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Studies on the Etiology of Glaucoma Part 2. Relation-ship Between Diencephalon and Intraocular Pressure

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Studies on the Etiology of Glaucoma Part 2. Relation-ship Between Diencephalon and Intraocular Pressure*

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Abstract

The author has carried out the investigations from various angles on the relationship between the function of diencephalon and the eye pressure, and has found that all the evidences in the investigations point to a quite important role being played by the diencephalon in regulation of the eye pressure. Today it is a common physio-anatomical knowledge that the functions such as respiration, pulsation, blood pressure, and digestive actions which are essential for the maintenance of life, all possessing autonomy, are performed and regulated by the centers existing in the diencephalon. Now, the eye pressure, having such an important relationship to the visual functions, can not possibly be a lone exception. From these, therefore, it may be concluded that at least an autonomic center of the eye pressure exists in the diencephalon.

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**STUDIES ON THE ETIOLOGY OF GLAUCOMA
PART 2. RELATIONSHIP BETWEEN DIENCEPHALON
AND INTRAOCULAR PRESSURE**

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It is well known that in a diencephalon there are many autonomic centers which regulate numerous important functions such as heart beats, respiratory rate, blood pressure, pupillary activity, thermoregulation, intestinal motility, tonus of the gall bladder, and other functions. Therefore, in our search for the autonomic eye pressure adjustment centers, diencephalon must be investigated first of all. In the past, MAGITOT¹, ELWYN², THIEL³, SCHMERL and STEINBERG⁴, and others have suggested that the eye pressure center might exist in the diencephalon. More recently, KUROZU⁵, NAGAI⁶, SALLMANN and LOWENSTEIN⁷ have provided evidences of centrally elicited changes in the eye pressure.

By the stimulation of diencephalon under various conditions, the author has investigated the influences of the stimuli on the intraocular pressure and on the other hand, pursued the variations of the eye pressure in the cases of the diencephalo-hypophyseal diseases. According to the results thus obtained, the relationship between the diencephalon and the intraocular pressure has been studied.

METHODS AND RESULTS

The experiments were carried out with the use of the method devised by Prof. KUROZU: KUROZU-SHIMIZU's instrument and du BOIS-RAYMOND's induction-coil were used. The primary coil was connected to a storage battery (2 volts) and then the intensity of stimulus was regulated by controlling the distance between the primary and the secondary coils. Animals: Adult rabbits were used, and as for the sites of stimulation, Prof. KUROZU's so-called b-sympathetic area (the ventromedial hypothalamic nucleus) and c-parasympathetic area (the lateral hypothalamic nucleus) were selected.

The variations by stimuli in intraocular pressure, blood pressure, the width of the lid fissures, the behavior pattern of pupils, and nicti-

tating membrane were recorded simultaneously.

Finally, after the experiments the author confirmed whether the proper anatomical points had been stimulated or not by histologic examinations of the serial section specimens obtained from each animal.

I. The relation between the stimuli in the diencephalon and the intraocular pressure⁸.

The rabbits used in the present experiment were 41 in all, but the ones in which the right anatomical points of the stimulus had been touched numbered only 17 (b-sympathetic area, 6; c-parasympathetic area, 11). The symptoms provoked by electric stimulation of sympathetic area varied in proportion to the intensity of the stimulus, provided of course, when the right anatomical points of the stimulus had been hit. In the cases of weaker stimulation, light mydriasis, widening of the lid fissures, exophthalmus, and retraction of the nictitating membrane can be observed, while in the cases given stronger stimuli these symptoms are more marked and are accompanied by systemic spasm.

The responses by the stimulation of parasympathetic area are more complex. When the stimulus is weaker, generally no response of pupils but light miosis can be seen, and practically no other responses. While in the cases of a stronger stimulation, the majority usually show mydriasis after transient miosis, and widening of the lid fissures, retraction of the eyeball or exophthalmus, and systemic spasm. In this instance, the symptoms are so complicated that they appear to be the symptoms arising out of the combined reactions for the sympathetic and the parasympathetic stimuli.

i. Stimulation in b-sympathetic area.

As the responses vary according to the intensity of stimuli (Table 1), these are divided into two, for the weak and strong stimulations.

a. Results in the cases of weak stimulation.

The intraocular pressure in the majority of cases show an extremely slight fall (0.1—1.00 mm.Hg), while the systemic blood pressure is variegated, some will show a marked rise, the others a marked fall, and still others show a rise followed by a fall. The decreasing curve of the eye pressure begins to fall rather gradually after stimulation but after the cessation of stimulation it rises slowly and finally reaches the original pressure. No evidence of parallel relationship seems to exist between the eye pressure and the systemic blood pressure, though a slight mydriasis is revealed in all cases.

b. Results in the cases of strong stimulation.

Strong stimulation in sympathetic area results in a rapid, marked

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Table 1 Stimulation in Diencephalon

No. of rabbit	Stimulation point	Intensity of stimulus	Variations of I. O. P. (mm.Hg)	Variations of blood p. (mm.Hg)	Pupillary changes	Widening of eye fissures	Systemic spasm
9	Sympathetic area	Weak	-1.0	+23	Mydriasis	+	+
	"	Strong	+3.5	+60	"	++	++
10	"	Weak	-2.0 → +0.5	+19	"	+	+
	"	Strong	+4.0	+77	"	++	++
13	"	Weak	-0.3	+5 → -5	"	+	+
15	"	"	-0.2	- 7	"	-	-
	"	Strong	+3.5	+50	"	++	++
81	"	Weak	-0.5	+10 → -4	"	+	+
	"	Strong	+5.0	+35	"	+	++
82	"	Weak	-0.1	- 9	"	-	-
	"	Strong	+1.0	+2 → -10	"	+	++
2	Parasympathetic area	"	+6.0	+33	Miosis ↓ Mydriasis	++	++
5	"	Weak	+1.0	- 3	Miosis	-	-
	"	Strong	+4.0	-5 → -10	"	+	++
6	"	Weak	+0.5	+10	"	-	-
	"	Strong	+2.0	+55	Miosis ↓ Mydriasis	++	++
12	"	"	+7.5	+29	"	+	+
16	"	Weak	0	-25	Miosis	-	-
	"	Strong	+2.0	+12 → -19	Miosis ↓ Mydriasis	+	++
17	"	Weak	+2.5	+8 → -20	"	+	+
84	"	"	+0.1	- 2	-	-	-
	"	Strong	+5.0	+8 → -15	Miosis ↓ Mydriasis	+	+
85	"	Weak	+1.5	+10	Miosis	-	+
86	"	Strong	+8.0	+30 → -15	"	+	++
87	"	Weak	+3.0	+10	"	+	+
88	"	"	+1.5	+25	"	-	++

elevation of the eye pressure (1—5 mm.Hg) without exception. As for the systemic blood pressure, however, some cases demonstrate a sudden rise while others show a rise at first then a temporary drop below the initial pressure. In the cases showing a rise in the eye pressure, all have been found to exhibit symptoms such as exophthalmus, widening of lid fissures, systemic spasm, and a rise of the systemic blood pressure simultaneously. Therefore, a sudden rise of the eye pressure provoked by strong stimulation seems in all likelihood to be a response accompanied to the contraction of intraorbital smooth muscles and to an elevation of the systemic blood pressure.

ii. Stimulation in c-parasympathetic area.

a. Results in the cases of weak stimulation.

Some are occasionally found to show no change of the eye pressure but the most of them reveal a moderate rise (0.1, 1.5 mm.Hg). As for the systemic blood pressure, on the other hand, there are various cases; some showing a rise while others a fall, and still others a rise then a fall. As for the reactions of pupils, the majority of the cases show miosis but there are some that reveal no change; and as a rule, no other changes can be seen.

b. Results in the cases of strong stimulation.

The eye pressure invariably rises rapidly and markedly (2—8 mm.Hg); and the systemic blood pressure in some cases rises at first then falls later, while in some it only keeps on rising. Pupils in general reveal miosis, but in rare instances, mydriasis or transient miosis immediately after the stimulation followed by mydriasis. The widening of lid fissures and the systemic spasm have been observed in all the cases. Viewing the eye pressure changes, the pressure rises tremendously rapidly after stimulation and falls suddenly after the cessation of stimulation. Moreover, it has been observed that the rise in the eye pressure always occurs simultaneously with the widening of lid fissures and with the systemic spasm. From this fact the rise in the eye pressure observed in the strong stimulation may be considered as being intimately correlated with the orbital and the systemic behavioral changes.

From these results, it may be said that in the stimulation of the sympathetic area the eye pressure generally falls while in that of the parasympathetic area it invariably rises, excepting the influences of the contraction of orbital smooth muscles, the systemic spasm, and the rise of the systemic blood pressure, all occurring simultaneously when the diencephalon is stimulated. In this instance, however, no evidence of parallel relationship between the changes of eye pressure and those of

systemic blood pressure can be found.

- iii. Relationship between the stimulation of diencephalon and fluorescein-inflow rate in the anterior chamber.

In order to investigate the production of aqueous humor, the rate of the inflow into the anterior chamber, of the fluorescein previously injected venously has been examined by AMSLER-HUBER's method (Figs. 1 and 2).

Fig. 1 Stimulation in Sympathetic Area (Average of 12 eyes)

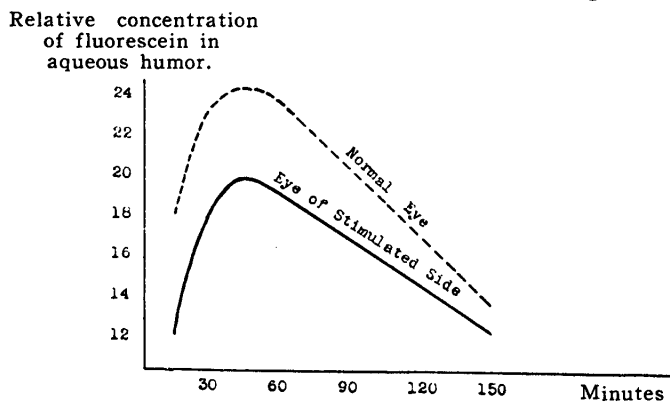
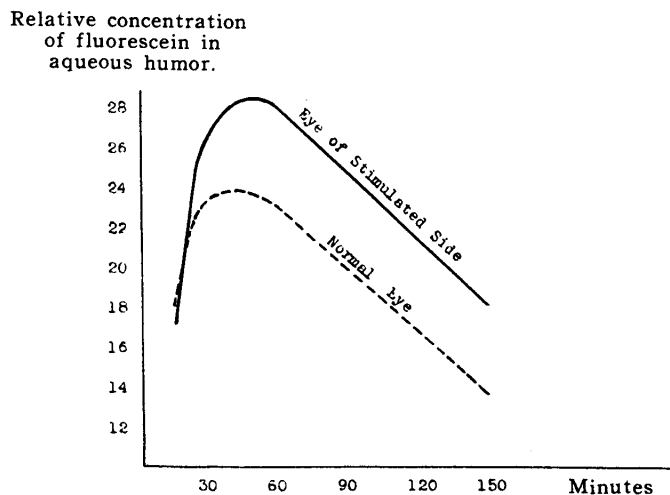


Fig. 2 Stimulation in Parasympathetic Area (Average of 10 eyes)



As the results, it has been observed that the rate of the inflow of fluorescein into the anterior chamber was inhibited by the stimulation of sympathetic area, whereas in the case of the stimulation in parasympathetic area it was accelerated. This fact is suggestive of the nervous regulating

mechanisms of aqueous humor production, inhibition by sympathetic stimulus but the acceleration by parasympathetic one.

- iv. Relationship between the unilateral stimulation in diencephalon and the pressure of the eye on the unstimulated side.

The changes of the eye pressure and the size of pupil on the stimulated side in the case of unilateral stimulation of diencephalon have been compared with the respective changes of those on the unstimulated side (Table 2). Even in the eye on the unstimulated side, the similar changes are revealed, as those in the eye on the stimulated side, though the degree of these changes seems to be slight.

Table 2 Relationship Between the Unilateral Stimulation in Diencephalon and the Pressure of the Eye on the Unstimulated Side.

No. of rabbit	Stimulation point	Intensity of stimulus	Duration of stimulation	Variation of eye pressure (mm.Hg)		Pupillary change	
				Stimulated side	Opposite side	Stimulated side	Opposite side
82	Sympathetic area	Weak	20	-0.1	-0.1	Mydriasis (±)	Mydriasis (±)
83	"	"	10	-0.2	0	"	-
85	Parasympathetic area	"	"	+1.5	+1.5	Miosis (+)	Miosis (+)
86	"	"	"	+8.0	+4.0	Miosis ↓ Mydriasis	"
87	"	"	"	+1.5	+1.0	"	Miosis ↓ Mydriasis

2. The eye pressure changes observed in the diencephalon-cauterized rabbits⁸.

If the adjusting center of the intraocular pressure, the so-called autonomic eye pressure adjustment center does really exist, it is reasonable to assume that some disturbances of eye pressure should be expected when that center is destroyed. Upon this assumption, the following experiment has been conducted.

Normal adult rabbits were divided into 3 groups and the first group was subjected to the unilateral cauterization of diencephalon, the second group to the unilateral cauterization of diencephalon as well as the ligation of vortex vein, and the third group to the cauterizations of diencephalon on one side and of the angle of anterior chamber on the same side.

Procedure: The diencephalon was cauterized for one minute with

the electrode, 26 mm. in length, 0.2 mm. the diameter and having its tip end uninsulated to the length of 0.1 mm., by KUROZU's method. By opening the bulbar conjunctiva and exposing the upper interior and the upper exterior vortex veins, these two veins were ligated with silk thread. To cauterize the angle of anterior chamber, a bow-shaped electrode was inserted into the anterior chamber and then a quarter of the whole circumference of the angle was cauterized. Using SCHIÖTZ's tonometer, the eye pressure was measured at a fixed interval for the period of two months after the cauterization.

i. The results of the first group: The phasic variations of the eye pressure on both the cauterized and the uncauterized sides were generally greater compared with those before the cauterization (min. 3.1 mm.Hg, max. 10.0 mm.Hg); and also the difference of the eye pressures between both eyes of the same rabbit as compared with the difference of those before the cauterization was greater (min. 3.1 mm.Hg, max. 10.0 mm.Hg). The maximum eye pressure, however, was 27.3 mm.Hg and there was none that exceeded 30 mm.Hg (Table 3).

Table 3 Changes of Eye Pressure of Rabbit Cauterized their Interbrains.
(Animals are cauterized only the right interbrains.)

No. of rabbit	I. O. P. (mm.Hg)	Before cauterization			After cauterization			Difference between both eyes	
		Max.	Min.	Difference	Max.	Min.	Difference	Before	After
62	R	23.5	17.3	6.2	27.3	17.3	10.0	3.1	10.0
	L	23.5	17.3	6.2	24.0	14.6	9.4		
64	R	20.4	17.3	3.1	24.0	17.3	6.7	3.1	6.7
	L	20.4	17.3	3.1	20.4	17.3	3.1		
65	R	20.4	15.9	4.5	22.4	17.3	5.1	3.1	3.1
	L	20.4	15.9	4.5	20.4	14.6	5.8		
69	R	18.8	14.6	4.2	20.4	14.6	5.8	4.2	5.8
	L	20.4	15.9	4.5	17.3	14.6	2.7		

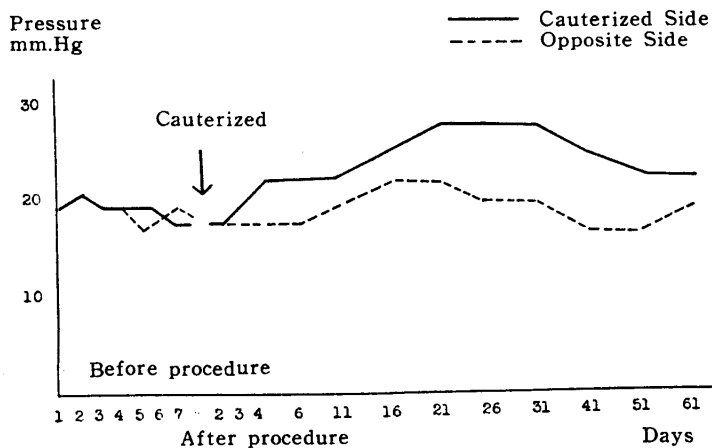
ii. The results of the second group: As a preliminary experiment, the changes in the intraocular pressure of five normal rabbits were investigated by the ligation of vortex veins. The eye pressure had shown a transient rise immediately after the ligation, but 24 hours later it fell markedly below the normal level. Subsequently it again rose gradually and 9 days after the ligation it returned approximately to the initial pres-

sure; and ever since the animals have been maintaining the normal pressure. With those rabbits whose diencephalon had been cauterized, the fluctuations of the eye pressures were greater (min. 5.8 mm.Hg, max. 11.7 mm.Hg) and the difference of the eye pressures of both of the same rabbit were also greater (Table 4). In one of these cases, its eye pressure was above 31 mm.Hg, for several days. (Fig. 3)

Table 4 Changes of Eye Pressure by Cauterization in Diencephalon and Ligation of Vortex Vein.

No. of rabbit	I. O. P. (mm.Hg)	Before procedure			After procedure			Difference between both eyes	
		Max.	Min.	Difference	Max.	Min.	Difference	Before	After
63	R	20.4	15.9	1.6	24.0	12.3	11.7	1.5	8.1
	L	20.4	18.8	3.1	20.4	17.3	3.1		
66	R	21.8	17.3	4.5	31.7	24.0	7.7	3.1	7.7
	L	21.8	20.4	1.4	24.0	17.3	6.7		
67	R	20.4	17.3	3.1	24.0	14.6	9.4	3.1	6.7
	L	20.4	15.9	4.5	20.4	17.3	3.1		
68	R	17.3	14.6	2.7	24.0	14.6	9.4	2.7	9.4
	L	20.4	15.9	4.5	17.0	14.6	2.7		
70	R	20.4	17.3	3.1	20.4	14.6	5.8	3.1	5.8
	L	17.3	17.3	0	17.3	14.6	2.7		

Fig. 3 Eye Pressure Curve of a Rabbit Which was Cauterized its Diencephalon and Ligated its Vortex Veins.



iii. The results of the third group: As a preliminary experiment, the changes in the eye pressure by electric cauterization of the angle of anterior chamber of 7 rabbits were investigated. The eye pressure showed a marked but transient fall after the cauterization, but on or about 12th day the pressure was found to have recovered to the initial level. None, however, showed rise in the eye pressure. On the contrary, in the rabbits with the cauterized diencephalon, the variations of the eye pressure after the cauterization became greater; and the author encountered one whose eye pressure reached even above 31 mm.Hg (Table 5). In view

Table 5 Changes of Eye Pressure by Cauterization in Diencephalon and Angle of Anterior Chamber.

No. of rabbit	I. O. P. (mm.Hg)	Before procedure			After procedure			Difference between both eyes	
		Max.	Min.	Difference	Max.	Min.	Difference	Before	After
71	R	20.4	18.8	1.6	20.4	10.4	13.6	3.1	6.9
	L	20.4	17.3	3.1	20.4	17.3	3.1		
72	R	20.4	17.3	3.1	24.0	17.3	6.7	3.1	3.6
	L	20.4	17.3	3.1	20.4	17.3	3.1		
73	R	22.5	20.4	2.1	31.7	12.3	9.4	3.1	7.7
	L	20.4	17.3	3.1	24.0	17.3	6.7		
74	R	20.4	14.6	5.8	17.3	7.3	10.0	3.1	13.1
	L	20.4	14.6	5.9	20.4	17.3	3.1		

of a small number of animals involved in the present experiment, it is difficult to draw a definite conclusion, but it seems that the phasic variation becomes greater when the diencephalon is destroyed, and furthermore, that when the local lesions such as the ligation of vortex vein or the cauterization of angle of anterior chamber is given, not only variations of the eye pressure become greater but also there is a tendency to accelerate abnormally the rise of the pressure. This experiment is quite interesting in that a possibility of the experimental induction of glaucoma has been found.

3. Influences of Philopon (methamphetamine hydrochloride) and Phenobital (phenobarbitalum solubile) upon the eye pressure of the normal individual⁹.

JEANSCH and THIEL³ reported that the eye pressure of the patient with glaucoma had been found to fall by administering the sedatives for

diencephalon such as Luminal or Ergotamine, but to rise by giving an excitatory drug, Pervitin. HEIM¹⁰, WIENER¹¹, GLAVAN¹², POPVICI¹³, GIFFORD¹⁴ and ABADII¹⁵ agree to this report, but recently AGARWAL¹⁶ has presented a contradictory opinion.

The author injected Philopon and Phenobital subcutaneously in the normal persons and obtained the results shown in Table 6. Namely, with Phenovital, a drug acting on the diencephalon sedatively, the lowering of the eye pressure, though slight, has been observed; but with Philopon, an excitatory drug, the rise in the eye pressure has been definitely recognized. In other words, even in normal person just as well as in the patients with glaucoma as proven by JEANSCH and THIEL, it has proven that the drug acting sedatively on the diencephalon lowers the eye pressure while the excitatory drug raises it.

4. Diurnal variations of eye pressure and the results of provocative tests in the patients with pituitary tumor¹⁷.

If an assumption is made that diencephalo-hypophyseal system is involved in the regulation of eye pressure, then it naturally follows that autonomic adjustment functions of the eye pressure would be in some way affected by the presence of tumor or inflammations in the vicinity of the pituitary body.

In the available literatures relative to this problem, IMRE¹⁸ claims that the pituitary body is one of the important centers involved in the adjustment of eye pressure and reports that one of

Table 6 Changes of Eye Pressure by Philopon and Phenovital
(Average of 16 cases)

	Variation of eye pressure (%)								Variation of blood pressure (%)						
	Before injection	After injection (Minutes)							Before injection	After injection (Minutes)					
		5	10	30	60	180	360			5	10	30	60	180	360
Philopon	100.0	105.7	103.7	105.7	108.4	105.6	105.5	Max.	100.0	102.9	105.2	99.4	102.1	105.0	106.6
								Min.	100.0	110.1	110.5	106.7	109.2	110.5	110.4
Phenovital	100.0	98.3	92.4	96.6	88.5	88.2	92.8	Max.	100.0	99.8	99.2	95.6	99.2	99.7	101.8
								Min.	100.0	95.5	97.1	95.1	91.7	93.9	90.5

Table 7 Results of Provocative Tests and Diurnal Variations of Eye Pressure in Diencephalo-Hypophyseal Diseases

No. of case	Kind of diseases	Diseases of eye	Diurnal variations of eye pressure (mm.Hg)		Provocative tests (mm.Hg)						
					Darkness	Lability	Massage	Coffee	Water drink	Philopon	Phenovital
1	Craniopharyngioma	Simple optic atrophy	R	3	0	12	0	4.5	12		
			L	6	-3	12	-2	0	8		
2	Pituitary adenoma	Conjunctivitis	R	8	6	9	0		14		
			L	7	0	11	-3		15		
3	"	Papillitis	R	5	0	13.5	-11	0	6	5.5	-7
			L	9	-3	16	0	8	11	7.5	-13.5
4	"	"	R	7	0	7	-2.5	3	3	3	-5
			L	9.5	1.5	9.5	-6	4.5	7	0	-6
5	Craniopharyngioma	Simple optic atrophy	R	29	8.5	3	-5	0	3	4.5	-1
			L	19	6	3	-3	0	0	2.5	0
6	Pituitary adenoma	Simple glaucoma	R	11	0	4	-8	3	15		
			L	6	0	0	-2	5	13		
7	Arachnoiditis	Choked disc	R	6	-3	10.5	-3	2.5	9	14	-3
			L	6	-1.5	3	-6	1	11	14	-3
8	"	Inflammatory optic atrophy	R	5	0	3	-4.5	3	7	0	-1
			L	4	-1.5	3	-4.5	5	9	0	-1

the symptoms observable at the early stage in the patient with pituitary tumor is the lowering of the eye pressure. JEANDELIZE¹⁹ mentions that glaucoma develops when a certain portion of the pituitary body is removed, while the lowering of eye pressure occurs when still certain another portion is removed. YAMASHITA²⁰ also proves that the eye pressure rises above 7—30 mm.Hg when the pituitary body is destroyed, and further he clarifies that, in this same instance, the protein concentration in serum and aqueous humor is altered. And SZILY²¹ says that if the function of the pituitary body is in jeopardy, there occurs a rise in the eye pressure. FREYTAG notices the lowering of eye pressure in one of the patients suffering from dystrophia adiposogenitalis. Thus, the existence of a close relationship between the eye pressure and the pituitary body has so far been amply stressed. The author, however, has investigated the diurnal variations of the eye pressure and the reactions to the various provocative tests, in the 6 patients with pituitary tumor and 2 patient with arachnoiditis and then has come upon an interesting finding in regard to the relationship between the two.

The results, as shown in Table 7, are as follows: the 10 eyes showed the diurnal variations of the eye pressure above 5 mm.Hg (max. 29 mm.Hg); one of them had the absolute value of the eye pressure of more than 30 mm.Hg; and in the provocative tests, the majority of cases gave positive results. Therefore, it will be able to conclude that eye pressure adjustment function seems to be perhaps impaired in patients with diencephalo-hypophyseal diseases. Such functional disturbances recovered somewhat by extirpation of the tumors.

5. Cases of diencephalo-hypophyseal glaucoma.

If there is an eye pressure adjustment center in the diencephalo-hypophyseal system, then in the cases of an impairment of the diencephalo-hypophyseal system, glaucoma should necessarily accompany. ZONDEK²², in his exhaustive examinations of the 22 cases with primary glaucoma, has found the impairment of various degrees in the diencephalo-hypophyseal system in the 16 cases. As already reported, the author²³ has also observed two cases with pituitary tumor accompanied by simple glaucoma.

CONCLUSION

The author has carried out the investigations from various angles on the relationship between the function of diencephalon and the eye pressure, and has found that all the evidences in the investigations point to a

quite important rôle being played by the diencephalon in regulation of the eye pressure.

Today it is a common physio-anatomical knowledge that the functions such as respiration, pulsation, blood pressure, and digestive actions which are essential for the maintenance of life, all possessing autonomy, are performed and regulated by the centers existing in the diencephalon. Now, the eye pressure, having such an important relationship to the visual functions, can not possibly be a lone exception. From these, therefore, it may be concluded that at least an autonomic center of the eye pressure exists in the diencephalon.

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