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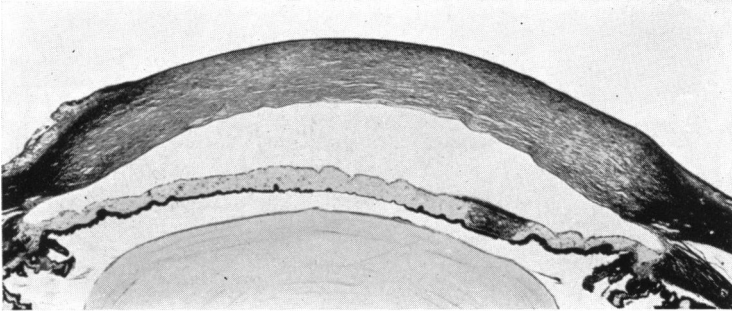
PIGMENT FRECKLES OF THE IRIS (BENIGN MELANOMAS): THEIR SIGNIFICANCE IN RELATION TO MALIGNANT MELANOMA OF THE UVEA*

ALGERNON B. REESE, M.D.
New York, N. Y.

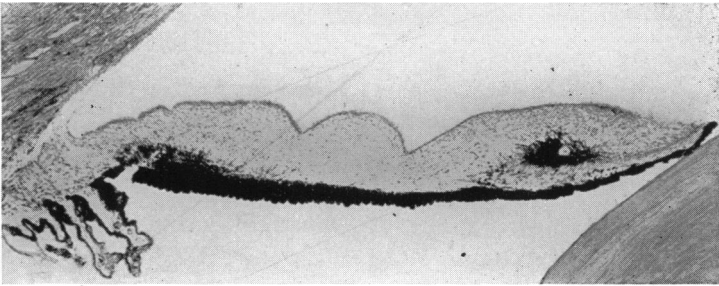
The presence of "freckles" on the anterior surface of the iris is common. Out of 300 adult patients with supposedly normal eyes, such freckles were seen on one or both irides in 145, or 48 per cent. In 93, or 31 per cent., of these the freckles were on both irides (about equal in 82, greater on one iris than on the other in 11) and in 52, or 17 per cent., they were unilateral. The statistics are based on the findings in adult eyes, as these pigment freckles do not appear before the age of six to eight years and rarely before twelve years. This is in keeping with the pigmented nevi of the skin, which also appear at this age. Although the term "freckles" seems convenient to employ clinically, these iris lesions really represent multiple benign melanomas.

The author has observed the more frequent occurrence of benign melanomas of the iris in the microscopic sections of eyes harboring malignant melanomas of the uveal tract. These have been observed in 13 eyes in which the malignant melanoma was present in the choroid, and in six eyes in which it was present in the iris or ciliary body.

* From the Institute of Ophthalmology of the Presbyterian Hospital, New York.



A

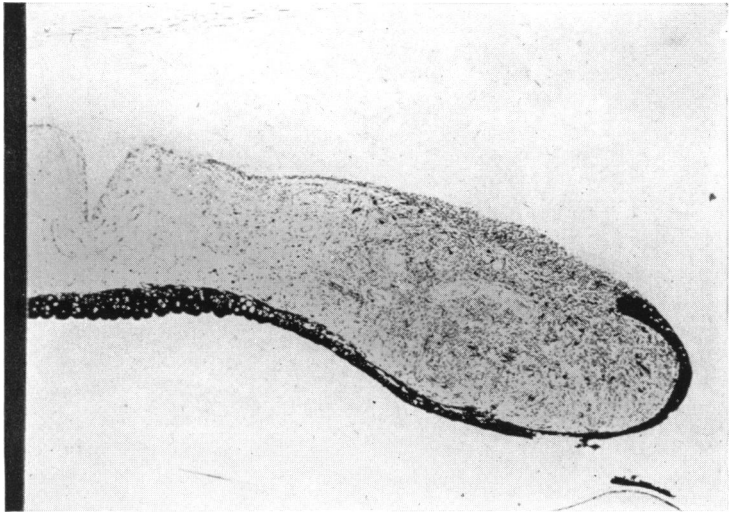


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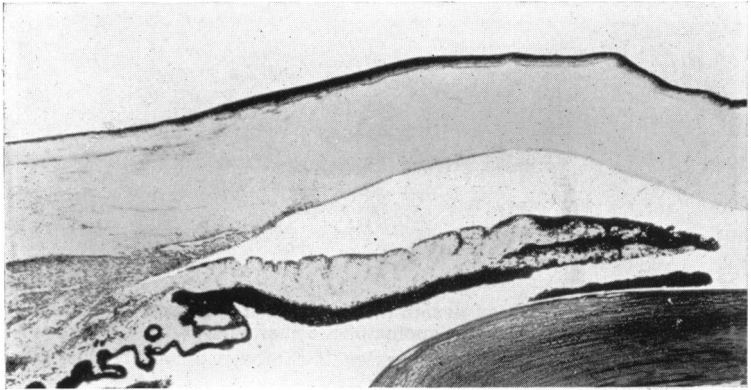
Fig. 1.—Four illustrations of benign melanoma of the iris in eyes with malignant melanoma of the choroid.

A, A benign melanoma of the iris extending through the entire thickness of the stroma.

B, A benign melanoma of the iris arising in the iris stroma.



C



D

Fig. 1.—Four illustrations of benign melanoma of the iris in eyes with malignant melanoma of the choroid.

C, A benign melanoma of the iris occupying the entire pupillary area, increasing the thickness of the stroma and causing an ectropion of the uvea (from the collection of Dr. Georgiana Theobald).

D, A benign melanoma of the iris occupying the pupillary area. The cells composing this resemble more closely the cells of the malignant melanoma of the choroid than in cases A, B, and C.

The histologic difference between melanomas of the iris seen in normal eyes and those seen in eyes with malignant melanoma seems to be one of degree. In the case of the normal eye the lesion is a localized accumulation of densely pigmented melanoblasts only a few cells thick along the anterior surface of the iris. In fact, the lesion could be characterized as merely a localized thickening of the anterior limiting layer of the iris, which in some instances has the appearance of being proliferated endothelium. Such a lesion may sometimes contain little or no pigment.

The melanomas of the iris in eyes with malignant melanoma are more extensive lesions (fig. 1, A, B, C, D). They tend to be slightly more elevated above the iris surface and to extend deeper into the iris stroma. Sometimes they actually arise in the stroma (fig. 1, B), and may even cause an increase in the thickness of the iris. In one instance an ectropion uveae was produced (fig. 1, C). The type cell is the melanoblast, varying in shape from plump, polygonal to long, branching, pigmented cells. When the cells spread through the entire thickness of the iris, they seem to have a predilection to abut on the dilator muscle layer in a manner similar to that which steel fragments assume toward a magnet. The cells are more matured than are those of the malignant melanoma, but sometimes they are less matured than are those comprising the physiologic melanomas of the iris. In one instance the cells of the iris lesion were of about the same maturity as those of the malignant melanoma in the choroid (fig. 1, D). No endothelium has been identified over their surface. There seems to be no predilection for any particular area of the iris. There is no tendency to encapsulation.

Sections of 100 eyes not the seat of malignant melanoma and with normal irides were examined, and iris melanomas were found in 26, or 26 per cent. Four of these were extensive enough to be comparable to those seen in eyes with malignant melanoma (fig. 2). It is interesting to note that the patients in three of these four cases had an extra-ocular tumor, but

not a malignant melanoma. However, most of the normal eyes that the author has available for microscopic study are those that have been enucleated because of a neoplasm of the adnexa.

Because these melanomas of the iris have been so frequently observed in the microscopic sections of eyes harboring malignant melanomas of the choroid, the author made an effort to identify them clinically. In three instances pigment freckles have been noted on the iris of the eye in which there was a malignant melanoma of the choroid, and were not present on the iris of the fellow-eye. In the first case (fig. 3), the choroidal tumor situated in the macular region was flat and non-pigmented, and a differential diagnosis from other conditions became necessary. In the second case, seen through the courtesy of Dr. Ramón C. Castroviejo (fig. 4, A, B), there was a retinal detachment over the choroidal tumor and the diagnosis was uncertain. The third case, seen through the courtesy of Dr. W. A. Boyce (fig. 5), was one in which the lesion occupied the macular region, was flat, and had no appreciable pigment content. In each of these three cases freckles were present on the iris of the involved eye and were not present on the iris of the fellow-eye. This finding was considered significant and was believed to lend substantiating evidence to the correct diagnosis. No difference was noted clinically between the appearance of these freckles and those seen in normal eyes, although the cases were not studied with this particular object in view. The fact that freckles were present on one iris and were not present on the other was considered most significant. What their appearance must be in order to be of significance in cases with bilateral physiologic freckles, or in cases with freckles normally more marked on one iris than on the other, is not known. From the microscopic picture there should be some clinical differences, if only for the reason that the one is more extensive than the other. A sufficient number of cases have not been seen clinically to warrant a statement as to any possible

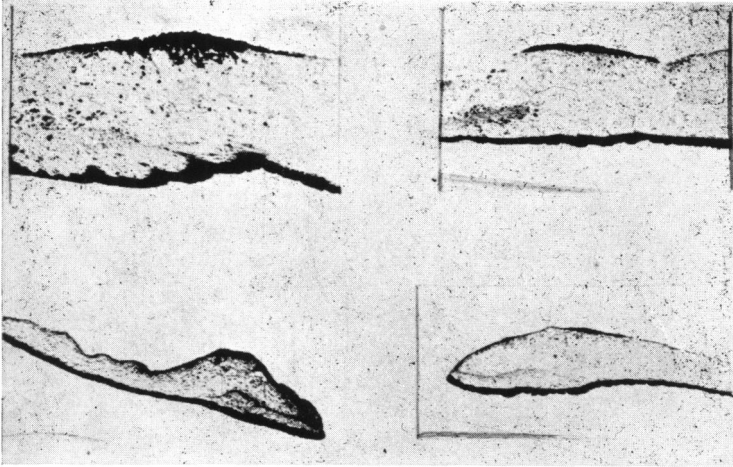


Fig. 2.—Four illustrations of benign melanomas of the iris in eyes with normal irides and not harboring a malignant melanoma of the choroid.

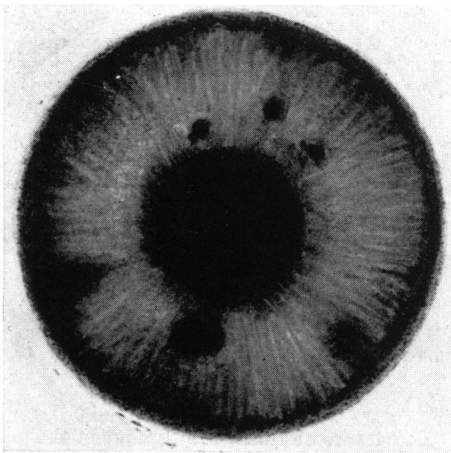
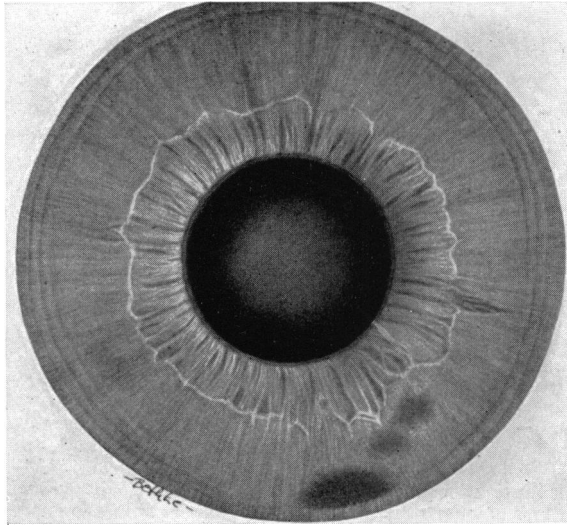
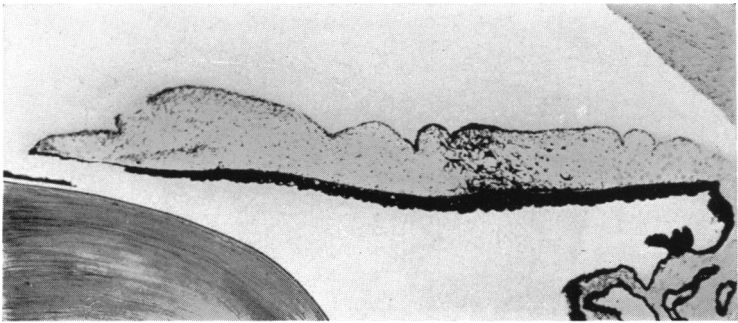


Fig. 3.—Freckles on the iris of an eye with a malignant melanoma of the choroid. There were no freckles on the iris of the fellow-eye.



A



B

Fig. 4.—A, Freckles on the iris of an eye with a malignant melanoma of the choroid. There were no freckles on the iris of the fellow-eye.

B, Microscopic section through the large freckle on the iris shown in figure 4, A.

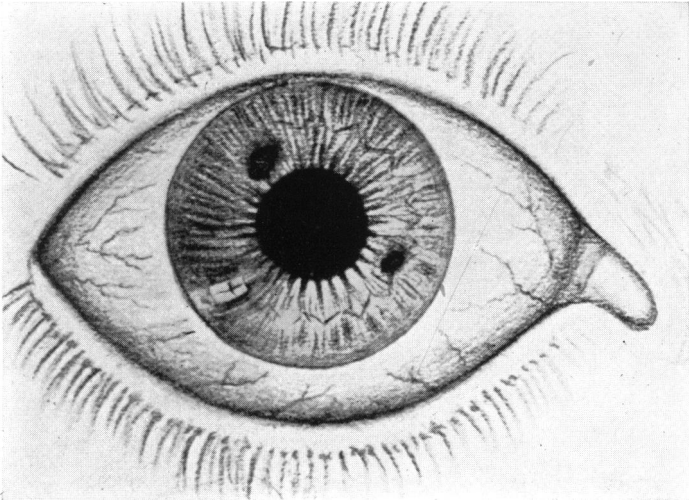
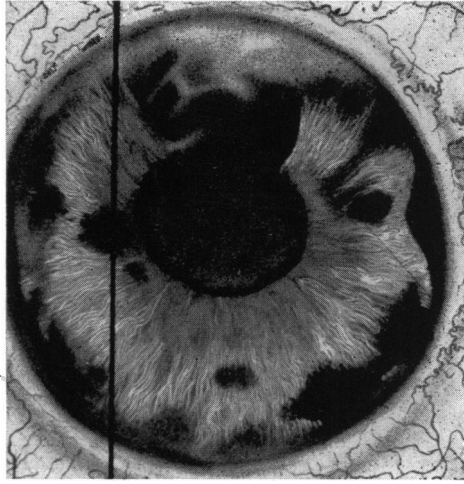
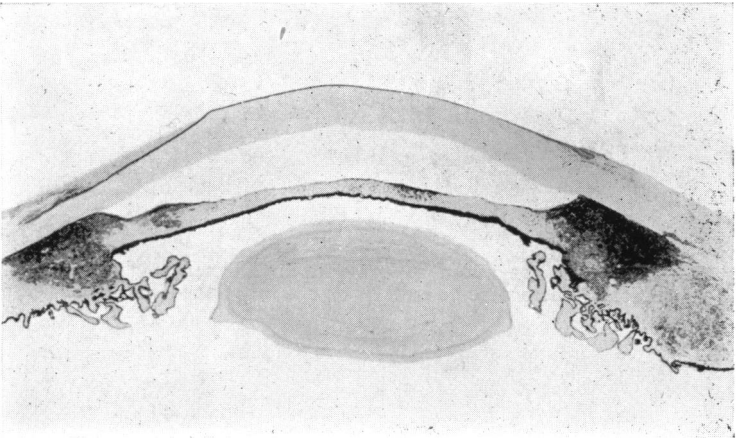


Fig. 5.—Freckles on the iris of an eye with a malignant melanoma of the choroid. There were no freckles on the iris of the fellow-eye.



A



B

Fig. 6.—A, Flat diffuse ring type of malignant melanoma of the iris and ciliary body. Operative coloboma above for secondary glaucoma. Line indicates the site of the section in figure 6, B.

B, Microscopic section of above case (line in figure 6, A, indicates site of section), showing one iris growth from implantation and one from direct extension along the anterior surface of the iris from lesion in the ciliary body. Other sections showed iris lesions which were instances of multiple origin.

differences. Even the most extensive ones seen microscopically were not noted clinically.

These melanomas of the iris are regarded as manifestations of the multiple origin of the tumor. They are composed almost invariably of more matured tumor cells than the main lesion, or of completely matured cells, and they are therefore benign, with little or no power of active growth. Similar instances of the multiple origin of melanomas are seen elsewhere in the uveal tract. In the cases studied here the main lesion is in the choroid and the lesser lesion in the iris, but it may be elsewhere in the choroid or in the ciliary body. Also, the main lesion may be in the ciliary body and the lesser one in the iris or choroid, or the main lesion may be in the iris and the lesser lesion also in the iris or in the choroid.

The question of whether or not these iris melanomas are implantation growths must be considered. Such manifestations of cancer are well known. In cases of retinoblastoma, implantation growths are frequently seen, and the anterior surface of the iris is not an uncommon site for their growth. Such manifestations in cases of malignant melanoma of the uvea occur, but are extremely rare. The growths are more frequently seen when the primary tumor occurs in the ciliary body and iris. In such cases the disseminated tumor cells have easy access to the anterior chamber, where they may implant themselves and grow along the iris and in the filtration angle. Such implantation growths around the circumference of the angle and iris are responsible for the ring character of some malignant melanomas (fig. 6, A, B).

The melanomas of the iris discussed in this paper do not appear to be implantation growths. The cells composing them are not comparable usually to the cells of the primary lesion. In only one instance were the cells of the iris lesion of about the same maturity as were those of the choroidal lesion (fig. 1, *d*). Furthermore, the melanomas studied here tend to involve the entire iris, whereas implantation growths

occur on the surface. The author has never seen an implantation lesion of the iris from a malignant melanoma of the choroid.

In cases of malignant melanoma of the skin daughter areas or freckles around the primary focus may occur, and these are generally said to be extensions along the lymphatics. The comparable iris lesions, however, do not seem to represent extension along the lymphatics from the primary focus, but are usually of multiple origin. Very exceptionally they may represent implantation, and, even more rarely, they may represent direct extensions by continuity along the iris surface from the primary lesion.

The question of whether the iris lesions are metastatic foci carried through the blood stream from the choroidal lesion hardly warrants consideration. The author has seen one instance of a metastasis by way of the blood stream from the primary site of the malignant melanoma in the uvea to a site elsewhere in the eye. In this case the primary lesion was in the choroid and the small metastatic focus was in the vascular layer of the ciliary body on the opposite side.

The Nature of These Multiple Origins.—Benign pigment lesions in the form of melanosis (café-au-lait spots) and nevi occur in the skin and tissue adjacent to and distal to such neurogenic tumors as neurofibromas. Also, the common skin nevus is believed to be neurogenic in origin. Thus there seems to be some relationship between pigment production and nerve tissue function or aberration. Assuming, therefore, that Dr. Georgiana Theobald's contention is correct, *i. e.*, that malignant melanomas of the uvea are neurogenic in origin, it can be argued that the multiple origin of melanomas of the uvea all emanate from some common neurotrophic influence.

This is borne out in a case reported by Goldstein and Wexler.* In their patient there were multiple neurofibromas

* Goldstein, I., and Wexler, D.: Melanosis Uveae and Melanoma of the Iris in Neurofibromatosis (Recklinghausen), *Arch. Opth.* 3: 288-296, 1930.

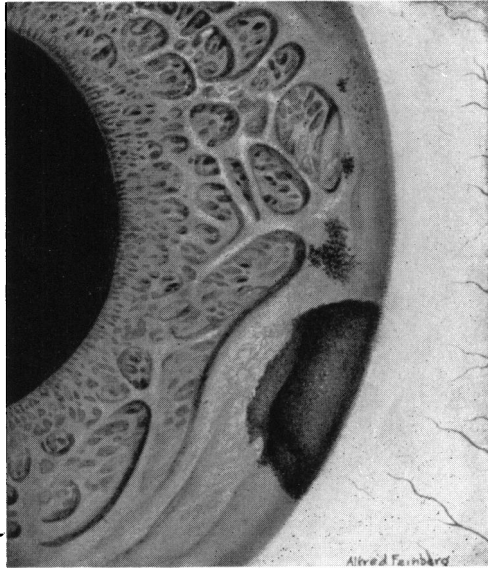
of the skin, multiple pigment lesions of the skin, fibrosarcoma of the back, and multiple melanomas of both irides. There were also stigmata of acromegaly and other features indicating tumor involvement of the central nervous system. This case illustrates the multiple origin of melanomas, associated with multiple neurogenic tumors, manifesting one malignant focus as well as innumerable benign foci all over the body, including the irides.

In some cases of neurofibromatosis the multiple manifestations of the disease, including the pigment lesion, tend to follow the distribution of a nerve. In cases of malignant melanoma of the uvea the iris melanomas do not seem necessarily to appear in the same quadrant or sector of the eye, indicating the same nerve distribution.

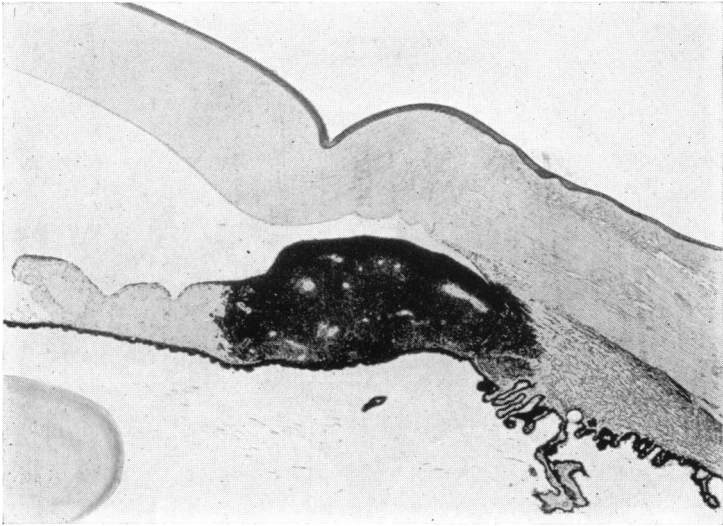
Another conception of the multiple manifestation of melanomas is that some cancerigenic agent acts on the whole uveal tract, causing a malignant melanoma at one site and more or less benign melanomas at other sites. There are similar occurrences elsewhere in the body. Among these may be mentioned cancerous lesions that occur simultaneously throughout the gastro-intestinal tract (mouth, esophagus, stomach, and rectum). Likewise, there may be papillomatous lesions over a wide area of the gastro-intestinal tract and one or several foci may become cancerous. Presumably, in these instances, some common agent acts throughout the gastro-intestinal tract. There may be epitheliomatous lesions over the face, with simultaneous and wide-spread multiple precancerous lesions, in which instance the cancerigenic agent is believed to be the effect of the actinic rays of the sun. In the mouth multiple carcinomas and precancerous lesions may occur which are considered by some to have a common cause in syphilis, in avitaminosis, or perhaps in the use of tobacco. Lymphosarcoma may manifest itself for a long time at one site as a localized tumor, and later show multiple tumors elsewhere. Both breasts and both ovaries may be affected simultaneously with cancer or precancerous lesions. The

multiple origin of a retinoblastoma, not only in the one eye, but in both eyes, is well known, and the primary site is malignant, whereas the secondary sites may be relatively benign. In all these instances there appears to be some common agent or factor at work that produces tumor changes of varying degrees over a wide area of a particular system. Dr. Verhoeff has suggested that some substance may emanate from the main lesion, causing a localized proliferation of melanoblasts elsewhere in the uvea.

Two instances in which the main lesion was in the iris or ciliary body and the lesser lesion in the iris serve to indicate certain characteristics. In the one case there was a malignant melanoma of the iris, with four pigment freckles on the iris at the opposite side to the tumor. There were two small freckles on the fellow iris. The tumor was excised locally by Dr. John M. Wheeler, and the microscopic diagnosis was malignant melanoma. Now, after seven years, there has been no recurrence of the tumor, and the pigment freckles which were not excised have not grown in size. This case bears out the fact that the freckles are composed of mature cells with little or no power of active growth. In the other case, a flat melanoma, measuring 1 x 3 mm. was discovered in the periphery of the iris during a routine examination (fig. 7, A). Presumably, the lesion had been present for an indefinite length of time. Observations were made regularly every three to six months. Gonioscopic examinations, drawings, and photographs were made at varying intervals. During the period of observation no change was detected until, after eight years, the gonioscope disclosed the fact that the anterior chamber angle could no longer be seen over the site of the tumor, indicating an increase in elevation. Also, at the same time, two freckles appeared on the iris above the main lesion. These had appeared in six months' time. After two and one-half months more a third freckle appeared above the other two. The main lesion still measured 1 x 3 mm. The eye was enucleated, and on microscopic examination the tumor



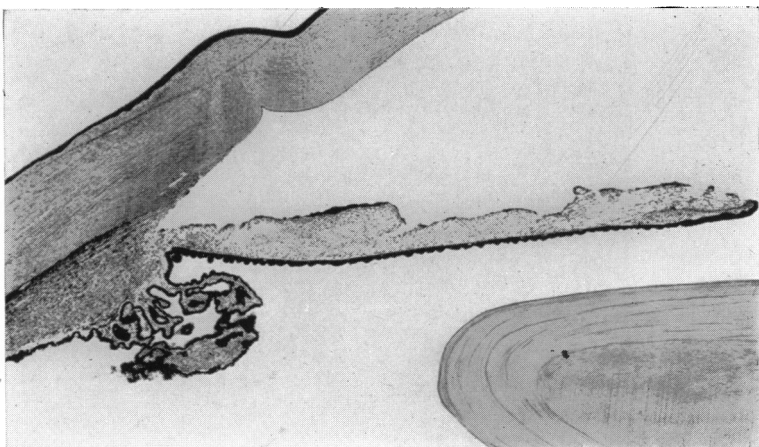
A



B

Fig. 7.—A, A melanoma of the iris observed for eight years before growth was detected coincident with the appearance of two iris freckles above the main lesion. After two and one-half months more a third freckle appeared above the other two.

B, Microscopic section of iris melanoma shown in figure 7, A. This is a malignant melanoma apparently arising from the site of a benign melanoma.



C

Fig. 7.—C, Microscopic section through the freckle shown in figure 7, A.

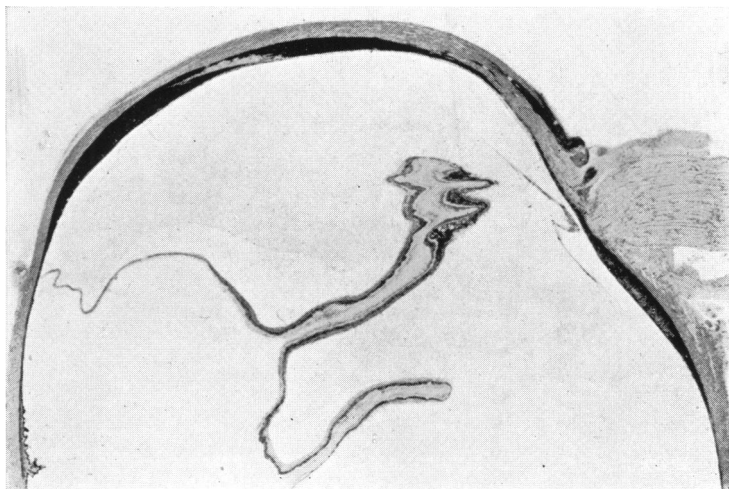
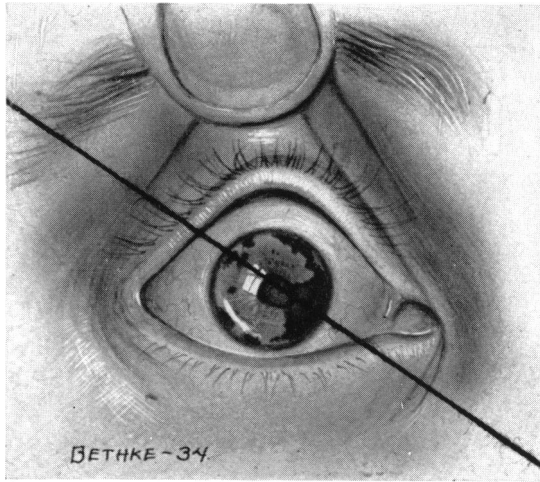
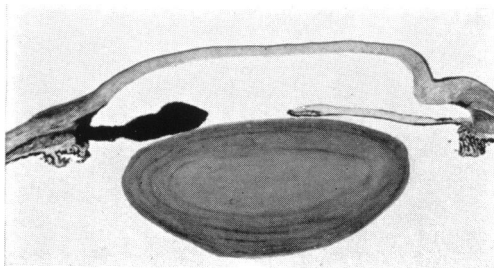


Fig. 8.—A diffuse malignant melanoma of the choroid which has extended out of the globe at the posterior pole. There is a detachment of the retina and secondary glaucoma.



A



B

Fig. 9.—A, A diffuse malignant melanoma of the iris. There was secondary glaucoma. Line indicates the site of section in figure 9, B.

B, Microscopic section of above case. Line in figure 9, A, indicates site of section.

proved to be a malignant melanoma arising apparently from the site of a benign melanoma (fig. 7, B). The pigment freckles were composed of more matured cells than the main lesion, and seemed to represent multiple origins of the tumor (fig. 7, C). They appeared coincident with active growth of the main lesion, and this suggests, therefore, that their presence on the iris indicates active or malignant growth of the main lesion.

Relation of the Iris Melanomas to Malignant Melanoma of the Uvea in General.—A malignant melanoma of the uveal tract is usually a localized tumor mass, but occasionally it manifests itself as a diffuse lesion involving sometimes the entire uvea (fig. 8). It may also appear as a diffuse lesion involving only a portion of the uvea, such as the iris (fig. 9, A, B), and/or the ciliary body (fig. 6, B). The malignant melanoma appearing as a localized mass in the uvea with benign melanomas elsewhere seems to be the bridge or link between the usual type of localized malignant melanoma of the uvea and the diffuse malignant melanoma. The cancerigenic factor has its effect at a localized site alone (usual localized malignant melanoma of the uvea), and to a lesser degree elsewhere (malignant melanoma at one site and benign melanoma elsewhere), or in a diffuse manner over the uvea (diffuse malignant melanoma of uvea or iris and ciliary body, or ring melanoma). The ring nature of a melanoma seems to be due in part to multiple diffuse origins as well as to implantation growths which logically occur around the filtration angle, where disseminated tumor cells in the anterior chamber would tend to gather. An important difference between a localized malignant melanoma of the uvea with benign melanomas elsewhere, and a diffuse and ring type of melanoma, is that the cancerigenic agent had a malignant effect at one site and a benign effect elsewhere in the one case, and a diffuse, multiple malignant effect in the other cases.

CONCLUSIONS

A melanoma of the uvea may be malignant at one site and benign at one or several other sites. This represents multiple origins of the tumor and the iris is a common site for the benign feature. The iris lesion is a diagnostic aid when seen clinically.

DISCUSSION

DR. F. H. VERHOEFF, Boston, Mass.: Dr. Reese's observations are highly suggestive and open up interesting questions. Freckles on the iris are so common that I have never recorded them in my cases of malignant melanoma of the choroid. In the future we should be careful to do this. It would be important to determine whether the freckles antedate the tumor of the choroid. Malignant melanomata may be neurogenic in origin, but I do not believe that Dr. Theobald has proved this to be so. In a fully developed malignant melanoma of the choroid she could easily find nerves in the tumor, whatever its origin might have been. As to possible explanations of the freckles associated with malignant melanoma, there is one not mentioned by Dr. Reese. This is suggested by an observation frequently made by me, namely, that a malignant melanoma of the corneal limbus causes an increase in the chromatophores in the tissue of the limbus for a considerable distance from the tumor. It would seem that from the tumor a substance is diffused which stimulates the chromatophores at a distance from it. In the case of a highly pigmented melanoma of the corneal limbus, with an implanted non-pigmented growth in the lower lid, I noted that the skin in a wide area around the implanted growth had become highly pigmented. This case seemed to prove that even an unpigmented malignant melanoma can stimulate the chromatophores around it.

DR. THEODORE L. TERRY, Boston, Mass.: At birth the iris is not very well developed, and the adult pigment characteristics are not evident. This change in pigmentation, or at least the appearance of iris pigmentation, is certainly not the development of freckles which Dr. Reese describes as occurring several years later. I wonder if Dr. Reese has been able to identify any such groups of cells that might be regarded as an unpigmented freckle.

Some iris freckles appear from his illustrations, extending deeply into the stroma and perhaps involving the muscle. Has he noticed any alteration in the motility of the iris locally in that region? I

make mention of this because I have always understood this alteration of motility to be strong presumptive evidence that the lesion is a malignant melanotic neoplasm of the iris. This sign of altered motility is demonstrated most graphically by use first of mitotics and later of mydriatics.

I had been using the term "malignant melanoma" and "benign melanoma" freely when it was pointed out to me by Professor Wolbach, a general pathologist, that to him the "melanoma" always carried with it an understanding of malignancy, whereas "nevus" was the term applied to the non-malignant pigmented tumor. Despite this general conception of terminology, in the eye there are benign pigmented neoplasms which we cannot call nevi, and which are certainly not malignant; thus ophthalmologists feel the need of the "benign" and "malignant" melanoma. Certainly one does find them used in the ophthalmological field.

It is my impression when malignant melanoma of the choroid is well enough advanced to have invaded the retina, it might free tumor cells in the eye, even giving implantations in the iris. Certainly iris implantations are to be seen in instances of retinoblastoma. Thus it is difficult to dismiss completely the evidence of the possibility of implantation here, yet it does not seem probable in the cases reported by Dr. Reese. In an eye removed because of melanoma of the iris, there was not only a definite melanoma of the iris but also in the ciliary body, some distance away, there was a mass of melanoma consisting perhaps of not more than 100 cells, resembling the tumor cells of the larger iris melanoma closely. Although this ciliary body mass represents a metastasis, most of these tumors of the iris are not extremely malignant and rarely give rise to metastases, especially within the eye itself, as iris melanomas appear to be related to the melanomas of the uveal tract approximately to the same degree that the basal cell carcinoma is related to the really malignant epidermoid carcinoma. The ciliary body lesion may, in turn, be a secondary lesion stimulated by the primary iris lesion if Dr. Reese is correct in his assumption about the association of iris freckles with more posterior uveal melanomas. It was my feeling that the immaturity of the cells in each region was of approximately the same grade. I will send one of these sections to Dr. Reese, and see what he can make out of it.

Another point to be considered is the possible relation of this disease to melanosis oculi. At one time Doherty pointed out that of those who had melanosis oculi, some 25 per cent. later showed

definite malignant changes in the uveal tissue. The association of freckles with malignant melanoma of the posterior uvea may indeed be similar to melanosis oculi in its relation to malignant uveal disease, the one being multiple and the other being diffuse. We often see a marked overproduction of retinal pigment epithelium adjacent to malignant melanoma of the choroid, but heretofore have thought this was a result of irritation, whereas it might, in turn, be related to this finding that Dr. Reese has presented.

It is considered by many that cancer is really a general disease; that it may manifest itself in certain locations typical of the type. Of course it may show itself in the eye more frequently than in other relatively resting tissues because the eye is composed of so many mixed, inter-related dependent parts that need organizers, one dependent on the other, especially since some of these do not differentiate well, such as the dilator pupillae, which never attain an appearance of well-developed muscle tissue. Some carcinogenic material, which is perhaps elaborated in the body, or perhaps derived extraneously, as in coal tar workers, can set off this process, as the eye might be more susceptible in certain individuals and it might well give rise to more than one neoplastic lesion such as uveal melanoma and iris freckles.

DR. ARNOLD KNAPP, New York, N. Y.: In confirmation of Dr. Reese's statement that this condition cannot be implantation processes on the surface of the iris, may I briefly mention a report of a woman, aged thirty-two, who came to me with the diagnosis of choroiditis and glaucoma? A trephining with iridectomy had been done, and she presented the usual coloboma. The color of the iris was almost inky black. A tumor could be easily seen behind one pillar of the coloboma. The trephine opening was definitely functioning, and the raised epithelium was studded with very small spots. The eye was removed, and microscopic examination showed that a tumor of the ciliary body had broken through at its apex, and that the surface of the iris was plastered with metastatic tumors which had also invaded the iris angle; the conjunctival spots were also examples of metastases, according to the opinion of Dr. James Ewing.

DR. REESE, closing: I wish to thank Dr. Verhoeff, Dr. Terry, and Dr. Knapp.

Dr. Verhoeff objected to my reference to the neurogenic origin of malignant melanomas of the uvea. However, it will be recalled that I prefaced this reference by saying that I was assuming that Dr. Theobald's contention was correct.

I think Dr. Verhoeff's idea that some substance may emanate from the main lesion and cause these pigment lesions elsewhere is a good one and possible.

The question which Dr. Terry brought up regarding the possible occurrence of unpigmented iris freckles is an interesting one. This possibility had occurred to me, and I intend to watch for them. The fact is that in the past we have overlooked even the pigmented ones.

Dr. Terry asked whether or not these benign melanomas of the iris caused any alteration in motility. I cannot answer this specifically, but I should judge that they do not, unless the lesion involves more than the anterior surface of the iris. In one of the cases shown you may recall that the lesion involved the entire thickness of the iris and produced an ectropian uvea. Such a lesion, I feel sure, altered the iris motility.

Dr. Terry mentioned the fact that the general pathologists use the one term "melanoma" and that it implies a malignant tumor. I am aware that this terminology is in common usage, and I am in accord with Dr. Terry's feeling that in the case of the eye we should further define melanomas as "benign" or "malignant" because in the eye we encounter mesodermal melanoblasts which are not present anywhere else in the body except at the Mongolian spot and the extra-sacral Mongolian spots. From these mesodermal melanoblasts both benign and malignant tumors arise.

Dr. Terry also brings up the question of the relationship between melanosis oculi and the lesions described in this paper. In the printed paper I cover the subject of diffuse melanomas of the uveal tract, and I conclude that the malignant melanoma of the uvea with these secondary benign manifestations is a connecting link between the usual malignant melanoma of the uvea and the diffuse lesions in which must be included melanosis oculi and the ring melanomas.

I think Dr. Knapp's case illustrates very well the metastatic foci which these lesions can manifest.