitrin was noted by Akamatsu [32] in 1931. He observed an increased action of the frog heart with decreased pulse rate and increased minute volume after their administration. Later studies by Szert-Gyorgyi showed the administration of hesperidin to result in decreased capillary fragility but have no effect on capillary permeability, while rutin is believed to be an essential substance other than ascorbic acid in regulating both capillary fragility and permeability. Hence it was recognized

with increased frequency that vascular accidents, especially of arterioles and capillaries were not solely the result of simple elevation of blood pressure with mechanical rupture, or of destructive atheromatous charges, such as might lead to massive hemorrhage or dissection of the wall in larger vessels, but are due to some defect in the architecture of the vessel. These are similar to but not identical with the disorders seen in scurvy, occurring in many persons with normal blood pressure and bearing no relationship to the actual level of pressure in hypertensives. Specifically, Duke Elder [40] in his discussion of edema and hemorrhage into the retina states "in most cases the escape of fluid from the circulation is through the capillary walls, and since it is probable that these preserve their permeability to a great extent so long as the endothelial cells are healthy, the appearance of edema is usually an indication of capillary or tissue damage." He considers as an essential factor in this process, "an increased transference of fluid to the tissues when the capillary permeability is increased, as in toxic and inflammatory conditions, a process which, when accentuated, leads to the escape of albumin and fibrinogen which coagulates in the form of exudates, and eventually to the escape of formed elements of the blood as actual hemorrhage." He further states, "It would seem that the essence of retinal hemorrhage is probably capillary dysfunction rather than high blood pressure itself."

Observations in constitutional medicine had long noted a certain type of woman- usually blond, well nourished or obese, with skin of fine texture, good complexion- whose arms and legs were covered with numerous bruises and ecchymoses which resulted from the slightest injury or pressure. These were not due to scurvy, and were not relieved by enormous quantities of ascorbic acid, and appeared in patients without other ascertainable causes. This interesting history probably prompted Scarborough [33] to demonstrate first that in the human, lack of vitamin P leads to spontaneous hemorrhage, lassitude, and rheumatic pains. The condition rapidly responds to vitamin P, while ascorbic acid was without effect. Also in the guinea pig and rat [34] vitamin P deficiency produces a decreased capillary resistance.

In an attempt to resolve an explanation for the effect of the "vitamin" Parrot and Lavollay [35] have suggested that the "vitamin" acts indirectly by inhibiting the oxidation of some product of adrenalin metabolism. This as yet unidentified compound is said to maintain normal capillary resistance. This action is supposedly antagonized by histamine, which decreases capillary resistance. The normal capillary state i s believed to be a balance between these two factors. Chambers and Zweifach [36] have cast doubt on the theory that histamine normally influences capillary permeability. Injections of histamine locally or I.V., in doses sufficient to produce arteriolar dilatation, fail to increase capillary permeability.

Only when the concentration of histamine is sufficient to produce visible endothelial damage, does increased capillary permeability occur.

Further, there is evidence to suggest that hyaluronidase might replace histamine in the schema of Parrot and Lavollay. Duran-Reynals [37] has recently reviewed the experimental findings which indicate hyaluronidase increases capillary permeability. He believes that hyaluronidase in small amounts are normally present in most, if not all, tissues. Wislocki, Burting and Dempsey [38] have shown that arteries, arterioles, and veins contain a metachronic ground substance, probably chondroitin sulfate. Meyer and Ragan [39] have suggested that this substance which is subject of attack by hyaluronidase may be a constituent of capillary walls. In view of the foregoing, the possibility suggests itself that widely distributed hyaluronidase normally maintains tissue and capillary permeability, and its overfunction is prevented by vitamin P. Thus a deficiency in vitamin P would lead to excessive hyaluronidase activity which would weaken all ground substances including that present in capillary walls, and would consequently increase tissue as well as capillary permeability. Further support was given this theory by Levitan [22], who has demonstrated in the rat that rutin does inhibit the intradermal spread of hyaluronidase.

One of the chief difficulties in the study of physiological and pharmacological actions of rutin to produce specific effects

upon capillary properties, is the lack of satisfactory methods to demonstrate such effects. In reviewing the literature it is apparent that attempts to demonstrate an effect of rutin upon capillaries by experimental methods have met with but limited success. Recently, Ambrose and DeEds [10] demonstrated that large doses of rutin in the rabbit reduced the capillary permeability (or trypan blue diffusion) after local irritation of the skin with chloroform etc. Griffith and coworkers [9] reported that rutin hastened recovery from irradiation injuries to experimental animals. Wilson and coworkers [11, 12] claim a slight decrease in histamine toxicity in guinea pigs by pretreatment with rutin. Raiman et. al [13] reported that rutin greatly reduced the fatality rate due to anaphylactic schock in guinea pigs; however, Roth and Sheppard [14], and Levitan [23], found only slight if any, protective action of rutin against anaphylactic shock, and none against $L.D._{100}$ histamine. Richards [15, 20] concludes that sodium bisulfite ($NaHSO_3$) exerts a specific influence and effect upon the capillaries which permit epinephrine to enter the blood stream at an accelerated rate. This effect was found to be abolished by previous administration of rutin but the toxicity of epinephrine HCl was not effected by rutin. Also rutin decreased the toxicity of procaine HCl solutions with and without sodium bisulfite (in contrast metrazol toxicity was not effected [23]). The importance is that it permits the use of this " bisulfite phenomenon " and the decrease of the absorptive toxicity of certain drugs,

as a tool for further research on rutin or other drugs which have specific effects on the capillaries. This phenomenon even makes quantitative studies possible.

One of the greatest difficulties in the study of retinal hemorrhages is obtaining some test through one might predict their occurrance in any given disease. To this end, the capillary fragility test is clinically applied. The correct determination of capillary fragility is also essential in selection of patients for rutin therapy as will become apparent in future discussion. At the present time a modification of the Wright and Lilienfeld method, the Rumpel-Leede, and Gothlin technic are the most popular. For pupose of review, the Gothlin positive pressure test for measuring capillary fragility, the technic is as follows: A circular area, 6 cm. in diameter, is marked in each antecubital space. A standard blood pressure cuff is then placed on the arm and a pressure equivalent to 35 mm. mercury is maintained for 15 minutes. The blood pressure is lowered, and all the petechiae within the cicular area are counted, a good magnifying lens being used. The process is repeated on the other arm, a cuff pressure equivalent to 50 mm. mercury being employed for the same period. THe pressure is lowered, and the findings noted. To determine the petechial index, the number of petechiae in the first stage is multiplied by 2, and the number accumulated in the second stage is added. The normal index is 8 (or less); an increased value is 13 (or more), and a borderline (probably increased), 9 to 12.

Capillary fragility has been found to be elevated in a host of conditions. Cutter and Marquardt[6] stated their belief that all chronic diseases predispose to increased fragility, for example rheumatic heart disease, hypertensive cardiovascular disease, diabetes mellitus etc., while Diem[7] showed lowered resistance in minor infections and intoxications, polyarthritis, epidemic hepatitis, glomerulonephritis, hepatic cirrhosis, gastric and duodenal ulcers, scarlet fever, and multiple sclerosis. Other conditions reported with increased capillary fragility are pulmonary hemorrhage, heart block[8], irradiated tissues[17], frostbite[18], and toxic reactions to sulfadiazine, gold salts, and aspirin[8]. But most pertinent to us, Shanno and his associates[19], found that 75% of a series of 79 individuals who had hemorrhage into the retina associated with hypertension, diabetes or both, had increased capillary fragility or permeability.

Perhaps the most important comprehensive work relative to the use of rutin in hypertensives was that of Griffith and Lindauer[24]. This work may be summarized as follows. He observed an increased capillary fragility occuring in approximately 18% of 1600 hypertensives, which was irrespective of blood pressure levels, is accompanied by an incidence of cerebral or retinal hemorrhages and death, varying from 6 to 10 times that found in hypertensives of comparable levels showing normal fragility. This abnormal fragility can be restored

by rutin therapy in 75% of the cases, becomes borderline in 15%, becomes normal but relapses in 4% and remaines abnormal despite large doses in 6%. Furthermore he found that restoration of normal fragility is followed by a decrease in vascular complications to the approximate frequency encountered in hypertensives with a normal fragility, only to be followed by a return of greater incidence in relapse due to discontinuance of therapy or failure of treatment. Finally, he showed that thiocyanate therapy, extensively used for the control of hypertension, produces in a significantly large number of cases an increased capillary fragility. Thus predisposing the patient to the hazard of vascular complications that are more serious than the uncomplicated hypertension.

Rutin is conventionally administered in doses of 80 to 100 mg. daily (available in 20 and 60 mg. tablets). However, even 500 mg. may be administered in resistant cases over long periods of time without any evidence of untoward or toxic effects. And when apparent dosage has been established the tourniquet test should be done every 4 to 6 weeks to forestall any relapses due to possible increase in rutin requirements, bearing in mind that the result of the tourniquet test is not valid if done within 3 weeks of a previous test on the same arm..

In the studies of Soloff and Bello[41] concerning 50 hypertensives, only 66% showed positive Rumpel- Leede tests: More important is the fact that 3 of the 9 patients in this

group with retinal hemorrhages gave negative Rumpel- Leede reactions. Hence they concluded,"there is obviously no correlation between a positive reaction (Rumpel-Leede) and the presence of retinal hemorrhages, as over 80% of our hypertensive patients with positive Rumpel-Leede reactions had no retinal hemorrhages."

Since the onset and cure of diabetic retinopathy has remained unknown despite nearly a century of investigation, its treatment has been directed along many lines. Among these many things rutin has been and is advocated. However, throughout the voluminous literature on this subject it is remarkable that these patients with diabetes mellitus seem to be the most refractory to restoration of the capillary state to normal. The incidence of retinopathy in diabetes mellitus is closely correlated with the duration of the disease rather than with the age of the patient. In unselected average groups the incidence of retinopathy run from about 5 to 18%. While in contrast Wagener[53] noted an incidence of 73% in cases who had the disease 20 years or more.

As stated, for the most part the treatment of diabetic retinopathy with rutin is attended by discouraging results. Dolger states rutin does not influence retinal hemorrhages significantly and unequivocally and Givner[42] is of the same opinion, and he has noted that several patients have had retinal hemorrhages during the course of rutin therapy. In contrast Palmer[43] reports,"We have used considerable rutin. I can not be too enthusiastic about it."

Friedenwald[44] related that he had observed an increase in the general capillary fragility, as determined by the arm-band test, in patients with diabetes mellitus. Wagener[46] referred to some as yet unpublished observations of Foxworthy of the Mayo Clinic. Where in a group of 85 nondiabetic patients of varying ages and in whom there was no evidence of hypertension, she found an average of 14 petechiae after application of the blood pressure manometer cuff for 10 minutes; 69 diabetics without retinopathy presented an average of 41 petechiae, and in 44 diabetics with retinopathy, the petechial average was 101. Donegan and Thomas[45] reported 45 cases of diabetes mellitus of which 25 presented retinopathy. The whole group averaged 53 petechiae; those presenting retinopathy averaged 60, and those without retinopathy averaged 16. After an average daily administration of 160 mg. of rutin there was a general reduction of capillary fragility, except in 3 cases, within 12 to 18 days. Despite this reduction there was no objective improvement in vision or in the appearance of the retinopathy in these 25 patients over periods of 3 to 12 months. However, it may be of significance that in approximately 66% of the cases with retinopathy, there was no decrease in vision and little or no change in retinopathy over a period of from 10 to 12 months.

Summary

1. A review of the history of rutin along with its theoretical effect and method of effect upon the capillaries has been presented.

2. The problem of future evaluation of rutin has been approached for the purpose of establishing foresight to the reader along hopeful lines.

3. The definition and a method of test for capillary fragility was reviewed along with numerous diseases showing an increased capillary fragility to stress the importance of the test in relationship to its use in selection of cases and treatment with rutin; yet, to show its inadequacies also.

4. Some clinical studies gathered from the literature were reviewed with particular attention and emphasis on the effects of rutin in hypertension and diabetes mellitus, (with their hemorrhagic retinal complications). It might be added that of the studies chosen, there were many more in the literature to augment the findings of any one particular report as summarized in this paper.

5. Dosages were reviewed.

Conclusions

Overenthusiasm inevitably follows the discovery of a new therapeutic agent, particularly that discovery which tends to be startling or which carries with it a dramatic appeal. After overenthusiasm in varying degrees, but in definite sequence come publicity, recognition of defects, etc., until finally such merits as exist become recognized in their true light and the new therapeutic agent reaches stability at its proper level of usefulness.

I do not think rutin is an exception in the process of its evaluation, even though it has been a number of years since its first use in humans. The drug has been used for nearly every disease which has shown an increased capillary fragility, for it is fairly well established by numerous investigators that rutin has the property of restoring increased fragility of the capillaries to normal values in a large majority of patients so afflicted. And in many patients this restoration is paralled closely by a simultaneous improvement in the clinical condition.

Without question the retinal complications of a diabetic are more refractory to treatment with rutin than are some of the other causes of hemorrhage into the retina; for example that due to hypertension or idiopathic Eales disease.

But even though there is lack of enthusiasm, probably due to the slow course of diabetic retinopathy so that there is little change seen from month to month, it is noteworthy that there is little and sometimes no significant progression of the blindness.

The work of Griffith and associates has established beyond doubt that rutin is of definite benefit in retinal hemorrhage due to hypertension. Also the literature is filled with universal acceptance of his views.

The question in general, however, of the use of rutin in retinal hemorrhages cannot be answered dogmatically. The entire situation may be summed up concisely by stating that extreme skepticism in one group is balanced by unbounded enthusiasm in another. And that one cannot withhold treatment with rutin, or withdraw it, in cases of hemorrhage into the retina, is true at the present time.

It is my belief that these conclusions, which are not based on my own opinions, are essentially those which any fair-minded person would inevitably reach after reading the same references.

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