OBSERVATIONS ON THE EFFECT OF RUTIN AND HESPERIDIN IN DIABETIC RETINITIS*

JOSEPH T. BEARDWOOD, JR., M.D.,
ELLA ROBERTS, M.D.,
ROBERT TRUEMAN, M.D.

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From 1856, when Jaeger first described changes in the fundi of patients with diabetes mellitus, a controversy has existed as to the specificity of these changes. Many clinicians and investigators have presented evidence both pro and con in this question and some, notably Wagener, in his career, have completely changed their ideas on the subject. In an excellent review of the subject of diabetic retinopathy, published in the *Proceedings* of the American Diabetes Association in 1945,[1] he stated that in 1921 he felt that "essentially, the retinopathy of diabetes mellitus was that of arteriosclerosis." However, in 1945 he felt that this was not true and that the lesions found in diabetes were characteristic of that disease, *per se*. The trend of thought in recent years has been definitely toward this point of view.

We feel that a brief review of the pros and cons of this question should be presented. Those that deny the specificity of the changes point out that the clinical appearance is frequently not typical and that transitional forms occur between the limits of arteriosclerosis and renal retinopathies. Against this is the fact that diabetic retinopathy is found in the younger age groups, often before arteriosclerotic and renal factors can be demonstrated. To this can be added the fact that in advancing years arteriosclerotic, hypertensive and renal conditions appear even in the absence of diabetes; in the presence of diabetes mellitus these complicating conditions may exist and modify the original picture caused by the diabetic changes.[2,3,4,5]

There is no relation between the severity of the diabetes and the extent of the retinopathy; varying degrees of retinopathy can occur in both mild and severe forms of the disease. It was previously thought that retinopathy was seldom seen in the young diabetic but only in older patients, with relatively milder forms and frequently complicated by arteriosclerotic and hypertensive changes. Barkan and Gray[5] in 1935, later O'Brian and Allen[6] were among the first to point out that diabetic retinopathy does occur in young people if the diabetes

has been present for a long enough time. Three cases of retinopathy occurring before the age of thirty are reported in this paper. Wagener, Dry and Wilder[3] and Waite and Beetham[4] have shown that sclerosis of the retinal vessels is no more frequent in diabetics than in non-diabetics of a similar age group.

The proponents of the specificity of diabetic retinopathy feel that a definite clinical picture exists, which, while not pathognomonic, has certain features which distinguishes it from renal or arteriosclerotic retinopathies. Elwyn[7] feels that the type of hemorrhages found in diabetes mellitus constitute the most characteristic feature, stating that they occurred only in diabetes mellitus and in "no other conditions I know." He felt that the hemorrhages combined with the exudates and glistening deposits complete the picture. Duke-Elder[8] points out the following differential points between the retinopathies of diabetes and renal disease.

1. The frequent unilaterality of diabetic retinopathy.
2. The occurrence of diabetic retinopathy in older persons.
3. Its relatively good vital prognosis.
4. Its response to therapy.

Incidence of Diabetic Retinopathy

The incidence of diabetic retinopathy reported in the literature varies greatly. Foster Moore in 1925 reported it as 10%[9]; Joslin in 1928 as 6.2%[10]; Shepardson and Crawford in 1931 as 23%[11] and Gray in 1933 as 13.3%.[12] Wagener in 1945 reported in his opinion a definite increase in the incidence. To substantiate this he compares the figures that he had reported in 1921, 8.3% and in 1934, 17.7% with similar figures in 1945, 30.6%. His figures also showed that the occurrence of diabetic retinopathy in younger patients had increased, in that in 1921 there had been no cases under the age of 40, in 1934 4.3% of the cases had been under the age of 40, while in 1945 12.8% of the cases had been below that age and 8.3% were less than 30. This period covers the "Insulin Era" of diabetes, and as juvenile diabetics live nearer their expected span of life, more and more cases of retinitis will be found in these individuals young in years but not in diabetes.

Studies of Duke-Elder[8] and Wagener[1] show that the "diabetic age, not the chronological age, is the dominant factor in the development of the retinopathy. Those cases in which the diabetes had been present less than one year only 10.7%

showed retinopathy; when it had been present 1-10 years 22% showed retinopathy; from 11 to 15 years 65% showed it; over 15 years 67% and over 20 years 73%. That the duration of the condition was more of a factor than the age of the patient was shown by the fact that in patients less than 30 years of age in which the condition had been present for more than 10 years 76% had retinopathy, while in patients over 30 years who had had diabetes for more than 10 years only 64% had retinopathy." One of the authors of this paper, (R. T.) saw recently for the first time a 24-year-old white female with apparently well-controlled diabetes for 12 years, who had in the fundus of the right eye four minute diabetic hemorrhages with perfectly normal retinal vessels. Two cases reported in this paper, with manifestations of Kimmelstiel-Wilson disease, had definite diabetic retinopathy while in their middle twenties and in each case the diabetes had been present for a little over 10 years before the retinopathy appeared. Observations of this type, in which vascular and infectious factors are not present at the time of the appearance of the retinopathy, lends evidence to the fact that there is some factor in diabetes itself leading to the development and progression of the retinopathy. The theoretical evidence at hand at the present time seems to point to the fact that in diabetes mellitus, the cause of the initial change of the retinopathy is due to changes in the capillaries, most probably an increase in the capillary permeability due to an unknown factor in the disease itself.

Clinical Picture of Diabetic Retinopathy

Descriptions and classifications of the fundus changes in diabetic retinopathy are numerous and varied, varying from simple descriptions to complex, morphologic and etiologic classifications. We are presenting one of the more generally accepted of these.

Wagener's[1] classification seems more practical and is as follows:

1. Hemorrhages only without vessel pathology.
2. Central punctate retinopathy.
   The appearance of "waxy" or "hard" exudates.
3. Mixed vascular retinopathy.
   The appearance of a suggestion of complicating hypertension. In this, "soft" or "cottonwool" patches appear into the picture in addition to the hemorrhages and exudates.

4. Venous disease.
   The less frequent but characteristic lesions of diabetic retinopathy—phlebosclerosis, localized constrictions or beadings, varicosities. This is usually accompanied by bleeding into the vitreous and subsequently a proliferative retinopathy.
5. Mixed toxic and diabetic retinopathy.

From the above description it can be seen that the characteristic initial lesion of diabetic retinopathy is the hemorrhages which are present without vascular changes. The hemorrhages are predominantly in the posterior polar region between the superior and inferior temporal vessels and around the nerve head. They may begin in the periphery and progress toward the posterior pole or begin in the posterior pole and extend peripherally. Most of the hemorrhages are small, round and deep, being found in the outer layers of the retina; some of them however may be superficial and flame-shaped. They may or may not be associated with a retinal blood vessel. Elwyn has pointed out that only in diabetes do the small, round and deep hemorrhages occur.

The exudates usually occur in the central area and Duke-Elder describes them as "solid, soapy or waxy looking with well defined, sharp cut edges . . . usually circumscribed but may become massive by accretion." They differ from the exudates of renal retinopathy in that they are solid and clear cut as compared to the fluffy, soft exudates of the renal type, they have an irregular arrangement at the posterior pole, there is an absence of a macular star, the association of the exudates with the small, round hemorrhages and finally the absence of edema in the picture of diabetic retinopathy. Pathologically the diabetic exudates are albuminous extravasations in the internuclear layer behind the retinal vessels with an outstanding lack of cells.

The glistening, yellowish-white deposits of varying sizes represent accumulations of cholesterol.

The severe retinal complications consist of large retinal and preretinal hemorrhages and massive vitreous hemorrhages which are fortunately few in number. When they do occur, they are usually catastrophic from a visual standpoint; they are extremely difficult in their absorption and are often replaced by a proliferative retinosis.

The mechanism of the production of the hemorrhages is, at the present time, unknown; however it is generally agreed that the fault lies in the capillaries, probably in increased permeability, so that the blood escapes by diapedesis rather than by increased intravascular pressure. The reason why the retinal capillaries allow this escape in an individual with diabetes mellitus poses the so-far unanswered question, although laboratory and clinical investigation seem to be heading toward a solution. That there are probably a number of factors concerned is brought out in the excellent review of the subject of diabetic retinopathy by Leopold.[13]

Long-standing subclinical vitamin deficiency and hypoproteinemia and other causes have been advanced as the "x factor" in this condition. It is important to bear in mind that whatever the factor or factors are which cause this condition, they are usually not present or active enough to produce retinal changes during the first five years of diabetes and it is more common to have ten years elapse before the onset of definite retinal changes.

Elwyn feels that in an individual with a continuous, mild hyperglycemia, with or without glycosuria or symptoms of diabetes, there is produced, in some unknown way, slight dilatations of the retinal capillaries with contraction of the artery above and a slowing of blood in the capillaries causing a condition which he calls "prestasis." The capillary wall becomes soft, openings occur through which the red blood cells pass resulting in the formation of a visible hemorrhage. Because of this prestasis a state of lowered nutrition and inadequate oxygen supply exists and hyalin and lipoids appear.

Ballantyne[14] stated that the "earliest unequivocal sign of diabetes" was the microaneurysms of the capillaries which occurred singly or in small numbers near the macula. Elwyn feels that these aneurysms were in actuality capillary dilatations which caused the state of prestasis. Ballantyne felt that this prestasis might exist before the formation of the microaneurysms.

Under any circumstance there is agreement that the basic pathology is in the capillary and that it most likely is a weakening in the resistance of the capillary wall. Wagener quoting Foxworthy states that there is a definite weakened resistance in the capillary walls in diabetics with retinopathy as com-

pared to diabetics without retinopathy. This is also substantiated by Conn[15] and by Rodriques and Root.[16]

Symptomatology in Diabetic Retinopathy

The symptomatology in diabetic retinopathy depends upon the state of the macula. The fundus may be peppered with hemorrhages, but if the macula has been spared the patient may have no visual complaints whatsoever. Conversely the entire fundus may be free of hemorrhages, but if a small hemorrhage is present in the macular area, marked visual impairment may result. As we have stated before, the occurrence of a large retinal or preretinal hemorrhage or a massive hemorrhage may be disastrous from a visual standpoint and even with absorption of the blood the subsequent proliferating retinosis or new blood vessel formation prevents adequate visual prognosis.

An interesting observation has been made in patients with absorbing diabetic hemorrhages in that, even without involvement of the macula, and with retention of normal or near normal central vision, the patient remarked on the improving vision as the hemorrhages disappeared. This was noted in a number of cases under observation.

The rôle that capillary fragility may play in this condition has but recently been appreciated and it is the object of this paper to present a study of consecutive cases of diabetes from the standpoint of capillary fragility and an attempt to correlate this fragility with certain retinal changes. In view of our experience this can only be a preliminary report.

Three hundred twenty-one consecutive white patients seen in the out-patient and ward services at the Presbyterian Hospital, Graduate Hospital of the University of Pennsylvania and the Abington Memorial Hospital, together with a smaller group of private patients, are included in this study.

The exact nature of increased capillary fragility is as yet not too well understood. It may be seen in certain toxic states and it has been well recognized that vitamin deficiencies will very directly affect the permeability of the endothelium. Baeser,[17] *et al.*, was one of the first to report on this subject. He found a greater incidence of increased capillary fragility in diabetics in the 5th and 6th decades and in those with hypertension. Griffith and Lindauer,[18] found a capillary fragility of 18% in 265 patients with hypertension and they felt that

this group of cases were more predisposed to retinal and cerebral hemorrhages.

In the correction of this condition, two drugs have been used. Scarborough and Stewart,[19] reported on the use of hesperidin (vitamin P). Subsequent investigators have suggested that this drug might be used as a method of controlling capillary fragility and prevent hemorrhagic complications. The second of the drugs used is rutin, which was first clinically studied by Couch,[20] *et al.* Further work had shown that both drugs have the ability, if given in proper doses, to restore the condition of the capillary vessels to normal in 86 to 90% of cases.

Complete review of the literature on these drugs has been reported by others and is not pertinent here. This present study was set up in the following fashion:

1. Each diabetic was given a capillary fragility test as modified by Gothlin. This consists in counting the petechiae appearing in two circles, 6 cm. in diameter, one in the antecubital space of each forearm, 15 minutes after the application of 35 mm. of mercury pressure to both upper arms, using standard blood pressure cuffs. Fragility is considered to be normal if two, one, or no petechiae appear, borderline but probably increased if three, four or five appear, and definitely increased if six or more appear. The index of fragility is obtained by multiplying the number of petechiae by 2. Examination should be made with an adequate white or "daylight" light, not tinted yellow, using a lens of 5 D or its equivalent. The common errors consist in using a poor light or even no light at all, too small or too low power a lens, or being careless in marking off telangiectases, et cetera, before starting the test. Moreover, since the same fragile vessels cannot be expected to break repeatedly, a negative test is of no significance if obtained within three weeks of a previous positive test.

These tests were all done by the same technician and were not repeated within three weeks. We feel it is very important in evaluating the capillary fragility of any group of patients that a definite procedure be followed, and the technique outlined above is the one of choice.

2. The patients were then alternately given (a) rutin, (b) hesperidin and (c) a placebo, because spontaneous

recovery has been reported in some cases.

3. The patients were then evaluated from the diabetic angle as regards diabetic control, presence or absence of complications and the chemical balance. The diabetic control consisted as far as possible in maintaining a normal blood sugar and sugar-free urine.
4. Ophthalmological examination was then made preliminarily by the same group of ophthalmologists who had followed them through the study. The examination was then repeated at intervals of one month. The format used is shown in Chart I.

CHART I

INIT	SEX	COL	AGE	DUR OF DIAB	INSULIN	CONTROL OF DIAB	VISIT	B.P.	GOEN INDEX	CLF	VISION OD	VISION OS	No Rx's	H's + EXUD. OD	H's + EXUD. OS	TREATMENT	REMARKS.
GN	F	W	57	6	Occas	Fair	1-48	134/70	10	Slight	6/9	6/12	0			Rutin 20m tid	Retinal art sclerosis, early senile macular changes.
							3-48	140/80	8	" "	6/15	6/15	0	As above	as above.	" " "	Subjective improvement.
							4-48	130/75	0	Norm	"	"	0	No change	No change	" " "	
							5-48	140/70	0	"	6/12	6/12	0	" "	" "	" " "	
SM	F	W	32	15	Yes	Fair	10-47	118/80	20	Incr.	HM	6/60	++	Vitr. Hemorr.	Mult. scattered	Rutin 20m tid	Acute retinitis recepsc. O.S.
							2-9	150/86	6	Incr.	HM	6/30	++	" "	" "	" " "	Vascular pict. in fundus normal.
							3-8	160/110	6	"	HM	6/30	+	" "	Marked improv.	" " "	Kimmelstiel Wilson Dis.
							5-10	170/110	0	"	L.P.	6/22	0	" "	No H's	" " "	
MF	F	W	74	8	Yes	Fair	11-47	148/80	12	N	6/9	1/60	5			Rutin 20m tid	Macular H. O.S. Advanced retin arteriosc. Circinate retin O.S.
							3-48	152/60	8	N	"	"	5	"	"	" " "	
							4-48	150/70	8	N	6/12	1/60	5	"	"	" " "	
							5-48	165/80	4	N	6/12	2/60	10			" " "	New H's in O.S.
MG	F	W	62	8	Yes	FAIR	1-48	150/80	6	N	6/6	4/60	16			Rutin 20m tid	EKG coronary art. dis.
							2-48	150/80	0	N	"	"	0			No Rx 3 wks	
							4-48	170/80	18	N	6/9	2/60	18			Rutin 20m tid	Pt. prob. not on medication.
SC	F	W	58	15	Yes	Good	11-47	160/40	18	N	6/12	6/12	0	0	0	Rutin 20m tid	
							2-48	155/85	8	N	"	"	0	0	0	" " "	
							3-48	150/90	6	N	"	"	0	0	0	" " "	
							4-48	150/80	4	N	6/9	4/12	0	0	0	" " "	
							5-48	148/84	2	N	6/9	4/12	0	0	0	" " "	
SM	M	W	55	7	Yes	FAIR	1-48	110/78	12	N	6/6	6/6	0	0	0	Rutin 20m "	
							3-48	135/80	0	N	"	"	0	0	0	" " "	
							5-48	132/80	0	N	"	"	0	0	0	" " "	
JT	M	W	59	15	NO	Good	11-47	130/72	2	N	6/12	6/60	2			Rutin 20m "	Bilat. complicat. cat. OS>OD
							12-47	140/70	0	N	1/60	1/60	8			" " "	Mac. H. OD: Cirrin. retin O.S
							2-48	138/75	0	N	3/60	1/60	-			" " "	
							4-48	135/70	0	N	6/60	3/60	14			" " "	Mac. H's OD. exud. same.
RG	M	W	48	4	YES	FAIR	2-48	150/94	10	N			59		V. Hemorr.	Rutin 40m "	Hypertens. 4 yrs.
							3-48	179/90	4	N			-		-	" " "	
							5-48	160/80	0	N			37		V. HEMORR.	" " "	
MD	F	W	50	6	YES	Good	1-48	160/80	12	Incr.	6/22	6/12	12			Rutin 20m "	Hypertension, art. sclerot. retin. yrs.
							2-48	170/100	4	Sl Incr	"	"	21			" " "	Some incr. in vasc. condition.
							6-48	165/90	2	N	6/15	6/15	3			" " "	Much subjective improvement
EM	F	W	69	20	YES	FAIR	1-48	120/80	12	N	6/6	6/6	0	0	0	Rutin 10m "	
							2-48	125/70	10	N	"	4/6	0	0	0	" " "	
							4-48	115/70	16	N	"	"	0	0	0	" " "	
							5-48	120/80	12	N	"	"	0	0	0	" " "	
							6-48	180/75	0	N	"	6/9	3			" " "	Emotionally upset, very worried and nervous.

Sample format used to follow these cases. The cross in the 15th and 16th column has as its centre the macula of the eye and the number of hemorrhages are prefaced by the letter H and of exudates by the letter E.

We feel it is very important to have a geographical appraisal of the exudates and hemorrhages and to check these on subsequent examinations.

Of the 321 consecutive cases tested, 46% showed capillary fragility. This is a smaller percentage than was reported by Rodriques and Root.[16] Of the total, 24% showed evidence of retinal change. There seemed to be no marked relationship to the duration of the diabetes and the capillary fragility except in those patients who had diabetes for more than ten years and

there was a definite increase of the incidence in this group. Approximately 50% of this group showed some elevation of the blood pressure and we accepted a persistent diastolic pressure over 90 as a criterion for such evaluation. There were in this group 24 who had retinitis. All but 4 had hypertension with normal indices. No marked change was seen with the antifragility drugs.

Kimmelstiel-Wilson's Disease, or Intercapillary Glomerular Nephrosclerosis, has become a condition of increasing interest during the last three or four years. Whether or not this is an entity peculiar to the diabetic is still not agreed upon by all pathologists. Certain it is, that it is seen much more frequently in diabetes and is a terminal condition in many cases. It has been our experience and that of many others that many juvenile diabetics will, in spite of adequate control for ten or twelve years, develop a condition of hypertension, retinal hemorrhage, albuminuria, proceed rapidly in a downward course and die, either as a result of kidney failure or one of the complications secondary to hypertension. It is not in the province of this paper to discuss this pathological entity. It is interesting, however, that we have observed during this study 9 patients who from the clinical standpoint might well be classified in this group. Five of these were juvenile diabetics starting their diabetes before the age of 10, the others starting in the early decades of life; they developed in a marked degree the triad of hypertension, albuminuria and extensive retinitis with varied degrees of vascular and kidney decompensation.

The interesting thing to us in this group was that they showed the most marked degree of capillary fragility of any of the cases studied. In one case with death from uremia, the capillary fragility was so great that it was practically impossible to read the Gothlin's index. The others had indices from 50 to 200. One of these patients is of particular significance . . . D. T., a girl of 23 years who had been a diabetic from the age of 12. Her diabetes had gone along under fairly satisfactory control. Two years before admission she rather suddenly developed many capillary hemorrhages of the retina and impaired vision. Her Gothlin index at that time was 50. She was placed on rutin and within a month her vision had improved; the hemorrhages had disappeared and there was no fresh bleeding. She left Philadelphia for a period of six months and stopped taking rutin. She was again seen after her

return, at which time she had multiple extensive hemorrhages of the retina and her blood pressure was 160/90. The urine showed a cloud of albumin, and there was evidence of peripheral edema. The blood urea nitrogen was 35 mgms. and her total proteins were 5.2 mgms. We felt that undoubtedly she was developing intercapillary glomerular nephrosclerosis. She was given 50 mgms. of rutin 4 times a day and after a period of two months her eye grounds had entirely returned to normal, her blood pressure is now 135/80, urinalysis showed only a faint trace of albumin and her blood chemistry has returned to normal.

It seems not illogical to conclude that possibly the primary cause of intercapillary glomerular nephrosclerosis may be associated with increased capillary fragility, causing as an initial lesion damage to the capillary walls in the kidney, from which develops the clinical picture which we see after some months progress. It is interesting that in spot checking, a relatively small group of non-diabetic patients with nephrosis, we did not find any marked increase in the capillary fragility. If such a supposition is true, it might well explain why one juvenile diabetic will develop this condition and another juvenile diabetic, whose diabetic control and whose over-all picture is relatively the same, fails to develop it. Further study and a longer period of further observation might indicate that these anti-fragility drugs could be of value as prophylactic measures in this condition.

In the past few years a discussion has arisen as to the retinopathy appearing in Kimmelsteil-Wilson's disease (diabetes, hypertension and albuminuria). Newburger and Peters[21]; Siegel and Allen[22] have reported the retinal lesions as either hypertensive or arteriosclerotic or a combination of both. Wagener[1] in discussing these findings disagrees with them and feels that the lesions are basically diabetic in character with the superimposition of changes of a vascular character. The findings in two such cases presented in this paper confirm the findings of Wagener.

Dosage

The initial dose of rutin in this study was 20 mgm. t.i.d., which was increased to 50 mgm. t.i.d. if the fragility did not come back to normal in four to five weeks. The dose of hesperidin was 50 mgm. twice a day. The average time required before the fragility came back to normal was five weeks with

rutin and 6.2 weeks with hesperidin in 80% of the cases. In the other 20% it was much prolonged and in some percentage of the cases the fragility had not come back to normal at the end of the six months' study. No toxic effects were noted in any of the cases.

To the 77 cases of the 321 where capillary fragility was increased were added 46 private patients who had retinopathy and whose Gothlin index was increased, making a total of 116 cases reviewed in this study. These are tabulated in Chart II.

CHART II

Analysis of Cases Studied

	Rutin	Hesperidin	Placebo
Gothlin Improved, No Change in Retina	20	22	0
Gothlin Improved, Improvement in Retina	10	10	0
Gothlin Improved, Retina Worse	5	5	0
Gothlin Same, Retinopathy Same	5	3	32
Gothlin Same, Retinopathy Improved	0	0	4
	40	40	36

Summary

A preliminary study of 321 consecutive diabetic patients is reported, of which 24% or 77 showed increased capillary fragility and retinopathy. To this group was added 46 private patients who also showed capillary fragility and retinopathy.

In this group of 116 patients after six months of anti-fragility drugs, 42 had no improvement demonstrable in the retina in spite of an improvement in the capillary fragility, although a few of these patients felt that their vision had been definitely improved after being on treatment. Twenty showed a definite improvement in the retinal picture with improvement in the Gothlin index and at the same time marked improvement in vision. Ten showed no improvement in spite of an improved index and 8 were unchanged. Of the 36 cases, in which placebo was used, 32 showed no improvement and 4 showed improvement in the retinopathy although the Gothlin's index did not change.

We feel from this preliminary survey that the evaluation of hesperidin and rutin requires:

1. Study of several years with patients who can be closely checked.
2. That there is little difference in this series of the results obtained with these two preparations.
3. That there is some indication that intercapillary glomerular nephrosclerosis may be definitely associated

with capillary fragility and that there is at least some rationale to suppose that this treatment may be used as a prophylactic measure.

4. That careful and competent retinoscopy, standard Gothlin technique, and adequate control of the diabetic, are of great importance in any series of cases so reported.
5. No improvement can be expected in our experience in those cases in which there was not evidence of increased capillary fragility.

Conclusions

In the 80 cases in which rutin and hesperidin were used, 20 showed definite improvement to ophthalmological examination. This improvement consisted in either cessation of further evidence of bleeding or absorption of exudates and hemorrhages already present.

It is obvious that drugs such as these cannot improve a retina scarred with extensive hemorrhages or one in which we have evidence of thrombosis of the deeper vessels, but with a definite improvement in 25% of selected cases, it is our opinion that these drugs warrant further trial and that the earlier they are used the more prompt and satisfactory results will be obtained.

It is our suggestion that capillary fragility determinations be made on all juvenile and young diabetics and if this is definitely elevated these drugs be given until this condition is corrected. It is also suggested that routine retinoscopy be done at least every three months on juvenile diabetics as a further check on the development of early diabetic retinitis.

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Discussion

Dr. J. Q. Griffith (*Philadelphia, Pennsylvania*): Dr. Beardwood's results were about the same as our own, except that our series contains diabetics only incidentally. There seems little doubt that retinal hemorrhage and increased capillary fragility are associated, in the non-diabetic as well as in the diabetic.

In our experience rutin and hesperidin will usually decrease the fragility to normal, though the required dose is usually larger in patients with retinal hemorrhage, suggesting, perhaps, that the metabolic need is greater.

Improvement in fragility makes the patient less subject to retinal hemorrhages in the future. This effect is most marked if there has been no previous hemorrhage; less marked if there has been previous hemorrhage.

The increased tendency of patients with past retinal hemorrhage to future hemorrhage, in spite of improvement in regard to fragility, may be explained in three ways:

(1) The vascular condition may represent a more advanced stage.

(2) The process of recovering from one hemorrhage leaves vessels more vulnerable.

(3) Chronic vascular dilatations may occur which may be confused with hemorrhage, or may themselves give rise to hemorrhage.

Dr. George F. Schmitt (*Miami, Florida*): I would like to ask Dr. Beardwood whether or not he is using Vitamin C or would that have any effect?

DR. HENRY DOLGER (*New York, New York*) : Looseness of terminology with respect to diabetic retinopathy precludes accurate evaluation of any form of therapy. Not only are there varying degrees of severity of the lesion, but more important, the rate of degeneration may bear no relation to the factor of severity. Each patient presents a highly individual course.

In some patients, the mechanical pull of scar tissue may provoke further hemorrhages regardless of the state of capillary fragility. On the other hand, many milder cases present spontaneous inexplicable remissions which should not be attributed to any specific therapeutic measure. The lumping together of all the cases of diabetic retinopathy cannot but confuse clear-cut analysis of the end results. Even advanced cases, as every ophthalmologist knows, may suddenly evince so-called "retinal immunity" by a cessation of hemorrhages and an arrest of visual deterioration.

I have used rutin, hesperidin, and hesperidin methyl chalcone with equivocal results. I do not believe that any known drugs strike at the heart of the problem of diabetic retinopathy.

DR. W. R. KIRTLEY (*Indianapolis, Indiana*) : I would like to mention two series; one series of only six patients was observed to determine whether the size of the dosage would have anything to do with the therapeutic effect. We started these patients on 300 mg. of hesperidin a day and the dose was doubled about every third day until they were receiving 15 grams a day. Four of these people received 15 grams daily for from four to fifteen days. Studies on the blood concentration of hemoglobin, petechial index, etc., gave us about the same results as reported here. The toxicity of this drug appears to be nil.

Another series of twenty-two patients was observed—these patients received 100 to 300 mg. a day for periods varying from six months to 32 months. Again our observations were very similar to those that have been described here.

DR. BEARDWOOD (Closing) : I particularly would like to thank Dr. Griffith who has probably done more work than any man in the country on rutin for his discussion. I appreciate it all the more because this is the first time that Dr. Griffith has reviewed this paper due to some irregularity in the United States mails and I appreciate that very much.

In regard to Dr. Dolger's remarks, we attempted to chart in the format the type and degree of retinopathy, and attempted to point out that it is the consensus of most men that there is probably a definite type of retinopathy which might be called diabetic retinopathy which obviously exists in varying degrees and in the format which we show, we attempt to break down the cases. Perusal of the charts will demonstrate the response obtained in various degrees of retinopathy.

In regard to the use of vitamin C, we did not include vitamin C with our rutin in this study because we did not want to complicate our results. Dr. Kirkley's observations were certainly very interesting.