THE PATHOLOGIC CHANGES IN THE ORBIT IN PROGRESSIVE EXOPHTHALMOS, WITH SPECIAL REFERENCE TO ALTERATIONS IN THE EXTRAOCULAR MUSCLES AND THE OPTIC DISCS*

JOSEPH L. McCOOL, M.D.†
San Francisco
AND
(By invitation)
HOWARD C. NAFFZIGER, M.D.†
San Francisco

We have seen a number of patients suffering from progressive exophthalmos following thyroidectomy in each of whom careful study revealed many findings of ophthalmologic interest.

For the treatment of these patients a surgical procedure was devised which, in six instances, proved highly satisfactory. In each case a similar mechanism for the exophthalmos was found, and the pathologic changes responsible for this disorder were proved.

The usual course of the condition is as follows: A thyroidectomy is performed on a patient with exophthalmic goiter presenting the usual elevated basal metabolic rate and cardiovascular and nervous manifestations. Clinical improvement follows, but the exophthalmos does not disappear. Over a variable period, often of three or four months, it becomes evident that the proptosis is increasing. As it proceeds an increased fullness of the lids is noted, after which lacrimation and epiphora appear. A watery appearance of the scleral conjunctiva is followed first by edema near the inner canthus and then by swelling, which spreads rapidly,

* From the University of California Medical School.

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with protrusion of the inferior palpebral mucosa. Diplopia and lack of parallelism of the eyes are followed by increasing limitation of movements of the globe. Downward movements are the only ones retained ultimately; in other directions there may be only slight movement. With increasing protrusion of the eye, the lids no longer completely cover the globe and the cornea becomes exposed.

Patients with these characteristic symptoms are said to be suffering from malignant exophthalmos, for although cases of less intensity may be seen, the severe ones have invariably progressed to the stage of corneal ulceration and infection. Many enucleations have been performed, but the usual termination has been an infected orbit, intracranial extension of the infection, and death.

Reports of progressive exophthalmos with blindness, enucleation of the eyes, and death, some of which are given here, appear all too often in the literature. Jessop[1] published three cases of his own and 22 collected from the literature. Additional reports were made by Saenger and Baer,[2] Juler,[3] Cross,[4] Coulter,[5] Thompson,[6] Paton,[7] Burch,[8] and Griffith.[9] Benedict[10] describes six cases from the Mayo Clinic, and in a personal communication from Lahey's clinic six more are added.

Many forms of treatment have been devised for these unfortunate patients: tarsorrhaphy and canthotomy, plastic operations on the conjunctiva, incisions of the lids, or removal of fat have been done by Saenger and Baer, Juler,[11] von Graefe,[12] Kuhnt,[13] and Harman.[14] Krönlein operations have been done by Chevallereau and Offret,[15] Meisner,[16] and Dollinger;[17] section or removal of the cervical sympathetics was performed by Jaboulay,[18] Jonnesco,[19] Balacescu,[20] C. H. Mayo,[21] Juler,[11] Reclus and Faure,[22] Adson,[23] and Bucy.[24]

Ruedemann[25] advised giving thyroid gland extract by mouth; other writers have recommended deep x-ray therapy. In severe cases these procedures have been found ineffective or futile.

Our operative procedure consists of complete removal of the orbital roof and that of the optic foramen by an intracranial approach. The orbital fascia and the ring of Zinn are opened for purposes of decompression, and to permit expansion of the contents of the orbit and the optic foramen. This wide exposure allows detailed study of the orbital structures, including the extrinsic muscles, the fat, the vessels, and the optic nerve. In our series over 20 specimens were removed from the muscles for microscopic study. In each instance abnormalities were found in the extra-ocular muscles, which were increased in size from three to eight times. Their color was altered, and varied from a pale, half-cooked appearance to a much deeper red with white fibrous streaks, depending upon the stage of the process.

Of additional interest is the fact that loss of vision occurs from causes other than changes in the cornea. In four of our six patients the optic nerves and retinas showed changes; most often there were swelling of the nerve head, hemorrhages, and atrophy. In each of these cases treatment proved effective, the loss of vision was arrested, and restoration of sight followed. The papillitis subsided, the hemorrhages underwent prompt absorption, and there remained only the fixed changes resulting from the preceding atrophy.

A search of the voluminous literature on exophthalmos and other eye conditions related to goiter proves to be of unusual interest. If one investigates the reports on exophthalmos and excludes those resulting from the various tumors of the orbit, arteriovenous aneurysms, mucoceles, orbital infections, and the like, there remains still an enormous number, in some of which the exophthalmos bore a relation to goiter, and others in which it was associated with cardiovascular disease, cerebral hemorrhage, and certain of the chronic diseases, particularly syphilis and tuberculosis. Lesser degrees of protrusion of the eyes are seen fairly often in persons with heart disease and with hypertension.

From this examination of the literature the conviction arises that the mechanism of the most severe cases of exophthalmos is similar in all, whether or not the individual suffers from hyperthyroidism. However, in this connection one point deserves emphasis, namely, that the term "exophthalmos" often is applied loosely. Frequently only a widening of the lid slit is present, and not a true protrusion of the globe.

Apparently the pathologic changes in the extrinsic ocular muscles which result in faulty eye movements have not received the attention their seriousness and importance merit. Diagnoses of neurologic disorders have been made frequently when primary alterations in the muscles were present.

The cause of exophthalmos in hyperplastic thyroid disease and in the so-called idiopathic cases has given rise to innumerable speculations. The theory of an increase of retrobulbar fat has been offered as an explanation by Basedow,[26] R. Foster Moore,[27,28] Bristowe,[29] Jendrassik,[30] Mendel,[31] and Carl Fisher,[32] and a number of postmortem examinations have been made. These investigations were not made in cases of progressive exophthalmos.

Since the experiments of Claude Bernard,[33] who produced a dilated pupil, widening of the palpebral aperture, and circulatory phenomena, other investigators have championed the rôle of sympathetic stimulation of the smooth musculature of the orbit. In 1860 Aran[34] supported Bernard, and in 1900, Edmunds[35] again repeated the experiments. Galezowski, Riche, Jaboulay, Gayme, and Abadie are cited by Landström[36] as believing that the contraction of the smooth musculature in Tenon's fascia produces exophthalmos, and Turner[37] has summarized data on the non-striped muscle connected with the ocular protrusion in men and mammals.

Since the work of H. Müller[38,39] on the unstriped orbital muscles which bear his name, other writers, prompted by their interest in exophthalmos, have described differences in

the arrangement and disposition of these muscle aggregations. Among them may be mentioned Landström, C. Hesser,[40] Krause,[41] and Whitnall.[42] Birch-Hirschfeld[43] reported studies on the lymph vessels in the orbit and described stasis occurring in them.

Experimental investigations directed toward the effect of cervical sympathetic stimulation have been carried on by Krauss,[44] who reported the production of exophthalmos in rabbits, cats, and dogs, but not in monkeys. Resection of Landström's muscle did not halt the ocular protrusion.

Muller and Wagner[45] stimulated the cervical sympathetic nerves in decapitated human beings, and Unverricht[46] performed clinical experiments on patients during the course of neck operations. In none of these investigations was exophthalmos produced, although other effects of sympathetic stimulation were present.

There are adherents to the theory that retrobulbar venous engorgement is the cause of exophthalmos. Goldscheider,[47] Schwerdt,[48] Fr. Muller,[49] and Unverricht are subscribers to this belief, and Sattler[50] also suggests that the engorgement is caused by a vasomotor toxin.

Landström cites von Graefe and McKenzie as believing in a widening of the orbital veins, and O'Day,[51] in a postmortem study, found varicose orbital veins. Fründ[52] is of the opinion that such widening results from compression of the ophthalmic vein as it passes obliquely through the smooth muscle of the orbital fissure. Bulson[53] and others object to the theory of venous engorgement because the orbitofacial veins show no enlargement.

The hypothesis that protrusion of the globe is caused by dilated orbital arteries has numerous proponents, among them Hervieux,[54] Buschan,[55] Mannatin,[56] Ehrich,[57] A. Kocher,[58] Fuchs,[59] Kraus,[60] Möbius,[61] and Haskovec.[62]

Wm. Cooper,[63] in 1849, explained exophthalmos on the basis of a weakening and elongation of the eye muscles.

Tilley[64] attributes exophthalmos to the fact that the wide-open lids exert no restraint upon the globe, and as a result an increase in the orbital content is permitted.

Hughlings Jackson[65] favored a pathologic change in the central nervous system, and referred to the work of Brown-Séquard and Filehne, who reported exophthalmos following injuries of the restiform body.

Experimental investigations along other lines have been carried out by Piorry[66] and Boddaert,[67] who ligated the jugular veins and excised the cervical sympathetic, producing exophthalmos by these two procedures, either one of which alone did not produce it.

MacCallum and Cornell[68] tied the jugular veins and stimulated the sympathetic, producing a mild exophthalmos, but Troell,[69] in 1916, was unable to confirm their work.

Certain pharmacologic experiments by Grunert,[70] Sato,[71] and Gibbs,[72] who injected paraphenylendiamin, produced edema about the lids and the orbit in dogs. Recently Marine, Spence, and Cipra[73] have reported thyroid hyperplasia with exophthalmos in rabbits after injections of methyl cyanid.

It may be worthy of comment that none of the theories expounded has proved to be satisfactory, and that none of the experimental work has been successful in producing marked or progressive exophthalmos.

Before considering pathologic studies, it should be noted that considerable comment has been made on changes in the optic nerve and retina in thyroid disorders. Sattler[74] reported one instance of retrobulbar neuritis and collected eight more from the literature. R. Foster Moore[27] also has noted the occurrence of retrobulbar neuritis. E. S. Thompson[6] quotes Sattler and von Hippel on the exophthalmos of thyroid disease associated with optic neuritis. Keogh[75] has observed optic atrophy. Fuchs[76] attributes these changes to tension upon the optic nerve caused by forward dislocation of

the globe. Benedict has referred to the frequent retinal changes and choroiditis seen in association with highly toxic goiters.

As to the eye-muscle palsies, various interpretations have been given of them, but they have been attributed, often erroneously, to neurologic causes. Willard[77] reports palsies; Bernhardt,[78] Sattler,[79] and Kappis[80] have also reported them, and considered them caused by a nuclear degeneration from a presumably infectious or toxic agent present in polioencephalitis or poliomyelitis. Jaensch[81] has written on eye-muscle palsies in thyrotoxicosis. Heuer,[82] in an article on neurologic associations of thyroid disease, commented on the frequency of eye-muscle disturbances.

It is instructive, in the light of our experience, to review the notes of various surgeons and to find that often there were indications of alterations in the extrinsic eye muscles, but that their significance was not appreciated. Basedow observed that in one case, "because of retrobulbar tension, the recti muscles compressed the globe and caused an indentation beneath each one." Moore,[28] while operating to remove retrobulbar fat, found large muscles but did not examine them. Burch, after an enucleation, discovered large muscles and submitted an excellent pathologic report, but reached no conclusion. Chevallereau and Offret, while doing a Krönlein operation, found large muscles that showed a myositis. Carl Fisher, and Silcock,[83] at postmortem examinations, noted that, in exophthalmos cases, there was interfascicular fatty muscle degeneration. Griffith reported that in a case of progressive exophthalmos, the orbits after enucleation were still so full of tissue that the lids could not be closed.

There are a larger number of pathologic reports from cases of idiopathic exophthalmos, and in these the findings are strikingly similar to those in our cases in which the association with thyroid disease is clear. Gleason[84] describes an

idiopathic myositis in which the muscles were eight times the normal size, and remarks that there are 35 cases in the literature. Rochon-Duvigneaud and Onfray[85] reported one case, finally concluding that it was caused by tuberculosis. Meisner published two cases occurring in patients with cerebral apoplexy, and one other.

Hensen,[86] Hessvert,[87] Nuel,[88] Mauch,[89] Busse and Hohheim,[90] Cords,[91] Thomsen,[92] and Buzzard[93] reported large eye muscles occurring in a variety of conditions and producing marked exophthalmos.

Each of the six patients reported[94] by us had hyperplastic goiter with characteristic symptoms, and each had some degree of exophthalmos prior to thyroidectomy. The basal metabolic rates varied from plus 17 to plus 75. Four patients were women, two were men. Their ages varied from twenty-eight to fifty-three years. The blood-pressure readings ranged from normal to 168/94.

All the patients were relieved of their general symptoms following thyroidectomy, but the exophthalmos persisted and increased in from two months to one year after the operation. Various treatments ranging from desiccated thyroid gland internally to canthotomy, sinus operation, and sympathectomy had been given in the attempt to check the progressive exophthalmos. During the progress of the exophthalmos the basal metabolic rate varied in the different individuals from normal to minus 32. All these patients showed marked puffiness of the lids, scleral edema in various stages, and lacrimation. The exophthalmos varied from 26 to 35 mm. Three patients complained of aching behind the globes and on movements of the eyes. In five of the six patients the motility of the globes was greatly impaired. Upward movements were most affected, and in some were lost completely; downward movements were affected least; lateral movements were limited in varying degrees. In four patients the lacrimal glands were enlarged and easily palpable. In

five vision was impaired seriously. Swelling of the optic discs occurred in five; retinal changes were present in one. The fields showed generalized contraction in two, and in one there was a loss of the inferior half of the fields. This last patient, who hardly could count fingers at two feet, exhibited no abnormality on ophthalmoscopic examination. Upon attempting to press the globes backward into the orbit there was great resistance.

A report upon the first patient of our series appeared in 1931.[95] Since then we have operated upon three others. This operation has been done also by Dr. Paul Bucy, of the University of Chicago, and by Dr. R. E. Semmes, of Memphis, upon a patient of Drs. Ellett and Rychener. We are grateful to these physicians for their communications regarding their patients and for the photographs and pathologic sections submitted.

In four patients both orbits were operated upon and one orbit each in the remaining two. Specimens of muscle for pathologic study were removed in all instances, and, in several, small bits of muscular tissue were removed from three or four muscles in each orbit. More than 20 specimens have been studied.

In every orbit the muscles were enlarged enormously. Some were measured and were found to be increased from three to eight times their normal size. Depending upon the duration of the process, the color varied from a pale, edematous, half-cooked appearance to a deep color, and there was much fibrous tissue present. The muscles were firm and at times of rubbery hardness. In the later stages, hyaline change was found and the muscles were gritty to the knife.

A summary of the histologic findings in the eye muscles so far studied shows varying degrees of muscle degeneration, fibrosis, and cellular infiltration.

The mildest lesion appears to be a swelling of muscle fibers, followed by a loss of striation; in other words, the early

changes associated with so-called Zenker's degeneration. Later, many muscle fibers are seen to be frayed out into a fibrillary substance which takes the stain for collagen. There is at the same time, in many of the sections, a definite interstitial edema. In the more pronounced cases, or perhaps in those of longer standing, there is a proliferation of round cells which appears to be coming from the intermuscular mesenchyme. Some of these cells are lymphocytes or immature plasma cells, but many are very embryonal in character. Small and large accumulations of these cells are present around the blood-vessels. This cellular reaction appears to be, in part, a response to muscle necrosis. What appears to be a still later stage is the condensation of fibrils into a comparatively dense scar tissue, although in no case can it be said that the condition is resting. One finds early, intermediate, and late stages in all the tissue. In addition to these changes, in some sections the walls of arterioles are somewhat thickened and are infiltrated by mononuclear cells. In places these cells appear beneath the intima, causing a slight bulging of the endothelium.

The operative procedure consisted of an intracranial removal of the orbital plate and the roof of the optic foramen, and opening of the ring of Zinn. The bone removal from the orbital plate extended from the frontal sinuses to the sphenoid ridge, laterally to the wall of the skull, and mesially to the ethmoid and sphenoid cells.

No deaths occurred in the series. Convalescence is characterized by a transiently increased edema of the lids and of the conjunctiva. As the edema subsides, the proptosis gradually lessens and the recession of the globes continues over a period of many months. In each instance there was early improvement in the vision, subsidence of the papillitis, and disappearance of the hemorrhages.

Recession of the globes continued over many months and varied from two to seven mm. on the exophthalmometer.

In no case has there been manifest any tendency to recurrence. In each instance the globes show faint pulsation, of which the patient is unaware.

In conclusion we feel justified in emphasizing the constancy of the pathologic change responsible for this type of progressive exophthalmos, and in stressing the importance of the recognition of impaired eye movements from intrinsic changes in the muscles. Treatment of this hitherto hopeless condition has proved adequate and highly satisfactory.

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DISCUSSION

DR. JONAS S. FRIEDENWALD, Baltimore: When the preliminary report of Dr. Naffziger's extremely interesting paper was published in the Annals of Surgery, the question arose as to whether or not this muscular change might be responsible for the ordinary exophthalmos of hyperthyroidism. We therefore examined the material that was available in our laboratory of autopsy specimens from cases of hyperthyroidism with exophthalmos. Among the material we found six cases of uncomplicated exophthalmic goiter which had come to autopsy in which the globe still had attached to it fragments of the extra-ocular muscles that could be investigated. All these showed perfectly normal extra-ocular muscles. There was a seventh case which was so remarkable that it is worth reporting. This patient came to the Johns Hopkins Hospital in 1924 stating that three months before he had had an acute upper respiratory infection, rhinitis, and fever, followed a week later by coma and convulsions which lasted for almost a week. Following this he had improved slightly, but noticed that his right eye began to protrude and was painful. Three months after the onset of the proptosis he came to the Eye Dispensary and was found to have moderate exophthalmos of the right eye with limitation of movement of the eyeball, beginning corneal ulcer, and the appearance of orbital abscess. There was no enlargement of the thyroid at this time nor any increase of pulse rate. A basal metabolism was not done, and attention was concentrated on the possibility of sinusitis and orbital abscess. A nasal examination was negative, and an *x*-ray examination of his sinuses revealed no abnormal condition. The patient remained in the hospital for a short time, and no diagnosis could be made. He returned three months later, having suffered great loss of weight. His thyroid was now palpable; there was bilateral exophthalmos with papilledema, and the pulse rate was much increased. The diagnosis of acute hyperthyroidism was now quite obvious, and the ocular condition was believed to be

a possible complication of a brain or an orbital abscess. After a few days in the hospital the patient became delirious, developed bilateral acute glaucoma, and finally died. At necropsy the orbits were carefully explored on account of the suspicion of orbital abscess, but no abscess was found and no record was made of any enlargement of the extra-ocular muscles. The extra-ocular muscles were preserved, and the specimen was sent to the laboratory. The sections showed the same changes as those found in the cases presented by Dr. Naffziger. This case will be reported in full in the Annals of Surgery.

From what has been said, I think we may conclude that this condition which Dr. Naffziger has discovered is a clinical entity which may appear as a complication of exophthalmic goiter, or in some cases may be complicated by exophthalmic goiter; that it is a special disease, distinct from the hyperthyroidism; and that the changes in the extra-ocular muscles which Dr. Naffziger has described are not the cause of the exophthalmos of ordinary hyperthyroidism.

Dr. E. C. Ellett, Memphis, Tenn.: I wish to mention the case of Mr. C., aged fifty-six years, in which a diagnosis of hyperthyroidism was made in July, 1929. This brief report has to do mainly with the exophthalmos which was present at that time. One year later, in July, 1930, a thyroidectomy was performed. In February, 1931, he was examined for the first time by an ophthalmologist, who found that the eyes were staring, but that the measurement was 20 mm. in each eye; V. each eye = 6/5; the lids were difficult to evert. In August, 1931, V.R.E. = 6/7.5; L.E. = 6/12. The exophthalmos measured R.E. 22 mm., and L.E. 24 mm., and the left nerve showed venous engorgement and slight edema. The vision failed somewhat rapidly, and in September, 1931, V.R.E. = 6/30; L.E. = 6/60, with loss of convergence. In October the lids did not cover the corneas, and V.R.E. = 15/200; L.E. = 10/200. Hemorrhages were present over the left swollen nerve head, and in the retinas faintly pigmented streaks were seen radiating temporally from each disc. The exophthalmos was R.E. 26 mm. and L.E. 27 mm. Alcohol injection of the sympathetic ganglia was without result. On December 2, 1931, a left orbital decompression was performed. December 17th the exophthalmos measured R.E. 23 mm. and L.E. 24 mm. January 1, 1932: V.R.E. = 6/15; L.E. = 6/21

with convergence normal. April 9th: V.R.E. = 6/30; L.E. = 6/6. May 31st: V.R.E. = 6/30; L.E. = 6/6 with glasses. The exophthalmos measured R.E. 25.5 mm. and L.E. 24 mm. The outlines of the right disc were blurred, the veins were engorged, and the vessels were tortuous. In the left eye the disc outlines were clear, with the disc a little pale. The vessels were straight and were of normal color. There was poor outward rotation in both eyes, and no inward movement of the right eye. Retinal striae were present as before.

On June 2, 1932, a right decompression was performed, the same as was done on the left side. The visual fields were always normal.

The changes in the muscles are shown in the photograph. They showed lymphocytic infiltration, and in the center of the infiltrates were larger cells, believed to be germinal centers. The main features in the orbit were the muscular enlargement and the absence of fat.

I saw this patient a few times, but he was under the surgical care of Dr. R. E. Semmes, and the eyes were cared for by my associate, Dr. R. O. Rychener, to both of whom I am indebted for the information and the permission to mention the case.

Dr. Arthur M. Yudkin, New Haven, Conn.: I am prompted, by the presentation of this splendid and instructive paper, to describe a clinical picture of a bilateral progressive proptosis produced in albino rats on a diet deficient in inorganic salts.

Soon after weaning, healthy albino rats were placed on a well-known basal diet which is low in inorganic salts and almost completely deficient in calcium. After a period of from sixty to seventy days on this diet the eyes of these animals showed considerable proptosis. It was also observed that their growth was stunted, for they were "dwarf-like" and had "pot bellies." Considerable nervous irritability was observed in these animals, particularly when they were handled or moved about, yet they showed no signs of scurvy. The teeth were soft and grew somewhat long, and some of them curled up in the mouth so that the mucous membrane was injured when the animal ate. An *x*-ray picture of the skull and spinal column showed that the calcium of the bone was diminished to the extent that it was difficult to outline the bony structure. The skull was easily dented on making the slightest pressure with the finger.

A pathologic study confirmed the *x*-ray finding; i. e., lack of

calcium in the bone. The spleen, liver, and adrenal and pituitary glands showed no abnormalities. A preliminary study of the ocular tissue revealed no pathologic change. The orbital fossae, however, were much shallower than normal, and it seemed that this lesion was responsible for the "popping" of the eyes. When I made my pathologic study I was unaware of the disease of the ocular tissue described by the authors, so that I cannot state whether or not such a lesion was also present in the tissue under study.

This experiment is being conducted at the Connecticut Agricultural Experiment Station under the supervision of Drs. L. B. Mendel, H. B. Vickery, and L. L. Reed, and a more detailed study will be presented in the future. (Photographs of the animals and x-rays of the bony structures were shown before the Society.)

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Dr. W. L. Benedict, Rochester, Minn.: The operation which Dr. Naffziger has presented affords mechanical relief of increased intra-orbital pressure, that is, it is a decompression which allows relief of the pressure on the intrinsic structures of the orbit. The bony walls of the orbit prevent lateral expansion, and the fascia orbitalis resists forward expansion of the contents of the orbit. As this fascia is elastic, however, the globe is pushed forward, and through the retracted lids exophthalmos occurs at the expense of exposure of the cornea and upper structures of the eye. An increase of water content in the tissues of the orbit is brought about by altered secretion of the thyroid gland, and occurs in many cases of exophthalmic goiter in some stage of the disease. The degree of exophthalmos is not influenced by the basal metabolic rate. A comparatively high metabolic rate can be induced either by toxicity of the gland or by thyroiditis, or it may be produced artificially by the administration of thyroxin without inducing exophthalmos. From the work of Dr. McCool and Dr. Naffziger, from the case reports of Dr. Friedenwald, and from our own observations, we have reason to believe that increased intra-orbital content in exophthalmic goiter is due to the increase in water content of the retrobulbar tissues. One of the substances secreted by the thyroid gland is known as thyroxin. Its function is to regulate the metabolic rate, its combination within the cell acting to control the rate of combustion as ethyl acts in an automobile engine. Another substance, of which we know little at present, has to do with bound water within the tissue of the body. In the

tissues of the orbit, as in other parts of the body, there is a disproportionately increased water content which is found in greater amounts in muscle. This explains the swollen appearance of the ocular muscles mentioned by the authors. There is a relative increase of water in the fat, in the fibrous tissues, and in the other loose tissues of the orbit behind the globe. The reason why the muscles are so large is because the muscle tissue everywhere contains a larger proportion of water than do other tissues, and we have no pathologic evidence to show that there is any other cause for the increased size of the ocular muscles in the early stages of exophthalmos. In the later stages inflammatory infiltration followed by fibrosis may be found.

In experimental work on the thyroid of the goat, examination of the eye muscles has shown similar conditions—edema in the early stages, cellular infiltration, and fibrosis later.

I think Dr. Naffziger is to be congratulated on having devised this operation, although it should be resorted to only in extreme cases, and it should be avoided whenever possible. The use of combined tincture of iodin (Lugol's solution) lessens the severity of the symptoms of exophthalmic goiter. By the use of thyroxin and Lugol's solution, marked exophthalmos can be kept under control so completely that there is little danger of losing the eye. I believe that through the combined action of these drugs we will be able definitely to control the exophthalmos in our goiter patients so that operation for orbital decompression will not be necessary.

Dr. Walter R. Parker, Detroit: I have been unfortunate enough, on one occasion, to witness the complete destruction of both eyes in a patient of my own belonging in the group reported by Dr. Naffziger, and I can assure you that on that particular occasion we would have welcomed even so radical a procedure as Dr. Naffziger has given us, if there were a possibility of saving some sight for this unfortunate man.

I have been struck by the similarity between the slides shown by Dr. Naffziger and the appearance of changes in the muscles seen in myasthenia gravis. I would like to ask Dr. Naffziger in closing to speak of the possibility of the presence of the latter disease.

A point of great interest to me in this report is the fact that there was a disappearance of the choked disc after operation. It possibly throws some light on the mechanism of papilledema. In general,

the conditions that may lead to choked disc of which we have the most knowledge are: brain tumor, nephritis, tumors of the orbit, and multiple sclerosis. The only factor that all these conditions have in common is pressure on the vessels in the optic nerve. In cases of nephritis with swelling of the nerve head there is increased intracranial pressure, so that the mechanism of papilledema might be the same as in brain tumor. The cases of multiple sclerosis with swelling of the optic nerve that have been carefully studied show plaques in that portion of the optic nerve that carries the blood-vessels, and it is held that the swelling incident to the formation of the plaques leads to pressure on the blood-vessels in this region. Orbital tumors that are accompanied by choked disc are usually situated just posterior to the globe and involve the nerve immediately back of the globe.

In the cases reported by Dr. Naffziger showing choked disc that disappeared after the superior orbital wall had been removed there might have been pressure exerted on the optic nerve that was relieved by the surgical procedure.

Dr. T. B. Holloway, Philadelphia: Shortly after Dr. Naffziger's original article appeared I was fortunate in having one of the reprints sent to me, and inasmuch as we see quite a number of thyroid cases at the University Hospital, where I am connected, I became much interested. In these cases I had always regarded edema or increase of orbital fat as the most likely factor in the exophthalmos. The cause of excessive increase of exophthalmos after operation was a little more difficult to explain.

I have been particularly fortunate in not seeing many patients with this complication. In fact, I recall only one case of this kind that has come under my observation in the past few years.

I agree with Dr. Benedict in this instance. We all realize what tremendous strides have been made in thyroid surgical procedures, and we are deeply indebted to Dr. Naffziger for developing this technique. He has accomplished a great deal, and I dare say will accomplish more in the future, but the fact remains that I consider that this operation should be a *dernier ressort*, and hence should not be used routinely in all cases with excessive exophthalmos.

One case that came under my direct observation was a patient who had been admitted with some question as to whether the exophthalmos was really dependent upon the thyroid disturbance, or whether there might not be some orbital or intracranial con-

dition. After a time it was shown that the exophthalmos was due to the thyroid disturbance and the patient was operated upon. Shortly after the operation the exophthalmos began to increase until the exophthalmometer showed 25 mm. for one eye and 26 mm. for the other. A sympathectomy was done by Dr. Frazier. Later, I did a somewhat excentric tarsorrhaphy. Following this the chemosis and exophthalmos gradually subsided until at the present time the patient's eyes would not impress you as indicating thyroid disease. Owing to the narrowing and shortening of the palpebral fissures, the stare so characteristic of many of these patients is absent.

Evidently in this case the tarsorrhaphy was just sufficient to turn the tide in favor of the patient.

It is interesting to note that in Dr. Naffziger's cases there was not more chemosis of the conjunctiva. I hope he will try an excentric tarsorrhaphy in some of his cases, if for no other reason than for its cosmetic effects.

Dr. Dewey Katz, Chicago (by invitation): I desire to present in greater detail the history of one of the cases—the one from Chicago—referred to by Dr. Naffziger.

The patient, a male, aged fifty-two years, developed Basedow's disease approximately two years previous to examination at Billings Hospital, University of Chicago. The basal metabolic rate was +105 per cent. In November, 1930, a partial thyroidectomy was performed. This was followed by complete subsidence of all the signs and symptoms of thyrotoxicosis, with the exception of slightly widened palpebral fissures. Four months after the operation a bilateral exophthalmos developed rapidly. The patient was seen ten months post-operatively, at which time it was noted that the exophthalmos of the right eye was more marked than that of the left. The conjunctiva of the right eye was markedly chemotic and protruded between the lower lid and the eyeball into the palpebral fissure. A right canthotomy was performed, but there was no improvement in the engorged and chemotic conjunctiva. The lids were markedly swollen and somewhat cyanotic. Fundus examination revealed a bilateral flat papilledema with peripapillary retinal hemorrhages. The basal metabolic rates at this time were found to be zero and −9 per cent. There were no other signs nor symptoms of hyperthyroidism.

Both middle cervical ganglia were removed by Dr. Paul Bucy

without reduction in the degree of the exophthalmos. A celloidin shield was worn constantly over the right eye. When this was not in place, a small corneal ulcer developed. A portion of the right orbital fat was then removed through an opening made in the floor of the orbit by way of the maxillary sinus.

In December, 1931, Dr. Paul Bucy removed part of the bony roof of the right orbit by the transfrontal route, without injuring the dura. Some of the orbital muscles were isolated, and these were seen to be three or four times the normal thickness. A piece of the external rectus was removed for examination. During the course of five weeks the exophthalmos of the right eye receded so that the exophthalmometer readings of both eyes were approximately the same. The amount of recession, measured by the Hertel exophthalmometer, was approximately 5 mm. The elevation of each disc was reduced, and the hemorrhages disappeared.

Histologically, the excised muscle presented the picture described by Dr. Naffziger. Most striking were the many areas of lymphocytic infiltration. These were usually present about the blood-vessels. Did this infiltration bear any relation to the lymphocytosis which frequently persists after the removal of the thyroid and the subsequent subsidence of the symptoms of thyrotoxicosis? Why was there bilateral reduction of the papilledema when only one orbit was decompressed, and that without injury to the cerebral dura?

Dr. Howard C. Naffziger, closing: As has been pointed out, there is a similarity between these pathologic changes and those found in myxedema. There are other analogies to be drawn; for example, the changes in these muscles are similar to those caused by Volkmann's palsy—the same infiltration, fibrosis, and edema are present. However, polynuclear cells, rather than lymphocytes, are found. In my paper I did not mention that sections from the temporal and quadriceps femoris muscles have been examined and that no abnormalities were found in them.

In connection with some of the points mentioned by Dr. Benedict, I would say that I feel as he does—that there must be an increase of fluid to account for the increased size of the muscles in the early stages. Later, following the infiltration of lymphocytes and the formation of fibrous tissue, there is an actual increase in solid tissue. It is not a hypertrophy of the muscle.

From the discussion it is apparent that all are familiar with

patients who have exophthalmos without accompanying thyrotoxicosis. Of these, some go on to the stage of corneal ulceration and loss of their eyes.

We have not operated on any patients for cosmetic purposes. The rule has been to operate when the exophthalmos is progressive. In addition, our patients showed other abnormalities; for example, all but one had limited eye-muscle movements, and five out of six were becoming blind very rapidly.

I am perfectly sure that Dr. Benedict will find that neither Lugol's solution nor any other preparation with which we are familiar will arrest the severe cases. Three of our patients had received such treatment as he outlined, without apparent effect. On the other hand, I believe that many of the milder cases will remain stationary with or without any treatment.

As to the lymphocytic infiltration, I think that it is comparable to that seen in other organs in thyroid disease. The underlying reasons for this myopathy or pseudohypertrophy are not clear as yet. I do not believe that the thyroid link is essential to the production of such muscle changes.

As to exophthalmos in animals, this is easily produced by various means, but none of the methods used has caused *progressive* exophthalmos. Marine has shown that methyl cyanid will produce thyroid hyperplasia with exophthalmos. Certain substances found in the anterior lobe of the pituitary gland have also been said to cause this condition. However, the condition in animals is quite different from that in man.

I am interested in the presence of choked disc with exophthalmos, and am pleased that Dr. Parker mentioned it. I am not certain that unroofing the optic foramen is an essential step in relieving either the exophthalmos or the choking. As to Dr. Parker's view that choked disc is caused by an increase of tension immediately behind the globe, I have grave doubts, for the following reason: We have been accustomed to think of the sequence of events as being something like this: Intracranial pressure is caused, for example, by a tumor, with a resulting increase in the cerebrospinal fluid pressure. This, in turn, is transmitted along the arachnoid sheath of the optic nerve and affects the venous outflow from the optic nerve and retina. As a result, these veins become engorged and tortuous. The tissue from which they drain becomes edematous and cellular infiltration occurs; later, fibroblasts appear, with the formation of scar tissue which ages and finally contracts so that atrophy is produced.

In such a sequence we assume that obstruction to the venous backflow is essential to the production of choked disc. There are certain points which such a theory does not explain. For example, if we consider that high venous pressure is important, we should find choked discs in every instance of cavernous sinus thrombosis, but this is not the rule. Again, when we are dealing with pulsating exophthalmos resulting from a fistulous communication between the internal carotid and the cavernous sinus, we usually do not find choked discs, and yet, in such cases, the venous pressure is raised to a degree well above that present in any other condition with which we are familiar. Therefore, while I believe that impairment of venous return may, under certain conditions, be a factor in the production of choked disc, I do not believe it can be regarded as an essential.

PREMONITORY LID EDEMA IN THE TYPHOID GROUP

S. J. BEACH, M.D.
Portland, Maine

There exists a tradition that edema of the eyelids occurs as a manifestation of typhoid fever. Although I have found no documentary evidence to substantiate this statement, I have more than once heard it mentioned. At what period in the disease the edema occurs, the nature, extent, and appearance of the swelling, and the length of its duration seem to be unknown. Competent observers dismiss the notion as not worth consideration. Therefore, having observed the phenomenon in two interesting cases, and, furthermore, having found in the literature the account of an epidemic[1] susceptible of this interpretation, I am placing it on record. These cases and the description of the epidemic alike indicate that the edema may be the earliest symptom of the disease, and therefore highly important as an aid to diagnosis; also that it is a soft, painless, non-inflammatory, bilateral swelling, extending to adjacent parts of the cheeks