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Abstract

From the results of the various tests thus far mentioned, it may be said that of the patients with primary glaucoma, be it. inflammatory or simple, the majority point to the functional disturbances and unbalanced conditions of the diencephalo-hypophyseal system as well as of the autonomic system, and that their autonomic adjustment functions of the eye pressure as compared with those of the normal are considerably disturbed and are in unbalanced state.

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STUDIES ON THE ETIOLOGY OF GLAUCOMA

PART 5. ON THE AUTONOMIC ADJUSTMENT FUNCTIONS OF EYE PRESSURE IN THE PATIENTS SUFFERING FROM GLAUCOMA

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INTRODUCTION

As has been reported previously, the author has proven that the eye possesses the functions which adjust the intraccular pressures autonomically so as to maintain a constant level at all time ; and that these functions are taking place through a functional cycle of "the eyeball → the ophthalmic nerve → the eye pressure center → the autonomic nerves → the eyeball."

In the present paper are presented the author's findings under what conditions the autonomic adjustment of eye pressure of the patients suffering from glaucoma are functioning and under what conditions the autonomic nerves are functioning ; and at the same time the author's interpretations on the causes of simple glaucoma are presented.

RESULTS OF EXAMINATIONS

1. Subjective symptoms : It is well known that when the autonomic nerve system or the diencephalon is in jeopardy and is not functioning properly, the patients often complain of gastro-intestinal disturbances such as constipation, diarrhea, and enteritis ; and vascular disturbances such as syncope, vertigo, quickened palpitations, and hemicrania ; and psycho-neurotic disorders such as anxiety, irritability, and insomnia. Therefore, with a view to acquaint himself more intimately about the conditions of functions of the autonomic nerve system and of the diencephalon, the author has examined 21 patients suffering from simple glaucoma and 18 patients with inflammatory glaucoma to see whether or not they present such symptoms as mentioned above ; and has obtained the results as shown in Table 1.

Table 1. Subjective Symptoms

Disturbances		Simple Glaucoma		Inflammatory Glaucoma	
		Case	%	Case	%
Gastro-Intestinal		13	61.9	5	27.8
Vascular		15	71.4	10	55.6
	Palpitations	7	33.3	5	27.8
	Hemicrania	12	57.1	6	33.3
	Vertigo	8	38.1	7	38.9
Psycho-Neurotic		16	76.2	15	83.3
	Anxiety	10	47.6	13	72.2
	Irritability	11	52.4	9	50.0
	Insomnia	9	42.9	5	27.8

As can be seen from the results in Table 1, the patients suffering from glaucoma complain of these symptoms to a quite high degree ; and these results are apparently suggestive of the existence of functional disturbances of the diencephalon or of an unbalanced condition of the autonomic nerve system.

2. Aschner's test : The phenomenon in which symptoms such as marked bradycardia and occasionally nausea and vomiting occur due to the compression of the eyeball is known as Aschner's test positive, and this phenomenon is thought to be indicative of parasympatheticotonia. With an ophthalmodynamometer applied over the eye-lid at the pressure of 150 gr. for 5 seconds, the author has conducted compression tests on 30 normal persons, 35 patients with simple glaucoma, and on 32 patients with imflammatory glaucoma in order to determine the pulsations both before and after the compression, and obtained the results as shown in Table 2. Namely, changes in the pulse counts of glaucoma patients are more marked than those of the normal persons, and this fact is suggestive

Table 2. Changes in the Pulse Counts

Subject	Max.	Min.	Average
Normal	9	0	2.8
Simple G.	20	0	4.9
Inflammatory G.	16	0	4.8

of that the majority of glaucoma patients in general are in the state of parasympatheticotonia.

3. Dermography : By making dermography as a method for estimating the conditions of the autonomic nerve system of glaucoma patients, the results as shown in Table 3, have been obtained. As is seen from Table 3, more than a half of the patients present the ectatic type of response ; and this fast seems to suggest that the autonomic nerve systen in the glaucoma patiects is in a rather unbalanced state.

Table 3. Dermographic Results

	Simple G.		Inflammatory G.	
	case	%	case	%
Normal	5	23.8	6	33.3
Dermographia alba	0	0	1	5.6
Dermographia rubra	16	76.2	11	61.1

4. Water test : Water test is known as one of the methods for indicating the conditions of vascular and renal functions. The method is to measure the specific gravity and the volume of urine excreted during the four-hour period after administering 800 c.c. of black tea to the patient early in the morning after urination, and finally to determine the vascular and renal conditions from these measurements.

The volume of 800 $\pm$ 300 c.c. excreted within the four-hour period is considered to be the normal limit, the volume exceeding 1,100 c.c. to be the accelerated excretion, while that less than 500 c.c. to be the inhibited excretion. In this instance the specific gravity of urine is also taken into consideration. When the glaucoma patients have been examined by this method, the urinoexcretory disturbances has been clearly indicated in more than one half of the glaucomatous patiens, as shown in Table 4. Especially in simple glaucoma, an extremely large number of patients have been found to present the inhibition of secretion.

Table 4. Water Test

	Simple G.		Inflammatory G.	
	case	%	case	%
Normal	9	42.9	6	37.5
Accelerated	2	9.5	5	31.2
Inhibited	10	47.6	5	31.2

5. Schellong's test : It is a common knowledge that the blood pressure usually decreases when one changes from reclining position to standing position and that in this change of the posture the decrease of blood pressure is marked where there is any distrubance in the blood-adjustment functin. With a purpose to examine the functional conditions of blood-pressure adjustment of glaucoma patients, the author has conducted Schellong's test ; and obtained the results as shown in Table 5.

Table 5. Schellong's Test

	Simple G.		Inflammatory G.	
	case	%	case	%
Negative	13	72.2	9	50.0
Positive	5	27.8	9	50.0

If the degree of decrease in the blood pressure of more than 15 mm. Hg be considered as positive, then, many of the glaucomatous patients subjected to this test have been found to be positive. Consequently, from the results of the test, there seems to be a quite few glaucomatous patients whose adjustment of the blood pressure is not functioning properly.

6. Pliocarpine test : Pilocarpine test has been performed in order to determine the conditions of the autonomic nerve system in glaucoma patients. By the subcutaneous administration of 0.13 c.c./kg. of 1% pilocarpine hydrochloride to the patients, the pulse rates, blood counts, the amounts of blood sugar, the volume of saliva and sweat excreted, and systemic symptoms (frequent uriesthesis, palpitations, frequent respiration, and flushing of face) have been examined both before the injection of pilocarpine and 15, 30, 60, and 120 minutes after the injection.

From the results thus obtained, the state of the autonomic nerves have been estimated.

In this test, any one whose pulse counts increases more than 30 ; the increase in the numbers of leucocytes or in the quantity of blood sugar, more than 30 percent ; the volume increase of saliva excreted over 75 c.c. ; or one whose sweat comes down in beads, has been adjudged positive. In this test a good percentage of the glaucomatous patients have been found as positive as shown in Table 6.

Consequently, among the glaucomatous patiens there seems to be quite a few who present parasympatheticotonia.

Table 6. Pilocarpine Test

	Simple G				Inflammatory G			
	+	%	−	%	+	%	−	%
Puls Rate	1	11.1	8	88.9	1	11.1	8	88.9
Leucocyte Rate	3	33.3	6	66.7	1	11.1	8	88.9
Blood Sugar	5	55.6	4	44.4	2	22.2	7	77.8
Salivation	8	88.9	1	11.1	8	88.9	1	11.1
Sudation	5	55.6	4	44.4	6	66.7	3	33.3
Systemic Sympt	7	77.8	2	22.2	7	77.8	2	22.2

7. Adrenalin test : This method is employed also for the purpose of examining the state of the adjustment function of the autonomic nerve system. In this test, 0, 13 c.c./kg. of epirenamine hydrochloride is given subcutaneously to glaucomatous patients, and the pulse rates, blood pressures, leucocyte counts, the amount of blood sugar, and systemic symptoms (palpitation thinking restlessness, chill and shudder, frequent respiration, and tremors of limbs), are checked both before medication and 15, 30, 60, and 120 minutes after injection and on the basis of this observation, the state of the autonomic nerve system is estimated.

In this case, an increase of the blood pressure above 30 mm. Hg, exacerbations of pulse counts of more than 30, and the leucocyte counts and the volume of blood sugar increasing over 50 per cent are all classified positive. It has been observed that the majority of the glaucomatous patients are positive in this test, as shown in Table 7.

Table 7. Adrenalin Test

	Simple G				Inflammatory G			
	+	%	−	%	+	%	−	%
Puls Rate	0	0	9	100.0	0	0	9	100.0
Blood Pressure	3	33.3	6	66.7	0	0	9	100.0
Leucocyte Rate	5	55.6	4	44.4	5	55.6	4	44.4
Blood Sugar	8	88.9	1	11.1	8	88.9	1	11.1
Systemic Sympt	7	77.8	2	22.2	7	77.8	2	22.2

8. Insulin test : This method is used to examine the functional conditions of the diencephalo-hypophyseal system. As for the method, 0.1

unit/kg. of insulin is injected subcutaneously before meal time; and the quantity of blood sugar is measured both before injection and 15, 30, 60, 90 and 120 minutes after injection. And from these measurements, the functional state of the diencephalo-hypophyseal system is determined.

The results of the test have been divided into 4 types following Birkmayer's classification ; namely, reaction exacerbated, reaction dull, no reaction, and reaction reversed. These results, as shown in Table 8,

Table 8. Insulin Test

Response	Simple G		Inflammatory G	
	case	%	case	%
Exacerbated	4	44.4	6	75.0
Dull	1	11.1	0	0
None	1	11.1	1	12.5
Reversed	2	22.2	0	0
Normal	1	11.1	1	12.5

demonstrate that the majority of the glaucomatous patients show the responses exacerbated and the amounts of blood sugar diminished, so there seems to be the dimunition of the function of the diencephalo-hypophyseal system.

9. Findings of blood : As is known that in general in the case of parasympathicotonia eosinophilia is indicated and in sympathicotonia lymphocytosis, therefore, the author has conducted a series of examinations of blood, as one of the methods in determining the state of the autonomic nerves in the patients.

In this test the rate of increase in acidophile leucocytes over 5 per cent is taken for leucocytosis ; and that in lymphocytes over 45 per cent, for lymphocytosis. As the results, as shown in Table 6, the majority of

Table 9. Blood Pictures

Type of Glaucoma / Condition	Simple G		Inflammatory G	
	case	%	case	%
Eosinophilia	7	43.8	4	26.7
Lymphocytosis	1	6.2	1	6.7
Leucocytosis	8	50.0	10	66.6

the patients have been found to present eosinophilia ; and this fact proves that the patients suffering from glaucoma are mainly in the state of parasympathicotonia.

10. The pulse and the blood sedimentation rates : Where there is an unbalanced condition in the autonomic nerve system, bradycardia is known to present itself.

In the present examinations conducted on the patients with primary glaucoma, though a few patients with simple glaucoma had shown a low rate of pulse, the average of pulse rates of all cases was within the normal limit, as shown in Table 10.

Table 10. Pulse Rates of Glaucoma Cases

Simple G			Inflammatory G		
Min.	Max.	Average	Min.	Max.	Average
42	88	70.9	64	104	79.4

As for the rates fo blood sedimentation, although there were some with abnormally high rate, the average rate of all cases was within the normal limit, as seen from the results in Table 11.

Table 11. Rates of Blood Sedimentation of Glaucomatous Cases

	Simple G			Inflammatory G		
	Min.	Max.	Ave.	Min.	Max.	Ave.
1 hour	1	32	m. 6.5 f. 12.5	2	30	m. 7.0 f. 12.7
2 hours	4	60	m. 18.2 f. 28.3	3	65	m. 16.2 f. 28.2

11. Diurnal variations of the eye pressures : That diurnal variation of the eye pressure of the normal eyes are small while those of glaucomatous eye big is well known. The author has measured diurnal variations of the eye pressure in 56 primary glaucomatous eyes and has compared these results with those of the normal eyes. The results of the comparison, as already described in Part One, in the normal eyes ones presenting diurnal variation over 5 mm. Hg amounted to only 4.5 per cent whereas in the glaucomatous eyes, ones showing such diurnal variations came to 86.4 per cent and in the inflammatory eyes as much as 91.6 per cent.

From the fact that the diurnal variations of eye pressure are great in glaucomatous eyes, it may be said that the eye pressure of glaucomatous eyes, is clearly unstable against various influences and lacks in resisting power against stimuli; in other words, it shows that the autonomic adjustment function is out of order.

12. Provocative tests: There are many provocative tests recommended for the diagnosis of glaucoma as supplementary methods. In any of these tests, the responses to the loaded stimuli of glaucomatous eyes differ from those of the normal. As a usual procedure the author is performing various provocative tests, and surveying the results of lability test, one of these routine tests, differences in the eye pressures of 20 normal eyes between those before loading and after loading have been found to be, minimum, 1.5 mm. Hg; maximum, 9.5 mm. Hg; and the average, 4. 6 mm. Hg. In contrast to these values, in the case of 45 primary glaucomatous eyes, the minimum variation has beon found to be 2 mm. Hg; maximum, 58 mm. Hg, and the average, 11.9 mm. Hg, proving that variations of eye pressures in the glaucomatous eyes are far greater than those of the normal eyes.

These results also suggest that glaucomatous eyes lack in the power resisting against various changes occurring in the body.

13. Phenovital and Philopon: In the previous report, the author has mentioned that the pressures of normal eyes either diminish or increase when Phenovital, a drug acting on the diencephalon as a tranquilizer or Philopon, a drug conversely acting as an excitator, is injected subcutaneously. The author, again, has studied to see how these drugs would act on the glaucomatous eyes. As the results, it has been verified that Phenovital acts as to decrease the eye pressures both in simple glaucoma and in inflammatory glaucoma whereas Philopon acts as to increase and that these variations of the eye pressures are far greater compared with the variations in the normal eyes. In other words, these data will become one of the evidences proving the unbalanced conditions of the center adjusting the eye pressures in the glaucomatous eyes.

14. The effects of chlorpromazine on the eye pressure: Assuming that the eye pressures are being adjusted by the eye pressure center in the diencephalon and the autonomic nerves and that glaucoma is brought about by the failure on the part of these adjustment functions, it seems only natural to expect that the eye pressures would be brought back to a balanced condition if the drugs that tranquilize and prevent the autonomic nerve center from wearying out on account of unnecessary reactions.

Entertaining such an expectation, the author, with the administra-

tion of chlorpromazine, a ganglion-blocking agent, has investigated the effects of this agent on the eye pressures in 15 patients suffering from simple galucoma and in 12 patients with inflammatory glaucoma. As the results, it has been found that the eye pressures decrease in all the cases, and that the phasic variation also become rather small. In Figures 1 and 2 are shown the typical ones of these cases. As for the falling patterns taken by the eye pressure, the eye pressures begin to decrease about 30

Fig. 1. A case of acute inflammatory glaucoma

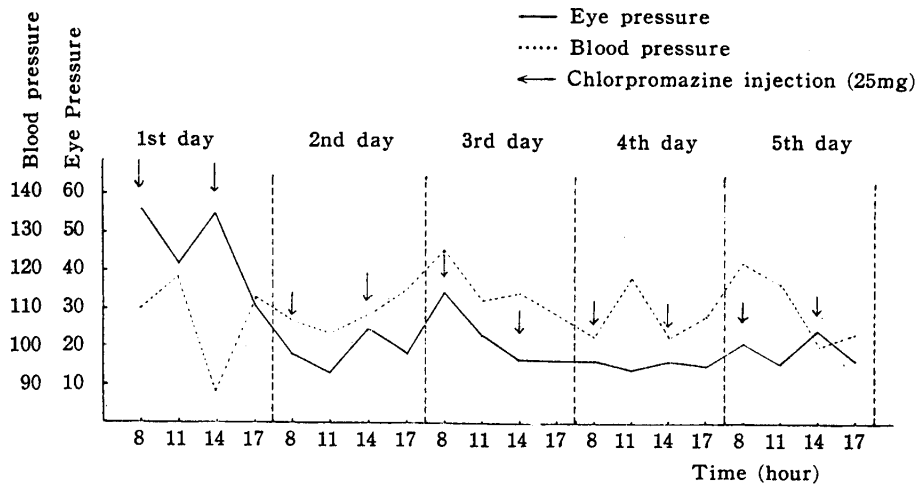
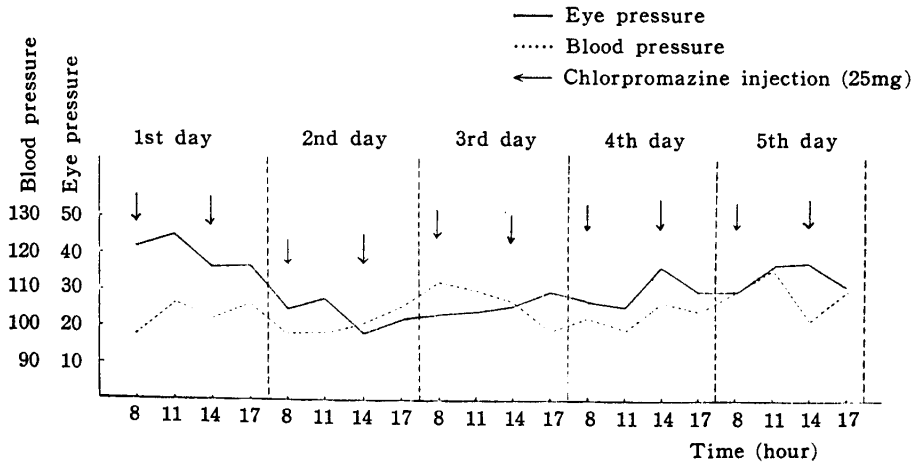


Fig. 2. A case of chronic inflammatory Glaucoma



minutes after injection ; and reaching the minimum level around 3 hours afterwards show a tendency to rise again. The systemic blood pressures also decrease, but no parallel relation have been recognized between the blood pressure and the eye pressure, nor can any change in the width of pupils be observed.

It has been, however, not possible to encounter a simgle case where glaucoma was cured completely by the administration of chlorpromazine alone. Whether this is due to a "get-used to" phenomenon arising in the body system or due to improper amounts of the drug and inadequate method of administration or due to an irreversible secondary change brough about by an abnormal rise in the intraocular pressures remains to be seen, and the answers to these problems must await future studies.

SUMMARY

From the results of the various tests thus far mentioned, it may be said that of the patients with primary glaucoma, be it inflammatory or simple, the majority point to the functional disturbances and unbalanced conditions of the diencephalo-hypophyseal system as well as of the autonomic system, and that their autonomic adjustment functions of the eye pressure as compared with those of the normal are considerably disturbed and are in unbalanced state.

DISCUSSION

The eye pressures of the normal eyes are known to be maintained almost at a constant level at all time despite innumerable changes of conditions both inside and outside of the body, occurring from time to time under all sorts of circumstances. The author has proven that this phenomenon is managed and controlled by the eye pressure center existing in the diencephalon the same as other important functions as the respiration, blood pressures, the body temperature, and so on. In other words, when an untoward change occurs in the intraocular pressure, that stimulus is transmitted to the eye pressure center by way of the ophthalmic nerve, causing an excitation of the center, the resultant impulse is in turn relayed to the eye by way of the autonomic nerve. Then in the eye there occur distension or contraction of the uveal vessels, a rise or a fall of blood pressure in the ciliary vessels, a necessary adjustment of aqueous humor production and a distension or a contraction of Schlemm's canal.

Thus, the volume of intraocular blood, the amounts of aqueous humor

produced, and the volumes of aqueous outflow, all being adjusted, the intraocular pressures seem to be automatically regulated. Under such circumstances, it goes without saying, the metabolism of salt, water, ptoein, sugar and so on, all controlled by the center in the diencephalon the same as the eye pressure, can be thought to exert influences on the intraocular pressure, This point has, however, not been clarified yet.

Next, the author studied from various angles the functional states of the diencephalo-hypophyseal system as well as of the autonomic nerve system in glaucomatous patients, and has proven that these functions are in the disturbed and unbalanced states. Namely, in the glaucomatous patients :

i) there are many who complain of such subjective symptoms as various gastro-intestinal, vascular, and psycho-neurotic disturbanses ;

ii) there are a considerable numbers who react positively to various tests such as the water, Schellong's, adrenalin, pilocarpine, insulin, and Aschner's tests ;

iii) diurnal variations of eye pressure are great ;

iv) the variation value in the lability test is great ;

v) in the diencephalo-hypophyseal diseases, diurnal variations in the eye pressure are great and the majority respond positively to the provocative tests for glaucoma ; and there have been bound some incorporated with glaucoma ;

vi) when a drug which acts either as an excitator or a tranquilizer upon the diencephalon is given, the eye pressure either rises or falls, markedly.

vii) the onset of acute glaucoma is often induced by over-work and over-excitation.

From these various reasons, it may be assumed that in the glaucomatous patients there are many whose functions of the diencephalo-hypophyseal system and the autonomic nerve systom are disturbed and their autonomic adjustment functions of the eye pressure are unbalanced.

However, as for deciding at once that the disturbances of the diencephalo-hypophyseal system or of the autonomic nerve system are the sole cause of glaucoma, there are some refuting and inconsistent facts against it such as :

i) of the diencephalo-hypophseal diseases, the incidences where glaucoma is accompanied are small ;

ii) of the patiens showing the unbalanced conditions of the autonomic nerve system, the incidences of accompaniment of glaucoma are small ;

iii) by chlorpromazine therapy glaucoma has been found to have been alleviated but none has been found cured completely ;

iv) when the diencephalon is damaged, the variations of the eye pressure become great ; but it has been found that the destruction of the diencephalon alone does not induce glaucoma.

Therefore, it seems difficult to explain all the causes giving rise to glaucoma by the disturbances of the autonomic adjustment functions of the eye pressure alone. In the case of glaucoma, on the other hand, there are such evidences as :

i) the facility of aqueous outflow is proven to be low by tonography;

ii) ones who possess sharrow anterior chamber are more liable to suffer from the disease; and the majority of glaucomatous patients posses narrow angle ;

iii) many are found to be cured by such treatments as miotics and filtering operations ;

iv) the disease may be induced by mydriasis ; and

v) in the cauterization test of the diencephalon, the cases have been encountered where the eye pressures increase abnormally when the operations such as the cauterization of the angle of anterior chamber or the ligation of vortex vein, in addition to that of the diencephalon, are performed, bringing about a little obstruction to the aqueous outflow.

These facts suggest that disturbances of the aqueous outflow exists in the glaucomatous patients. In glaucoma, however, such facts as described below have been found :

i) no small numbers of cases show the angle of anteror chamber opened ;

ii) the diurnal variations of the eye pressure are great, and furthermore, even when the lowering of intraocular pressure is successful by the treatment, the variations as compared with those of the normal eyes are, more often than not, still greater ;

iii) even when the eye pressures are successfully brought down to the normal level by operation or miotics, there are cases whose disorders of sight and visual field continue to aggravate ;

iv) when the cases cured by iridectomy are examined by a gonioscope, the iris root is often found not cut but remains still attached to the angle of anterior chamber ; and

v) even when the rate of aqueous outflow is impeded by the ligation of vortex vein or by the cauterization of the angle of anterior chamber, the eye pressure, instead of rising, on the contrary, has decreased.

For these reasons, it is difficult to attribute definitely the onset of primary glaucoma only to the disturbances of aqueous outflow.

In summarizing the various facts stated so far, the author believes it

is proper that the mechanism leading to glaucoma should be considered as follows :

Primary glaucoma would occur mainly to the ones having functional disorders of the autonomic adjustment of eye pressure when additional, local factors such as vascular and aqueous outflow disturbances occur in the eyeball.

CONCLUSION

The author has verified that the intraocular pressure like the respiration, the blood pressures, and the body temperatur, is adjusted automatically ; and has elucidated the mechanisms of these autonomic adjustment functions : namely, the intraocular pressure is managed and controlled by the eye pressure center located at the diencephalon and if any abnormal change of the intraocular pressure should occur, the resultant stimuli are transmitted to the eye pressure center via the ocular nerve, causing an excitation of the center. The impulse created in the center by these stimuli are in turn relayed to the eyeball by way of the autonomic nerve ; and by inducing distension or contraction of uveal vessels, a rise or a fall of the blood pressure in ciliary veins, regualting the volume of aqueous humor produced, and by distending or contracting SCHLEMM's canal, the volume of intraocular blood, the quantity of aqueous outflow, are adjusted in the eyeball. By these, the intraocular pressures are thought to be adjusted automatically. Furthermore, likewise the salt, water, and protein metabolisms having their center in the diencephalon like the eye pressure, may be assumed to exert influences on the intraocular pressure.

Moreover, after a series of studies on the functional conditions of the diencephalo-hypophyseal system and of the autonomic nerve system as well as on those of autonomic adjustment functions of the eye pressure, in the patients suffering from primary glaucoma, the author has verified that the majority of the patients have the functional disturbances in all these systems.

From these data of the above mentioned studies, the author believes that the primary glaucoma originates in the patients whose automatic adjustment functions of the eye pressure have already been not functioning properly, with the advent of additional local factors such as the disturbances of aqueous outflow or vascular disturbances, in the eyeball.