A NEW ADRENERGIC BLOCKING AGENT IN THE TREATMENT OF GLAUCOMA

by

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A THESIS

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It is the purpose of this report to describe some of the ocular effects of a new class of autonomic drugs and to present a preliminary report of their use in recalcitrant acute glaucoma. Our investigation of these drugs represents a final phase in a comprehensive study of the ocular effects of the various classes of autonomic drugs. In the past the studies were largely concerned with the corneal penetrability and ocular effects of stimulatory drugs, both cholinergic, e. g., acetylcholine derivatives and synergists, and adrenergic drugs, e.g., epinephrine[1,2,3]. The second phase of this program has been concerned with the development and study of the ocular effects of specific blocking agents. First a new class of autonomic drugs with a peripheral cholinergic blocking action was synthesized by Kenneth Swan and Norman G. White[4]. The most effective of these compounds, dibutoline, specifically blocks the stimulatory action of acetylcholine on the iris and ciliary muscles[5], but seems to have no direct influence on the ocular tension. The next step was to develop and investigate drugs with a specific adrenergic blocking effect; that is, drugs which would specifically block the stimulatory action of epinephrine and sympathin. The ocular pharmacology of acetylcholine and epinephrine and the action of cholinergic and adrenergic blocking agents are illustrated in figure 1.

We are not aware of an adrenergic blocking agent which produces consistent ocular changes when administered locally, but a number of compounds effectively block the stimulatory action of epinephrine when administered systemically. Dibenamine is the best known of these new agents. SKF#194 is another closely related compound of considerable promise (fig. 2)*. Dibenamine was discovered by Nickerson and Goodman to block specifically

*Dibenamine was provided by the Givaudan-Delawanna, Inc.
SKF:194 was provided by Smith, Kline and French Laboratories.

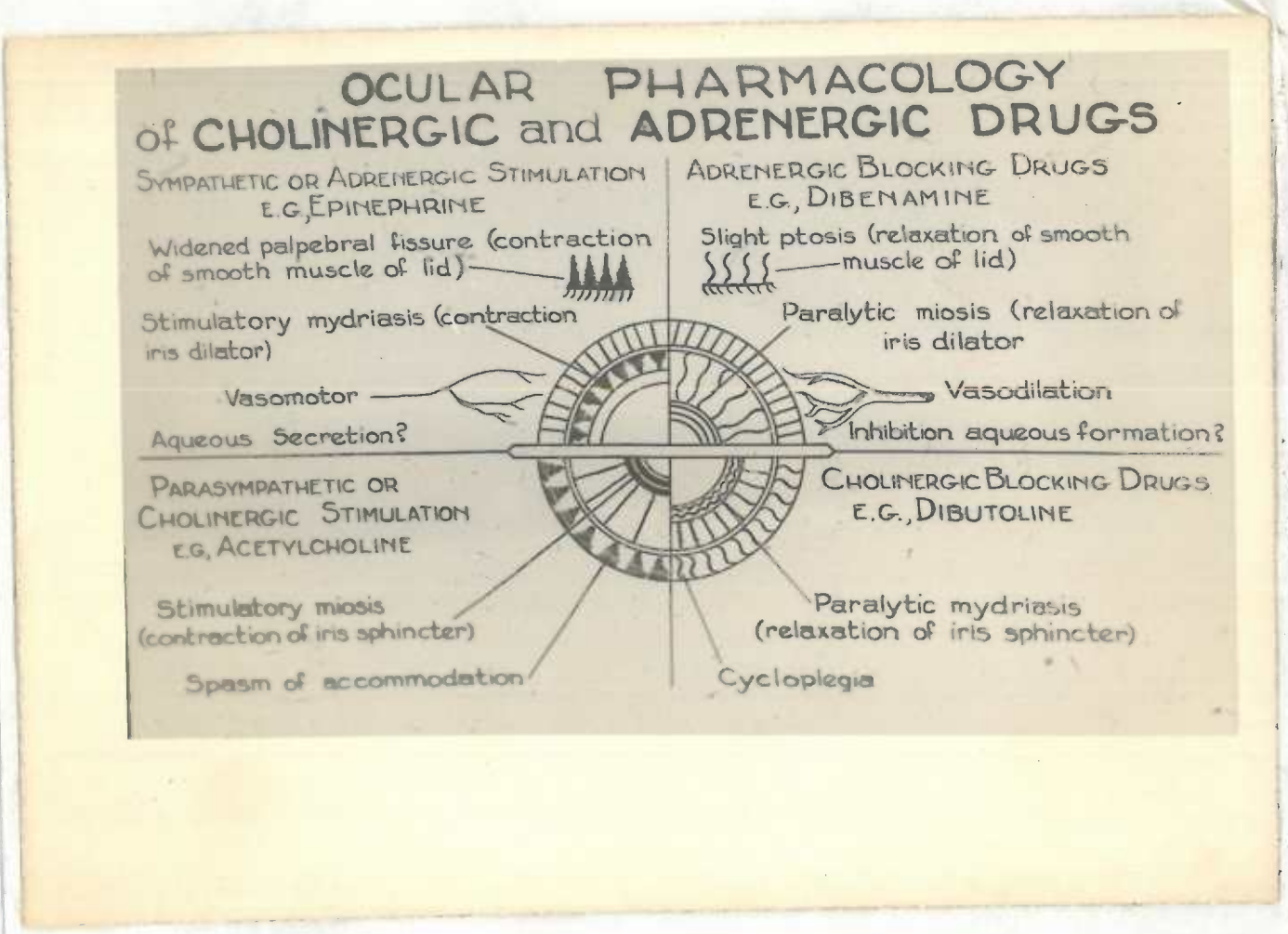

OCULAR PHARMACOLOGY
of CHOLINERGIC and ADRENERGIC DRUGS
SYMPATHETIC OR ADRENERGIC STIMULATION
E.G, EPINEPHRINE
Widened palpebral fissure (contraction of smooth muscle of lid)
Stimulatory mydriasis (contraction iris dilator)
Vasomotor
Aqueous Secretion?
ADRENERGIC BLOCKING DRUGS
E.G., DIBENAMINE
Slight ptosis (relaxation of smooth muscle of lid)
Paralytic miosis (relaxation of iris dilator
Vasodilation
Inhibition aqueous formation?
PARASYMPATHETIC OR
CHOLINERGIC STIMULATION
E.G, ACETYLCHOLINE
Stimulatory miosis
(contraction of iris sphincter)
Spasm of accommodation
CHOLINERGIC BLOCKING DRUGS
E.G., DIBUTOLINE
Paralytic mydriasis
(relaxation of iris sphincter)
Cycloplegia

Figure 1

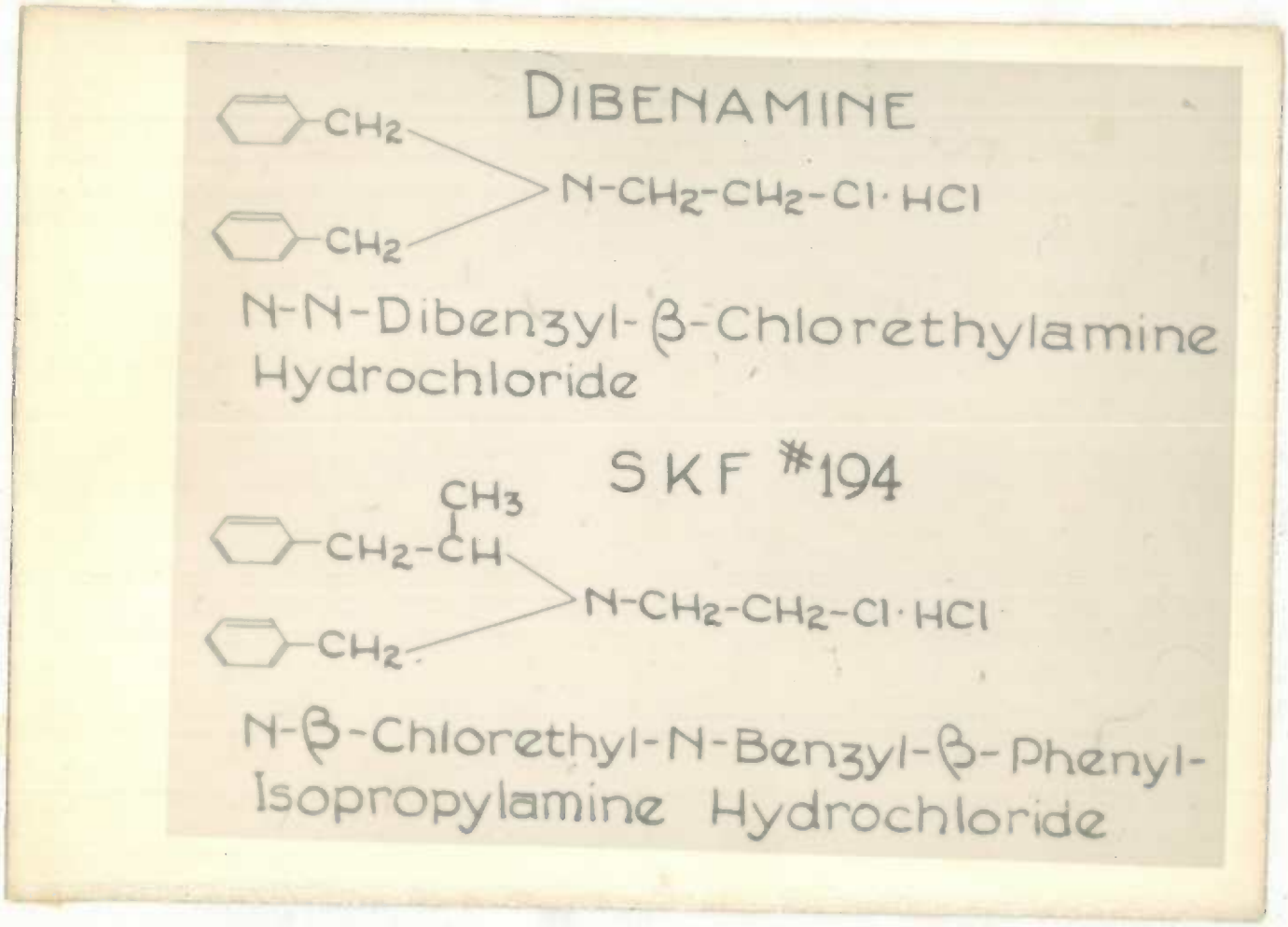

DIBENAMINE
CH2
CH2
N-CH2-CH2-Cl·HCl
N-N-Dibenzyl-β-Chlorethylamine
Hydrochloride
SKF #194
CH3
CH2-CH
CH2
N-CH2-CH2-Cl·HCl
N-β-Chlorethyl-N-Benzyl-β-Phenyl-
Isopropylamine Hydrochloride

Figure 2

the excitatory effect of epinephrine in laboratory animals, e.g., if dibenamine had been administered previously, epinephrine effected a drop in blood pressure in place of the usual rise[6]. It seems to have a direct action on the receptor substance in cells innervated by excitatory adrenergic nerves, and does not alter or destroy epinephrine or sympathin. Administered slowly in full blocking doses, dibenamine seems to cause no consistent cardiovascular changes in normal patients other than orthostatic hypotension. The only toxic effect observed by Nickerson and Goodman has been stimulation of the central nervous system, which consists of confusion, emotional lability, restlessness and some hallucinations[7]. These undesirable side effects are transient and usually can be prevented by slow administration of the drug. Accumulative toxicity from repeated clinical doses has not been observed.

Dibenamine may effect a considerable decrease in arterial blood pressure in hypertensive patients; consequently, the administration of this drug to hypertensive patients in the University of Oregon Medical School Hospitals under the direction of Drs. Morgan Goodman and Jarvis Gould, provided an opportunity to study effects of dibenamine on the normal eye and to correlate them with changes in the cardiovascular system.

Dibenamine is an irritant to the tissue. Christensen, Swan and Gould observed it to be ineffective as well as irritating when administered to the conjunctival sac; therefore, it must be administered intravenously even when prescribed for its ocular effects[8]. In this study, dibenamine was administered intravenously in doses of four to five milligrams per kilogram of body weight. The drug was added to 300 cc of saline solution and injected by the drip method over a period of one and one-half hours. Patients were cautioned to remain supine for the first thirty-six hours to avoid the undesirable side effects of orthostatic hypotension. This hypotension usually lasted less than twenty-four hours. Dibenamine seems to

increase peripheral blood flow which was evidenced in some of our patients by congestion of the nasal mucosa. Central nervous system excitations were observed in only two of a series of eighteen patients.

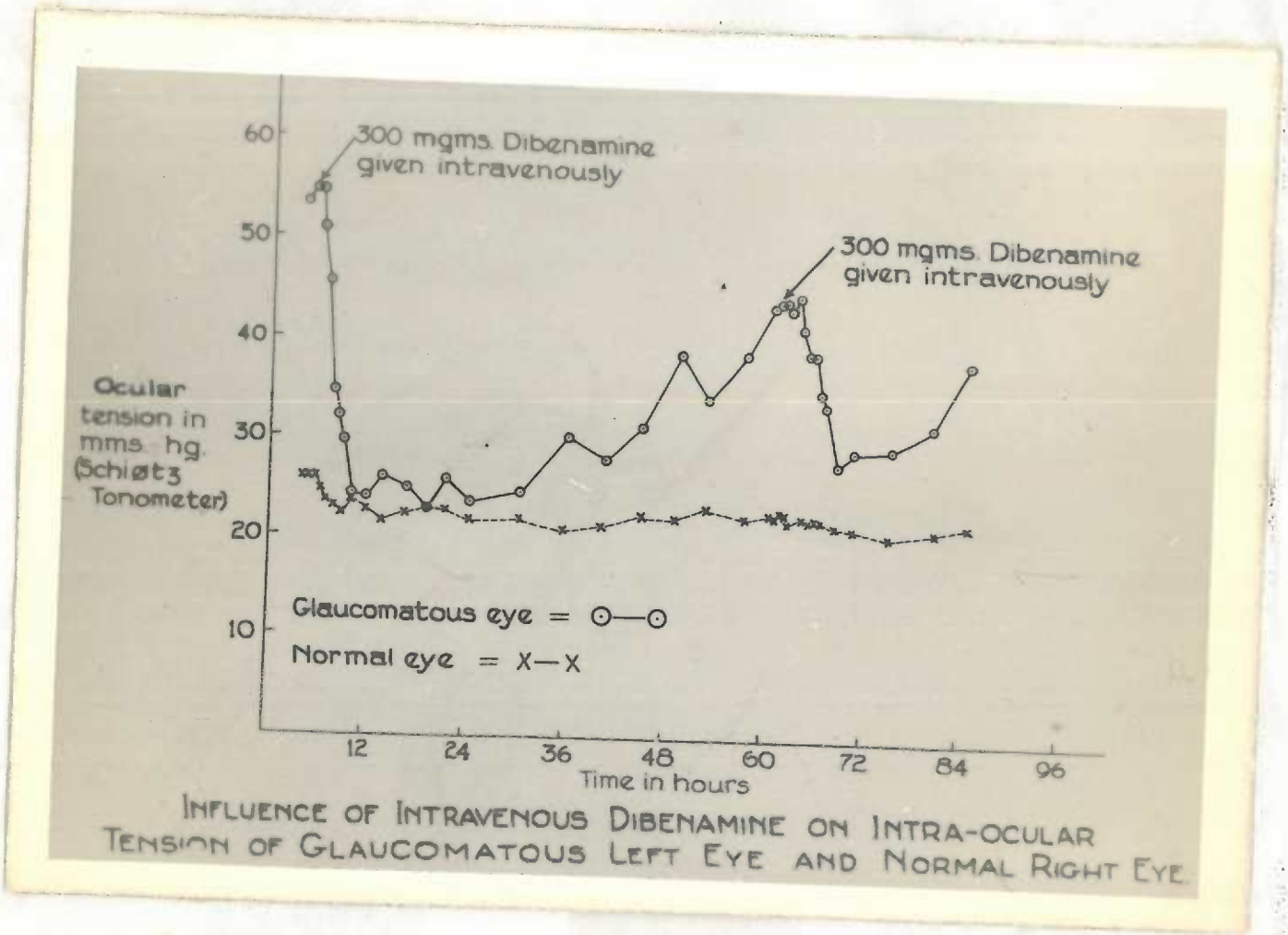
The ocular effects of dibenamine in the normal eye were not striking. A miosis due to relaxation of the iris dilator fibers was observed to develop in most patients with normal irides, but this was not marked. Dilatation of the conjunctival vessels and a narrowing of the palpebral fissure was evident in some patients. When ocular tension was within normal limits before the administration of dibenamine, a drop of several millimeters of mercury (Schiøtz) occurred quite consistently after the intravenous administration of the drug and persisted for approximately forty-eight hours. The drop in tension could not be correlated with the onset, intensity or duration of the pupillary changes. A change in accommodative mechanism was not detectable by retinoscopy and nearpoint tests. Also, there seemed to be no definite correlation between fluctuations in arterial blood pressure and the decrease in intraocular tension. It seemed evident that the ocular hypotensive action of dibenamine was unlike that of any previously known agent and justified its trial in glaucoma.

Dibenamine was administered to eighteen consecutive cases of acute glaucoma of diverse etiology and recalcitrant to the usual medical measures. The results summarized in the accompanying tables indicate a drop in intraocular tension in each of the eighteen patients to whom it was administered. The average decrease in tension effected by the drug was 35 millimeters of mercury (Schiøtz).

There were seven patients with acute glaucoma of the shallow chamber type, which did not respond to maximal doses of the stimulatory type of miotics commonly used in the treatment of acute congestive glaucoma (Table I). The response of these otherwise recalcitrant cases to dibenamine

was spectacular. The typical response is shown by the tension curve of one of these patients (fig. 3). In another patient the attack of glaucoma was precipitated by atropinization. The case was referred to the University of Oregon Medical School Hospitals when it became evident that the widely dilated pupil would not contract and tension remained elevated despite maximal doses of eserine repeated at frequent intervals. The tension was promptly controlled with dibenamine (fig. 4). This case was one of several in which it was demonstrated that the hypotensive action of dibenamine was not blocked by local administration of mydriatic and cycloplegic drugs. In these additional cases the acute glaucoma was secondary to iridocyclitis (Cases HF and HL Table II). Administration of dibenamine permitted control of the intraocular tension until the acute stage of the inflammatory process could be controlled.

It is noteworthy that dibenamine produced a drop in tension in two cases in spite of an obstruction of the circulation of the aqueous from the posterior to anterior chamber. In one of the patients,(DS Table II), with chronic non-congestive glaucoma, an acute rise in tension occurred following an attempted filtration operation. In this case the surgeon had performed a sclerectomy but had failed to do an iridectomy. Prolapse of the iris into the opening and formation of a pupillary membrane were associated with the development of an iris bombe and an acute glaucoma. The eye became congested, hard, and painful. Two injections of dibenamine three days apart controlled the tension and permitted performance of an iridectomy on an eye with normal tension. In another patient, (AJ Table II), the iris bombe wa s due to a post inflammatory seclusion of the pupil. The dramatic drop in ocular tension which occurred in this patient was associated with a noticeable deepening of the anterior chamber, but there was no evidence of formation of a new communication between the anterior and posterior chambers (fig. 5).



INFLUENCE OF INTRAVENOUS DIBENAMINE ON INTRA-OCULAR TENSION OF GLAUCOMATOUS LEFT EYE AND NORMAL RIGHT EYE

Figure 3

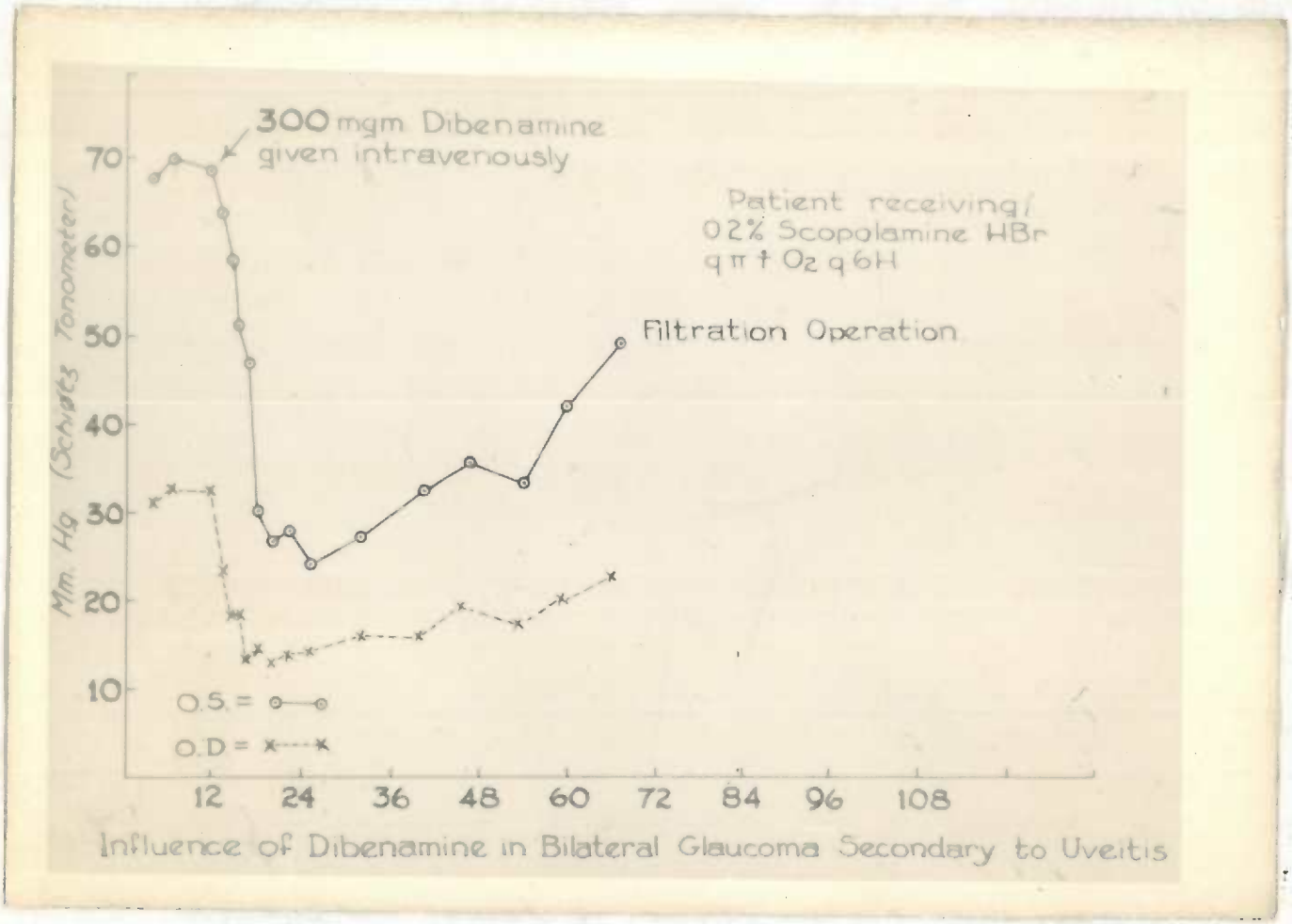

300 mgm. Dibenamine
given intravenously
Patient receiving
0.2% Scopolamine HBr
q π + O2 q 6H
Filtration Operation
Mm. Hg (Schiötz Tonometer)
70
60
50
40
30
20
10
O.S. =
O.D =
12
24
36
48
60
72
84
96
108
Influence of Dibenamine in Bilateral Glaucoma Secondary to Uveitis

Figure 4

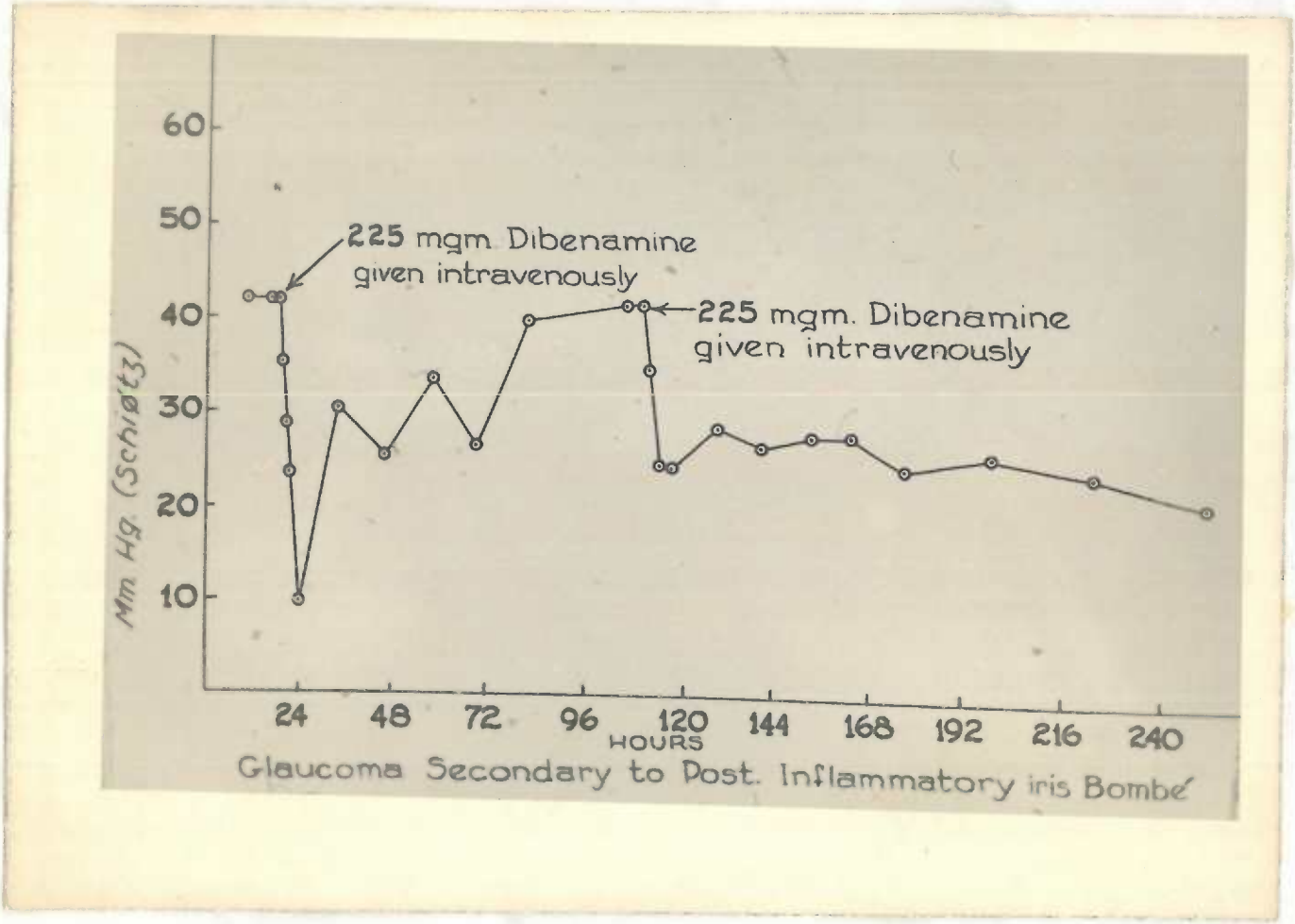

60
50
40
30
20
10
Mm Hg. (Schiøtz)
225 mgm. Dibenamine
given intravenously
225 mgm. Dibenamine
given intravenously
24
48
72
96
120
144
168
192
216
240
HOURS
Glaucoma Secondary to Post. Inflammatory iris Bombé

Figure 5

These two cases suggest that the drug may interfere with formation of aqueous by the ciliary body.

There were two patients in whom gonioscopy indicated that the glaucoma was secondary to obstruction of the chamber angle. In one (JA Table II) patient the glaucoma was post-inflammatory and in the other (CC Table III), it was associated with a massive exfoliation of the lens capsule and the formation of extensive peripheral synechiae. The ocular tension in these advanced cases had not been influenced by maximal doses of the stimulatory miotics including DFP. The dramatic decrease in ocular tension induced by dibenamine was not associated with detectable pupillary changes or alteration in the gonioscopic picture.

The hypotensive effects of dibenamine were transient in three cases listed in Table III, that is, they were of only a few hours' duration. It is noteworthy that a massive hyphemia was present in two of these patients. In the third case, the glaucoma was in association with an epithelial ingrowth into the anterior chamber, which had been treated by irradiation. This was a severely damaged eye with advanced degenerative changes. A larger series of patients than are included in this preliminary report will be necessary to determine which cases of glaucoma will be recalcitrant to dibenamine, but the short duration of its action in these few cases indicates that the drug will not prove infallible.

The summary of the above mentioned patients provided an indication of the action of dibenamine in acute congestive glaucoma, notably that a dose of four to five milligrams per kilogram of body weight induces a drop in ocular tension in glaucomatous eyes usually beginning one to two hours after administration and becoming maximal within eight hours. The tension usually remains at the lowered level for at least twenty-four to forty-eight hours. In a few cases the formerly glaucomatous eye may actually become hypotonic. The drug seems effective in advanced or neglected

cases of diverse etiology which are usually recalcitrant to other medical measures, but an occasional case, the hypotensive effects may be transient. The local administration to the eye of cycloplegic and mydriatic drugs does not block this hypotensive course, nor does dibenamine interfere with their paretic effects on the intraocular muscles. It is not yet possible to ascertain with certainty whether stimulatory miotics such as pilocarpine and eserine, have synergistic hypotensive effects when administered with dibenamine. Serious systemic complications are not to be expected in patients with a relatively normal cardiovascular system, provided the patient is kept in bed, but for the present it would seem wise to limit the use of dibenamine to hospitalized patients of known cardiovascular status.

The seeming development of a tolerance to dibenamine in several of our patients merits special attention because it has not been reported in relation to the systemic effects of the drug. In some of our patients several doses of dibenamine were administered several days apart. In each instance the hypotensive action of the drug decreased with successive doses; however, even in these instances, it was possible to maintain the ocular tension at a low level for a week or longer. This proved sufficient time to permit control of the primary processes responsible for the glaucoma. Whether a tachyphylaxis could be avoided with a different dosage schedule, e.g., less frequent intervals of administration and smaller doses, remains to be established.

DISCUSSION

Dibenamine is only one of a number of adrenergic blocking agents which we are investigating. The possibilities for synthesis of less toxic and more effective drugs of this type seem excellent because at least three chemically different groups of compounds exert some degree of adrenergic blocking power. Another compound (SKF#194) closely related to dibenamine has demonstrated greater hypotensive effectiveness than dibenamine on the

eyes of laboratory animals. It is obvious, therefore, that the final role of these drugs in the treatment of glaucoma will not be established for some years, but our experience with these compounds indicate that already they have an important place in ophthalmic therapeutics, that is, in emergency control of the ocular tension in acute glaucoma of diverse etiology. The drugs produce potentially dangerous changes in the cardiovascular system, and tachphylaxis may develop, but in our, as yet limited experience they have consistently effected a dramatic drop in intraocular tension in cases of acute congestive glaucoma which did not respond to the usual medical measures. Also, the systemic administration of dibenamine has permitted the local treatment of the eyes even with the continued local administration of mydriatic and cycloplegic drugs, e.g., in several instances dibenamine controlled marked glaucoma during a period of acute iridocyclitis until this primary condition could be brought under control. In a number of other cases of acute congestive glaucoma of the shallow chamber type, which did not respond to miotics and dehydration therapy, the administration of dibenamine permitted the performance of precise operative procedures under ideal circumstances rather than upon a hard, painful, and congested eye. In several instances eyes were saved by the use of dibenamine which otherwise would have been lost.

Whether the oral or local administration of adrenergic blocking agents will be of value in the management of chronic non-congestive glaucoma remains to be established. Experiments with the oral administration of adrenergic blocking agents alone and in conjunction with miotics are promising, but not yet conclusive. Also, the minimal effective intravenous dose may prove to be considerably smaller than those used in this study.

Although the mechanism of hypotensive action of the adrenergic blocking agents in glaucoma has been the subject of extensive laboratory

experimentation, a contemporary discussion must be largely on theoretical grounds. It seems possible that the ocular hypotensive action of these drugs may be upon the vascular system. Although the changes in ocular tension can not be correlated with the arterial blood pressure as measured in the brachial artery, a relationship to alterations in capillary pressure and permeability is possible. That the hypotensive action of the drug is not related to their mechanical effects on the intraocular muscles seems certain because the onset, duration, and intensity of the miosis which these drugs produce has shown no measurable relationship to the drop in tension in glaucoma. Also, it has occurred, on one hand, in eyes in which maximal miosis had already been effected by parasympathetic stimulation with miotics and on the other hand in eyes in which complete paralytic mydriasis and cycloplegia had been induced with scopolamine or atropine. A third possibility is that these drugs effect osmotic relationships between the plasma and the intraocular fluids in a manner similar to that induced by the intravenous injections of hypertonic sorbitol; however, there is no clear cut evidence that dibenamine induces appreciable changes in the osmotic pressure relationships of the blood or the state of systemic hydration. The most likely explanation would seem that drugs like dibenamine have some blocking action on the formation of aqueous against an excessive pressure gradient. The fact that the drug was effective in lowering increased intraocular tension secondary to iris bombe formation is indicative of a posterior site of action. Friedenwald has produced evidence that epinephrine plays a role in the mechanism of the ciliary body and has demonstrated that reformation of the aqueous is delayed in adrenalectimized animals[9]. Although the mode of action of these drugs can not, therefore, be stated with certainty, the least that can be said is that their action is unlike that of any previously studied drugs, that they demonstrate the feasibility of systemic control of glaucoma and

that they offer a new approach to the problem of the nature of the aqueous humor.

SUMMARY AND CONCLUSIONS

New drugs have been developed which seem to inhibit the stimulatory effects of epinephrine and sympathin on adrenergic receptors. Of these compounds, dibenamine has received most attention. It induces a transitory miosis through relaxation of the iris dilator fibers, dilates the blood vessels, may narrow the palpebral fissure, and slightly lower the ocular tension; otherwise, it has little effect on normal human eyes. Administered intravenously dibenamine usually effects a dramatic drop in the ocular tension in glaucomatous eyes. This hypotensive action seems unrelated to the pupillary effects of the drug and, therefore, it has a range of effectiveness exceeding that of autonomic drugs previously used in the treatment of acute glaucoma. This action is not blocked by the local administration of a mydriatic and cycloplegic drug, and occurs even in the presence of an iris bombé. Also, it seems to bear no direct relation to the state of systemic hydration, or arterial blood pressure. The mode of action of adrenergic blocking agents can not therefore, be stated with certainty, but it seems unlike that of any previously known autonomic drugs.

During the past several years dibenamine has been used in the treatment of eighteen consecutive cases of acute glaucoma of diverse etiology which did not respond to previously known medical measures. These cases are reviewed and discussed. It will be years before the most effective of the adrenergic blocking agents is determined and their full toxic and therapeutic effects established; however, this preliminary clinical investigation indicates that in the emergency control of acute glaucoma recalcitrant to the usual medical measures dibenamine has a great effectiveness than any previously known agent. Also, the adrenergic blocking agents demonstrate the feasibility of

specific systemic treatment of glaucoma and provide a new approach to the problem of the nature of the aqueous humor.

We are indebted to Doctors John E. Harris, Morton Goodman, Garvis Gould, and William Youmans of the faculty of the University of Oregon Medical School for their advice and assistance in this study.

TABLE I

Case No.	Age	Etiology	Initial Tension (mm. Hg. Schiotz)	Minimal Tension after Dibenamine (mm. Hg. Schiotz)	Remarks
MM-35375	30	Associated with degeneration of uveal pigment	56	16	No secondary rise in tension
GH-54783	65	Shallow chamber Iris block	80	34	There was a reduced response to second dose
LS-6628	73	Shallow chamber Iris block	76	42	Did not receive full dosage
MD-62929	64	Shallow chamber Iris block	62	30	
HB-165766	65	Shallow chamber Atropinization	95	16	Lowered tension maintained with DFP & Pilocarpine
FS-134707	70	Shallow chamber Intumescent lens	51	35	
GN-54283	75	Acute intumescence of the lens	64	10	No secondary rise in tension
Average	66		69	26	

TABLE II

HYPOTENSIVE EFFECT OF DIBENAMINE UPON GLAUCOMA OF INFLAMMATORY ORIGIN

Case No.	Age	Etiology	Initial Tension (mm. Hg. Schiotz)	Minimal Tension after Dibenamine (mm. Hg. Schiotz)	Remarks
HF-149803	52	Acute uveitis	50	18	Secondary rise followed by a spontaneous decrease to normal with subsidence of inflammation
HL-4938	80	Acute uveitis	68	22	No response to oral
AJ	30	Iris Bombe Postinflammatory	42	10	
OS-158871	56	Iris Bombe	54	26	Chronic noncongestive glaucoma with postoperative iridocyclitis
JA*115886	46	Postinflammatory	34	28	Preceding luetic uveitis and keratitis
Average	52		53	20	

TABLE III

HYPOTENSIVE EFFECT OF DIBENAMINE UPON RECALCITRANT GLAUCOMA OF VARIABLE ETIOLOGY

Case No.	Age	Etiology	Initial Tension (mm. Hg. Schiotz)	Minimal Tension after Dibenamine (mm. Hg. Schiotz	Remarks
AW-128810	46	Rubeosis iridis Absolute glaucoma	46	26	Transient effect, developed mental confusion ; Oral administration of Dibenamine unsuccessful
ED-135770	72	Rubeosis Hyphemia	95	54	No response to several days of miotics
PH-171972	44	Contusion with hyphemia; subluxation of the lens	48	26	Transient effect
IB-149095	14	Contusion with hyphemia	44	31	
LH*164957	69	Epithelial ingrowth postoperative	46	28	Transient effect; anterior chamber obliterated
CC-67730	54	Exfoliation of lens capsule	79	28	Less hypotensive response to a second dose of Dibenamine
Average	49		59	32	

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