A CONTRIBUTION TO THE THEORY OF THE VASCULAR ORIGIN OF GLAUCOMA

BY

E. DIENSTBIER, J. BALÍK and H. KAFKA

PRAGUE

INTRODUCTION

It appears to-day that, after nearly a hundred years of controversy, the solution of the problem of pathogenesis of glaucoma has entered its final phase. The literature concerning this theme was immense. Some of the authors approached the problem with a modern outlook, but Leber's classical theory, with which their results did not agree, could not be rejected. After a time they formed a new conception based on their own observations.

Though the vascular system was often mentioned, the old conception of the pathogenesis of glaucoma remained unchanged. One thing was clear, namely, that primary glaucoma was not a local disease of the eyes, but an eye complication of some organic or constitutional disturbance still unknown (Gordon 1938, Duke-Elder 1945).

It was apparent that the problem of the pathogenesis of glaucoma could only be solved analytically. This method was used in the study of glaucoma, published in 1946. When analysing the origin of hypertension, the anatomical findings, clinical observations and the effects of treatment, the following conclusions were made, glaucoma is the expression of stasis in the venous system and the eye capillaries. It has its origin partly in organic vascular changes with a more or less marked spastic factor and partly in changes in function (vasoneurosis).

When ocular hypertension was analysed, it was clear that the problem was one of the intra-ocular fluid and blood circulation. These problems, which are so closely connected, are identical with the question of the peripheral circulation and of fluid-balance. It is therefore necessary to observe the function of the peripheral arterial circulation in glaucoma. The disorders of the peripheral arterial circulation in glaucoma, as already mentioned, are not only local but general. Some of the authors noticed a possible pathogenic connection with the circulation; on the contrary the majority

* Delivered at the XIVth Congress of the Ophthalmological Society of Czechoslovakia on October 2, 1948, in Prague.

† Received for publication, May 9, 1949.

From the first ophthalmic clinic, Director, Professor R. Kadlický, and from the second internal clinic, Director, Professor A. Vancura of the Charles University, Prague.
were satisfied with the old conception. They believed that ocular hypertension caused all the disorders which appear in the evolution of glaucoma, including the circulatory disorders. The word glaucoma and ocular hypertension were synonymous. Nothing changed this belief, not even the so-called glaucoma without hypertension—the disease where the second main sign of glaucoma is predominant, namely, the excavation of the papilla of the optic nerve without an increase in intra-ocular pressure. This form of glaucoma has a long history. It begins with Graefe's "amaurosis with excavation," then the term glaucoma without hypertension and pseudoglaucoma and later the term incomplete glaucoma. It was necessary to change this term, because the excavation which could have its origin in hypertension, can exist without it. Regarding the influence of eye hypertension it was said that the hypertension might be only small or transitory (Donders). No proof could be obtained from anatomical findings. Schnabel (1892-1905), described the lacunar degeneration of the nerve-fibres in the optic nerve with glaucomatous excavation. This condition, which was similar to changes occurring in the brain, was called "status lacunaris" by Pierre Marie. He described vacuoles formed in the optic nerve by the joining of the lacunae, and causing depression of the papilla. The author himself discovered that the causes of these disorders were angiosclerotic retrobulbar lesions, namely lesions of Haller's arterial circle. Thus Schnabel definitely rejected the view of the pressure-origin of excavation. In spite of his clear proofs and the work of his followers, his opinion of the origin of glaucomatous excavation is not generally accepted, even to-day (Elschnig, Ichikawa, Langrange, Beavieux, Gallanga, Magitot, etc.). Experimental results and clinical experience are not sufficient. Artificial hypertension produced by ligature of the veins did not give rise to excavation even after five months. Clinical cases are well known where the function of the eye restored by operation, deteriorates progressively, even without hypertension. This might be considered as evidence of disturbed tissue-nutrition.

REPORT OF THE METHODS USED AND OF OUR OWN OBSERVATIONS

When estimating ocular hypertension it is seen that there are problems which are in close connection with the peripheral blood circulation and fluid-balance. As already mentioned, these problems led to our examination of patients suffering from glaucoma, with particular reference to the examination of the cardiovascular system. The colloid osmotic pressure of the plasma-proteins was estimated, and the investigation completed by a series of tests leading to the explanation of the plasma-protein spectrum. The
blood cholesterol and urine were examined, and Wassermann reactions ascertained.

A total of 97 patients were examined: 23 with acute inflammatory, 14 with chronic simple, 37 with chronic inflammatory and 23 with secondary glaucoma.

A. Examination of the cardio-vascular system

A statistically important relation was found between vascular hypertension and glaucoma — hypertension being found in our series more frequently than in patients of the same age using the hypertension table of Robertson and Brucer from Vančura. In the group of secondary glaucoma, deviations were not so striking.

Because even the highest diastolic readings are comparatively low, hypertension due to loss of elasticity of the vascular wall can be excluded. Systolic hypertension could be expected in our patients on account of their age, but radiological findings show signs of arteriosclerosis. The ECG showed mostly left ventricular preponderance, which is usually caused by hypertension. Some findings, such as auricular fibrillation, prolonged P-R interval, infarctions and possibly bradycardia are signs of coronary sclerosis.

In conclusion it may be said that glaucoma with hypertension is quite evident in 95 cases where the examination of the cardio-vascular system was made. It is not possible to characterize this co-existence more closely. But it can be stated with certainty that the patients of this group suffer from vascular disease.

It is necessary to complete the examination of the peripheral abnormalities of the vascular system by the determination of the oscillatory index and capillaroscopy. Before making the examination a detailed family and personal history was taken for evidence of cardiovascular disease.

Patients suffering from acute glaucoma often complained of paraesthesia of the limbs, digití mortui, cyanosis, intermittent claudication, migraine, hypertension, diabetes, varicose veins and their complications and urticaria, as seen from their personal histories. These complaints confirm the presence of vascular disease. This positive history was more frequent in chronic inflammatory glaucoma (42), than in acute inflammatory glaucoma (22), and in secondary glaucoma (12). Excitability is considered a sign of a labile vascular system by many authors. This was found in chronic inflammatory glaucoma 16 times, in acute inflammatory 10 times, in secondary glaucoma 9 times, and in chronic simple glaucoma only twice.

Oscillation was determined by means of the oscillotonometer in the usual way above the ankle, above and below the knee-joint,
and on the arm. According to Prusik the loss of the oscillatory index to 50 per cent. and more was regarded as a decrease from the normal. The signs which were reasonably supposed to be of vascular origin, were verified by the symptoms of the patients. A decrease in the oscillatory index was found in acute inflammatory glaucoma in 11 cases (12 normal values), in chronic simple glaucoma in 8 cases (6 normal values), in chronic inflammatory in 15 cases (22 normal values) and in secondary glaucoma in 4 cases (19 normal values). In 97 cases a distinct decrease of values above the knee-joint was seen 4 times. This decrease indicated the necessity for appropriate therapy.

When making a critical evaluation of these facts two striking points are seen: decreased oscillations in all groups except secondary glaucoma, and the obvious predominance of this decrease in chronic simple glaucoma.

Capillaroscopy: the capillaroscopic determinations were made by the Zeiss capillaroscopic microscope. The capillaries of the nailrim, the flexor sides of the fore-arm, the outer part of the arm above the olecranon and the left infraclavicular region were examined. From the findings it was possible to estimate the condition of the capillaries.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Vasoneurosis</th>
<th>Transitory forms</th>
<th>Arteriosclerosis</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gl. ac. infl.</td>
<td>14</td>
<td>4</td>
<td>5</td>
<td>—</td>
</tr>
<tr>
<td>Chr. simple</td>
<td>2</td>
<td>1</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Chr. infl.</td>
<td>16</td>
<td>9</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Sec.</td>
<td>6</td>
<td>1</td>
<td>4</td>
<td>12</td>
</tr>
</tbody>
</table>

When making a microscopic examination of the capillaries none of the 23 cases of acute glaucoma gave normal findings. This group showed an absolute predominance of vasoneurosis. In chronic simple glaucoma the relationship is quite different, giving evidence of arteriosclerosis. In chronic inflammatory glaucoma both groups are the same and finally in secondary glaucoma the microscopic findings of the capillaries are mostly normal.

In making a general estimation of the cardio-vascular findings, the most striking thing is the tendency to disease in our patients. The cardio-vascular findings show that the patients with glaucoma often suffer from hypertension with all its consequences and electro-cardiographic findings. X-ray findings show the presence of arterio-sclerosis, which is not surprising, considering the age of the patients. The oscillatory findings indicate anatomical and, considering the age, mostly arteriosclerotic changes in the peripheral arteries. The most common occurrence in chronic simple glaucoma may well illustrate the findings of those authors who
found sclerotic changes in the intra-ocular vessels. The microscopic examination of the capillaries shows the same condition in the smallest vessels. In general our cardio-vascular findings are in agreement with the extensive literature.

B. Biochemical examination

The protein spectrum was examined first to estimate the colloidal osmotic pressure from the absolute values of the serum protein. This osmotic pressure, as was known, plays an important part in the formation of the tissue fluid against the hydrostatic blood pressure of the capillaries. It was also necessary to verify the influence of local changes on the plasma-proteins; in this way the importance of other associated illness and their possible aggravation of the increased intra-ocular pressure was seen. The erythrocyte sedimentation-rate was estimated using the Westergren method, and read after the first two hours and after 24 hours. The flocculation test with cadmium sulphate according to technique of Wuhrmann and Wunderly and the Takata reaction were performed and estimated according to these authors. The nephelographic curve was examined instead of Weltmann's turbidimeter band. But the findings had only a relative value because for technical reasons it was not possible to measure the turbidity by means of the nephelometric arrangement of Pulfrich's photometer. The turbidity was ascertained fluorophotometrically by its transmission of light. The absolute plasma proteins were estimated by the Kjehldal method.

The normal erythrocyte sedimentation rate was 10 mm. for men, 13 mm. for women during one hour.

<table>
<thead>
<tr>
<th>Normal</th>
<th>Increased</th>
<th>Not explained</th>
</tr>
</thead>
<tbody>
<tr>
<td>gl. ac. inf.</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>chr. s</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>chr. infl.</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>sec.</td>
<td>18</td>
<td>5</td>
</tr>
</tbody>
</table>

We suppose therefore that glaucoma itself does not lead to an increase of the erythrocyte sedimentation rate even in the presence of acute inflammation. When higher values during the first two hours were found these could be nearly always explained by concurrent disease leading to an increased sedimentation rate (inflammatory or degenerative kidney diseases, inflammatory diseases of the urinary tract, diabetes mellitus, arteriosclerosis univ.). This increase was then explained by the primary ocular findings in secondary glaucoma.

The cadmium test was positive in four cases. This cannot be explained by the glaucoma and an explanation similar to that given for the erythrocyte sedimentation rate was suggested. The Takata test was always negative. Its positive result would have indicated the necessity for a further liver investigation.

In nephelogram the most striking change was a shift to the left. A clear shift to the left was seen only once (—2). This could be explained by the general serious condition of the patient where the acute glaucoma occurred with nephrosis, diabetes and severe cachexia. The shift to the left (3,4) was seen 21 times, in 11 cases in chronic inflammatory glaucoma. It is likely that this shift has nothing to do with the glaucoma itself, because it did not occur in 3/4 of the cases. We did not always succeed in finding a connection with other disease. A shift to the right was not noticed. Comparing the heights of our curves we nowhere saw the clear fall which is an unfavourable prognostic sign when considering the general condition of the patients.

The colloidal osmotic pressure was estimated according to the paper of Wunderly and Wuhrmann. We next wanted to determine whether the decrease of the COP was the cause of glaucoma and under which conditions. The normal COP is given as 300-400 mm. H_2O by the above-mentioned authors. This means nearly 22-29 mm. Hg. The decrease below 300 mm. H_2O was found in 33 cases (see the table).
C. As a supplement to the blood examination the Wassermann test and gonorreatic reaction were performed. Positive results were rare and unassociated with the condition.
Discussion

The examination of our patients suffering from glaucoma showed that the pathological findings were to a large extent lesions of the cardio-vascular system. This confirmed our conclusions about the functional and organic changes in the vascular system. These conclusions are in agreement with the findings of many authors. When the rest of the war literature accessible only to-day is reviewed, and the literature since 1945, many authors are found to agree with the vascular origin of glaucoma. Magitot considers the increase in intra-ocular pressure to be due to an increase in capillary permeability occurring as a result of vascular disease. On the contrary, atrophy of the optic nerve indicates another process, which causes vascular obliteration and lacunar degeneration. This obliteration is probably an anatomical obstruction which is the result of sclerotic narrowing of the lumen of the arteries. The spastic factor contributes in the early stages as in all vascular processes. Only later are the walls under the influence of obliterative degeneration. Redslob also considers lacunar degeneration of the optic nerve to be the main cause of excavation. Sjögren holds the same opinion. Weekers considered that changes in the ocular vascular system were the cause of glaucoma. The lesions affect the uvea, retina and optic nerve. The three main symptoms of glaucoma correspond to these three localizations: ocular hypertension, loss of the visual field and atrophy with excavation of the papilla. These three symptoms appear generally together but not always. Thus the author deals with the expression of incomplete glaucoma (mono- and bisymptomatic glaucoma). Gérard agrees with Weekers. In the pathogenesis of glaucoma the vascular phenomena are primary—this is said by Venco. Cristini considers that changes in the arteriolar vessels of the uvea are the cause of glaucoma. Morax in his contribution to the study of the pathogenesis of glaucoma considers that the vascular changes which are so constant in glaucoma are the dominating influence.

In the second group there are authors who say that glaucoma is caused by vascular disorders originating in the vegetative centres. To this group belongs L. Hess, who declares that the vascular and circulatory changes in glaucoma are angioneurotic changes due to central irritation. An important part is played by the diencephalic centre at the base of the brain (Karplus-Kreidl). Morreau considers glaucoma to be an oculovascular disorder caused by a disorder in the equilibrium of the sympathetic and parasympathetic system under endocrine influence. According to Marquenze glaucoma has its origin in vascular changes in the anterior and posterior segment of the bulbus oculi. These changes
result from imbalance of the vasomotor nerves. This imbalance is sometimes caused by the thalamus and at other times by the endocrine glands. Zondek and Wolfsohn show that glaucoma is connected with the di-encephalo-pituitary system. Magitot, perhaps influenced by these authorities, especially by Hess, concludes (1947) that glaucoma is not only a disease of the organ of sight but also a disease of the affect (which is far from his original conception). The importance of the central nervous system (either vegetative centres or centres of the autonomic nervous system) on the increase in intra-ocular pressure is emphasized by Podljasak, Fradkin, Levina, Archangelskij. Lucena considers that general and local vegetative dystonia is responsible for glaucoma.

These papers stress the vascular pathogenesis of glaucoma, and mention the participation of the organo-vegetative system and the ductless glands — partly in isolation, and partly in connection with the autonomic nervous system. Indisputably the autonomic nervous system has an influence, especially through innervation of the arterial walls, but this influence is inconstant and accessory. Sympathetic hypertension helps to promote an ischaemic crisis, just as parasympathetic hypertension discourages local angiospasm but is not able to neutralize it. The di-encephalic centres play an important part in the general regulation and co-ordination of the various autonomic centres as observed in all the higher centres of the autonomic system. Though their importance is considerable they do not always participate. As in all other higher autonomic centres of the cerebrospinal system, a loss in function after the phase of transient damping causes a freeing of activity of the lower centres which will take over autonomy. Failure may be to a certain extent compensated by the activity of the lower centres. This was proved experimentally, and many clinical observations also confirm it, e.g., extensive destruction of the di-encephalic sphere (by tumour, inflammation, etc.) were associated with no autonomic symptoms. In two cases Cushing removed the whole infundibulo-tuberal area, but he saw no important signs (Tinel).

It is evident that some authors explaining the influence of emotion on glaucoma failed to mention the activity of important intra-mural centres. There is a new danger that we shall not succeed in discovering the pathogenesis of glaucoma. The final explanation of the whole problem will be again postponed. Surely the autonomic centres have an influence, but these are the peripheral and intramural centres which form with the vessel together an anatomical and functional unit. Only in this sense it is possible to speak about the influence of the autonomic system in glaucoma.

Many syndromes can appear as well as increased and decreased
irritation of the central regulative systems. Syndromes showing excessive activity or functional inactivity of some peripheral autonomic centres do not depend on functional changes in the sympathetic or parasympathetic system. The changes in activity are brought about directly by disorders of the mural systems. This increased or decreased irritation can be constitutional, congenital and hereditary. Other conditions associated with increased irritation are certainly acquired. This acquired increase of irritation has different causes: (1) repeated reflex excitation (approximating to 'conditioned reflexes'); (2) humoral, autotoxic causes, perhaps in connection with slight renal and hepatic insufficiency, intestinal intoxications, arthritic diathesis, etc.; (3) glandular causes, e.g., Graves' disease, puberty, menopause or the menstrual cycle; (4) anaphylactic manifestations; (5) psychological disorders, especially emotion. These different factors nearly all lead to the activity and fixation of the different active or paralysing substances on the automatic nervous centres (Tinel).

It is the increased and decreased irritation—namely, dystonia of the autonomic vascular intramural system—which enables us to explain the signs occurring in the course of glaucoma, the so-called inflammatory signs, especially in young subjects where we cannot expect structural vascular lesions. It is similar to the simple vasomotor syndromes of other peripheral arteries, especially Raynaud's disease, which is a vasomotor neurosis in which spasm plays a primary part. Sclerotic vascular lesions are found only in the later stages of the disease as a consequence of prolonged vasomotor ischaemia. These lesions complicate and aggravate the syndrome, making the changes irreversible. According to Claude, it is one of the most striking examples of a change from a functional, dynamic and paroxysmal lesion into an organic, permanent and irreversible syndrome (Tinel). There are also cases where the spasm is secondary to a primary arterial lesion. In these cases there is a more marked narrowing of the vessels. It is generally known that angiospasm is associated with arteriosclerosis. The familial occurrence of inflammatory glaucoma, the marked incidence of glaucoma in certain families, the appearance of acute crises and their spontaneous disappearance, the effect of temperature, the influence of emotional factors all suggest a spastic factor. Some clinical manifestations are otherwise quite unexplainable; e.g., the crisis of transitory amblyopia, the changing of scotomata and all the disorders which subside after disappearance of the inflammation. On the other hand, chronic simple glaucoma which tends to come later and to get progressively worse is probably the result of a predominantly anatomical lesion.
From this point of view it is necessary to understand the influence of the endocrine glands. Glaucoma rarely occurs as an early or late complication of disorders in endocrine function. When glaucoma and endocrine disorders occur together, either hyper- or hypo-function of the endocrine glands may be present. The disorders of hyper- and hypo-function — i.e., the quantitative disorder—are not always the cause of endocrine disorders, but more often dysfunction—a qualitative disorder. The influence of the intramural autonomic vascular apparatuses on changes of irritability can be compared to the last drop which causes the glass to run over.

Finally, secondary glaucoma should be mentioned. Previously when workers have sought for the pathogenesis of glaucoma they have considered the primary and secondary forms as two distinct diseases. We consider that this view is incorrect. The difference is this: In primary glaucoma the primary lesion is the vascular disease, functional or organic; but secondary glaucoma is caused by other ocular lesions. The mechanism of origin may be the same. In the peripheral arteries we found signs not only of vasoneurosis, but also of arteriosclerosis. But not all secondary glaucoma is caused by these disorders. In some cases the influence on the vessels is direct, and after cessation of this the glaucoma spontaneously disappears. The most typical instance of this is acute serous iritis. The vascular disease is not primary in this case, as is confirmed by the fact that the ocular function is not injured when the glaucoma lasts a long time. Secondary glaucomas show only an increase in intraocular pressure. This is a proof that hypertension does not lead to the functional loss of the eye. On the contrary, there are diseases which cause ocular hypertension. These diseases, based on axon-reflexes, can in time lead to a functional condition which develops into an organic lesion with all its consequences. Ultimate loss of ocular function is not only due to changes in the vessels of the optic nerve, which lead to changes in the integrity of the nerve fibres. Nutritional disturbances play an important part. They have their origin in the damaged circulation of the choroid. Glaucoma during thrombosis venae centralis retinae occupies a special place in this category of secondary glaucoma. We know that it does not often occur. In the literature secondary glaucoma is mentioned as a complication in 20 per cent. of cases, but is this a true secondary glaucoma? It would seem that the same vascular lesions which lead to thrombosis cause glaucoma. The simultaneous appearance depends on the localisation of these lesions (retina, choroid).
The result of work on the estimation of acetylcholine, histamine, cholinesterase and amino-oxydase in the aqueous humour and blood-serum in patients suffering from glaucoma are not yet numerous, but indicate a vascular genesis. Bloomfield found a substance in the aqueous humour influencing the parasympathetic system 17 times in 20 normal eyes. In 7 cases acetylcholine was found, in 3 cases the substance was not acetylcholine. On the other hand the result was negative in 20 glaucomatous eyes. A feebly active parasympathicomimetic substance was found only 5 times. He concludes that this cholinergic lack is related to glaucoma. A substance was found by Halbertsma in the aqueous humour of glaucomatous patients. This substance was similar to histamine, judging by its effect on the vessels of the guinea-pig. This agrees with the previous findings of Chopra and Ridley regarding epidemic dropsy.

Bruckner (1943) was the first to consider the problem of cholinesterase. He was also the first to find cholinesterase in the aqueous humour of man. He does not consider that cholinesterase has its origin in blood. Esterase in the vitreous probably comes from the retina. In another work he determines the level of cholinesterase in isolated eye tissues. Rados (1943) was the first to estimate the level of cholinesterase in the blood of patients with glaucoma. In glaucoma its level is not different from the normal. On the contrary an increase in the serum level of cholinesterase in some patients suffering from glaucoma was found by Gallois and Herschberg. Thomas, Verain, Cordier, Henry (1946) have inconsistent results in estimating the level of the blood cholinesterase. They did not find cholinesterase in the aqueous humour or in the plasmoid. But Vidal and Malbran (1946) found an increase in cholinesterase in the aqueous humour in patients suffering from chronic glaucoma.

Our conception of glaucoma has therefore changed very much during the last few years. Two fundamental things are necessary: a careful diagnosis of glaucoma and the revision of our treatment. These are the problems with which we must concern ourselves.*

* We wish here to express our sincere thanks to Prof. J. Horejši, the director of the biochemical laboratory of the First Internal Clinic of Prof. K. Hynek, for enabling this work to be carried out and for his useful advice.

REFERENCES


Bruckner, R. (1943).—Ophthalmsiologia, 105, 37 and 200.


Hess, L. (1948).—Arch. d'Ophthal., 8, 197.


Magitot, A. (1938a).—Documenta Ophthal., 1.

——— (1947b).—Ann. d'Ocul., 180, 1 and 321.


Moreau, A. (1946).—Arch. d'Ophthal., 6, 344.


BOOK NOTICES


This book contains useful information with regard to the selection and care of cases of strabismus suitable for orthoptic treatment. There is, however, a lack of appreciation of the scope of early surgical treatment.

The author states in discussing the treatment of concomitant convergent strabismus in children that "where the squint is alternating and the vision equal in both eyes, the squint can be safely left, provided due care and attention are paid to the refractive error. The patient reports periodically for exercises, but as a rule no orthoptic treatment is given until the child can appreciate what is meant by "mental effort." This may be all very well if there is some contra-indication to operation on general grounds, but if such a procedure is universally adopted it means that the squinting child is left to battle with the adverse psychological effect that his physical deformity may cause, and is allowed to consolidate the secondary sensory and motor correspondences which subsequently may prove so difficult to remove. In the case of squint, as in any other physical deformity, an attempt should be made to cure the condition forthwith, not only cosmetically but also functionally.

The chapter entitled "The selection of Orthoptic Cases of Strabismus" is good and clearly set out, but it would have been better entitled "The selection of Cases of Strabismus for Orthoptic Treatment."

The section of the book dealing with practical lines of treatment is good, and it is refreshing to find that Mr. Giles appreciates the value of simple forms of apparatus. It is a pity that the author, although realising that ocular palsies are outside the scope of the book, has included two misleading diagrams (Figs. 16 and 21) which are intended to show the actions of the extrinsic ocular muscles. It ought to be recognised by now that the vertically acting recti