CAUSES OF HETEROCHROMIA IRIDIS WITH SPECIAL REFERENCE TO PARALYSIS OF THE CERVICAL SYMPATHETIC.

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This abstract of a candidate's thesis presented for membership in the American Ophthalmological Society, includes the reports of cases, a general review of the literature of the subject, the results of experiments, and histologic observations on the effect of extirpation of the cervical sympathetic in the rabbit, the conclusions reached from the investigation, and a bibliography.

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 Aristotle¹. 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 Hutchinson² (1869) credit for first describing a difference in the color of the irides, with which cataract was associated. I by chance discovered that Lawrence³ (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 Wilde⁴ who mentioned 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; Weill⁵ uses the word *heterophthalmus*; *anisoiridochromia* is mentioned by Scalinci⁶ and *chromoheteropia* is suggested by Malgat⁷, who also

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, Butler⁸ uses the term "heterochromic cyclitis," but the "Chronic Cyclitis with Decoloration of the Iris" as described by Fuchs⁹ 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 (ἑτερος *other*, χρομα) color. Other newly coined words only add disorder to an already chaotic classification of diseases.

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 as obvious as the term heterochromia iridis, unless the reader possessed a working knowledge of Greek.

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 cata- ract.	par-
Secondary..	{	Acquired..	{	With or without	{	Sympathetic paralysis, Cyclitis or cata- ract.	par-
Secondary..	{		{		{	Injuries. Sidero- sis bulbi. Uveal infection— Myopia. Glaucoma.	

Strictly speaking, as Sym¹⁰ 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 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 and Scalinci who maintained that we should reserve the term heterochromia iridis for the instances in which there has not been any obvious pathologic 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 than¹⁰ 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 of

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 I and II 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.

Galezowski¹¹, Bistis¹² and Scalinci⁶ 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 Priestley Smith's¹³ 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."

Osborne¹⁴ 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 fifteen brothers and five 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. Gunn¹⁵ 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 Gossage¹⁶ 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, altho 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."

From a genetic point of view, Przybram's¹⁷ work on angora cats is interesting. He found that the union of an

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

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.

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 classical Horner's Syndrome (ptosis, myosis, anhidrosis, hemiatrophy

facialis) heterochromia iridis as a symptom. Mayou¹⁸ in 1910 was probably the first to accurately describe these changes, although Horner (quoted by Samelsohn²⁰) 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 thirty-three cases have been reported, ten of which were complicated either with cataract or a slow uveitis.

The following authors reported: Galewski¹¹, 2 cases, 1 complicated; Horner's case reported by Samelsohn²⁰; Dethleffsen²¹, 5 cases, 1 complicated; Lutz²², 13 cases, 3 complicated; Hutchinson², 1 case; Alexander and Lander²², 5 cases, 2 complicated; Bistis³⁰, 2 complicated cases; Mayou¹⁸, 3 cases and Scalinci⁹, 1 case.

From my own observation I can report four cases; the first two being of the same family with positive symptoms of a sympathetic paralysis. Case III gave less prominent symptoms, and case IV presented only slight evidences of any sympathetic disturbance. My reason for here reporting case V 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, age 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 blonde 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 II) 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 have 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. 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 reacted well to light; the iris was blue, vision 20/20 and fundus was normal

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

with no corneal deposits (without mydriasis). The left eye was normal and the iris brown. (Fig. 2.)

Case II. Master D, age 5. The family history is the same as case I, 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 I) 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.

Examination: Right, drooping upper lid, facial hemiatrophy, palpebral fissure measured 5 mm., pupil active to light, 2 mm. in diameter. Color of iris was blue. Two drops of 1-1000 solution epinephrin did not dilate pupil. Cocain

not used. Fundus normal, no corneal deposits. Vision 20/20. Left, dark blue iris, with brownish pigmentation surrounding pupil, which measures 4 to 5 mm. Fundus normal. Vision 20/20.

The grandmother states 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 III. J. L. M., male, age 57. States that all of 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 refractive 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: Right 20/15 corrected. Palpebral aperture 12 mm. Iris brown; pupils active to light and measure 2.5 mm. Fundus shows 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. Left 20/20 corrected. Palpebral aperture 10 mm. Iris light grey and active to light. Pupil measures 3 mm., does not dilate to epinephrin, but actively and widely to cocain. Fundus no corneal deposits, but similar vitreous opacities and retinal changes as in right. Decided left facial hemiatrophy and apparent enophthalmos. No anhidrosis. Tonometer 20 mm., Hg. Visual fields contracted peripherally. Systolic blood pressure 172 mm. Hg.

Case IV. J. E. M., male, age 38. Family and hereditary history negative. Father's eyes brown, mother's blue. Patient is only member in family with differently colored irides and he states that he has had this difference all of his life. He consulted me for pain in eyes after reading.

Examination. Right eye comp. H.

astig. Vision 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. astig. Vision 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 use of one drop of cocain. Left did not dilate. The only additional evidence of a sympathetic paralysis was a slight ptosis on the lighter side.

Case V. P. R. R., male, age 43, consulted me on account of defective sight of long duration in the right eye. Several members of his family have had 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 several months of age he was paralyzed on the entire left side of body and face. He states that the left eye has always been of lighter color than the right. The patient 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 and there were no positive evidences of a sympathetic paralysis. The eye examination is as follows: Right, vision, light perception, extraocular 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. Typi-

cal cupping with atrophic changes of glaucoma simplex. Tension 52 mm. Hg. Corneal anesthesia. Left, vision 20/30. Small pterygium. Pupil 2.5 mm., wide, active, iris gray, slightly shallow A. C., 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 nor scotoma. There was 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 thirty-three cases reported it is very 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 III which I believe to be of sympathetic paralysis (having ptosis and facial hemiatrophy), 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's²³ well known experiment in which he caused a dilation 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.

Pollock concluded after his experiments that "evidence is given that a motor plexus with nerve cells exist in the sphincter and in the dilatator pupillae 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 intestines."

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 dilation of the pupil. The phenomenon has been observed by Langendorff²⁴, 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.

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 difference in the color of the irides developed at the natural time when changes take place in the color of the iris. In several cases (Mayou¹⁹) 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 paralysis from forceps delivery without iris decoloration (Reese²⁵ and Burrows²⁶) altho in many of these reports no reference is made to the color of the iris. This lack of depigmentation in light colored irides of blondes with an associated sympathetic paralysis can easily be explained. Mayou²⁷ has also mentioned cases of sympathetic paralysis without iris decoloration associated with cervical rib. Of all the reported cases of sympathetic paralysis developing in adult life Bistis²⁸ reports the only positive case where a change in the color of the iris subsequently developed; and the case is well worth reviewing.

Bistis' case. Female age 38. 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 had failed and the color of the right iris has changed. There was pain around the right eye, facial hemiatrophy with anhidrosis of same side that appeared at same time as heterochromia. Author had seen patient much before onset of trouble and the condition described did not then exist. The eye showed ptosis, enophthalmus, descemetitis, blue iris, pupil does not dilate as well to cocaine as opposite side, no effect by epinephrin. Aqueous slightly turbid, tension subnormal and lens changes.

Metzner²⁹ 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 practiced 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 III 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. Mendel³⁰ mentioned a similar change in one of his cases. It is well known that deafness is often present in albino cats (Beaumont³¹) and in two cats which had heterochromia iridium and deafness, Alexander and Lander³² 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 Collins³³, might have in producing a depigmentation of the iris. According to Griffin³⁴ these glands control the amount of pigment in the eye, as 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, Alt³⁵ and Rutteman³⁶, who were not even able to find their lumen. Finnoff³⁷ 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 cross-wise. 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, Angelucci³⁸ 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. Bistis³⁹ produced similar changes in the iris, and in one case he was able to demonstrate a cloudiness of the aqueous, and find in sections deposits on the posterior surface of the cornea, which to his mind was highly suggestive of an inflammatory process. Later Metzner and Wolflin²⁹ 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 nictitat-

ing 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 generally accepted physiology of the sympathetic system.

In this connection it is of interest to know that Galezowski 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 was made in the rabbit.

Guinea pigs were first employed in our experiments, mainly to perfect the operative technic of the removal 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 iodine. 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 afterwards. 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 northerly 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 milligram 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 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 microscopic 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 and later disappeared. The detailed account of these experiments is published in the Transactions of the

American Ophthalmological Society v. 16, p. 291-298.

TABLE 1.

Tonometric readings of the right eye before and after operation:

Rabbit No. 1—Average tension before operation, 22 mm. hg.; total average after, 24 mm. hg.

Rabbit No. 3—Average tension before operation, 27 mm. hg.; total average after, 22 mm. hg.

Rabbit No. 4—Average tension before operation, 26 mm. hg.; total average after, 21 mm. hg.

Rabbit No. 5—Average tension before operation, 25 mm. hg.; total average after, 14.8 mm. hg.

Rabbit No. 6—Average tension before operation, 27.3 mm. hg.; total average after, 22 mm. hg.

Rabbit No. 7—Average tension before operation, 21 mm. hg.; total average after, 12.1 mm. hg.

Rabbit No. 8—Average tension before operation, 7 mm. hg.; total average after, 17.8 mm. hg.

Rabbit No. 9—Average tension before operation, 16 mm. hg.; total average after, 14.3 mm. hg.

General average tension before operation, 21.5 mm. hg.; after operation, 18.5 mm. hg.

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.

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 24 days after operation. The longer the animal lived usually the more distinct was this discoloration; 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, altho 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, at 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 operated 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 does terminate in cataract. These complicated cases may or may not be associated with the apparent disturbances of the sympathetic. Of the thirty-three cases of iris decoloration associated with sympathetic paralysis, ten cases were complicated with uveitis or cataract.

Lawrence and Hutchinson were among the first to describe the association of cataract with heterochromia iridis, and Fuchs⁴¹ 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 thirty-eight cases, twenty occurred within the first three decades, nine 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.

Butler⁸ 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, altho 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, altho 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 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 innervation. Finally Dor⁴⁸ 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 our 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 cyclitic 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 physiochemic 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's⁴⁶ 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 of his cases, the patients have reacted to the tuberculin test, and in a large number they have done well with tuberculin therapy.

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 represents 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, that 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 decolorated 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 is much reduced and appeared in small aggregations. 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 in 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 is scanty and occurs around the nucleus like a seal ring. Lymphocytes were only occasionally found and no polynuclear leucocytes 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.

Lagleyze⁴⁵ confirmed Fuchs' observations except there was greater atrophy and more 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, altho a suggestion of decoloration 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, altho all of the iris vessels are characterized by a thickening of adventitia. We could not detect other 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 glance 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 substantiated 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 pathologic specimens, but simply "freaks" of nature.

Regarding the inheritance of 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 changes in those cases occurring in early life, where the iris pigment has developed. These changes can only be explained by nutritional disturbances of trophic origin—first a vasodilation, then a hyaline degeneration of the adventitia, and finally a contraction of the vessel lumen.

The great number of clinical reports show that 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 disease, and where a sympathetic paralysis is associated, it may properly be reckoned as the cause, pro-

ducing 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 thru 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 experimentally: First a decoloration of the iris (Bistis, Metzner, et al.); 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 be-

gin in youth and have the train of symptoms described by Butler, but hardly as severe and usually without the severe 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 changes in the aqueous.

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

- (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.

In closing I wish to acknowledge my debt of gratitude to Dr. G. Bachman, professor of physiology in the medical school of Emory University, in whose department our experiments were conducted. His advice was valuable, and the abstracts which he made of the foreign journals greatly facilitated the preparation of this paper.

REFERENCES.

1. Hirschberg. Wörterbuch der Augenheilkunde.
2. Hutchinson, J. "Notes of Miscellaneous Cases." Royal London Oph. Hospital Reports. 1869. Vol. VI., p. 44.
3. Lawrence, W. "Treatise of Diseases of the Eye," by W. Lawrence 1843, 3rd Amer. Edition, by Isaac Hays, Philadelphia.
4. Wilde. Dublin Quart. Journal. Nov., 1848.
5. Weill. "Über Heterophthalmus." Zeitsch. f. Augenhlk. Vol. XI, 1904.
6. Scalinci. "Eterocromia e paralisi del Simpatico." Arch. di Ottalmalogia. Feb., 1915.
7. Malgat. "La Chromheteropie." Recueil d'ophtalmologie. Vol. XVII. 3, 1895, p. 449.
8. Butler, T. Harrison. "Heterochromic Cyclitis." Ophthalmoscope, Vol. IX, No. 7, 1911, p. 501.
9. Fuchs, E. Klin. Monatsb. für Augenhlk., 1906.
10. Sym, Wm. Geo. Review of Scalinci's Article, Ophthalmic Review, Vol. XXXIV, 1915, p. 167.
11. Galezowski, J. "Heterochromie de l'iris, cataracte et troubles sympathiques." Recueil d' Oph. XXXIII, p. 76.
12. Bistis, J. "Heterochromie und Kataraktbildung." Centralbl. f. prakt. Augenhlk., Vol. XXII, p. 138, 1898.
13. Smith, Priestley. "Notes on the origin of familial and hereditary disorders." Oph. Review, Vol. XXV, p. 70, 1916.
14. Osborne. Dublin Quart. Journal, Vol. VII, p. 33.
15. Gunn, Marcus. "Congenital malformation of the eyeball and its appendages." Ophthalmic Review, Vol. VIII, p. 239, 1889.
16. Gossage, A. M. "The inheritance of certain abnormalities." Quart. Med. Jour. Oxford. I, p. 341, 1907.
17. Przibrams. Arch. für Entwicklungsmechanik. Vol. XXV, p. 260.
18. Mayou, M. S. "Heterochromia iridis associated with paralysis of the sympathetic in early life." Ophthalmic Review, Vol. XXIX, p. 190, 1910.
19. Mayou, M. S. "Paralysis of the Sympathetic (birth injury), with slight heterochromia iridis." Ophthalmoscope, Vol. XIV, No. 8. p. 421, 1916.
20. Samelsohn. Arch. für Ophthalmol., 1875.
21. Dethleffsen, A. "77 Fälle von Heterochromia iridum." Kiel Dissert, 1911.
22. Lutz, A. "Über einige weiteren Fälle von Heterochromia iridum." Deutsche med. Wochenschn, XXIV, p. 1125, 1910.
23. Pollock, W. B. I. "The presence of the nerve plexus of the iris after excision of the ciliary and superior cervical ganglion." Arch. f. vergleichende Ophthal, Vol. IV, pt. 1, 1914.
24. Langendorf, O. "Über die Beziehungen des oberen sympathischen Halsganglion zum Auge und zu den Blutgefäßen des Kopfes." Klin. Monatsbl. f. Augenhlk., Vol. XXXVIII, p. 129, 1900.
25. Reese, Robt. G. "A case of traumatic paralysis of the Cervical Sympathetic with oculo-pupillary symptoms, following forceps delivery." N. Y. E. & E. Inf. Reports, Jan., 1896.
26. Burrows, Harrold. "Two cases of paralysis of the cervical sympathetic following forceps delivery." Ophthalmoscope, Jany., 1915.
27. Mayou, M. S. "Two cases of paralysis of the sympathetic associated with cervical rib." Ophthalmoscope, Vol. XIV, No. 6, p. 313, 1916.
28. Bistis, J. "La paralysis du sympathique dans l'etologie de l'heterochromie." Archives d'Ophthal., Vol. XXXII. p. 578, 1912.
29. Metzner and Wolflin, "Klinische und experimentelle Untersuchungen über Halssym. "Arch. f. Oph., Vol. LXXXIX, p. 308, p. 1915.
30. Mendel. Recorded by Metzner and Wolflin.
31. Beaumont, W. M. "Heterochromia iridum in cats." Ophthalmoscope, Vol. IX, p. 630, 1911.
32. Alexander and Lander. Quoted by Lutz. See reference No. 22.
33. Collins, Treacher. Trans. Oph. Society United Kingdom, Vol. XI, 1890.
34. Griffin, John. "Criticism concerning recent views as to the secretory function of the ciliary body." Oph. Review, Vol. XIII, p. 247.
35. Alt, A. "On Treacher Collins' so-called glands of the ciliary body." The Amer. Journal of Oph., Vol. XIII, p. 3.
36. Rutteman, C. "Die sogenannten Drüsen von Treacher Collins in achen Abschnitt des Ziliarkörpers." Dissertation, Amsterdam, 1914.
37. Finnoff, W. C. "The Ciliary Glands." Arch. of Oph., Vol. XLIV, No. 6, p. 626.
38. Angelucci. "Studi sulle influenze fisiologiche del ganglion cervicale superiore del simpatico, &c., &c." Arch. di Ottolmol. I, p. 71, 1893.
39. Bistis, J. "Clinical and experimental investigations on the etiology of heterochromia." Arch. of Oph., Vol. XLIV, No. 4, 433, translation Arch. f. Augenhk., 1913.

40. Metzner and Wolfflin. Clinical and experimental studies of paralysis of the cervical sympathetic. *Graefe's Arch. für Oph.*, Vol. 91, p. 167.
41. Fuchs, E. "Über Komplikationen der Heterochromie." *Zeitsch. f. Augenhk.*, Vol. XV, p. 105, 1906.
42. Galezowski, J. "Heterochromie de l'iris, etc." *Recueil d'Oph.*, Vol. XXXII, 169, 1919.
43. Dor. *Encyclopedie Francaise*, Vol. VII, p. 189.
44. Brown, E. V. L. Trans. of German text of "The Anatomy and Histology of Human Eye-ball, etc.," by M. Salzman, Chicago, 1912.
45. Lagleyze. "L'oeil des albinos." *Arch. d'Ophthal.*, Vol. XXVII, p. 280, 1907.
46. Ellett, E. C. Heterochromia Iridis, Heterochromic Cyclitis and Allied Conditions." *Tr. Am. Oph. Soc.*, 53 Meeting, May 29, 1917.

SYMPATHETIC IRIDOCYCLITIS AND POSSIBLY RELATED PROCESSES IN OTHER PARTS OF THE BODY.

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This argument supports the idea that the essential causative agent of sympathetic ophthalmia may exist in the body outside of an injured eye, and be transmitted through the blood currents. Microorganisms entering the exciting eye through injury might become established elsewhere in the body. Submitted as a Candidate's Thesis to the American Ophthalmological Society.

It is a fact accepted by most observers that sympathetic iridocyclitis is dependent upon a chronic plastic uveitis of the first eye. Preceding the fibrinous inflammatory process, the capsule of the eyeball must have been opened; usually by trauma, occasionally by an ulcer, or by operation, such as for cataract or iridectomy. Certain cases, however, have been reported in which the so called typical findings were present, the capsule not having been opened, following certain intraocular growths.

In my opinion, these dogmatic statements should be regarded circumspectly, for the reason that, while the establishment of a sympathetic iridocyclitis may require the occurrence of these events, it must not be overlooked that they are only events in the process, for underlying there is an agent inaugurating these changes. The agent may be a toxin or bacteria, specific in nature, or of special affinity for uveal tissue.

Clinically, sympathetic iridocyclitis shows no characteristic features to differentiate it from so called idiopathic or nontraumatic iridocyclitis; that is, as regards involvement, cause, and end

results. Those of known origin, due, as for example, to focal infections, syphilitic, or tubercular invasion, are particularly difficult of discrimination. Histologically, there may be specific differences.

This contribution was suggested by a recent experience which recalled to my mind the only case of sympathetic iridocyclitis which has occurred in my own practice. I have, of course, observed several cases of so called sympathetic irritation. That is, certain evidences of irritation were present in the fellow eye, but prompt removal of the injured eye was immediately followed by a cessation of these signs. In view of what is about to be stated, it is extremely doubtful whether they would have actually developed into cases of true sympathetic iridocyclitis.

One frequently encounters instances where trivial injuries to one eye, such as a small particle of foreign material on the cornea, will entail considerable irritability in its fellow. May not the irritability in the fellow eye, following more serious injury, frequently partake largely of this character? Clinically we have no means of determining, def-