A CONSIDERATION OF THE CAUSES OF HETEROCHROMIA IRIDIS, WITH SPECIAL REFERENCE TO A PARALYSIS OF THE CERVICAL SYMPATHETIC.*

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That curious condition which consists in a difference in the pigmentation of the two eyes is regarded by the casual observer as a play or caprice of nature. This phenomenon has for centuries been noted, and was called *heteroglaucus* by Aristotle.[1] One who seriously studies the subject is at once impressed with the complexity of the situation and soon learns that nature plays a comparatively small part in its causation. It is, however, only within a comparatively recent time that the pathologic aspect has been considered, and in this discussion I especially wish to draw attention to that part played by the cervical sympathetic.

Many writers have given Hutchinson[2] (1869) credit for first describing a difference in the color of the irides, in which cataract was associated. By chance I discovered that Lawrence[3] (1853) described irregularities in the color of the iris and cited two cases, in one of slowly changing color and another of changed color of the iris with cataract. He also quoted Wilde,[4] who mentions the fact that heredity plays an important part in many of these abnormalities.

NOMENCLATURE.

Various terms have been applied for this inequality in the color of the irides, such as heteroglaucus of the ancients;

* Candidate's thesis for membership accepted by the Committee on Theses.

heterophthalmus (Weill[5]), aniso-iridochromia (Scalinci[6]), and chromoheteropia (Malgat[7]). The last named thinks that the word heterochromia should apply to those cases in which parts of the same iris have different colors. In those cases where a cyclitis accompanies the iris decoloration Butler[8] uses the term "heterochromic cyclitis," but the "chronic cyclitis with decoloration of the iris," as described by Fuchs,[9] undoubtedly gives a more accurate description of the disease, notwithstanding its long title. The commonly accepted and most universally used term, *heterochromia iridis*, exactly expresses and implies the picture from its derivation (ἕτερος, other; χρῶμα, color). Other newly coined words only add disorder to an already chaotic classification of diseases.*

CLASSIFICATION.

Any exact classification of this condition is almost an impossible task, and, mindful of its limitations, I venture to submit the following as a working basis of study:

Primary	Congenital	with or without	Heredity. Sympathetic paralysis. Cyclitis and cataract.
	Acquired	with or without	Sympathetic paralysis. Cyclitis or cataract.
Secondary			Injuries. Siderosis bulbi. Uveal infection—Myopia. Glaucoma.

Strictly speaking, as Sym has pointed out, there could be no such thing as a congenital form of heterochromia iridis, since it is about the twelfth or sixteenth month that the

* Dr. Willis H. Bocock, my friend and former professor of Greek at the University of Georgia, has suggested the word *irideterochromia*. "The *o* (as in iridoplegia) is not used in composition before a vowel; therefore *irid* in the word above. *Hetero* (as in heterochromia) loses the *h* in composition, therefore *irideterochromia*."

While it would be advantageous to have the meaning so expressed in one word, its derivation would not be so obvious as the term heterochromia iridis, unless the reader possessed a working knowledge of Greek.

child's iris ceases to be light and takes on color. Brown pigment has, however, been noted to appear on the iris as early as six months.

I am not in accord with Sym[10] and Scalinci, who maintained that we should reserve the term heterochromia iridis "for the instances in which there has not been any obvious pathological process in the eye, such as glaucoma or iridocyclitis." The term expresses the condition regardless of the cause. I have recently seen a case in which there was a decoloration of the iris in an adult negro who, at first glance, presented evidences of a sympathetic paralysis, namely, a smaller pupil and a narrower palpebral aperture than in the opposite eye. The case proved to be the result of an injury received during childhood, and the presence of a foreign body in the choroid could be demonstrated. The ptosis was traumatic, the myosis was due to posterior adhesions, and the iris decoloration was probably a siderosis bulbi, or caused from a low-grade iridocyclitis. I can see no objection to classifying this as one of heterochromia of the iris of secondary origin, due to an old injury (foreign body with uveitis).

HEREDITY.

Heredity as a cause for heterochromia iridis has not received the same consideration from modern writers as from those of a generation ago. I am firmly convinced that there are many such congenital cases without sign or development of a pathologic lesion; and one reason why more cases are not so classified is that the observer, indifferent to the causes of heredity, does not stress its influence, and also that too few of our patients, clinical patients especially, know enough of their ancestry.

The history of cases 1 and 2 from the same family (more fully described under the heading of sympathetic paralysis), where the paralysis and lighter iris were all on the same side, in a manner substantiates the fact that heredity does

play an important part. If the paralysis was the cause for the iris decoloration, it would be proper to consider it as the disorder inherited.

Galezowski,[11] Bistis,[12] and Scalinci[6] report cases of sympathetic paralysis where one or more children in a family had iris decolorations which were inherited. But we should bear in mind Priestly Smith's[13] words that "heredity is not in any real sense a cause. It may account for the presence of a disorder in an individual or family, but it tells us nothing as to its origin. In some former generation there must have been a first departure from the normal."

Osborne,[14] as early as 1849, drew attention to the difference in color of the irides of a person (that is, they were irregularly marked) who had 15 brothers and 5 sisters who all possessed the same abnormality which was derived from the mother, whose three sisters and one brother had the same, which were again derived from the mother's side. Gunn[15] mentions similar cases and classifies them as "piebald iris."

It has been stated many times that in congenital heterochromia iridis the color of one eye is inherited from the father, while the color of the other is derived from the mother. In many instances this has been true, but the reverse is as often the case, and even eyes of an entirely different color to either parent have been observed. This contradictory observation, however, would not refute the hereditary theory of transmission, bearing in mind the principles of Mendel's law.

The family reported by Gossage[16] is the only recorded case beyond the second generation that I find mentioned. A detailed description and examination of the eye unfortunately is not given, although the author states that "in this family heterochromia of the iris tended to appear when one eye, always the left, was grayish blue in color, with chestnut-brown patches. Of the offsprings of the affected

members of the family, eight were affected and twenty-two free" (Fig. 1).

From a genetic point of view, Przibram's[17] work on Angora cats is interesting. He found that the union of an asymmetrically colored animal having one blue and one yellow eye, with a symmetrically colored animal having two blue or two yellow eyes, resulted in the production of both asymmetrically (heterochromia iridis) and symmetrically pigmented offsprings. He concluded that asymmetric animals can be traced back to asymmetric ancestry, and that either color of an asymmetric parent can appear in the symmetric form of an offspring.

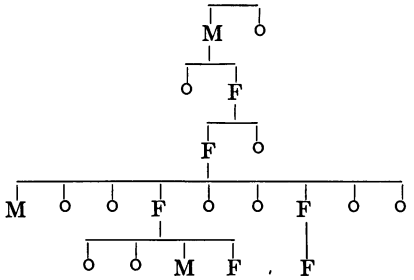


Fig. 1.—Gossage's case. M, affected male; F, affected female; o, sex undetermined.

PARALYSIS OF THE CERVICAL SYMPATHETIC.

Within the past few years attention has been directed to the association in heterochromic eyes of alteration of a paretic nature of the cervical sympathetic. In fact, some observers, notably Bistis, are so enthusiastic over the close association that they have added to the classic Horner's syndrome (ptosis, myosis, anhidrosis, hemiatrophy facialis) heterochromia iridis as a symptom. Mayou[18] in 1910 was probably the first accurately to describe these changes, although Horner (quoted by Samelsohn[20]), as early as 1875, did draw attention to a case in which a light iris occurred on the same side with a ptosis of sympathetic origin. In

all only 33 cases have been reported,* 10 of which were complicated either with cataract or a slow uveitis.

From my own observation I can report four cases, the first two being of the same family, with positive symptoms of a sympathetic paralysis; the third gave less prominent symptoms, and the fourth presented only slight evidences of any sympathetic disturbance. My reason for here reporting case 5 along with the others is that we may assume that the heterochromia was due to certain trophic disturbances from a complete hemiplegia. Properly it belongs under the acquired classification if the history is correct.

CASE 1.—Baby R., male, aged ten months, seen September 30, 1908; parents first noticed a drooping of the upper lid and a lighter color of the right eye when only a few weeks old. The father and mother are blonds and have blue eyes. The mother of the patient has a paternal aunt whose right eye is of lighter color; her brother has a drooping right upper lid with a lighter colored iris on the same side. This brother has a son (case 2) with the same abnormality on the right side. There is also another brother whose eyes are of the same color, and whose son has a drooping upper lid and light eye on the right side. This patient (baby R.) was born normally and has been healthy. The parents noticed that the child did not perspire on the right side of his brow.

The examination showed on the right side a decided ptosis, small pupil, light-blue iris, and a dryness of the skin of the right forehead as compared to the opposite side. As well as I could detect without a dilated pupil (the parents refusing eye drops), the fundus was normal and there were no corneal deposits. In July, 1915, nearly seven years later, I again examined the child. He had been well and healthy. The upper right lid still drooped, but not greatly, there was some suggestion of a facial atrophy on the same side, the pupil was still quite small compared to the left eye, yet it

* The following authors reporting: Galezowski,[11] 2 cases, 1 complicated; Horner's case, reported by Samelsohn;[20] Dethleffsen,[21] 5 cases, 1 complicated Lutz,[22] 13 cases, 3 complicated; Hutchinson,[2] 1 case; Alexander and Lander,[32] 5 cases, 2 complicated; Bistis,[39] 2 complicated cases; Mayou,[18] 3 cases, and Scalinci,[6] 1 case.

reacted well to light; the iris was blue, V. = 20/20, and fundus was normal, with no corneal deposits (without mydriasis). The left eye was normal and the iris brown (×192).

CASE 2.—Master D., aged five years. The family history is the same as case 1, the patient being his first cousin. The maternal grandmother gave me the history of the family and patient, and she stated that the condition to be described existed from birth. The patient's father (uncle to case 1) has blue eyes, and the mother's eyes are hazel, and I am told she is blind in one eye "from the rupture of a blood-vessel." At birth there was some abnormality (a breech presentation), although no instruments were used. There are two younger children with normal eyes of the same color.

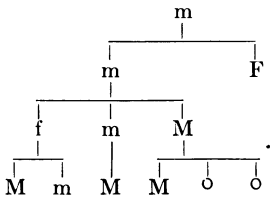


Fig. 2.—Author's case. M, affected male; F, affected female; m, normal male; f, normal female; o, sex undetermined.

Examination: Right, drooping upper lid, hemiatrophy facialis, palpebral fissure 5 mm., pupil active to light, 2 mm. in diameter. Color of iris was blue. Two drops of 1: 1000 solution of epinephrin did not dilate pupil. Cocain not used. Fundus normal; no corneal deposits. V. = 20/20. Left, dark-blue iris, with brownish pigmentation surrounding pupil, which measures 4 to 5 mm. Fundus normal. V. = 20/20.

The grandmother states that when the child is unwell, the drooping of the upper lid and the narrowing of the pupil of the right eye are perceptibly increased. Perspires on left side of face only (Fig. 2).

CASE 3.—J. L. M., male, aged fifty-seven years, states that all his life the left eye has been smaller than the right and of a lighter color. Family history negative; all children have dark eyes. The patient was brought to me as a re-

fractive case on account of headaches and dizziness. Patient is a brunette. Two years ago he had a stroke of apoplexy causing left hemiplegia, which now partially exists. He gives a positive luetic history, and has taken appropriate treatment, including salvarsan.

Examination: V. R. E. = 20/15 corrected. Palpebral aperture, 12 mm. Color of iris brown; pupil active to light and measures 2.5 mm. Many small vitreous opacities, but no corneal deposits. Typical retinal arteriosclerosis, *i. e.*, beaded and corkscrew arteries. Pupil does not dilate to epinephrin, and sluggishly to cocain, as compared to left. Tonometer, 20 mm. V. L. E. = 20/20 corrected. Palpebral aperture, 10 mm. Iris light gray and active to light. Pupil measures 3 mm., does not dilate to epinephrin, but actively and widely to cocain. No corneal deposits, but similar vitreous opacities and retinal changes as in right. Decided left hemiatrophy facialis and apparent enophthalmos. No anhidrosis. Tonometer, 20 mm. Hg. Visual fields contracted peripherally. Systolic blood-pressure 172.

CASE 4.—J. E. M., male, aged thirty-eight years. Family and hereditary history negative. Father's eyes brown, mother's blue (?). Patient is only member in family with different colored irides, and he states that he has had this difference all his life. He consulted me for pain in eyes after reading.

Examination: Right eye, H. + A. H. V. = 20/20. Pupil same size as left and reacted to light. Color of iris gray. Slight drooping of upper lid. Palpebral aperture 6 mm. Fundus normal. No corneal deposits.

Left eye: H. A. V. = 20/20; pupil active to light. Color of iris brown. Palpebral aperture, 8 mm. Decided bluish discoloration of sclera, arranged in patches above and out, and down and out. After using the same number of drops of homatropin in each eye for an hour to dilate the pupils for retinoscopy, it was observed that the right (light iris) was dilated to maximum with loss of accommodation, whereas the left pupil still reacted to light, with little loss of accommodation. Prolonged use of the drops did produce cycloplegia. Seen one month later. Slight ptosis on the right side, and right pupil 2.5 mm., whereas left 2 mm. No

response to epinephrin, and right pupil dilated to 4 mm. after twenty minutes from one drop of cocain. Left did not dilate. The only evidence of a sympathetic paralysis was a slight ptosis on the lighter side.

CASE 5.—P. R. R., male, aged forty-three years, consulted me on account of defective sight of long duration in the right eye. Several members of his family have bad eyes, evidently refractive errors, and perhaps from ocular injuries. Blue or gray colored eyes predominate in the family. The patient is a decided brunette, with black hair, and states that when seven months of age he was paralyzed on the entire left side of body and face; that the left eye has always been of lighter color than the right. Is a farmer of moderate intellect. A general physical and neurologic examination was made by Dr. H. Crenshaw, who reported nothing abnormal except a general left hemiplegia. There were no positive evidences of a sympathetic paralysis. The eye examination is as follows: V. R. E. =light perception, extra-ocular muscles normal, pupil dilated and inactive, measures 5 mm. Iris light brown, with one area of intense brown pigment above and a sector-shaped area of gray below. Media clear. Typical cupping with atrophic changes of glaucoma simplex. Tension, 52 mm. Hg. Corneal anesthesia. V. L. E. = 20/30. Small pterygium. Pupil 2.5 mm., active, iris gray, slightly shallow anterior chamber, no drooping of upper lid. Fundus normal, cornea sensitive, no deposits. Field contracted peripherally, with an encroachment on nasal side. No enlargement of blind spot or scotoma. No anhidrosis, but there existed a decided asymmetry to the face; the left side much sunken, with a deepening of facial furrows. We assumed that the facial atrophy was due to the general hemiplegia and not to a seventh nerve involvement. It is difficult at this late day to explain in this case any direct connection between the light iris and facial hemiatrophy or hemiplegia on the left side, unless we can imagine that in infancy certain trophic disturbances developed as a result of the hemiplegia, but even this gives nothing very definite.

In closely reviewing the 33 cases reported, it is noticeable that in a good percentage the only evidence of a sympathetic

alteration was a narrowing of the pupil in the lighter eye. While this is evidence of a sympathetic paralysis, it is not altogether positive. In case 3, which I believe to be of sympathetic paralysis (having ptosis and hemiatrophy facialis), the pupil was larger and dilated under cocain more readily than its fellow. I take for granted that the authors have eliminated the many other influences which would cause a small pupil before positively declaring the case as one of sympathetic disturbance. In this connection it is interesting to note Pollock's[23]* well-known experiment, in which he caused a dilatation of the pupil from a mydriatic and a contraction by direct light in cases where he had completely excised the superior cervical sympathetic and the ciliary ganglia.

It should also be borne in mind that in rabbit experiments, where the superior cervical sympathetic ganglion has been completely removed, there is often a paradoxical dilatation of the pupil.†

Another fact to be noted, from the reported cases of heterochromia iridis associated with undoubted sympathetic paralysis, is that the paralysis was usually congenital or first noticed in early infancy, and the differences in the color of the irides developed at the natural time when changes take place in the color of the iris. In several cases (Mayou[19]) there was a history of forceps delivery, which was naturally supposed to be the cause of the paralysis. However, it is not difficult to find equally as many reports of a sympathetic

* Pollock concluded, after his experiments, that "evidence is given that a motor plexus with nerve-cells exists in the sphincter and in the dilator pupillæ of the rabbit's iris. This plexus lies between the individual cells of the muscles and contains fibers of extreme tenuity. The plexus persists after separation of the iris from the central nervous system. It may, therefore, be regarded in the same nature as the plexus of Auerbach and Meissner in the intestine."

† This phenomena has been observed by Langendorff,[24] where, several days after the ganglion has been removed, the pupil markedly dilates, and he explains it by vasomotor changes, *i. e.*, dilatation of the iris vessels causes the pupil to contract, while a narrowing produces a dilatation of the pupil. This vasomotor change also takes place in the ear: at first an increased warmth, and then later a coldness.

paralysis from forceps delivery without iris decoloration (Reese[25] and Burrows[26]), although in many of these reports no reference is made to the color of the iris. This lack of depigmentation in light-colored irides of blonds with an associated sympathetic paralysis can easily be explained. Mayou[27] has also mentioned cases of sympathetic paralysis without iris decloration associated with cervical rib. Of all the reported cases of sympathetic paralysis developing in adult life, Bistis[28] reports the only positive case where a change in the color of the iris subsequently developed; and the case is well worth reviewing.* Metzner[29] reports Mendel's case, in which there were certain suggestive peripheral depigmented changes in the iris.

A traumatic paralysis of the superior cervical ganglion or nerve in adult life is by no means an uncommon accident, and as yet no reports have been made of a subsequent iris decoloration. I personally have followed two such cases. I have also inquired of the older ophthalmic surgeons of large experience, who at one time advocated and practised sympathectomy for glaucoma, and in no instance has there been noted any subsequent change in the color of the iris.

SUGGESTED ALLIED CAUSES.

It is noted that in case 3 there existed slight deafness, which, from the history and examination, suggests nerve impairment. I can offer no opinion from this limited experience as to whether there is any association between the auditory, ocular, and sympathetic disturbances. Mendel[30] mentioned

* Bistis' case. Female, aged thirty-eight years. The mother showed differences in the color of the irides, and the lighter eye showed cataract in an advanced age. For two years the patient's sight has failed, and the color of the right iris has changed. There was pain around the right eye, and facial hemiatrophy, together with anhidrosis of same side, appeared at same time as heterochromia. Author had seen patient often before onset of trouble for refraction, and the condition described did not exist. The eye showed ptosis, enophthalmus, descemetitis, and blue iris; pupil did not dilate as well to cocain as opposite side; no effect to epinephrin. Aqueous slightly turbid, tension subnormal, and lens changes.

a similar change in one of his cases. It is well known that deafness is often present in albino cats (Beaumont[31]), and in two cats which had heterochromia iridis and deafness Alexander and Lander[32] studied the anatomy of the eyes and ears. They found an absence of pigment in the perilymphatic cells of the auditory organ, and, on the other hand, the mesodermal pigment was absent in the lighter iris. These same authors called attention to the influence which certain gland-like structures at the posterior part of the ciliary body, first described by Collins,[33] might have in producing a depigmentation of the iris. According to Griffin,[34] these glands control the amount of pigment in the eye, shown by their absence in albino eyes and their imperfect development in feebly pigmented blue eyes. As plausible as this theory seems, the presence of these glands are nevertheless doubted by other able men (Alt[35] and Rutteman[36]), who were not even able to find their lumen. Finnoff[37] finds these so-called pigmented glands, but thinks that they are pigmented plugs, and, while he admits that gland-like bodies may be demonstrated, he considers the lumen an artefact, produced by the process of hardening, and a section of such tissue would resemble a tubular-like gland cut crosswise. Therefore, with this apparent uncertainty we could hardly accept at the present time the suggestion that the so-called ciliary glands of Collins have any influence in causing heterochromia iridis.

EXPERIMENTAL WORK.

In regard to the experimental work, which has been done on animals by dividing the sympathetic nerve or excising the superior cervical ganglion, Angelucci[38] found that section of the ganglion produced trophic alterations of the eye, among them being a disappearance of the pigment of the iris, with an atrophy and depigmentation of the choroid, besides certain well-defined alterations of the blood-vessels of the iris. Bistis[39]

produced similar changes in the iris, and in one case he was able to demonstrate a cloudiness of the aqueous, and found in sections deposits on the posterior surface of the cornea which, to his mind, was highly suggestive of an inflammatory process. Later, Metzner[29] and Wolfflin added evidence that a sympathetic paralysis caused a distinct loss of pigment in the iris, and also recorded other changes which had previously been observed, such as epiphora, flattening of the cornea (Angelucci), changes in the motility of the nictitating membrane, and hypotonia. This latter observation was to a certain extent agreed with in our experiments.

By more recent experiments on rabbits these same authors concluded that the superior sympathetic ganglion must have an independent tonus as regards the dilatation of the pupil, for if on one side division of the nerve was made below the ganglion, and on the opposite side the ganglion was extirpated, the pupil was smaller on the extirpated side. Their experiments also showed that the extirpation of the ganglion was never accompanied by a depigmentation of the iris, but that a resection of the nerve below the ganglion was followed by a decoloration of the iris.

These last-mentioned experiments present new phases to the subject with which we have had no experience, and which are quite contrary to the general accepted physiology of the sympathetic system.

In this connection it is of interest to know that Galezowsky reported a case of heterochromia where, in the lighter eye, the pupil and the palpebral fissure were wider, and the eye was more prominent, than its fellow. Obviously, there were symptoms of a sympathetic stimulation or irritation.

THE AUTHOR'S EXPERIMENTS.

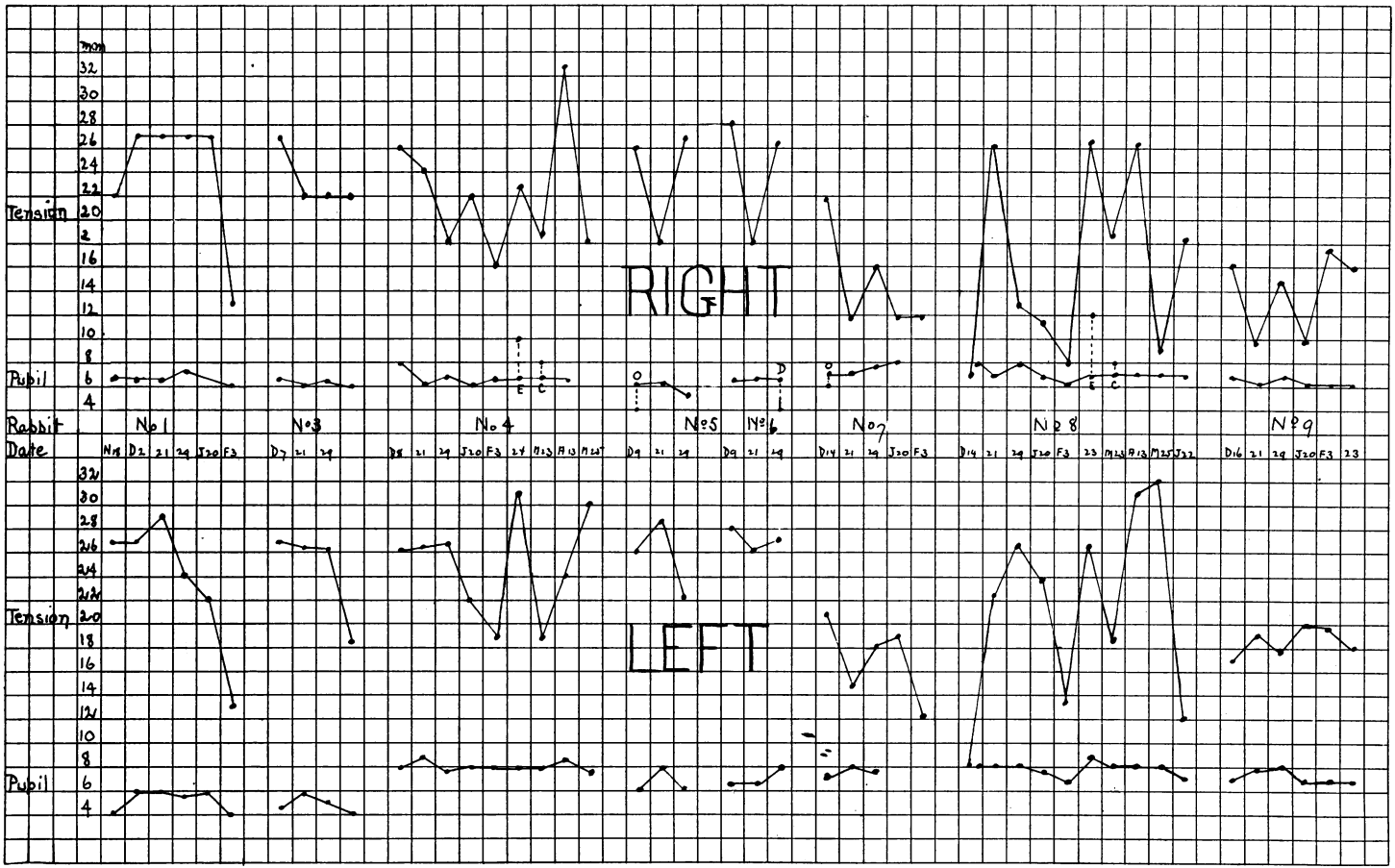
An Excision of the Cervical Sympathetic Ganglion in the Rabbit.—Guinea-pigs were first employed in our experiments, mainly to perfect the operative technic of the re-

moval of the superior cervical ganglion, and later Belgian hares were used. After the operation the ganglion was preserved in normal saline solution, later stained with methylene-blue (vital stain) and examined microscopically.

Light ether anesthesia was administered, the fur on the under surface of the neck was shaved, the part washed with soap and water, sponged with alcohol, and then painted with tincture of iodin. The ganglion was rapidly exposed and grasped with a pair of tissue forceps and excised with scissors. The skin incision was closed with continuous silk sutures, and a sterile gauze dressing applied with adhesive tape. Apparently the animals did not suffer in any way from the operation, and were quite alert shortly afterward. There were no infections.

As the rabbit's pupil is often oval (the vertical diameter being the greatest), pupillary measurements were made with a millimeter rule along the horizontal meridian of the cornea —that is, from canthus to canthus. The eyes were exposed to daylight from a northernly direction. Tonometric readings were made with the Schiötz instrument, and it was applied the moment after an instillation of one drop of a 4 per cent. aqueous solution of cocain. The lids were gently retracted with the fingers, and usually the readings were easily and presumably accurately made, although at times the animals were exceedingly nervous and frightened, which apparently accounted for the wide variations in the intraocular tension. The 7.5 mg. weight was employed, but when there was doubt of the accuracy, other weights were used as controls and the readings usually corresponded.

It was exceedingly difficult to distinguish early decoloration of the irides, and it is possible that one's imagination had its influence in causing certain discrepancies made in our early observations, but when a decided change was noted, this opinion was concurred in by three or four other observers. Eyes which showed no great change in the color



The above chart represents the intraocular tension and pupillary measurements of the rabbits used in the experiments. The first readings indicate the tension and size of the pupil of the right eye of each rabbit before operation, while all other readings were made after operation. The letters indicate the following: E, epinephrin; C, cocain; O, operation, and D, death.

during life presented a marked difference after enucleations, and when held side by side for a closer comparison.

Five guinea-pigs were used, and the four that survived all showed a narrowing of the palpebral aperture and myosis, but no macroscopic change in the color of the iris on the operative side even seven months after the operation. Weeping of the eye on the operative side was noticed as a symptom in three cases after recovery from ether anesthesia, which later disappeared.

Rabbit No. 1.—November 18, 1915: Male, weight 1620 gm. Color of irides light brown. Size of right pupil 6.5 mm.; contracts to light. Left, 6 mm., contracts to light. Tension: Right, 22 mm. Hg; left, 27 mm. Hg. Fundus normal.

Operation: Removal of right superior cervical sympathetic ganglion. Right pupil immediately contracted, and grows smaller; left dilated and does not respond to light. Lacrimation right eye.

November 19th: Right pupil smaller than left.

November 22d: Pupils of equal size; reaction to light—right more sluggish. Palpebral aperture same size.

November 27th: Right pupil smaller than left.

November 30th: Right pupil 6 mm.; left, 8 mm.

December 2d: Right pupil 6.5 mm.; left, 8 mm. Nictitating membrane not affected. Tension: Right, 27 mm. Hg; left, 26 mm. Hg. Right palpebral aperture narrower than left. No increased lacrimation. Color of iris same. Fundus normal.

December 21st: Pupils: Right, 6.5 mm.; left, 7 mm. Tension: Right, 27 mm. Hg; left, 29 mm. Hg. Right iris appears to be of lighter color than left.

December 29th: Narrowing of right palpebral aperture. Pupils: Right, 7 mm.; left, 8 mm. Tension: Right, 27 mm. Hg; left, 24 mm. Hg.

January 20, 1916: Slight ptosis, right side. Pupils: Right, 6 mm.; left, 7 mm. Tension: Right, 27 mm. Hg; left, 22 mm. Hg. The iris has in the upper part a "washed-out" appearance.

February 3d: Slight ptosis, right side; pupils equal,

5 mm. Fundus normal. Tension: Right and left, 13.5 mm. Hg.

February 7th: Rabbit died of unknown cause. Pupils: Right, 4 mm.; left, 6 mm. Eyes enucleated. Color of right iris distinctly lighter than left. (See description under histopathology.)

Rabbit No. 2.—December 2, 1915: Male, weight 2310 gm. Irides dark brown. Pupils 7 mm. in horizontal diameter. Tension each eye, 26 mm. Hg.

Operation: Removal of right superior cervical sympathetic ganglion. Rabbit did not react from anesthetic.

Rabbit No. 3.—December 7, 1915: Female; weight 1220 gm. Irides dark brown. Pupils, 7 mm. Tension: Right and left, 26.5 mm. Hg. Fundus normal.

Operation: Removal of right superior cervical sympathetic ganglion. Right pupil contracts to 5 mm. and both react promptly to light. No weeping or ptosis.

December 8th: Pupils: Right, 5 mm.; left, 6 mm.; slight ptosis.

December 14: Pupils: Right, 6 mm.; left, 7 mm.; slight ptosis. Nictitating membrane shows slightly on right and not at all on left.

December 21st: Pupils: Right, 6 mm.; left, 8 mm. Tension: Right, 22 mm. Hg; left, 26.5 mm. Hg. No change in color of iris. Fundus normal.

December 28th: Pupils: Right, 6.5 mm.; left, 7 mm.; right ptosis. Fundus normal. Tension: Right, 22 mm. Hg; left, 26.5 mm. Hg.

January 20, 1916: Pupils: 6 mm.; right ptosis. Tension: Right, 42 mm. Hg; left, 18.5 mm. Hg. No change in color of iris. Fundus normal.

January 31st: Died. No change in size or color of iris. Eyes enucleated.

Rabbit No. 4.—December 8, 1915: Male; weight, 1530 gm. Color of irides brown. Pupils, 8 mm. Fundus normal. Tension, each eye, 26 mm. Hg.

Operation: Removal of right superior cervical sympathetic ganglion. Immediate contraction of right pupil—right, 6 mm.; left, 8 mm.

December 9th: Pupils: Right, 7 mm.; left, 9 mm.; ptosis right; nictitating membrane not visible on either side.

December 13th: Pupils: Right, 6 mm.; left, 8 mm.

December 21st: Pupils: Right, 6 mm.; left, 7.5 mm. Tension: Right, 24 mm. Hg; left, 26.5 mm. Hg. Fundus normal. Right ptosis; lighter color to right iris.

December 29th: Pupils: Right, 7 mm.; left, 8 mm. Tension: Right, 18.5 mm. Hg; left, 26.5 mm. Hg. Fundus normal. Right ptosis.

January 20, 1916: Pupils: Right, 6 mm.; left, 7 mm. Right ptosis. Fundus normal. No apparent change in color of iris. Tension, each eye, 22 mm. Hg.

February 3d: Pupils: Right, 6.5 mm.; left, 8 mm. Right ptosis. Tension: Right, 16 mm. Hg; left, 18.5 mm. Hg.

February 24th: Same as above. No change in color of iris. Fundus normal.

March 2d: Pupils: Right, 6 mm.; left, 7 mm. One per cent. aqueous solution homatropin in each eye; after fifteen minutes in dark room, right, 8 mm.; left, 9 mm.

March 16th: Pupils: Right, 7 mm.; left, 8 mm. One drop 1:1000 epinephrin solution in each eye; after fifteen minutes in dark room, right pupil, 10 mm.; left, 9 mm.

March 23d: Pupils, 7 mm. Slight right ptosis. Tension, each eye, 18.5 mm. Hg. Two drops 4 per cent. aqueous solution cocain in each eye; after fifteen minutes in dark room, pupils 8 mm.

April 13th: Pupils: Right, 7 mm.; left, 8 mm. Tension: Right, 24 mm. Hg; left, 31 mm. Hg. Right ptosis. Fundus normal. Slight discoloration of right iris. One drop 4 per cent. solution cocain in each eye; after fifteen minutes in dark room, pupils, right, 7 mm.; left, 8 mm.

May 4th: Pupils: Right, 6.5 mm.; left, 8 mm. One drop 4 per cent. cocain solution in each eye; after twenty-five minutes, right pupil, 7 mm.; left, 8.5 mm. One per cent. homatropin solution in each eye; after twenty minutes, left pupil dilates more than right. No fundus change.

May 25th: Pupils: Right, 7 mm.; left, 8.5 mm. The right iris is slightly lighter than the left. Tension: Right, 18 mm. Hg; left, 30 mm. Hg. Aqueous in right eye appears turbid, but there are no corneal deposits. Attached to the

under surface of the right iris, or rather hanging from it at twelve o'clock, is a small black tag which moves with the iris excursions. In the horizontal diameter of the cornea, near the limbus of the temporal side and within the cornea proper, is a refractile body.

June 22d: Pupils: Right, 6.5 mm.; left, 8 mm. The difference in the color of the irides does not appear to be so marked. The aqueous in the right eye is not so turbid as at the previous examination, and the iris tag is not present. Homatropin dilated both pupils evenly. The general view of the fundus of the right eye does not appear to be as clear as the left. After mydriasis the iris tag is seen, but it is not so large.

July 6th: Very slight difference in the color of the irides. There is a second pigment tag of the iris at about 1 o'clock.

July 27th: Pupils: Right, 7 mm.; left, 8 mm. Very slight difference in the color of the irides, but one pigment tag hanging from the iris, and that at twelve o'clock. There are two distinct opacities seen in the posterior portion of the lens. Epinephrin solution 1: 1000 dilates the right pupil to 11 mm. but the left remains the same.

August 10th: Opacities in lens still present. It has been noticed for some time that it is more difficult to see the fundus in the right than in the left eye, due to detritus on cornea. It was also noticed that after the instillation of epinephrin the cornea became clearer.

August 24th: There is a slight difference in the color of the irides.

October 19th: Pupils: Right, 7 mm.; left, 8 mm. There is only a slight difference in the pigmentation of the two irides. The pigment tag hanging from the iris is still present. The opacities in the lens noted at previous examinations are not seen.

January 4, 1917: Rabbit in good health. Pupils: Right, 6.5 mm.; left, 8 mm. There is a decided difference in the pigmentation of the two irides. No opacities seen in the lens or vitreous. Iris tag still present.

January 29th: Rabbit died of unknown cause. Eyes enucleated for examination.

Rabbit No. 5.—December 9, 1916: Male, two months old;

weight, 810 gm. Color of irides, brown. Pupils: 6 mm. Fundus normal. Tension (obtained with difficulty, as animal was nervous): right and left, 26 mm.

Operation: Removal of right superior cervical sympathetic ganglion. Immediately right pupil contracts to 4 mm. Nictitating membrane invisible.

December 9th: Pupils: Right, 6 mm.; left, 8 mm. Right ptosis.

December 21st: Pupils: Right, 4.5 mm.; left, 6 mm. Tension: Right, 17.5 mm. Hg; left, 27.5 mm. Hg.

December 29th: Pupils: Right, 5 mm.; left, 6 mm. Right ptosis. Tension: Right, 26.5 mm. Hg; left, 22 mm. Hg.

January 18, 1916: Died. Pupils of equal size. Eyes removed (hemorrhage in right orbit); when held together the right iris is paler than left, and the decrease of the pigment seems to be more marked toward the pupillary margin. (See description under histopathology.)

Rabbit No. 6.—December 9, 1915: Male, two months old; weight, 800 gm. Color of irides, brown. Pupils, 6.5 mm. Fundus normal. Tension (obtained with difficulty as animal was nervous): Right, 27.5 mm. Hg; left, 28 mm. Hg.

Operation: Removal of right superior cervical sympathetic ganglion. Pupil on right side, 6 mm.; left, 8 mm. Nictitating membrane not visible.

December 10th: Pupils: Right, 5.5 mm.; left, 6.5 mm. Right ptosis.

December 21st: Pupils: Both, 6.5 mm. Tension: Right, 17.5 mm. Hg; left, 26.5 mm. Hg. Slight right ptosis.

December 29th: Pupils: Right, 6 mm.; left, 7 mm. Right ptosis. No change in color of iris. Tension, both eyes, 26.5 mm. Hg.

January 13, 1916: Died. Pupils: Right, 4 mm.; left, 8 mm. Eyes removed (extensive hemorrhage in bottom of orbits). Right iris distinctly paler than left.

Rabbit No. 7.—December 14, 1915: Male; weight, 2800 gm. Brown irides. Pupils, 7 mm. Fundus normal. Tension, each eye, 21 mm. Hg.

Operation: Removal of right superior cervical sympathetic ganglion. Right pupil immediately contracted to 6 mm.; left, 9 mm. (cocain).

December 21st: Pupils: Right, 7 mm.; left, 8 mm. No difference in palpebral aperture. Tension: Right, 9.5 mm. Hg; left, 14 mm. Hg.

December 29th: Pupils, 7.5 mm. Slight ptosis in right side. Fundus normal. Tension: Right, 16 mm. Hg; left, 18.5 mm. Hg.

January 20, 1916: Pupils, 8 mm. Tension: Right, 11.5 mm. Hg; left, 18.5 mm. Hg. Right iris slightly paler than left, especially in upper posterior quadrant.

February 3d: Animal apparently paralyzed in hind legs. Pupils, 8 mm. Fundus normal. Slight ptosis right side. Tension: Right, 11.5 mm. Hg; left, 9.5 mm. Hg. Right iris slightly lighter than left.

February 5th: Died.

Rabbit No. 8.—December 14, 1915: Male; weight, 2620 gm. Brown irides. Pupils, 8 mm. Fundus normal. Tension (obtained with great difficulty as animal was frightened and nervous): Many readings of the tonometer, using different weights to check results; right, 7 mm.; left, 8 mm. Hg.

Operation: Removal of right superior cervical sympathetic ganglion. Right pupil contracts to 7 mm.; left, 10 mm. (cocain).

December 21st: Pupils: Right, 7 mm.; left, 6 mm. Slight ptosis right side. Tension (with difficulty): Right, 26 mm. Hg; left, 22.5 mm. Hg.

December 29th: Pupils, 8 mm. No difference in palpebral apertures. Tension (animal quiet): Right, 12.5 mm. Hg; left, 26.5 mm. Hg. Right iris slightly lighter in color than left.

January 20, 1916: Pupils: Right, 5.5 mm.; left, 7 mm. Slight ptosis right. Right iris slightly lighter than left, especially in upper temporal quadrant. No change in fundus. Tension: Right, 11.5 mm. Hg; left, 23.5 mm. Hg.

February 3d: Pupils: Right, 6.5 mm.; left, 7.5 mm. Tension: Right, 9.5 mm. Hg; left, 12.5 mm. Hg.

February 23d: Pupils, 7 mm. Tension, each eye, 26.5 mm. Hg. Right iris lighter than left.

March 2d: Pupils: Right, 6 mm.; left, 7 mm. One drop aqueous solution homatropin in each eye. Animal placed

in dark room, and after fifteen minutes pupils dilated equally to 9 mm.

March 16th: Pupils: Right, 7 mm.; left, 9 mm. One drop 1: 1000 epinephrin solution in each eye, and after fifteen minutes in dark room, right pupil, 13 mm.; left, 9 mm.

March 23d: Pupils: Right, 7 mm.; left, 8 mm. Tension, each eye, 5 mm. Hg. Right iris of lighter color than left. Two drops of 4 per cent. aqueous solution cocain in each eye, and after twenty minutes in dark room pupils did not dilate, *i. e.*, right, 7 mm.; left, 8 mm.

April 13th: Pupils: Right, 7 mm.; left, 8 mm. Slight ptosis right. Tension: Right, 31 mm. Hg; left, 31 mm. Hg. Right iris distinctly paler than left. A drop of 4 per cent. cocain solution in each eye, and after twenty minutes both pupils measured 8 mm.

May 4th: Pupils measure 7.5 mm. After twenty-five minutes use of 4 per cent. cocain solution in each eye; right pupil measures 7.5 mm.; left, 9 mm. The right iris is distinctly paler than the left. A drop of 1 per cent. homatropin solution was instilled in each eye, and after twenty minutes the left pupil dilated wider than the right. There was no appreciable fundus change.

May 25th: Pupils: Right, 7 mm.; left, 8 mm. Tension: Right, 11 mm. Hg; left, 32.5 mm. Hg.

June 22d: Pupils, 7 mm. Tension: Right, 18 mm. Hg; left, 12 mm. Hg.

July 6th: Right iris still lighter in color than left.

July 27th: Right pupil smaller than left, and color of right iris lighter than left. No fundus change. Animal killed by blow on back of neck. Eyes enucleated and placed in 10 per cent. formalin solution. (See description under histopathology.)

Rabbit No. 9.—December 16, 1916: Female; weight, 2600 gm. Brown irides. Pupils, 7 mm. Fundus normal. Tension: Right, 16 mm. Hg; left, 17 mm. Hg.

Operation: Removal right superior cervical sympathetic ganglion. Right pupil contracts to 6.6 mm.; left, 8 mm.

December 21st: Right pupil, 6 mm.; left, 7.5 mm. Slight ptosis right. Tension: Right, 11 mm. Hg; left, 18.5 mm.

December 29th: Slight ptosis right. Pupils: Right, 7 mm.; left, 8 mm. Fundus normal. Tension: Right, 14 mm. Hg; left, 17.5 mm. Hg.

January 20, 1916: Pupils: Right, 6 mm.; left, 7 mm. Slight ptosis right. Tension: Right, 11.5 mm. Hg; left, 20 mm. Hg. Right iris generally paler than left.

February 3d: Pupils: Right, 6 mm.; left, 7 mm. Slight ptosis right. Tension: Right, 17.5 mm. Hg; left, 17 mm. Hg.

February 23d: Slight ptosis right. Pupils: Right, 6 mm.; left, 7 mm. No change in fundus. Tension: Right, 16 mm. Hg; left, 18.5 mm. Hg.

February 27th: Died in labor. Pupils: Right, 3 mm.; left, 8 mm. Eyes enucleated. Right iris distinctly paler than left.

TABLE 1.—TONOMETRIC READINGS OF THE RIGHT EYE BEFORE AND AFTER OPERATION.

Rabbit	Mm. Hg		Mm. Hg
No. 1	Average tension before operation	22	Total Average after 24
No. 3	Average tension before operation	27	Total Average after 22
No. 4	Average tension before operation	26	Total Average after 21
No. 5	Average tension before operation	26	Total Average after 14.8
No. 6	Average tension before operation	27.5	Total Average after 22
No. 7	Average tension before operation	21	Total Average after 12.1
No. 8	Average tension before operation	7	Total Average after 17.8
No. 9	Average tension before operation	16	Total Average after 14.3
General average tension before operation,		21.5	after operation 18.5

A summary of the above experiments on the nine rabbits, after a complete excision of the right superior cervical sympathetic ganglion, shows:

1. No marked influence on lacrimation. There was an increase in one case immediately after operation; the observation made August 10th on No. 4 was probably due to a disturbance of lacrimation.

2. The nictitating membrane was not affected by the operation.

3. A paresis of Müller's muscle, which caused drooping of the upper lid in all cases on the operated side.

4. The average horizontal diameter of the pupil before

operation was 7.6 mm. It contracted immediately after the operation, and usually so remained, the average diameter then being 6 mm. In those cases where epinephrin was instilled into the conjunctival sac it caused a dilatation of the pupil on the operated side.

5. There was no appreciable ophthalmoscopic change in the retina and choroid. In rabbit No. 4, as seen from the notes, there were certain interesting developments in the iris which I was not able to explain. The tags of pigment undoubtedly developed from the epithelial layer, but what influence the operation had in causing them is a matter of conjecture. While I could not detect deposits on the posterior surface of the cornea, a cloudiness of the aqueous was surely present at one time; also there were opacities in the media, which I placed in the posterior part of the lens, as the rabbit's lens is very thick. These opacities later disappeared.

6. There was an appreciable gross change in the color of the iris on the operated side in all cases except one (rabbit No. 3 died twenty-four days after operation). The longer the animal lived, usually the more distinct was this decoloration, and where the eyes were enucleated and placed side by side for closer comparison, the change was more decided. About five weeks after operation changes in the color of the iris were first detected, although in one case (rabbit No. 8) a suspected change took place in fifteen days, which was more positive during the fifth week. Unquestionable variations in the color of the iris were noted in rabbit No. 4; that is to say, one time the change was barely perceptible, and at other times the decoloration was decided.

7. The intraocular tension (see chart and table) shows varying estimates, without any uniformity. Taking an average first reading before operation, the right eye was 21.5 mm. Hg and left, 22 mm. Hg. A combined average of all readings after operation (omitting the first reading)

on the right was 18.5 mm. Hg, and the average of all readings on the left was 21.2 mm. Hg. This observation would lead us to believe that the removal of the superior cervical sympathetic ganglion lowers the intraocular tension in the eye on the operative side.

8. The age or weight of the animal apparently had no influence in these experiments.

CASES COMPLICATED BY CATARACT OR UVEITIS.

There is another classification of primary heterochromia iridis to be considered, namely, those cases in which there is an uveal affection, evidenced by deposits on the posterior surface of the cornea, which may and usually do terminate in cataract. These complicated cases may or may not be associated with the apparent disturbances of the sympathetic. Of the 33 cases of iris decoloration associated with sympathetic paralysis, 10 cases were complicated with uveitis or cataract.

Lawrence and Hutchinson were among the first to describe the association of cataract with heterochromia iridis, and Fuchs[41] claims priority for first calling attention to the fact that chronic cyclitis with deposits occurred in the lighter eye. He also called attention to the fact that in his series of 38 cases, 20 occurred within the first three decades, 9 in the fourth decade, and the remaining number scattered. It was his opinion that heterochromia was usually due to some anatomic difference in the stroma of the iris, and when the retinal layer was affected (which condition he had observed), it was then due to a chronic inflammation. He often noted that the pupil was larger on the lighter side.

Butler[8] regards the cause as unknown, but when associated with a sympathetic paralysis, the chronic cyclitis may be comparable to the iritis and iridocyclitis which are occasionally seen in herpes ophthalmia, and are usually regarded

as trophic disturbances. The same author also describes a train of symptoms which in part are as follows:

The change in the color of the iris may last several years before other complications set in, but sooner or later the patient complains of bad sight in the blue eye. There is never pain or redness, possibly a ciliary blush. There is no associated dyscrasia, although patients look "out of sorts." Occasionally there is a transient albuminuria. The eye shows fine keratitis punctata, which soon covers the whole posterior surface of the cornea, although in other cases it is arranged sector shape. An exudation may develop in the vitreous, followed by opacities of the lens, which are often punctate, and glaucoma is not an infrequent complication. Choroiditis and optic neuritis have been observed. The prognosis is generally bad. The disease usually begins in youth, and is slow and may extend over a period of years or even decades.

Contrary to the views of Butler and other observers, Galezowski is of the opinion that the depigmentation is preceded by a chronic inflammatory condition. On the other hand, Malgat regards the heterochromia as due to a difference in the blood circulating in the iris or ciliary body, and from a lack of nourishment to the lens, a cataract being the natural consequence. Hirschberg is of this same opinion, but thinks that the defective circulation starts *en embryo* or before the development of the iris pigment. This condition may remain stationary for years, to again become active and cause a uveitis and cataract. Gunn refers to the iris which contains sectors of different colors, and which subsequently regains its color, and he thinks that it is suggestive of an abnormal enervation. Finally Dor thinks that, besides the congenital heterochromia (he does not mention sympathetic paralysis), there exists a disease of the eye yet unknown, which begins in heterochromia and ends in cataract.

It is natural to ascribe the formation of cataract in these cases directly to the absence of iris pigment, and also to the influence of the action of ordinary daylight. But Sym has drawn attention to the fact that albinos are no more liable to cataracts in proportion to their number than are the normally pigmented.

Others attribute the cataracts to the chronic cyclitis which frequently accompanies heterochromia, and, as certain other intraocular changes are frequently noted, and as occasionally serious complications follow extractions, it is a commonly accepted cause.

Scalinci regards the cataract as due to changed physiochemical relations with the circulating nutritive fluids, or to biologic alterations in the content of the nutritive fluid itself, due to vasomotor paralysis.

Knapp, discussing Ellett's[46] paper on "Heterochromia Iridis, Heterochromic Cyclitis, etc.," was of the opinion that disturbances of the sympathetic system had very little to do in producing these changes (cyclitis). In practically all his cases the patients have reacted to the tuberculin test, and in a large number they have done well with tuberculin therapy.

HISTOPATHOLOGY OF THE IRIS.

A brief review of the histology of the iris may be helpful to those (as it was to the author) who study the microscopic changes in an heterochromic iris. Brown's[44] translation of Salzmann's "Anatomy of the Eye" is my authority for the following description:

The arrangement of the layers of the iris is regular in the middle part of the ciliary zone. It consists—(1) of an endothelial layer, which is difficult of histologic demonstration, continuous from the inner layer of the cornea. It lies in intimate contact with (2) the anterior border layer, made up principally of cells, which in reality is only a modification of the iris stroma. The cells are chromophores, like

the stroma cells, and usually possess two or three processes. It gives color to the iris, not alone through its pigment content, but also in its density; blue irides have a delicate border layer and almost unpigmented cells, while brown irides have a thick border layer and heavy pigmented cells. A complete absence of pigment in the border layer and stroma probably occurs in the new born or in very young children. These, therefore, at times actually have blue eyes, for the blue color is due only to the fact that a clouded but colorless medium (border layer and stroma) lies in front of a dark background (pigment epithelium). This difference also comes out when color in different sectors of the iris varies. Next (3) is the vessel layer which forms the main mass of the iris. It contains the blood-vessels and nerve plexuses, held together by a loose delicate stroma. The blood-vessels enter the iris root in large bundles and branch into finer branches and pass through the ciliary zone in a radial direction in several layers. The vessels show a corkscrew arrangement to adapt themselves to the changing contraction of the iris tissue. In the pupillary zone the course is altered by the formation of circles from anastomosis.

The vessels of the iris are characterized by a thick adventitia consisting of a finely fibrillated collagenous tissue, which often exceeds the diameter of the vessel lumen. The arteries have a thin muscularis and a weak intima, and the veins have perivascular sheaths bordering immediately upon the endothelium.

The nerves of the iris likewise advance through the iris root in large trunks, and build a plexus in front of the larger vessels. Nerves are practically not to be demonstrated in cut sections. The nerve-fibers end partly in the stroma (sensory fibers), partly in the vessels (sympathetic fibers), partly in the sphincter pupillæ, and partly in the dilator (motor fibers).

The spaces between the blood-vessels and the nerves are filled by the iris stroma proper, which is a loose collagenous tissue consisting of discrete fibrillæ containing pigment stroma cells (chromatophores), non-pigmented stroma cells, and clump cells. The chromatophores are grouped principally about the vessels and nerves, and each cell shows a small oval body which stains well and an oval nucleus not sur-

rounded by pigment; the processes are slender and long, and unite into a plexus with those of their neighbors. Other pigment-cells are also found which are termed clump cells; they are large and more densely pigmented, and are found in the neighborhood of the sphincter pupillæ.

The back surface of the iris is termed the ectodermal layer, and it is a continuation forward of the pars ciliaris retinæ. It is divided into an outer leaf (the dilator pupillæ) and the inner leaf (the pigment epithelium). The dilator pupillæ, like the sphincter, is an epithelial muscle or a "myoid plate," as it is called, *i. e.*, its fibers develop out of epithelial cells, and while a complete transition from an epithelial cell into a muscular cell occurs in the sphincter pupillæ, this takes place in only a part of the cell in the dilator pupillæ. When typically developed, it consists of a spindle-cell formation with an oval nucleus and a moderately pigmented protoplasm, extended at each end into an unpigmented fiber layer process. From the position of these cells two layers are recognized—one a posterior border layer and then the layer of pigmented spindle-cells.

This pigmented muscle or myoid plate extends along the posterior surface of the vessel layer of the iris, from the ciliary border of the sphincter pupillæ almost to the root of the iris, and at the sphincter zone the elements of the dilator are united to those of the sphincter.

The inner leaf or pigment layer has an epithelial character throughout, and is a direct continuation of the tunica interna of the ciliary body. Its cells are so densely filled with dark-brown pigment granules that cell borders or nuclei are not visible, except in bleached preparations.

But few writers have attempted to explain the alterations in the iris associated with a sympathetic paralysis; or, in other words, how a sympathetic paralysis caused an iris decoloration. The investigation of Angelucci on rabbits and dogs offers us a reasonable explanation. He concluded that the eye resents trophic disturbances on account of the influence which the cervical sympathetic exerts on the movements of the walls of the blood-vessels (vasomotor effect). It is well known that for a time after the superior sympathetic

has been excised there is a dilatation of the blood-vessels, which in the case of the rabbit can easily be demonstrated in the ears. Later it is followed by a thickening of the vessel-wall which tends to contract the lumen. With the weakening of the nutritive changes thus brought about there is an arrest of development of the eye, and in the case of the iris there is a more or less pronounced degree of simple atrophy, with its accompanying decoloration.

I cannot find recorded a report of a microscopic examination of a human decolored iris associated with sympathetic paralysis. Bistis, in his examination of rabbit eyes, found a great reduction in the pigment and a thickening of the vessel-wall. The pigment in the anterior layer was much reduced and appeared in small aggregation. The iris stroma possessed no pigment cells, but contained a large number of nuclei which occupy the place of the stroma cells. These nuclei are round or oval, and are situated in a basement substance composed of fibrillary connective tissue. He was also able to detect deposits on the posterior surface of the cornea. These findings, together with a cloudiness of the aqueous and the vessel-wall changes, he thinks are suggestive of an inflammatory condition.

Fuchs was the first to examine a heterochromic iris occurring in cataracts. In one case he could demonstrate cells on the back of the cornea. There was some depigmentation in the anterior layer, principally of small pigment granules. In the deeper layer there were only isolated remains of the branching pigment stroma cells, and these had lost their shape and had become round. These should not be confounded with clump cells found near the sphincter and Bruch's membrane. The retinal pigment layer was normal. The texture of the stroma had entirely changed, and the network of the branching stroma cells had been replaced by nucleated cells of a different character. There was no accumulation of nuclei around the blood-vessels, as is seen in

an inflammatory infiltration of the iris. Protoplasm was scanty and occurred around the nucleus like a seal ring. Lymphocytes were only occasionally found, and no polynuclear leukocytes were seen. The blood-vessels showed a hyaline degeneration; the nuclei were scarce, as were the endothelial nuclei. Complete closure of the lumen was observed.

Lagleyze[45] confirmed Fuchs' observations, except there were greater atrophy and depigmentation in the anterior layers.

AUTHOR'S FINDINGS.

Rabbit No. 1.—Interval of eleven weeks and two days between operation and death. The notes show that after enucleation the right iris was "distinctly lighter" than the left, although a suggestion of discoloration was noted some time before death. Microscopic study of each eye did not show any decided variation from the normal, except in a few of the thinnest sections there was noted an appreciable difference in the general pigmentation in the extreme anterior border layer.

Rabbit No. 5.—Interval of five weeks and four days between operation and death. After operation the right iris appeared lighter than the left, but no difference was detected microscopically.

Rabbit No. 8.—Interval of approximately twenty-eight weeks between operation and death. There was noted before and after enucleation a decided difference in the pigmentation of the irides. Our findings did not differ materially from those of Bistis, Fuchs, and Lagleyze. The greatest changes were noted in the anterior border layer, where there was a general atrophy of the branching pigment cells; this atrophy was likewise present to a large extent in the chromophores of the vessel layer. In certain areas along the margin of the anterior border layer there appeared to be a disorganization or absorption of the pigment cells, which probably corresponded to the lighter areas seen on the iris during life. The pigment epithelium was unaffected, and there was no sign of inflammation. There was a difference in the

thickening of the vessel-walls, due to a hyaline degeneration, although all the iris vessels were characterized by a thickened adventitia. We could not detect the marked vessel changes mentioned by other observers, which was probably due to the short interval between the operation and enucleation in this particular animal, as compared to Fuchs' examination of the human heterochromic eye.

Rabbit No. 4.—Interval of thirteen months and twelve days between the operation and death. Before operation there was a noticeable difference in the color of the irides. With the low magnification the general comparison of the sections showed a marked difference. In the section of the right eye there was a "washed-out" appearance in the anterior border and vessel layer, with a noticeable depigmentation of the cells surrounding the larger vessels. These changes were especially noted in the middle and upper thirds of the iris, and to some extent in the ciliary region.

The sections did not reveal any cause for the changes detected during life (*i. e.*, the iris tags and lens opacities (?) described in the notes).

With the higher magnification, the changes were similar to those described in rabbit No. 8, except for an increase in adventitia thickening.

ACQUIRED SECONDARY HETEROCHROMIA IRIDUM.

Cases of heterochromia iridum occurring secondary to some acquired intraocular state are common to all ophthalmologists of any experience. A severe iridocyclitis, foreign bodies (metal) in the globe, degenerative changes of myopia, and chronic glaucoma are the common causes.

COMMENT.

Those who have studied the literature of heterochromia iridis, or even casually glanced over the many reports and discussions which I have very briefly collected, must have been impressed with the vastness of the subject and the lack of unity of opinion of the many authors. I, therefore, with trepidation hesitate to express an opinion, unless substan-

tiated by facts, and unfortunately in this character of investigation "cold" positive facts are very few. I shall then confine myself to a systematic arrangement of the cases and causes of heterochromia, and express my personal opinion only where experience warrants it. I do not feel, however, that the last word on heterochromia iridis has been written, yet we do know a great deal concerning it.

I firmly believe in the influence of heredity, and with the subject under consideration I am convinced that in a proportionate number of these cases certain tendencies are inherited which cause a difference in the color of the irides. This statement especially applies to the cases in which there is not even the suggestion of any alteration of the cervical sympathetic system. In this country, where our people are not only a mixed hue, but of many nationalities, a proportion of our fairly numerous cases of heterochromia are not all pathologic specimens, but simply "freaks" of nature.

Regarding the inheritance of a sympathetic paralysis, I believe that its cause may be transmitted, and its manner of producing heterochromia is similar to any other form of congenital sympathetic paralysis, including those of traumatic origin (forceps deliveries). Assuming then this sympathetic disturbance in fetal life, it would not be difficult to explain the arrested development of the iris pigment on the involved side, and we could suppose the same changes in those cases occurring in early life where the iris pigment has developed. These changes can be explained only by nutritional disturbances of trophic origin—first, a vasodilatation, then a hyaline degeneration of the adventitia, and finally a contraction of the vessel lumen.

The great number of clinical reports show the difference in the color of the irides to have taken place within the first few months or years of life, when the pigment cells were young and apparently easily absorbed; on the other hand, I have not found a record where a sympathetic paralysis

in the adult, produced by trauma or operation, ever caused iris depigmentation.

A chronic uveitis (deposits on the posterior corneal surface) is often recognized in association with heterochromia with or without an accompanying sympathetic paralysis. Many such cases may have escaped close observation. It is claimed that the lighter iris renders the eye liable to a chronic cyclitis, while others are equally sure that the cyclitis precedes the decoloration; in fact, produces it. In support of either opinion, we have no real proof. From our clinical observation and experimental study the corneal deposits which often accompany the heterochromia should be regarded as a symptom of a disease, and where a sympathetic paralysis is associated, it may properly be reckoned as the cause, producing the passive hyperemia of the iris and ciliary body which Sym and Scalinci describe. Precipitates have been found on the posterior surface of the rabbit's cornea, and I have observed a turbid aqueous after an excision of the sympathetic ganglion, and if we could at will observe our clinical cases, I believe we would find similar changes at some time. To my mind there is much to be said in favor of Scalinci's theoretic consideration of the cause for these precipitates and the formation of cataracts. He maintains that there are abnormal substances which percolate through an abnormally pigmented iris and ciliary body due to vasomotor paralysis. The normal aqueous does not contain albumin, but when the anterior chamber is emptied, that which is then formed contains it, and fibrin may be demonstrated. This rapidly formed fluid is regarded as a transudate from the superficially placed vessels in the ciliary body, rather than a secretion of the body itself, and it is produced by a lowering of the intraocular tension. This change may account for the cloudy aqueous and precipitates noted in rabbits, and for the precipitates seen in man.

The following ocular changes have been produced experi-

mentally: first, a decoloration of the iris (Bistis, Metznen, etc.); secondly, a cloudiness of the aqueous (author); thirdly, the formation of corneal deposits (Bistis); and lastly, uncertain lens opacities. The experiments have not been continued long enough to note more decided lens changes; in fact, it might take years for them to develop—far beyond the natural life of the rabbit.

This, however, does not explain the other type in which there is no evidence of a sympathetic alteration, and yet clinically we have the same picture, namely, heterochromia, precipitates, and finally cataract.

It is, as Dor expressed, an unknown disease. It may and usually does begin in youth and have the train of symptoms described by Butler, but hardly as severe and usually without the serious complications. From the investigations of Fuchs and others it is not a true inflammatory type of disease, such as iritis or cyclitis, and its precipitates may be produced from the same type of passive congestion which takes place in sympathetic disturbances. The origin appears to be in the vessels themselves, a type of sclerosis with obliteration. Whether or not this vasomotor disturbance is of trophic origin, due to a sympathetic alteration without external evidence, is only a suggestion which other investigators of more original thought might consider.

In regard to the formation of cataract, it also appears that its origin is especially due to a lack of nutrition or to altered changes in the aqueous.

Finally our investigations have led us to make the following conclusion:

(1) That the difference in the color of the irides should be called heterochromia iridis.

(2) That in a small number of cases it is inherited.

(3) That in all other cases it is a symptom of some abnormal ocular state.

(4) That in a large percentage of the cases a paralysis of

the cervical sympathetic is the responsible cause for this heterochromia through its trophic disturbances. This paralysis may be inherited.

(5) That besides a congenital heterochromia there is an eye disease of unknown origin, which begins in heterochromia and ends in cataract.

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