of straight vitreous on the cornea. I am not sure that vitreous alone produces corneal changes. I think the changes I have observed have occurred as the result of the hyaloid membrane. This membrane has a definite structure and it is the effect of this against the cornea which promotes symptoms and signs.

I was glad to hear Dr. Verhoeff state that he felt a deliberate rupture of the hyaloid membrane is indicated sometimes. I have thought that this might be beneficial sometimes in cases with permanent adhesion of the membrane to the cornea, and in cases with secondary glaucoma.

Dr. Beetham mentions the value of air injection. I think it has value not only in pushing the iris back but in pushing the hyaloid back.

I recall the case which Dr. Perera quoted, and I feel, as he did, that the injection of air was beneficial.

Dr. Rychener asks how long miotics are used. I think a period of about 2 to 3 days is adequate.

I know of Dr. Cowan's work. I referred to the hyaloid as a membrane which is in agreement with his ideas.

I thank Dr. Bedell for calling my attention to the article which he wrote in 1925 pertinent to this subject.

Thank you.

THE EFFECT OF DICUMAROL ON THE VISUAL FIELDS IN GLAUCOMA. A PRELIMINARY REPORT

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The problem of progressive loss of visual field following a successful filtration operation in glaucoma is one that has plagued ophthalmologists for years. The general consensus seems to be that these changes are due to an irreversible vascular process which is set up while the tension is above normal limits and has progressed sufficiently so that when the tension is reduced, either by surgical or medical means, there is no regression, but apparently a continued progression of the vascular process.

As far as can be determined, no completely satisfactory

pathologic observations have been made on the ocular vascular system in early cases of chronic simple glaucoma. Duke-Elder[1] states that there is a vascular stasis and quotes 3 individual case reports by Levinsohn, 1908, Ronne, 1913 and Hanssen, 1918, in which all showed evidence of circulatory stasis and vascular lesions, either of periphlebitis or endophlebitis of the episcleral or vortex veins, with areas of leukocytic infiltration. Knapp,[2] in reporting on cases of atrophy of the optic nerve with cupping and low tension states that "atheromatous carotid arteries cannot alone cause this descending atrophy, but the condition must be caused by simultaneous circulatory disturbances in the optic nerve from arteriosclerotic vascular changes." Best[3] called attention to the fact that arteriosclerotic changes in the small nutrient vessels may damage the optic nerve, while Siegert[4] and von Stief[5] believed that the cause of optic atrophy in cases of "pseudoglaucoma" are the result of arteriosclerotic changes in the vessels supplying the optic paths.

Gradle,[6] in discussing glaucomatous cupping and atrophy of the optic nerve in cases where the tension was never found to be elevated, held that the condition begins as a low-grade neuritis limited to the anterior third of the optic nerve, the vessel-bearing portion, and leading to an absorption of the nerve fibers, producing the cavernous changes in the nerve described by Schnable.[7] Lagrange and Beauvieux[8] found sclerosis and obliteration of the small nutritive vessels of the nerve in several cases of primary glaucoma. Loewenstein[9] demonstrated changes in the walls and thromboses in the small vessels of the optic nerve, producing cavernous degeneration and sclerotic plaques. He concluded that the degenerative changes found in the nerve in glaucoma are the result of vascular damage with impairment of nutrition rather than the effect of increased intra-ocular tension. It is interesting to note that the recent studies of Putnam[10] and his co-workers on the etiology of disseminated sclerosis present some evidence that vascular thrombosis has a definite bearing on the

formation of the plaques found in nerve tissue in this disease. This group has recently treated a series of cases of acute disseminated sclerosis with dicoumarin and report encouraging results in those cases which are characterized by remissions and exacerbations.

Rintelen[11] has described the histologic findings in cases of arteriosclerotic atrophy of the optic nerve. He believes that sclerosis of the central retinal artery has little or no effect on the nerve and that the damage in these cases is due to sclerosis of the small nutrient vessels. Vail[12] states, "It is entirely probable that vascular disease of the nerve may account for the progress of cupping, atrophy and field changes that frequently occur after the ocular hypertension has been quite controlled in true glaucoma, especially in the aged."

In view of these facts and hypotheses it would seem that the most reasonable explanation for the progressive field changes in chronic simple glaucoma is arteriosclerotic changes in the nutrient vessels of the optic nerve. These changes may involve slowing of the blood stream, narrowing of the lumen of the vessels, formation of atheromatous plaques in the endothelium and formation of mural thrombi.

In searching for some method to treat these patients, many of whom seem to be in desperate straits, it was believed that a vasodilator might be of benefit if the vasodilatation could be prolonged. Further, it seemed that a drug with anticoagulant properties which would inhibit the formation of thrombi might possibly be of value in the treatment of these cases. The only drug which met both of these requirements was dicumarol.

Schofield[13] in 1924 and Roderick[14] in 1929 reported on hemorrhagic disease in cattle following ingestion of spoiled sweet clover hay. In 1939 Link[15] and his associates isolated and crystallized the active principle in spoiled sweet clover hay that was responsible for this disease of cattle. Since that time a great number of experimental and clinical investigations have been made on 3,3′-methylenebis (4-hydroxycou-

marin), better known as dicoumarin or dicumarol. Meyer, Bingham and Axelrod[16] reported that the administration of the chemical, either orally or intravenously is succeeded by a protracted prolongation of the prothrombin time and coagulation time. This effect follows an initial latent period of 24 hours following administration of the drug. In therapeutic amounts no untoward symptoms were produced but excessive quantities produced spontaneous hemorrhages and fatalities in dogs.

Bingham, Meyer and Pohle[17] first noted that the most constant pathologic change produced by the substance is a widespread dilatation of capillaries, arterioles and venules, and this finding has been confirmed by Wright and Prandoni,[18] Bollman and Preston[19] and Townsent and Mills.[20] It is of interest to note that this vasodilatation occurred in animals whether they died from overdose of the drug or were destroyed for study following therapeutic dosages. In treating patients suffering from arteriosclerosis obliterans or thromboangiitis obliterans with dicumarol, Wright and Prandoni[18] noted an increased tendency to bleed at the site of ulceration and attributed it to the dilatation of minute vessels. Allen, Barker and Waugh[21] believe that something in the body is necessary for the action of dicoumarin because if the drug is added to drawn blood, the prothrombin time is not affected. The bleeding time is not affected by the clinical use of the drug but the sedimentation rate is routinely increased.

The method used in administration of the drug in the cases to be reported consisted in hospitalizing the patients and, on the first day of hospitalization, the administration of 300 mg. of dicumarol by mouth. Routine determination of the prothrombin time, according to the method of Quick[22] was started on the second day in the hospital and carried out daily thereafter. According to this method the normal prothrombin time runs around 11 to 13 seconds. By the administration of dicumarol the prothrombin time was elevated to

between 35 and 45 seconds and maintained at that level during the period of hospitalization. The amount of dicumarol to be given each day is determined by the reported prothrombin time of that day. On the average it was found that after the initial dosage of the drug a daily dosage of 100 mg. was sufficient to maintain the desired level in the blood, although on occasion the dose had to be decreased or increased for a day or so. It is of interest to note in this connection that if there appears to be some danger of hemorrhage the prothrombin time can be reduced dramatically by the intramuscular injection of 50,000 units of penicillin. This will reduce the prothrombin time but will not prevent it being raised again to the desired level by the administration of dicumarol, while the intravenous use of vitamin K will not only reduce the prothrombin time but keep it at low levels for several days in spite of the continued use of the anticoagulant.

Of the 9 cases to be reported in this paper, dicumarol was initially administered for a period of 2 weeks only. However, several patients have had a second course of the drug because, while some improvement was noted after the first course, it was felt that further improvement was desirable and consequently further treatment was advised. The first case reported was perhaps the most dramatic of all. After the first course of dicumarol, from which there was a most striking, and to me unbelievable, response, the fields held well for a period of 10 months. At this time it was noted that there was again a marked lower nasal field cut to within 10 degrees of fixation. He was given a second course of the drug and 1 month after this the field had again become almost normal while a month later it was within normal limits and has remained so until the present, 8 months after the last course of dicumarol. This quite naturally brings up the question as to whether it is necessary to give repeated courses of the drug and at what intervals these should be given, or whether, as in the case of some patients who have suffered thrombosis of the coronary artery, a maintenance dose of

the drug should be given for some months or years. I am not prepared to definitely answer this question at the present time although I do have 3 elderly patients with advanced field changes on a maintenance dose at this time. These patients all had increased intra-ocular tension which was reduced by operation but I believe that the field changes in them were more characteristic of an arteriosclerosis of the vessels supplying the optic pathways than of those which we ordinarily associate with glaucoma. It is too early to speculate what the outcome will be in these elderly patients for if, after further study, this therapy proves to be of value in treating the visual changes in long-standing glaucoma, it is my belief that the older patient with advanced field changes, due in all probability to arteriosclerosis, will prove to be the most intractable type of case for such treatment. Again, although I have not yet carried out such a procedure, I have the feeling that if dicumarol proves to be of value in these cases probably the most advantageous use of the drug would be its long-continued administration over a period of years with weekly checks on the prothrombin time after the blood level is finally stabilized.

Case Reports

Case 1.—W. G., aged 44. This Negro was first seen on December 12, 1944, complaining of early presbyopic symptoms. He stated that the vision in the right eye had been failing for some years but he thought the left eye was all right and that all he needed was some reading glasses. There was no history of pain or congestion in the eyes at any time. Vision O.D., hand movements at 1 foot, vision O.S., 20/30. External examination was negative with the exception of the pupils which were semidilated and reacted poorly. The media were clear while the fundi showed a minimal arteriolar sclerosis and a deep cupping of each disc of the glaucomatous type, the pallor of the nerve head being more marked in the right eye. The vision in the right eye could not be improved while in the left it was improved to 20/20 by+0.50 sphere. Intra-ocular tension was O.D. 29, O.S. 42 (Schiötz). No visual field was obtainable in the right eye while that in the left eye revealed a marked defect in

both the upper and lower nasal quadrants. Pilocarpine 2% was ordered to be instilled 4 times daily and the patient asked to report in 2 weeks. At this time the tension was O.D. 25, O.S. 35 and operative intervention was advised for the left eye.

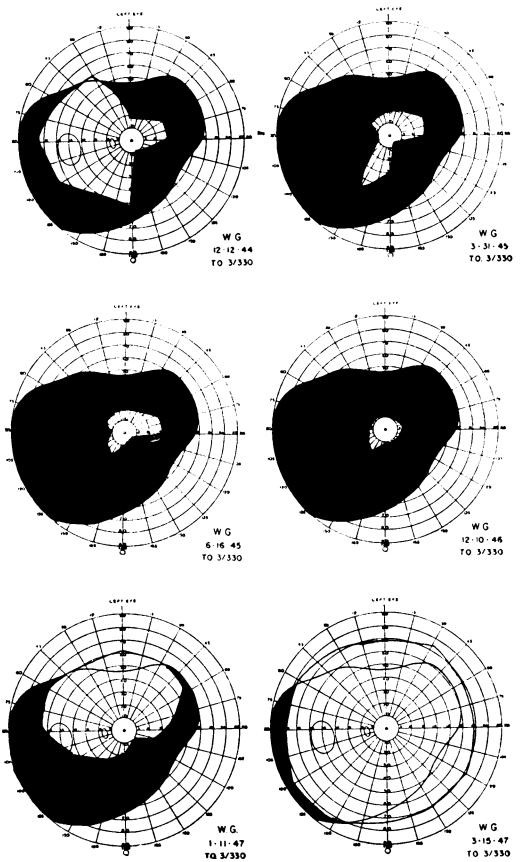


Fig. 1.—Case 1.

On January 7, 1945, a modified Lagrange operation was performed on the left eye. The postoperative course was uneventful, and 1 month after the surgical procedure tension was O.D. 25, O.S. 17. From that time until the present the tension in the left eye has never been above 17 nor below 13 on repeated examinations. However, on March 31, 1945, almost 3 months after operation, the

field in the left eye showed a good deal more contraction, and 3 months later the contraction was even more marked. Following this there was a more gradual contraction of the field until December, 1946. At this time the best corrected vision in the left eye

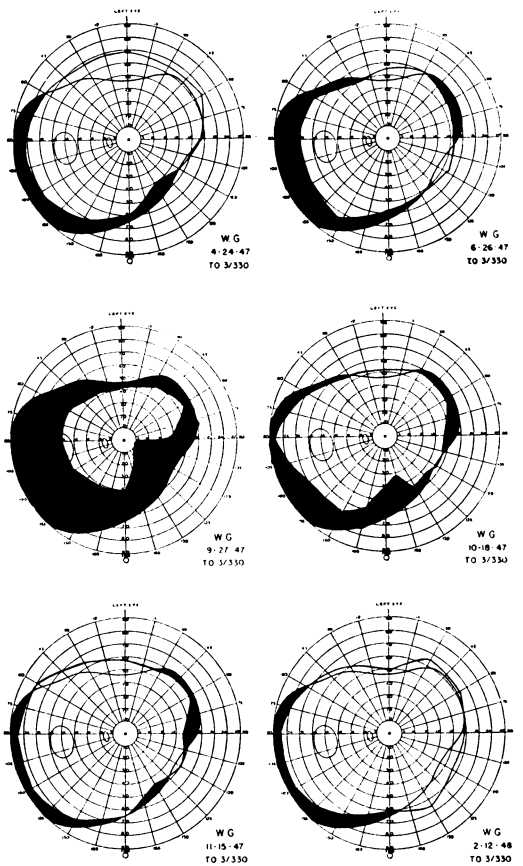


Fig. 2.—Case 1.

was 20/30 but it should be emphasized that at no time during the observation of this patient had the blindspot showed any variation from normal. Dicumarol therapy was ordered on December 12, 1946, and the patient was kept on the medication for 10 days. He was seen again on January 11, 1947, and the field was found to be much improved. Two months later, on March 15, 3 months after

the dicumarol therapy, he was again checked and the field found to be full in all meridians.

In June of 1947 the field remained normal and he was asked to report again in 3 months. On September 27, 1947, the field had begun to show a temporal contraction and a marked lower nasal quadrant cut to within 10 degrees of fixation. The blindspot remained unaffected and the best corrected vision was 20/25. At this time he was put on dicumarol for 2 weeks and on October 18, 1947, the field had shown marked improvement while 4 weeks later, on November 15 the field had again returned to normal limits and the corrected vision was 20/20. He was last seen in February, 1948, and the field was holding well.

CASE 2.—M. W. P., aged 60. This white male was first seen in October, 1936, when he stated that he had lost the sight in the right eye 4 years previously. He had not consulted a physician and came in merely to see about getting some reading glasses. There was no history of pain or inflammation in either eye. There was no light perception in the right eye while the vision in the left was 20/20. The external examination was negative with the exception of the right pupil which did not react to light and was partially dilated. The media were clear. The fundi showed marked glaucomatous atrophy of the right nerve head and some shallow cupping of the left disc. There was a slight upper nasal contraction of the left field. Intra-ocular tension was O.D. 48, O.S. 35. Pilocarpine was ordered for each eye and under this regimen the tension was reduced to O.D. 30 and O.S. 17. No essential change was noted in the eyes until the middle of 1940, 4 years after the patient was first seen, when, in spite of the continued use of miotics the tension began to rise slightly in the left eye. Between May and December, 1940, the tension varied between 17 and 35 in the left eye with a base curve which was showing a slow but constant increase. On December 31, 1940, a trephining was done on the left eye, following which the tension was reduced from 40 to 15, in which neighborhood it remained for several years.

During late 1943 the patient developed an acute exacerbation of the glaucoma in the blind right eye and a complete iridectomy was performed by Dr. Louis S. Greene in January, 1944. This served to reduce the tension for only a few months and then the patient began to develop spontaneous hemorrhages from the iris in the right eye and the globe was enucleated in May, 1945. In the meantime the tension and the field in the left eye had been holding well. In August, 1946, it was noted that the field in the left eye had

begun to show a little more contraction and a 48-hour tension curve was done with the highest tension recorded at 22 mm. of Hg. (Schiötz). In May, 1947, the field was found to be more contracted

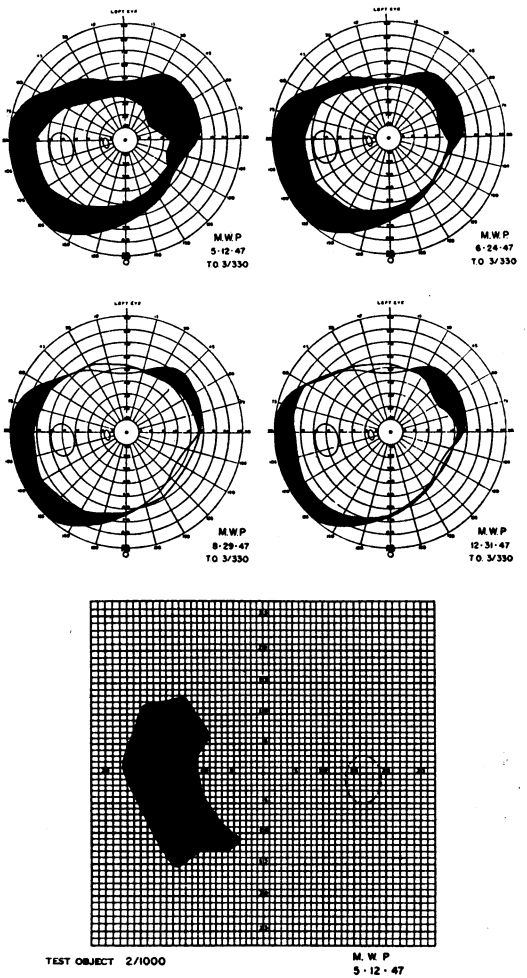


Fig. 1.—Case 2.

and the blindspot definitely enlarged. Dicumarol therapy was advised and the patient entered the hospital for this therapy on May 15, 1947. He had 2 weeks on the drug and on June 24 it was noted

that the nerve head was of better color and the field was improved. On August 29 the field showed continued improvement and the blindspot was about normal in size, while the fields were maintained at the same level on December 31, 1947. In this case the

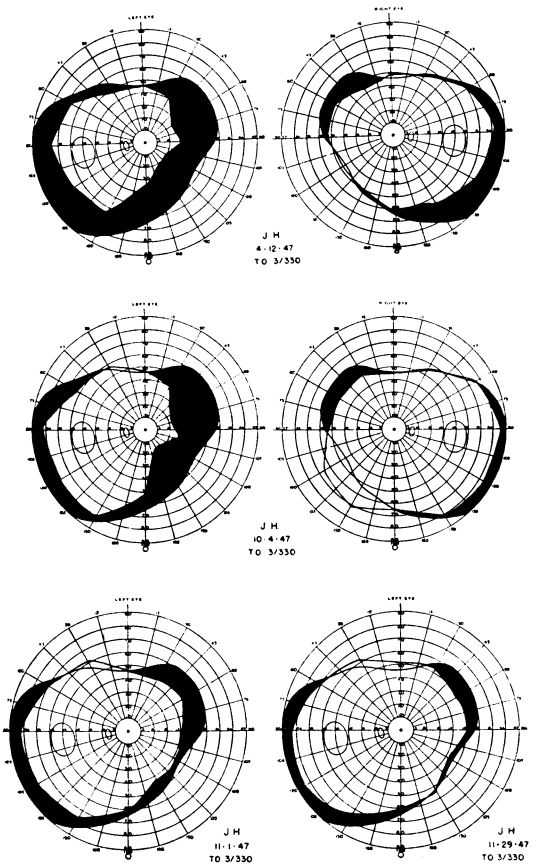


Fig. 1.—Case 3.

central vision in the left eye has never been worse than 20/30 corrected and when the patient was last seen it was corrected to 20/20.

CASE 3.—J. L. H., aged 45. This white male was first seen in August, 1944, when he came to the office for a change of glasses. There was no history of ocular trouble other than the usual pres-

byopic symptoms. The vision was 20/20 in each eye, corrected to 20/15 in the right eye and to 20/15 in the left. The external examination was negative and the media were clear. The fundi were normal with the exception of the left nerve head which showed a moderate pallor and a shallow cupping. Intra-ocular tension was O.D. 17, O.S. 29. The right field was full while the left showed some upper nasal contraction, although this was not marked. The patient was placed on pilocarpine but the tension remained unchanged. On December 2, 1944, a trephining was done on the left eye. Following this procedure the tension dropped to 6 but within a month had risen to 35. Miotics were again ordered and the tension was slowly reduced to normal limits.

From June, 1945, until April, 1947, the patient did not report for a check and when he finally was seen on April 12, 1947, he reported that his eyes had been comfortable but that he thought he needed more help in reading. At this time the corrected vision was 20/15 in the right eye and 20/25 in the left. The fundi showed no appreciable change, tension O.D. 17, O.S. 22. The left field showed more contraction. On October 4, 1947, the field showed even more contraction and the blindspot a marked enlargement. Dicumarol therapy was advised. The patient entered the hospital on October 8 and received dicumarol for 2 weeks. On November 1 the field showed marked improvement and on November 29 slightly more improvement was apparent while the blindspot had been materially reduced in size. At this time the corrected vision remained at 20/25 and the tension at 22 in the left eye. When last seen in April, 1948, the field and blindspot showed no appreciable change over a period of almost 5 months.

Case 4.—G. W. M., aged 74. This white male was first seen in April, 1944, with a vision of 20/200 in each eye, corrected to 20/70 O.D. and 20/20− O.S. There was a nuclear sclerosis in each lens and a shallow cupping of each disc. Intra-ocular tension was O.D. 29, O.S. 40, and there was a slight concentric contraction of the visual field in each eye. The patient was ordered to use miotics and was followed in the office at intervals. By April, 1947, the tension had risen to 40 in each eye and the fields showed more cut in each eye. In May, 1947, a flap sclerotomy was done bilaterally and dicumarol was administered for 2 weeks. Following operation the tension has remained within normal limits and in October, 1947, the field showed marked improvement. At the last visit, October, 1947, the nuclear sclerosis had increased markedly and the best corrected vision was 20/100 in each eye. In spite of being advised to return

for periodic checks this patient, who lives at a considerable distance, has not returned and I have, unfortunately, lost contact with him.

CASE 5.—Mrs. H. A. S., aged 67. This white woman was first seen in June, 1945, when she stated that she thought she needed a change of glasses. Upon questioning she stated that for several years she had noticed that she could not see objects to the side of her direct line of vision but that she had paid no attention to this phenomenon. Vision in the right eye was 20/50− corrected to 20/20 and in the left 20/70− corrected to 20/40−. The media were clear

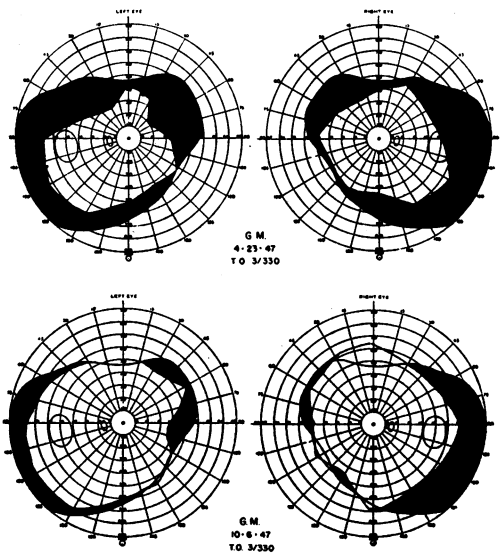


Fig. 1.—Case 4.

and the fundi revealed a grade 2 retinal arteriolar sclerosis and a marked cupping of the glaucomatous type in each nerve, associated with an extreme pallor. Both visual fields showed a great deal of constriction, the left being more marked than the right. Tension O.D. 25, O.S. 35. Pilocarpine 2% was prescribed 4 times daily.

There was no appreciable change in conditions until March, 1940, when the patient was hospitalized for a 24-hour tension curve. During this period, and in spite of the continuance of pilocarpine as before, the tension was found to be elevated in the early morning hours to O.D. 35, O.S. 48. Iridencleisis was performed on

each eye with an interval of 1 week between operations. Immediately after operation the tension was reduced to O.D. 19, O.S. 11 and since operation has never been found above 22 in either eye. While the patient was still convalescent it was noted that the vas-

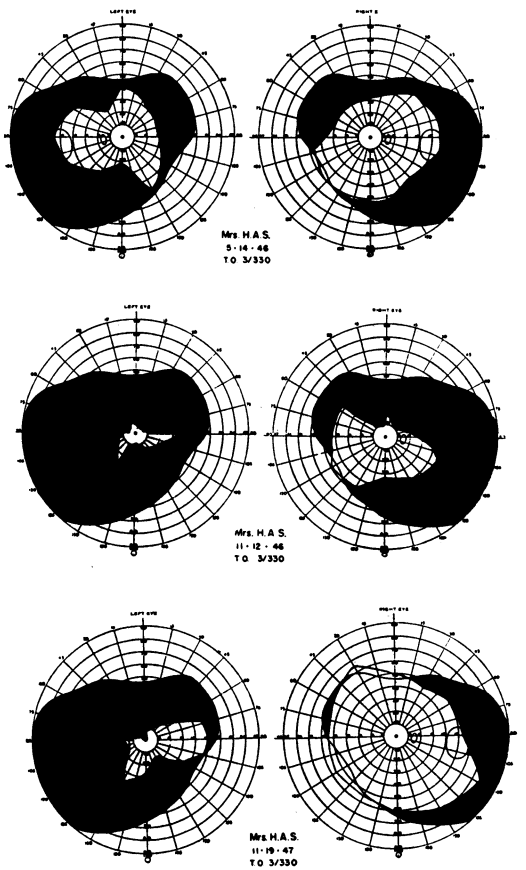


Fig. 1.—Case 5.

cularity in each nerve head was improving, so much so in the left eye that the vessels on the left disc looked like a Medusa head of capillaries, and the color of the discs in general was much improved. When the fields were checked in May, 1946, 2 months after operation, they were found to be much improved, but by November 12

of the same year they had again begun to contract. They remained in about the same stage until August, 1947, when the patient en-

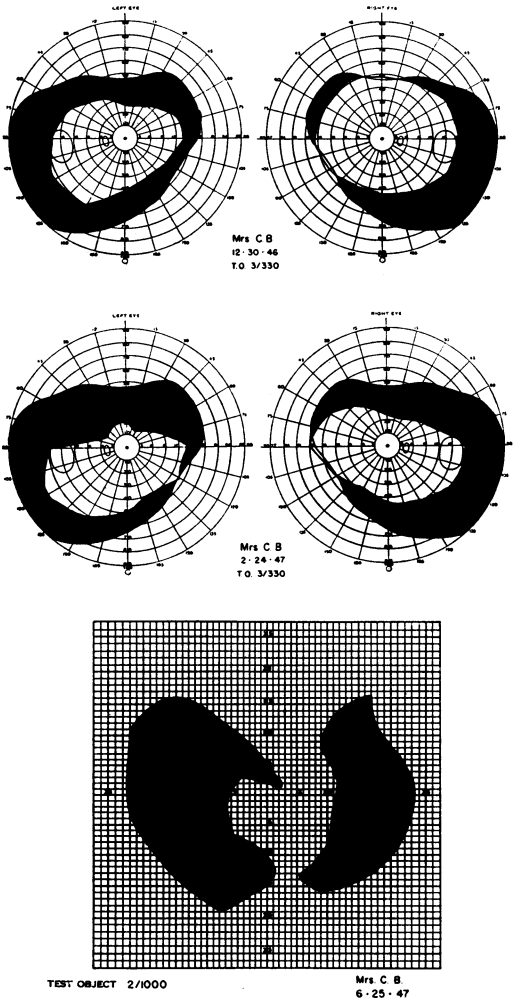
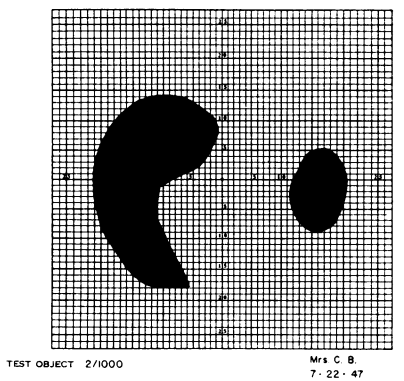


Fig. 1.—Case 6.

tered the hospital for dicumarol therapy which she had for 2 weeks. On November 19, 1947, the right field had improved very strikingly while the left showed marked contraction with a central de-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Mrs C. B.
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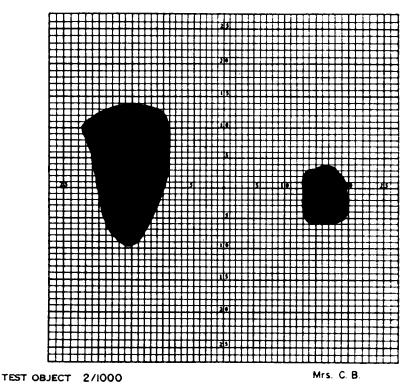
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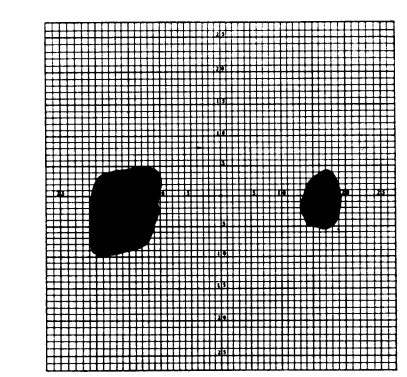
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Fig. 2.—Case 6.

fect. At this time the corrected vision in the right eye was 20/20— and in the left 20/60 eccentric.

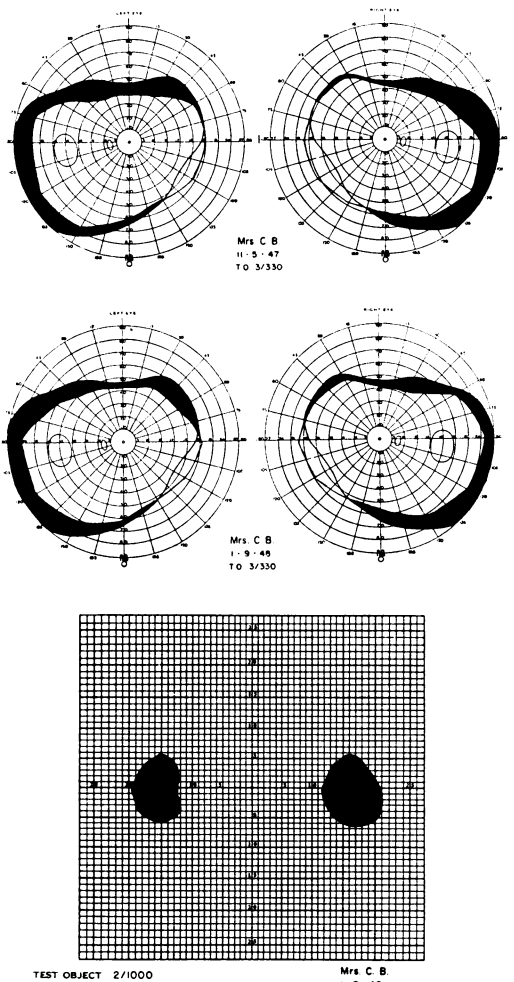


Fig. 3.—Case 6.

CASE 6.—Mrs. C. B., aged 73. This white woman was first seen in January, 1946, with a corrected vision of 20/20 in each eye. Tension was O.D. 26, O.S. 22. There was a faint nuclear sclerosis in

each lens and a shallow cupping with some pallor of each disc. The fields showed some slight bitemporal contraction and there was some enlargement of the blindspots. Roentgen examination of the skull was negative with the exception of calcified posterior clinoid ligaments. In spite of the use of miotics the tension varied between 22 and 30 in each eye and in June, 1946, a bilateral iridencleisis was done. Since operation the tension has remained within normal limits but by February, 1947, the fields showed more contraction, particularly in the upper portion, while by June 25 of that year the blindspots had markedly increased in size. The patient was placed on dicumarol for 2 weeks and 1 month later the central fields had improved to some extent. On August 25, September 24, November 5, 1947, and January 9, 1948, a progressive improvement was noted in both the peripheral and central fields. The corrected central vision in each eye has steadily become worse due to the development of lenticular opacities. This patient was last seen in April, 1948, when it was found that the fields and blindspots were virtually unchanged in the 3-month period.

CASE 7.—Mrs. G.L., aged 47. This white housewife first presented herself on September 4, 1947, stating that she did not think she saw well enough with the glasses that she was wearing. She had had them for several years. Her husband was a photographer and she had made a practice of helping with work in the developing room. She had noticed that recently, after working in the darkroom for several hours, she would have a headache and pain in the eyes. Vision in the right eye was 20/30– and in the left 20/40–, each correctible to 20/15−. The media were clear. The fundi were normal with the exception of the left disc which showed a very shallow cupping with a questionable pallor. Intra-ocular tension was O.D. 22 and O.S. 26. Visual fields showed an upper nasal cut in the left eye and a slight concentric contraction temporally in both eyes with a beginning enlargement of the blindspot in the left eye. Two per cent pilocarpine was prescribed for each eye 4 times daily and when the patient was next seen in early November the tension was O.D. 19, O.S. 22. There was no change in the fields and the patient still complained of the same symptoms following work in the darkroom. An iridencleisis was performed on the left eye on November 19, 1946, and on the right eye the following week. The postoperative course was uneventful and upon repeated checks since operation the tension in either eye has not varied from a low of 15 to a high of 19 mm. There was no material change in the fields through June, 1947, but at this time the best corrected vision had decreased to O.D. 20/20 and O.S. 20/25−.

Two months later, on August 23, 1947, the fields were unchanged from the preoperative appearance but the left blindspot had enlarged slightly while the right was a little larger than normal. Dicumarol therapy was advised and during the first 2 weeks in September the patient was in the hospital for a course of the drug.

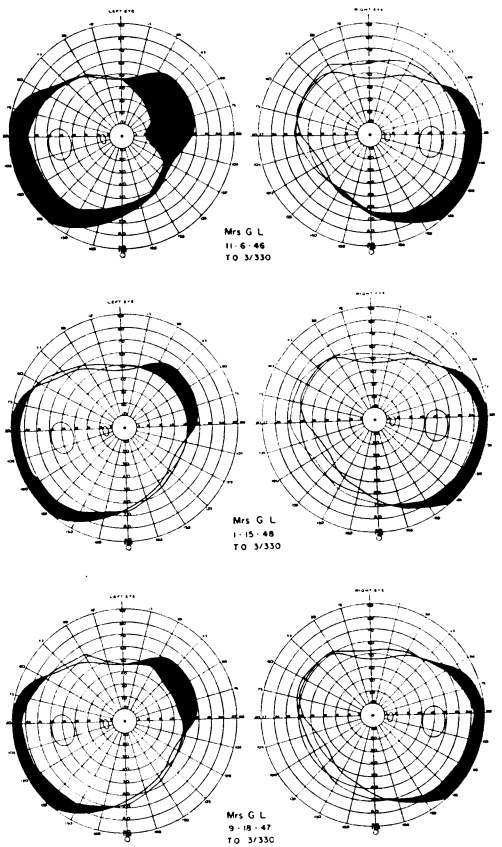


Fig. 1.—Case 7.

On September 18, 1947, the field and blindspots showed some improvement, while on January 15, 1948, the blindspots were normal in size and the only remaining peripheral field defect was a slight concentric contraction in the upper nasal quadrant of the left eye. At this time the corrected vision in each eye was 20/15−.

CASE 8.—Mrs. M. F., aged 52. This white woman was first seen in the office in June, 1945, at which time she complained of gradual loss of vision in the left eye. Vision in the right eye was 20/100

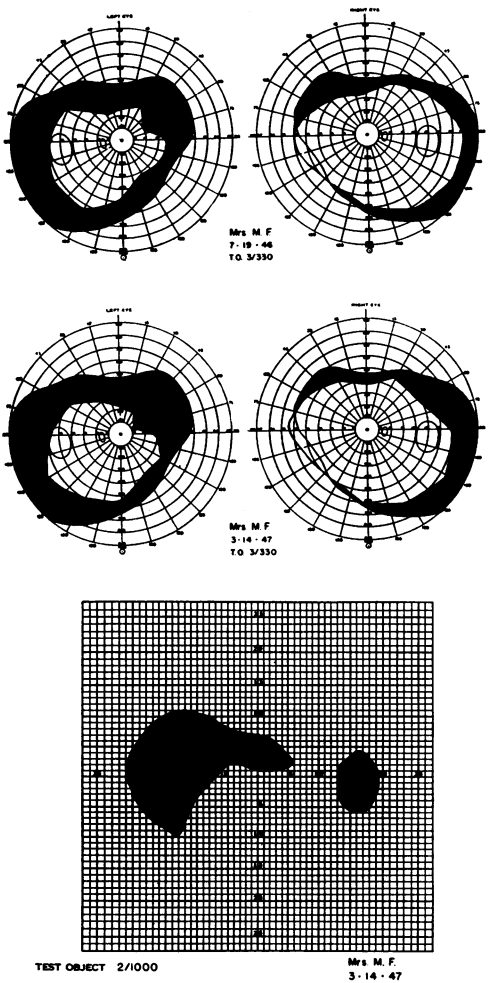


Fig. 1.—Case 8.

corrected to 20/15, while that in the left eye was 20/70−, unimproved. Tension was 19 in the right eye and 35 in the left eye. Nothing remarkable was noted in the examination other than a

rather marked cupping and pallor of the left disc with some loss of field and a large Bjerrum scotoma above in the left eye. The patient

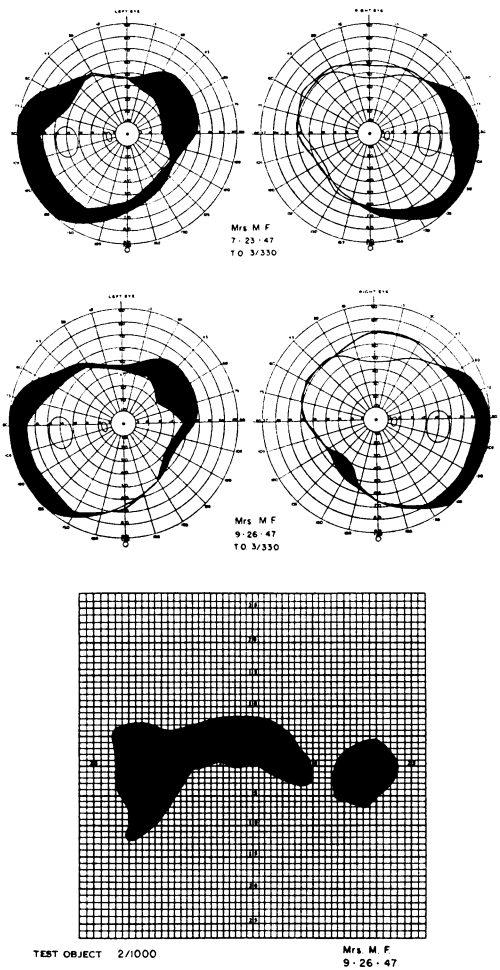


Fig. 2.—Case 8.

was placed on miotics and the tension was found to be O.D. 19, O.S. 22, when she was next seen several weeks later.

One year later, in spite of maintaining normal tension at every office visit the field showed more cut, while in March, 1947, there

was an even greater defect in the field. At this time a flap sclerotomy was performed on the left eye and the patient was given dicumarol for 2 weeks. Following this the field improved somewhat

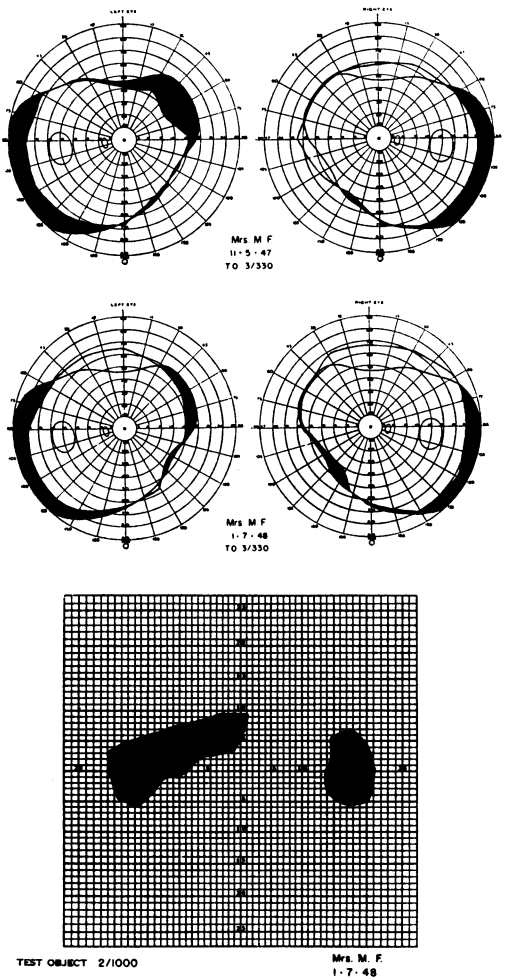


Fig. 3.—Case 8.

but the tension in the left eye rose to 30 and remained at that level in spite of the continued use of miotics, also the blindspot increased in size. Consequently in October, 1947, an iridencleisis was done on

the left eye followed by 2 additional weeks on dicumarol. In November, 1 month after operation, the tension was 19 in each eye and has remained at that level since, while at the same time the field showed considerable improvement. In January, 1948, the field was

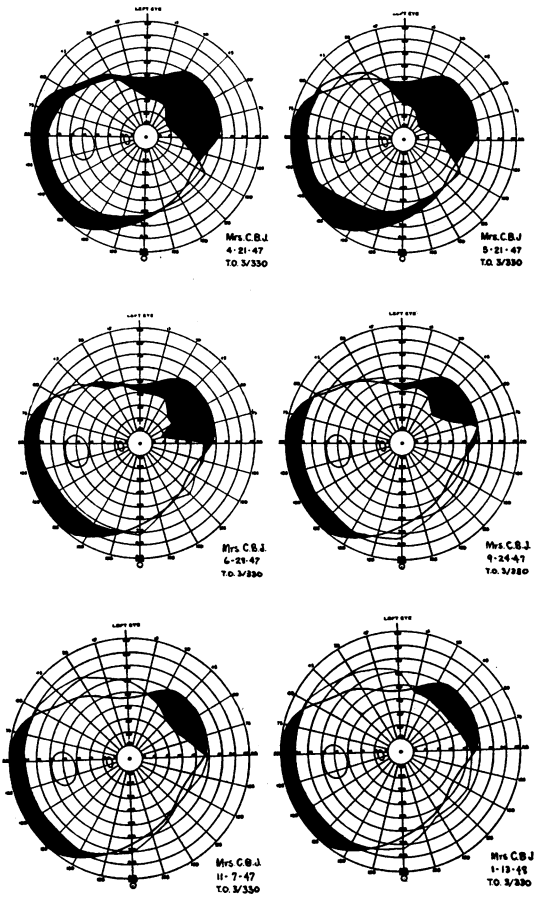
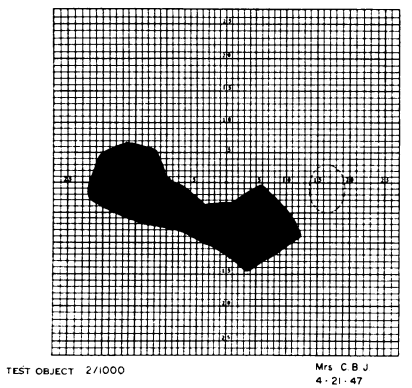
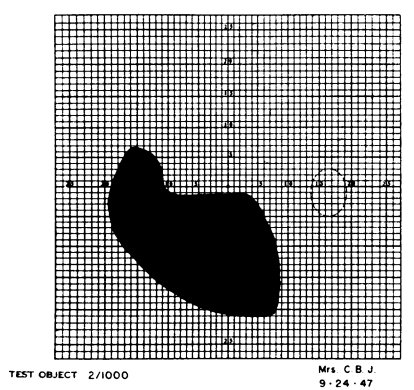


Fig. 1.—Case 9.

almost normal in all meridians and the Bjerrum scotoma has shown some improvement but the central vision has not been improved.

CASE 9.—Mrs. C. B. J., aged 36. This white woman was first seen on April 21, 1947. She stated that she had been born blind in


TEST OBJECT 2/1000
Mrs. C B J
4 · 21 · 47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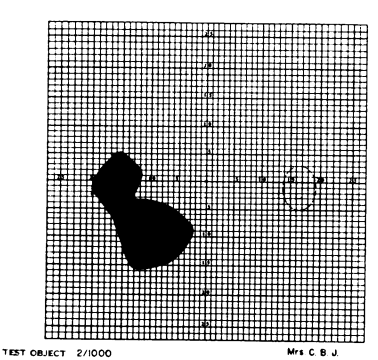
Mrs. C B J.
9 · 24 · 47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Mrs. C. B. J.
1 · 13 · 48

Fig. 2.—Case 9.

the right eye and that while she was still an infant it had begun to enlarge. It had been enucleated because of pain by Dr. Louis S. Greene 10 years before I had seen her. She said that Doctor Greene had prescribed drops for the left eye and had cautioned her about constant observation of it but she had not seen him for 8 years and had not used the drops for 6 years. There had been no pain nor inflammation in the left eye. Left vision was 20/40−, unimproved by refraction; the media were clear and the fundus normal with the exception of the disc which showed a wide and deep cup with marked pallor. The cornea measured 12.5 mm. in diameter and the intraocular tension was 52. The peripheral field showed a marked upper nasal defect and the central field a large Bjerrum scotoma below.

On the following day a flap sclerotomy after the method of Cruise was done and the patient placed on dicumarol for 10 days. One month after operation the tension had been reduced to 17 and has remained in that vicinity since. There was no improvement in the field a month after the surgical procedure, but on June 28 an improvement had begun. The peripheral field showed continued improvement on September 24, 1947, but the blindspot had not responded and consequently in early October she was again hospitalized for 2 weeks of dicumarol therapy. By November 7, 1947, the field and blindspot showed marked improvement and when last seen on January 13, 1948, no further changes were noted. The central vision has improved to 20/20−.

COMMENT

Until recently there has been no alarming increase in the prothrombin time of any patients undergoing treatment with dicumarol. However, there are 2 recent cases who have been taking the drug at home with weekly checks of the prothrombin time, after it was thought that their maintenance dosage had been adequately determined, who have suddenly developed hematuria with all the symptoms of renal calculus. Upon examination by a urologist, nothing of note was found except a marked increase in the prothrombin time. Because of the experience of these 2 patients I feel that it probably will be safer in using the drug to have daily checks of the prothrombin time for some weeks rather than let the patient be checked weekly after a supposed stabilization of the blood

level during a 1-week or 2-week period of frequent observation.

Of the 9 cases reported in this preliminary report, 6 had dicumarol with benefit some months or years after the tension had been reduced by surgery but, in spite of the reduction of tension, the field changes showed continued progression. One patient had dicumarol immediately following operation and 5 months later had a second course following which there was marked improvement in the fields. The remaining 2 patients had dicumarol immediately following operation with improvement in the visual fields. Therefore, it is impossible to say whether dicumarol was the effective agent in the gain in field or that surgery played the important role. However, it has generally been assumed in the past that the field that was lost in glaucoma was not restorable by any means except in very rare instances.

There are many questions that come to mind in relation to this problem which I cannot answer at this time. This report is presented because it has seemed to offer some hope in what has formerly been an almost hopeless condition and, while the work that has been done is purely preliminary, it would seem to warrant further investigation by many more ophthalmologists.

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DISCUSSION

DR. JOHN H. DUNNINGTON, New York City: I had not intended discussing Dr. McGuire's presentation because I have had no experience with the use of dicumarol in glaucoma. I did study his field charts some weeks ago and the improvement is most striking. The central field defects show similar improvement. At my suggestion they were not presented today because of lack of time. Changes such as he has shown are certainly most interesting and encouraging. I hope that these findings will stimulate many others to try this form of treatment.

DR. PAUL A. CHANDLER, Boston, Mass.: I have had no experience with this drug in the treatment of glaucoma. I should like to make a few remarks, however, on the cause of loss of field. We know if there is an acute rise of pressure in the eye one may find field defects of the same type seen in advanced glaucoma, and these field defects are reversible. They disappear if the tension is brought down promptly. When the pressure rises fairly rapidly and is sustained for a relatively short period of time we see a predominance of atrophy and a minimum of cupping of the disc. Where the pressure is moderately elevated for a long period of time we see a predominance of cupping, but the type of change in the visual field is much the same, whether we observe a marked cupping with atrophy, or a marked atrophy with minimal cupping. This suggests that the defects in the visual field in glaucoma are all caused by changes which take place at the nerve head.

We know also that there is a great difference in the strength of the disc, as witnessed by the fact that some eyes will tolerate a tension of 30, 35 or 40 without atrophy or cupping, and this over a period of years, whereas other eyes with a much lower tension show a steady progression in the degree of cupping and atrophy. There is, therefore, a great difference apparently in the strength of the optic disc, and the amount of damage which is done is the balance between the strength of the disc and the degree of pressure.

In the syndrome of so-called pseudoglaucoma which we observe in older people, the damage cannot be attributed to hypertension, because the pressure is never elevated. Nevertheless, we see a

progression of the cupping and a steady loss of field. However, in many of these older patients the time may come when no further cupping takes place and no further loss of field occurs, without any treatment whatever. The process appears to come to a standstill. This suggests that the pressure in the eye has reached a state of balance with respect to the lamina; no further cupping takes place, and no further loss of field occurs. It would appear, therefore, if we are going to prevent progressive cupping and atrophy of the disc, that we must either reduce the pressure or in some way increase the resistance of the disc.

I know it is a very controversial subject as to what causes the continued loss of field after operation, after normalization of tension. I cannot help but feel that the relation of the ocular tension to the strength of the disc in the individual case is the important factor, and that in the postoperative continued loss of field the majority of patients will have a tension of 17, 22 or 25. We have all observed patients who, after operation for advanced glaucoma, with a small field, might be expected to have continued loss of field after operation, but who fail to do so. If one analyzes the records on these patients, I think one will find in the majority of instances that it is these particular patients who do not continue to lose field that have postoperatively a hypotony, 6, 8, 10 or 12. The continued loss of field in my experience is by no means so evident in these cases as in those where the pressure ranges from 17 to 25. It may well be that once cupping has become well established, it requires less pressure to cause a further weakening of the disc.

Dr. McGuire's work has certainly been very impressive to me. The mechanism which makes the treatment effective, he suggests, consists in changes in the nutrient vessels of the optic nerve. It could well be, however, it seems to me, due to a change in the nutrient vessels of the lamina, so that he has succeeded by his treatment, in part at least, in strengthening the optic disc and thus preventing further cupping with atrophy following.

I think we all must feel grateful to Dr. McGuire for presenting this adjunct to the treatment of a disease which causes us all so much trouble.

Dr. Alexander E. MacDonald, Toronto, Canada: We have just had evidence of a very spectacular change, and I imagine many of us will want to try this new treatment. I have not used it in glaucoma, but from my work with heparin and dicumarol in occlusion of the central vein I have had a fairly considerable experience

in the use of dicumarol, and I think our enthusiasm to obtain results such as Dr. McGuire has shown should be well considered, because dicumarol is a fairly dangerous drug.

Last Christmas I sent home for the holidays a patient whom I treated for occlusion of the central vein. He had had a very good result, normal vision. We used heparin for 3 days intravenously; I then used 300 mg. of dicumarol, then 200 and 100 and carried him at 100 while he was in the hospital. Over the Christmas holidays I sent him home with a prothrombin time of 32. He was to report for prothrombin times, but for some reason or other the laboratory staff over the holidays did not do his next prothrombin test until 3 days had passed, at which time it had risen to 58. The drug was immediately stopped, but in a couple of days we again gave him 50 mg. and permitted him to go home to a mining district north of Toronto. He had hematuria during the trip; the drug was stopped at that time. I think Dr. McGuire is well advised to keep these patients under daily observation for their prothrombin times.

DR. ANGUS L. MACLEAN, Baltimore, Md.: Dr. McGuire has made an extremely interesting and original observation and has added another condition to the rapidly growing list of uses for this amazing substance, dicumarol. If the visual field improvement noted occurred as a result of what is believed by many to be clinical doses of dicumarol, then I believe he has made a real contribution in the realm of glaucoma.

Two years ago, Dr. Bramble and I reported our results with the use of dicumarol in certain retinal vascular conditions. Almost from the start of our work we have had in mind the possible effect dicumarol might have on intra-ocular tension. We were able to observe its effect on one patient with chronic glaucoma simplex. The tension was readily controlled by miotics but rose quickly if these were discontinued. Following a period of dicumarol administration for other conditions, it remained normal for as long as 5 days following omission of the miotics. It did not occur to us, however, to try its effect on the type of case Dr. McGuire has described. Improvement in the vision and visual fields in retinal occlusion cases has been attributed to the use of dicumarol. Recently, in a case of cerebral thrombosis with right homonymous hemianopsia and aphasia, following conservative treatment with dicumarol for 2 months the fields returned to normal and the patient regained his ability to read and write.

Dr. McGuire has related the usual causes given to explain progressive visual field loss following successful reduction of intra-ocular tension by operation. There is another possible explanation

which has not been mentioned, namely, "blood sludging." Biochemists and other investigators have led us to believe that increased intra-ocular tension might cause a change of some of the fibrogen of the blood to fibrin and that deposition of this fibrin onto the red blood cells could lead to sluggishness of the circulation. After successful control of the tension by surgery this process once started might continue but would be checked by the anticoagulant effects of dicumarol. A very plausible theory and one which is still being investigated but one which has not as yet been fully proved. Certainly dicumarol has no effect on the walls of the blood vessels themselves. It causes no retardation of sclerotic processes and assays concerning dilatation of blood vessels following its administration have not been satisfactory. True, pathological studies of the liver and other organs on animals following lethal doses of the drug have shown dilatation of the capillaries and other vessels but there are no conclusive reports on the dilating effects of clinical doses of the drug in humans. Personally, although hoping to find increase in retinal vessel caliber, I am not sure that I have ever seen any. I would therefore like to ask Dr. McGuire if he was able to detect any increase in the caliber of the retinal vessels in any of his cases. If this drug can produce dilatation of vessels such as is reported by Dr. McGuire, why is it not being used extensively in the treatment of essential hypertension?

Regarding the matter of dosage, I again find myself at variance with Dr. McGuire. I believe that raising the prothrombin time to around 35 to 45 seconds is extremely hazardous. This is equivalent to the prothrombin activity of blood diluted down to 15 or 20% of normal. Such levels are definitely in the hemorrhagic zone. Although such levels have been recommended by other clinical investigations, notably Barker of the Mayo Clinic, they are thought by the more conservative group of clinicians and investigators to be too high and too hazardous. A safe and effective level of prothrombin activity and a level we employ in treating our cases is between 20 and 25 seconds or around the level of prothrombin activity of blood diluted to around 50% of normal. Patients can be maintained at this level for indefinite periods, even as long as 2 to 3 years without harmful effects. Furthermore, if such a level is maintained, hospitalization, which is an expensive proposition, is not necessary. Most of our patients have been ambulatory. To determine an individual's pattern of response to the drug requires prothrombin determinations every 2 days for a week or more. Then determinations are necessary only every 1 to 2 weeks. Our patients have been permitted to pursue their usual activities uninterrupted

unless hospitalization was required for reasons other than control of the dicumarol administration.

In spite of these differences of opinion concerning the effects and methods of administration of dicumarol, I think Dr. McGuire's report is most interesting and his observations entirely original, and I plan to try this therapy on 2 of these cases just as soon as I return home from this meeting.

DR. WILLIAM P. McGUIRE, closing: I want to thank the discussers for their remarks.

Dr. Chandler mentions optic atrophy and cupping, and Dr. MacLean asked a question about the dilatation of the retinal vessels. From my limited experience I will answer both of these questions as well as I can. I have noticed no change in cupping of the disc in any of these patients; that is, the cupping is seen to remain constant after the use of dicumarol. I have noticed, however, that the color of the disc has improved, and I think that is almost a constant finding in these patients.

Whether there is any dilatation of the retinal vessels or not I cannot say. It is just a clinical impression that there is slight dilatation of the retinal vessels, but I certainly cannot say it is definitely so.

Dr. MacDonald mentioned this is a dangerous drug to use, and I agree with him to a certain extent. I mentioned in my paper that there were 2 patients who developed all the signs of renal calculus with marked hematuria; these patients were taking the drug outside the hospital. The prothrombin times had been regulated in the hospital over a period of several weeks, and we thought they were doing all right. The prothrombin time was checked once a week. However, when they developed hematuria their prothrombin times were respectively 99 in the first patient, and 59 in the second, both of which are too high. I have felt that if the patient is hospitalized under extremely limited activity that we did not run too much danger from carrying the prothrombin time up to around 35 or 40 seconds. That is what I have done with these patients I have reported today. However, in view of the experience of these 2 patients with hematuria I believe I am going to cut the prothrombin time down to 25 or 30 seconds, and try some of them at that level.

I have had no experience with intra-ocular tension after the use of dicumarol because all the patients on whom I have used the drug have had a normal tension following operation. I have had no experience or, as a matter of fact, I have never heard of blood sludging, but I think it is an interesting theory.