VON HIPPEL-LINDAU DISEASE: THE RECOGNITION AND TREATMENT OF EARLY ANGIOMATOSIS RETINAE AND THE USE OF CRYOSURGERY AS AN ADJUNCT TO THERAPY*

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THE VERY NAME VON HIPPEL-LINDAU DISEASE imparts a certain air of fascination and intrigue to a syndrome which has been referred to in the literature on several hundred occasions. This vast number of references is indeed numerical testimony of the great interest in this disease and stems from the fact that it is a systemic disease which embraces the fields of general medicine, ophthalmology, and neurosurgery, as well as the sciences of medical genetics and pathology. It is a prime example of the happy union of a variety of medical disciplines.

In August 1968, Newell[1] noted in summarizing the meeting of the American Ophthalmological Society that von Hippel-Lindau disease was "almost the favorite topic of the society" and that "nearly all reports in the American literature have been initially presented there." The knowledge of his statement has created both incentive and diffidence in the presentation of this material.

The present study is based upon the observations made on members of a single family with von Hippel-Lindau disease. This large pedigree, spanning four generations, has been assembled through their cooperation, and the majority of the living members have been personally examined. From these observations certain clinical features of this disease have been solidified and new concepts have been brought to light. These include (1) the full appreciation of this clinical entity as a systemic disease. This is well exemplified by the strong association of pheochromocytoma in a segment of our pedigree. (2) the recognition of early retinal lesions. By the use of indirect ophthalmoscopy and fluorescein angiography, minute retinal lesions

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TR. AM. OPHTH. SOC., vol. 68, 1970

were discovered which long precede the earliest clinical stage recorded in various classifications in the literature. (3) the ability to treat these early lesions with uniform success and with little chance of complication by the technique of Zeiss photocoagulation. A perusal of the entire literature shows clearly that ordinarily the diagnosis is obvious when it is made and that this alone accounts for results of treatment being only reasonably good when excellence might have been obtained. (4) the observation of the transformation of an early lesion from an area of nonfluorescence to a typical early lesion with feeder vessels is demonstrated by fluorescein angiography. (5) the chance to observe the genetic pattern of a hereditary disease from a large pedigree which explains clinical features of this disease that hitherto have not been expressed clearly, and (6) the use of cryotherapy to successfully treat angiomas of the retina. In the essayist's experience this modality may be utilized as a reliable type of therapy that accounts for a minimum of discomfort and risk. The success of this form of therapy is demonstrated by clinical observation and fluorescein studies. Although histological studies of these treated lesions would be of great interest, the essayist is happy to state that none have become available to date as all eyes treated have been saved.

HISTORICAL REVIEW

Von Hippel-Lindau disease is named for two brilliant investigators who interestingly enough both had a great interest in pathology. The ophthalmologist Eugen von Hippel (1867–1939) of Halle, Germany, is well known for his interest in the pathology of congenital ocular defects. It was his classic paper[2] in 1904 which brought to light the entity of angiomatosis retinae; however, it was not until 1926, when the Swedish pathologist Arvid Lindau (1892–1958) described angiomatosis of the central nervous system,[3] that an association between the two was established and a systemic disease recognized. Lindau began his study with an investigation of cerebellar cysts and observed a group which were characterized by a small angioblastic tumor in the cyst wall. In studying the postmortem material of these cases he noted the great frequency of cystic and adenomatous lesions in other organs. When he found reference in the clinical protocol of one case to a retinal arteriovenous aneurysm, he had the eye sectioned and found a small capillary hemangioma of the retina. From his observations of this case, as well as pathologic material from Sweden and Europe and a review of the reported cases of angiomatosis retinae (v. Hippelsche Krankheit), he was able to

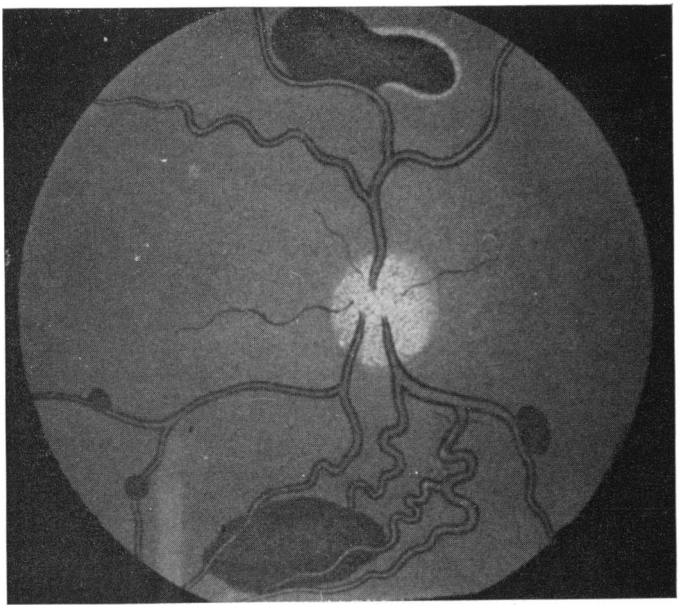

FIGURE 1
The earliest case in the literature of von Hippel-Lindau disease. From Galezowski's Atlas, 1886.

present a disease entity which he called "central nervous system angiomatosis."[4] This entity was characterized by hemangioblastomas of the cerebellum, medulla oblongata, and spinal cord, angiomatosis retinae, and visceral organ involvement including cysts and hypernephroid tumors of the kidneys, cysts of the pancreas, and tumors of the adrenal glands and epididymis.[5]

As in all aspects of medicine the often quoted cliché "there is nothing really new in medicine" certainly applies here. A study of the literature reveals that case reports typifying angiomatosis retinae were abundant prior to 1904, and reports typical of hemangioblastoma of the cerebellum had also been published. Indeed the association between retinal and brain involvement was found in a number of case reports between 1904 and 1926. The pieces of the puzzle were all there waiting to be properly assembled. Thanks to Arvid Lindau the puzzle was completed and the picture took form.

The earliest case in the literature[6] appears to be that of a patient of Drs Vigla, Duchenne, and Dolbeau who died in 1864 from a brain tumor and who had retinal tumors in the right eye. A fundus painting of this patient's eye and description of the case appears in Galezowski's Atlas published in 1886[7] (Figure 1). The earliest description of

a typical hemangioblastoma of the cerebellum appears to be that of Hughlings Jackson in 1872.[8] It is of interest that his patient's sister died with seizures which suggests a familial relationship. Panas and Remy in 1879[9] are given credit for the first pathologic description of angiomatosis retinae while Darier later presented a clinical description of the patient's other eye (1890).[10] The first classic description and illustration of the fundus picture was by Fuchs in 1882[11] who described a case as arteriovenous aneurysm and ascribed its etiology to trauma. Lagleyze in 1884[12] reported a typical case in the South American literature. Returning to the central nervous system aspect of this syndrome, Pye-Smith gave an interesting case report in 1885 of a patient who had a cerebellar cyst as well as pancreatic and kidney cysts.[13]

In 1892, D. J. Wood[14] of London presented a case of "Retinal detachment with unusual dilatation of retinal vessels and other changes." This clinical report is important because in 1894 Treacher Collins[15] gave the pathological description of the eye from Wood's case as well as the description of the patient's sister's eyes. This was the first clear indication that the condition was familial and the first proof that the basic pathology was a capillary angioma. From the other side of the world in Australia came Barrett's [16] case report in 1897 which described the fundus of a 21-year-old patient with enormous dilatation of a retinal artery and vein. Goldzieher[17] in 1899 further enriched the literature with a good clinical and ophthalmological report of a case. This was important as Czermak[18] was later to describe it histologically following the patient's death. In the American literature, a case described by Millikin[19] from Cleveland in 1904 probably represents a typical case when one examines the accompanying fundus painting.

This then was the background to von Hippel's classic paper in 1904. In this paper he presented two patients with a retinal mass fed by an enormously dilated artery and vein with associated retinal detachment and exudation. His first case was a patient who he had originally seen in 1893 and whom he had presented at the Heidelberg Congress in 1895.[20,21] In his paper he referred to earlier reports by Fuchs (1882), von Dzialowski (1900),[22] and Leplat (1901)[23] who had described cases under the term arteriovenous aneurysms. Fuchs had felt that his case was traumatic, but von Hippel leaned toward an inflammatory etiology and suggested the possibility of tuberculosis. Although his initial impression was soon to be disproven by his own pathological observations, he nevertheless publicized a new and fascinating clinical entity which soon bore his name as an eponym. In 1905, Czermak

reported on the histological findings of Goldzieher's case. He found retinal nodules of dense capillaries with large arteries and veins entering into them. Glial proliferation was felt to be of the reactive type.

In 1908, Coats[24] presented his classic paper on retinal disease with massive exudation and divided the patients into three characteristic groups. His group III consisted of cases which were later shown to be obvious examples of angiomatosis retinae and which he referred to as cases with formation of arteriovenous communication. Although none of the case reports which he presented in his paper belonged to this group, he was able to assemble 18 cases from the literature many of which are included in the references just cited. Following this article Pooley[25] in 1910 presented a beautiful description and fundus painting of a case and stated "a full description of the literature of these cases was given by Mr. George Coats." He stated that the case fulfilled all the requirements of an angioma of the retina.

In 1911, von Hippel[26] examined the enucleated eye of his first case. He was aware of the studies of Czermak and Collins and his pathologic findings confirmed their discoveries. He found capillary clusters in the tumorous part of the retina and felt that the basic lesion was angiomatous. He used the term angiomatosis retinae. Meller,[27] in 1913, disagreed with the previous investigators and stated that the basic pathology was a proliferation of neuroglia and that the vascular changes were reactive proliferation. This report coupled with papers by Ginsberg and Spiro (1914)[28] and Guzmann (1914)[29] temporarily sidetracked the attainment of a true understanding of the disease. All these investigators were confused by the secondary changes which occur. While the basic pathology was being debated, Seidel,[30] in 1912, made some important observations on the relation of retinal lesions to cerebral problems. In his case with a retinal angioma, the patient developed papilledema and was operated upon for a cerebellar cyst. The patients' brother also had a cerebellar cyst. Seidel mentioned that other observations in the literature related eye and cerebral problems (Czermak,[18] Jacoby,[31] and von Dzialowski[22]). In 1921, Brandt[32] presented the autopsy findings on von Hippel's first patient. This revealed tumors of the central nervous system as well as cysts and tumors in the visceral organs. He also presented two other cases, one of which showed histologic sections of a retinal angioma before secondary gliosis had become established. This study further strengthened the angiomatous etiology of the retinal lesions and weakened the theory of those who advocated a gliotic basis for the problem. In

1922, Berblinger[33] described another case of retinal angioma with multiple tumors of the nervous system. With this background awaiting his discovery, Lindau, in 1926, presented his classic thesis. In 1927, Schuback[34] presented a case and coined the eponym Lindau's disease (Lindausche Krankheit). In 1928, Cushing and Bailey[35] classified vascular growths of the nervous system into two groups (1) angiomatous malformations and (2) the hemangioblastomata or true neoplasms of blood vessel elements. They confirmed Lindau's observations that the favorite site of the latter group was the cerebellum, and secondarily the medulla and spinal cord. They pointed out that the hemangioblastomas differed from ordinary capillary angiomata by having a network of reticulin brought out by Perdrau's silver nitrate stain. In 1930, Lindau[36] restudied his material and confirmed the value of the Perdrau staining for the cerebellar tumors. He also tried Perdrau's stain on the eye lesion with the same good result.

Van der Hoeve[37] in 1932 presented the Doyne Memorial Lecture and brought von Hippel-Lindau disease into his group of phakomatoses which included Bourneville's and von Recklinghausen's disease. He pointed out that their principal symptoms were "the presence of spots, tumifactions, and cysts joined to other congenital malformations in various parts of the human body, especially in the nervous system." By his use of the word "phakos", he denoted a "spot, congenital in origin, often hereditary and familial in appearance which can be found in different parts of the human body, either be present at birth or appear later on, which can vary in size, enlarge by proliferation of any part of the tissue, grow to a real blastoma, and even turn to malignancy, but does not contain naevus cells." His description certainly applies to all the aspects of von Hippel-Lindau disease.

The hereditary aspect of this disease was first demonstrated by Collins although the first real pedigree was recognized by Rochat.[38–40] Moller[41] first demonstrated in his family study that there was a dominant mode of inheritance. Lindau[4] pointed out that hereditary transmission occurs in 20 per cent of the cases reported.

CLINICAL PICTURE

The classical ophthalmologic picture of angiomatosis retinae is that of a tremendously dilated artery, often appearing beaded and showing great tortuosity, leading from the disk to a peripheral tumor of pinkish color in the temporal fundus. From this mass an accompanying vein with similar engorged characteristics leads back to the disk.

The color of the two vessels may be almost identical demonstrating the admixture of arterial and venous blood and requiring one to examine the vessels near the disk to properly identify them. It would appear that the presence of arterial and venous communication within the angioma, as well as anastomoses which have been reported between the vessels leading to the angioma, is responsible for the hypertrophy of the feeder artery and vein. It has been noted that the dilated vessels are poor in lateral branches and greatly elongated.[42,43]

In 1912, Moore[44] showed that pressure on the globe caused narrowing of the blood stream in the large vessels and a blanching of the angioma which clinically seemed to be a spongy vascular tissue. Others have noted that pressure on the globe causes pulsation of the vessels but not the nodule[2,24,45] (proof that the lesion is not an arteriovenous aneurysm). The clinical observations by these investigators, without the benefit of modern-day techniques, is a tribute to their astuteness and clinical acumen. With the development of the technique of fluorescein angiography[46,47] one now has an excellent method of observing the nature of angioma and can demonstrate the consecutive filling of the feeder artery, capillary angioma, and efferent vein[48] (Figure 2).

Although the angiomas are usually located in the periphery with predilection for the temporal fundus, they may occur in the posterior pole either near the macula[49–51] or at the optic disk.[52–55] The retinal angiomas are bilateral in from 30 per cent (Usher[56]) to 50 per cent (Cordes and Hogan[57]) of the cases gathered from the literature, while in individual series all the eyes may have bilateral involvement (Saebo[58]). Multiple angiomata occur in about 33 per cent of involved eyes.[32,57] The average age for the development of signs and symptoms of angiomatosis retinae is 25 years according to Lindau,[3] although they have been reported in a premature infant and young children by von Hippel,[59] Appelmans,[60] and others,[61] and in patients in their sixth decade by Wood,[62] and Craig, Wagener, and Kernohan.[63] Twenty-five per cent of the patients with retinal involvement eventually develop central nervous system disease according to Lindau.[36] The average age for the development of the cerebral involvement varies in reported series from 33 to 39 years.[3,35,64] The hemangioblastomas of the brain form about two per cent of all intracranial tumors,[65] their site of predilection being in the hind brain and especially the cerebellum. When located there the patient usually complains of occipital headache as an initial symptom. Vertigo and projectile vomiting as well as physical signs of cerebellar dysfunction

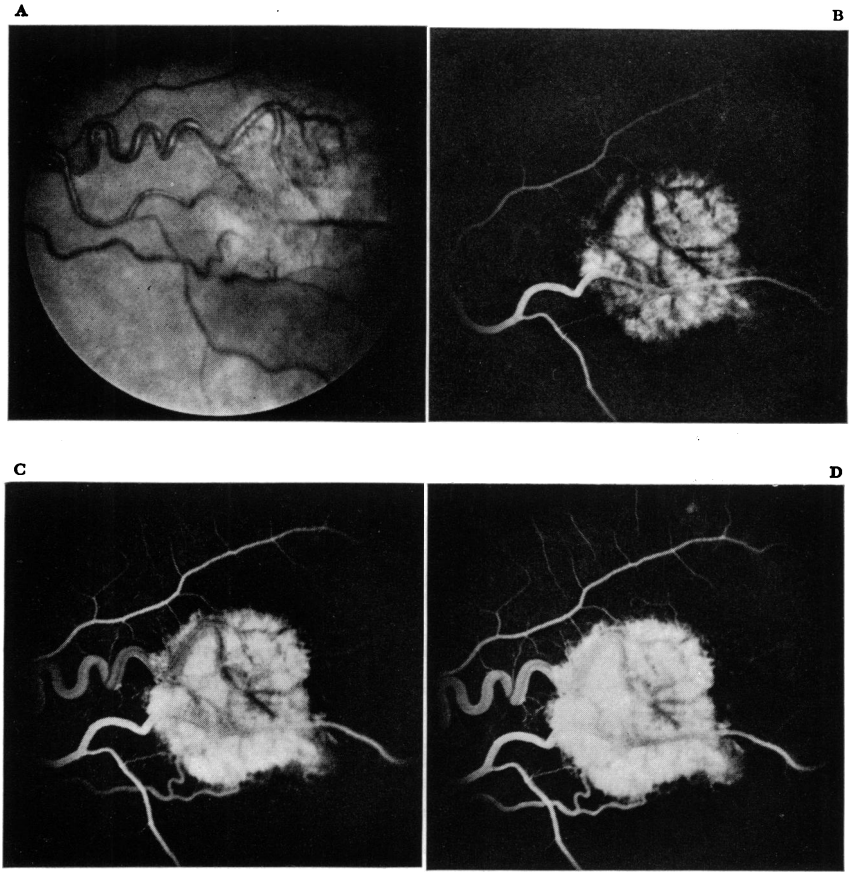

FIGURE 2

A, Four o'clock angioma left eye, Case IV-7. The remaining photographs B, C, D, are sequential fluorescein photographs demonstrating the consecutive filling of the feeder artery, capillary angioma, and draining vein.

gradually become manifest. When the lesion is in the medulla oblongata there are no specific features although syringobulbia may be associated. Moller's report of paresis of upward gaze in a number of patients with a cyst in the roof of the fourth ventricle is worthy of note.[66] Spinal cord hemangioblastoma may cause no symptoms and thus be more common than realized. Levin,[67] in 1936, stated that the spinal cord was involved in every proven case in which post-mortem examination of the spinal cord was made. Cox and Trumble[68] also emphasized this by pointing out that autopsy of cases with von Hippel-Lindau disease frequently revealed hemangioma of the

TABLE I. SYSTEM INVOLVEMENT IN VON HIPPEL-LINDAU DISEASE

A. Retina	Angiomatosis retinae—classic picture of dilated and tortuous artery and vein-feeding angioma (capillary hemangioblastoma)
B. Central Nervous System	(almost always below the tentorium)
1. Cerebellum	Cysts with mural hemangioblastomas
2. Medulla oblongata	Hemangioblastomas with cysts may lead to syringobulbia
3. Spinal cord	Hemangioblastomas with syringomyelia; may be unrecognized—may lead to spastic paraplegia
C. Visceral Organs	
1. Pancreas	Adenomata, cysts
2. Kidney	Hypernephroma, cyst
3. Adrenal gland	Pheochromocytoma, cyst
4. Epididymis	Hypernephroid tumor, cyst
5. Ovary	Adenomata, cyst
6. Bones	Hemangioblastoma, cyst
7. Cutaneous lesions	Naevi, cafe-au-lait spots
8. Spleen	Angioma
9. Liver	Angioma, cyst
10. Miscellaneous	
a. Thyroid	Cyst, adenomata
b. Urinary bladder	Hemangioblastoma
c. Lung	Cyst
d. Omentum	Cyst

spinal cord when there was no clinical evidence. Otenasek and Silver[69] reported six cases in a single family with spinal hemangioblastoma. They stress that three of these cases had had a parietal craniotomy because of the combination of focal signs referable to the extremities and generalized increased intracranial pressure caused by unrecognized cerebellar or brain stem hemangioblastoma. Thus spinal cord involvement ranges from asymptomatic lesions to syringomyelia and even spastic paraplegia.

The visceral lesions of von Hippel-Lindau disease usually take a back seat in the disease and only occasionally present the primary clinical picture; however, they should be kept in mind for Lindau[4] reported a palpable epididymal mass in a patient who subsequently died with central nervous system disease. Others have noted epididymal tumors and other palpable abdominal masses during life and sometimes prior to the development of ocular or brain symptoms.[70–72] From a study of the literature, our present pedigree, and other patients seen by the author, the entire syndrome with various system involvement is summarized in Table I.

The usual clinical course of the retinal involvement has been divided into stages by several authors. Thus, Duke-Elder[73] and Vail[74,75] separate the disease into four stages. Stage I: An early stage of arterial and venous dilatation with the formation of an angioma

which may be single or multiple. Stage II: The development of hemorrhages and exudation. Lipid deposition may occur around the angioma as well as in the macula. Stage III: Massive exudation and retinal detachment, and Stage IV: Absolute glaucoma, uveitis and loss of the eye. Bedell[76] described three types of retinal picture, (1) immense venous enlargement and fullness of the paralelling artery, (2) whip cord artery and widened straight vein, and (3) swollen, rounded, elevated nerve head suggesting a choked disk. Thus the appearance of large tortuous vessels leading to a large pinkish mass in the periphery of the fundus has become the hallmark of this disease to the average ophtholmologist; however, from our present study, it will be demonstrated that a much earlier clinical lesion may be recognized.

PRESENT STUDY

This study began in May 1966, when a 15-year-old white female was referred to me with a vitreous hemorrhage in the right eye. (Pedigree Case IV–7). The child had been followed elsewhere because of poor vision in the left eye. Photographs of the left fundus had been taken, but the nature of the fundus problem was unrecognized. At the time of our examination there was a fresh vitreous hemorrhage in the right eye. In spite of the blood, a dilated artery and vein were seen coursing to a large angioma inferiorly. There appeared to be an early detachment around the angioma. The left eye showed four large angiomas with edema of the disk and a large amount of lipid material in the macula. Because of the recognition of classic von Hippel-Lindau disease, a study of the family was begun and the accompanying large pedigree was assembled. (Figure 3).

SUMMARY OF THE PEDIGREE

Generation I

Case I-4 Great-grandfather of our initial Case IV-7. Died age 86 with good vision both eyes. No manifest neurological symptoms.

Cases I-1,2,3 Brothers of above patient. No known visual or neurological problems but a son (II-1) of Case I-1 died from a brain tumor.

Cases I-5,6 Sisters of above patient. Both blind in one eye. Died age 80.

Generation II

Case II-5 Son of I-4 and grandfather of our initial Case IV-7. Died age 76 with carcinoma of the lip. No ocular or neurological problems. This patient had eight siblings.

Case II-2 Died age 79. Blind in one eye. No other problems. No children.

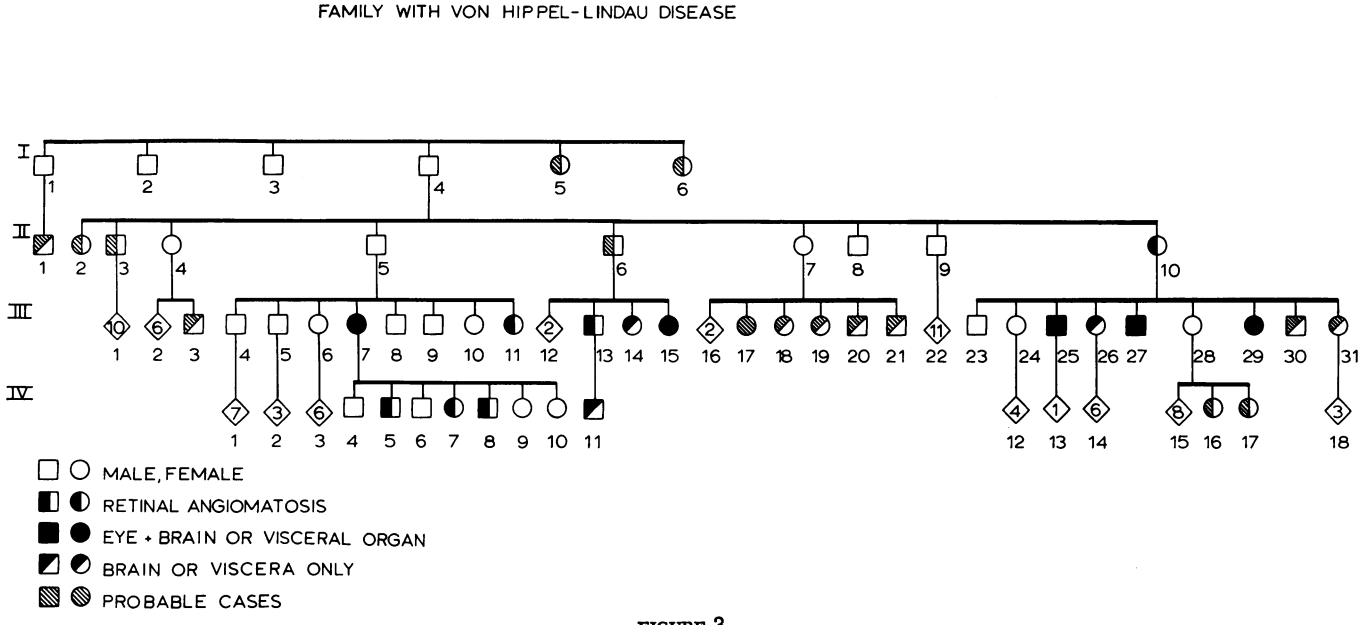

FIGURE 3

Pedigree of family in present study with von Hippel-Lindau disease.

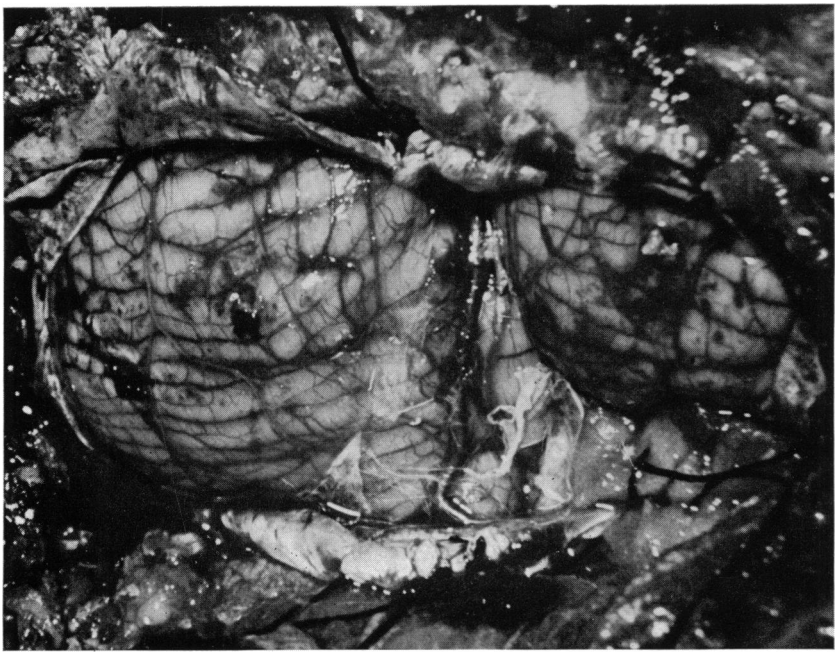

FIGURE 4A

Case II-3 Died age 79. One eye removed for probable angiomatosis retinae. Children unaffected to date.

Case II-4 Died age 79. No known problems but one son (III-3) died age 30 from kidney tumor (hypernephroma).

Case II-6 Died age 89. Blind in one eye. Five children with three affected (see Generation III).

Case II-7 Died age 79. No known problems. Five of seven children affected (see Generation III).

Cases II-8,9 Free of disease.

Case II-10 Age 74. Blind in both eyes from angiomatosis retinae. One eye enucleated at Wills Eye Hospital in 1917. No other symptoms. Nine children with six affected (see Generation III).

Generation III

Case III-7 Age 48. Daughter of II-5 and mother of IV-7. Lost vision in right eye at age 12. Eye now NLP, soft, occluded pupil. Left eye normal in 1966 except small pigmented scar at 10 and 1 o'clock posterior to equator. In November 1968, onset of cerebellar symptoms with increased intracranial pressure and papilledema. Severe left occipital headaches. Referred to neurosurgeon with diagnosis of left cerebellar hemangioblastoma. On 22 November 1968, patient had a bilateral suboccipital craniotomy (Figure 4) which revealed the left cerebellar hemisphere to

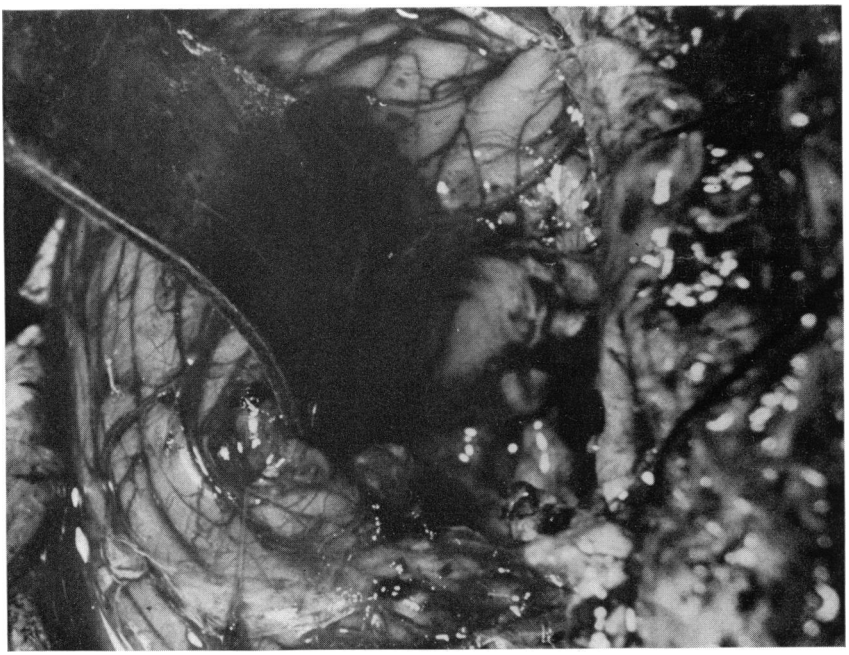

FIGURE 4B

Photographs at operation of Case III-7. A: Tremendous enlargement of left cerebellar hemisphere. B: Retractor in large left cerebellar cyst.

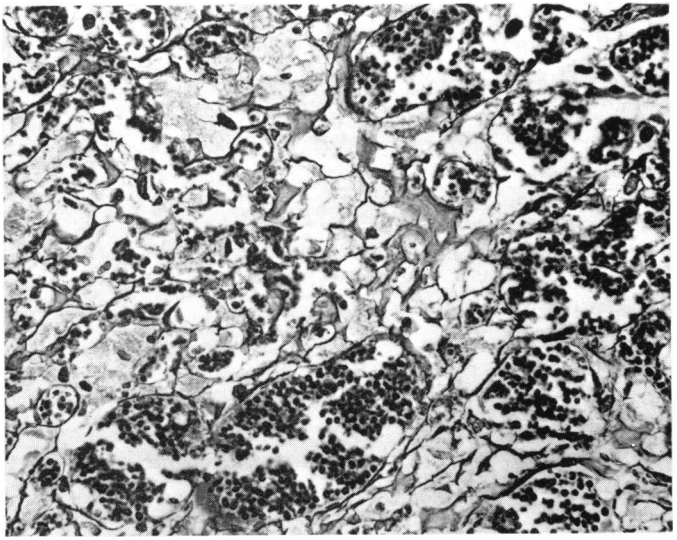

FIGURE 5

Photomicrograph of section through mural tumor removed from cerebellum of Case III-7. Classic hemangioblastoma. Gomori's reticulin stain. (× 279)

be much larger than the right and cystic to palpation. The cyst cavity was entered and a mural nodule found superomedially. This was resected and proved to be a classic hemangioblastoma (Figure 5). The patient has done well to date.

Case III-11 30-year-old sister of above patient. No complaints. Very early lesion right eye (see Early Lesions).

Cases III-13–15 Children of II-6.

III-13 Age 65. Blind in one eye from angiomatosis retinae. One son IV-11 had cerebellar tumor.

III-14 Died age 38. Probable pheochromocytoma.

III-15 Died age 31 from cerebellar tumor. Had angiomatosis retinae in one eye.

Cases III-17–21 Children of II-7.

III-17 Age 63. Blind in one eye and ovarian cyst.

III-18 Age 62. Cystic kidney.

III-19 Died age 24 from brain tumor.

III-20 Age 52. Has had cystic lesion removed from mandible.

III-21 Died age 40 from brain tumor.

Cases III-25–31 Children of II-10.

III-25 Age. 47. Angiomatosis retinae one eye, pheochromocytoma removed 1948, hemangioblastoma of spinal cord with paraplegia.

III-26 Age 36. Bilateral pheochromocytomas removed. Cafe-au-lait spots on extremities.

III-27 Age 34. Eye enucleated at Walter Reed Army Hospital for angiomatosis retinae in 1955. Pheochromocytoma removed from right adrenal gland.

III-29 Died age 49. One eye removed in 1949 with angiomatosis retinae. Cause of death probably pheochromocytoma.

III-30 Died age 16 from pheochromocytoma.

III-31 Age 46. Has had cystodenomata of the ovaries.

Generation IV

Case IV-7 15-year-old female child, daughter of III-7. Initial case seen. Bilateral multiple angioma. First seen May 1966 (see section on Treatment).

Case IV-5 21-year-old brother of above. Bilateral angiomatosis retinae. The right eye very early lesion (see Early Lesions). The left eye a classic peripheral tumor (see section on Treatment).

Case IV-8 18-year-old brother with bilateral angiomatosis retinae found on routine examination (see Early Lesions).

Case IV-9 14-year-old sister with small greyish white lesion in the right eye (see Early Lesions).

GENETIC STUDY – THE PEDIGREE

A study of this pedigree is fascinating and permits us to observe firsthand

the genetic make-up of a family with von Hippel-Lindau disease, which has been shown in the literature to be of incomplete dominant autosomal inheritance.[77] In studying any genetic disease we should keep in mind that even in dominant inheritance there is phenotypic variability. This may be due to the fact that we are dealing with a pleiotropic gene (having multiple action with simultaneous influence on several tissues or organs) with variation in penetrance, expressivity, and specificity. Since a gene may manifest itself phenotypically in some cases, and not at all in others, we speak of it as having high or low penetrance. It is this fact that makes it difficult to establish a type of inheritance with study of only a few individuals. Thus a case with a disease of dominant inheritance may be thought to be recessive or even nonfamilial if the parent carrying the gene shows no obvious effects because of low penetrance. Expressivity of a gene refers to the quantity or degree of phenotypic manifestations, while specificity refers to their quality (morphology) and localization.

In this family we see that the inheritance is incompletely dominant with varying penetrance, expressivity, and specificity among the generations. The mother of our first case (Case III-7) lost the vision in her right eye at age 12, yet did not develop cerebral involvement for 36 years. Her father (Case II-5) died at the age of 76 with good eye sight and no evidence of cerebral involvement. In turn, his father (Case I-4) died at age 86 also without any manifest evidence of von Hippel-Lindau disease. Thus in the case of the earlier generations the gene was showing extremely low penetrance, expressivity, and specificity. Without knowledge of other siblings in generations I and II, we would have been unable to establish a genetic pattern of dominant inheritance. Whereas the grandfather (II-5) of our first case (IV-7) showed no evidence of von Hippel-Lindau disease, his sister (II-10) has had bilateral angiomatosis retinae and is still living at age 74, blind in both eyes. She is otherwise healthy. It would appear that the gene was just "warming up" in her, for her children manifest a gene high in penetrance, expressivity, and specificity. Thus, of her nine children, three have retinal angiomata (III-25,27,29), five have had pheochromocytomas (III-25,26,27,29,30) and one is paraplegic from a hemangioma of the spinal cord (II-25). One has had cystadenomata of the ovaries (III-31) without other involvement to date. A similar picture of gene penetrance is seen in the children (III-17–21) of Case II-7 who died at age 79 without evidence of the disease.

This pedigree then graphically illustrates the phenomenon of incomplete dominant inheritance and demonstrates just how penetrance, expressivity, and specificity can affect the portrait of a disease. It is of interest to note the longevity of many members of this family. Also of great interest is the large number of cases with associated pheochromocytoma. This fact seems to solidify the inclusion of von Hippel-Lindau disease as one of the phakomatoses since the association of pheochromocytoma and von Recklinghausen's disease is well known.

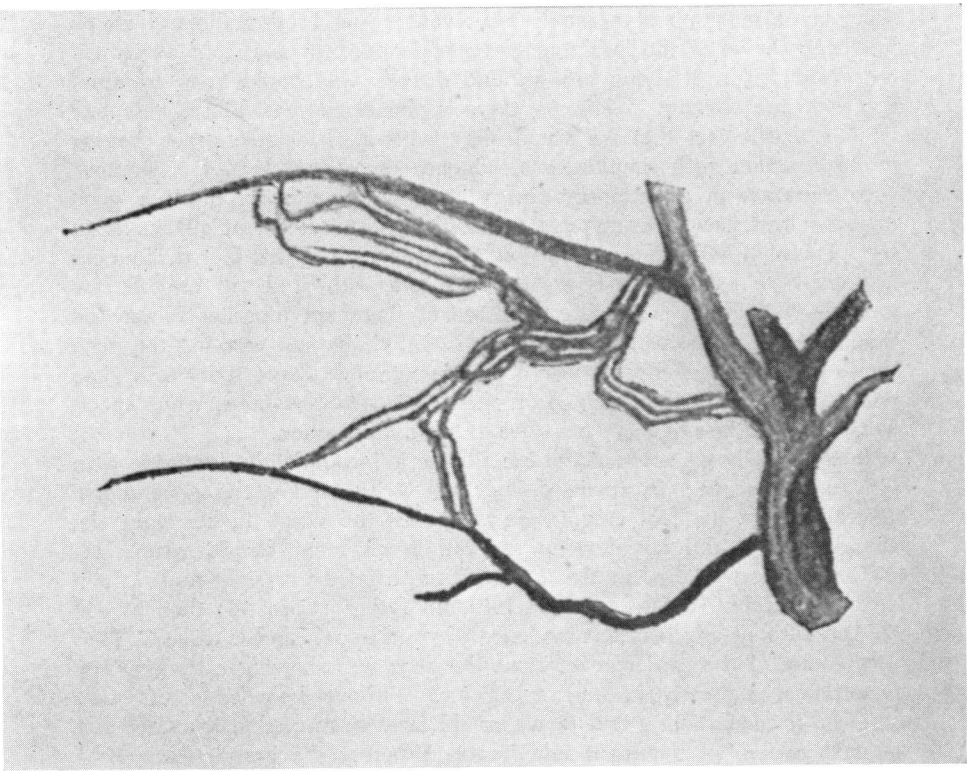

FIGURE 6
Drawing from Stern (1913) showing an early lesion of angiomatosis retinae.

EARLY LESIONS

In examining various members of this family, very early retinal angiomas were found. These lesions presented as minute reddish retinal nodules with afferent and efferent vessels which were not dilated, tortuous, or grossly abnormal. Thus we were seeing a stage of this disease which preceded that recorded in the literature as Stage 1. With the recognition of these early lesions a careful review of the literature was undertaken to see if others had recognized changes that preceded the classic appearance of angiomatosis retinae.

It is apparent that even in the early days an earlier stage of retinal involvement was recognized. Stern,[78] in 1913, noted in his case report that all the affected vessels and angiomatous nodules were connected in a channel system, and that in a relatively normal part of the fundus

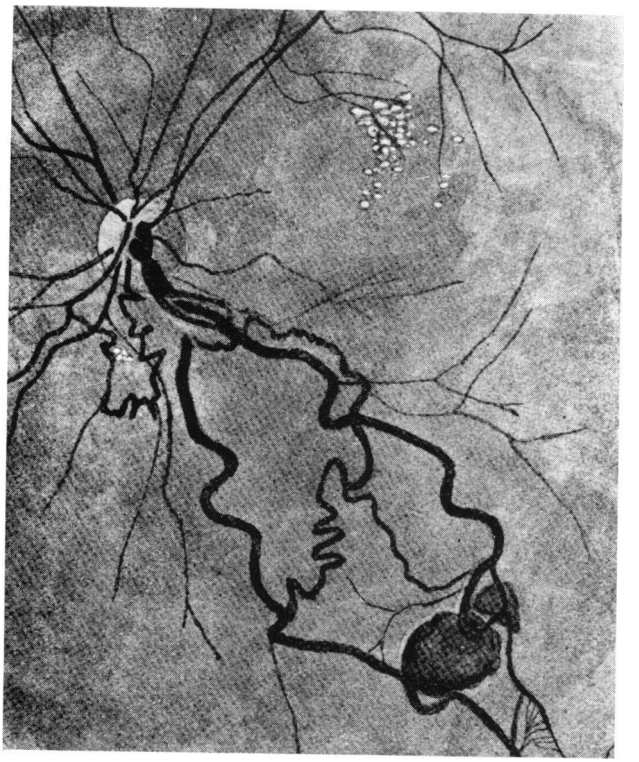

FIGURE 7A

there were delicate vessels between an artery and vein converging toward a small angiomatous nodule (Figure 6). Ditroi[79] also showed a channel system of angiomas with a peripheral anastomosis of fan-like vessels. Approximately two years later, this fanlike anastomosis was replaced by a tumor nodule (Figure 7). Gamper,[80] in 1918, noted a bilateral case of angiomatosis retinae. One eye had all the classic findings, but the other eye showed only a small red nodule without changes in the vessels. Observation over several years showed enlargement with dilatation of adjacent vessels. The fact that there may be unrecognized angiomas in the retina is further illustrated by one of Lindau's cases[4] which had shown only a choked disk clinically. The patient died from a brain tumor and histological examination of the eye revealed a hemangioma of the retina of microscopic size. Cushing and Bailey[81] presented a patient in 1928 who had had an ophthalmologic examination on eight different occasions with negative findings. Finally, five years after a cerebellar

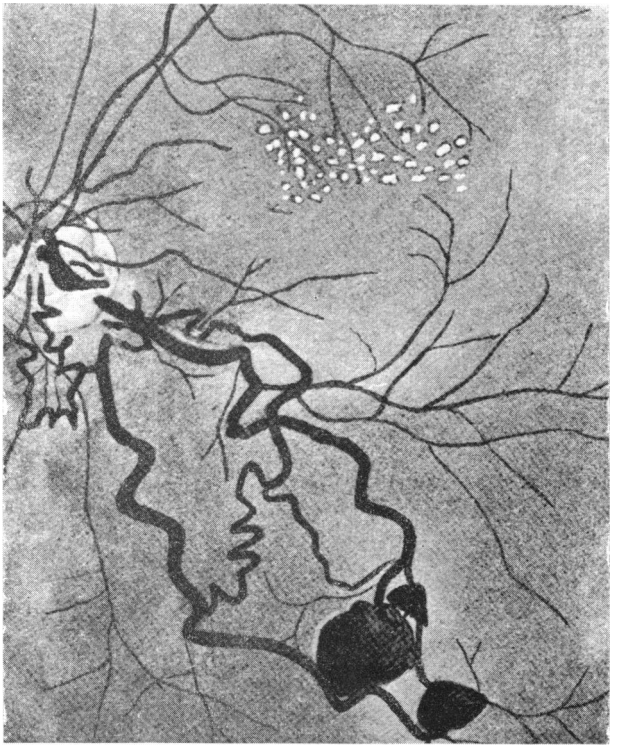

FIGURE 7B
Retinal drawings from Ditroi (1917). A: Note peripheral lesion of fanlike anastomotic vessels. B: Two years later this area replaced by an angiomatous nodule.

operation a retinal angioma was found. A beautiful fundus painting of this patient's retina by the late Annette S. Burgess appeared in Dr William Holland Wilmer's *Atlas Fundus Oculi* in 1934.[82] In recent years other reports have mentioned early lesions. Thus Joe and Spencer,[83] in 1964, reported a small angioma found only on histologic examination. Goldberg and Duke,[84] in 1968, demonstrated an early angioma by the trypsin digestion-flat mount technique. This lesion had been recognized by only one of many observers during the patient's life. It is thus obvious that early diagnosis of angiomas of the retina has been a problem since the recognition of the disease although it has been alluded to since 1913.[77]

In our present study some of the patients in whom we found early lesions had been examined previously by ophthalmologists but with-

out knowledge of a family history of von Hippel-Lindau disease (Case IV-5); however, one patient (III-11) who resided out of town was specifically referred for examination because of the family history and was said to be negative.

These cases emphasize two important points in fundus examination. The first is the sensitization of the doctor to a problem when he is performing ophthalmoscopy, and the second is the necessity of an adequate method of observing the fundus. With the advent of indirect ophthalmoscopy and scleral depression, the entire fundus has come into view and one is able to view large areas of the retina in one image field. This is especially true when using the 30-diopter indirect lens (American Bifocal Co, Cleveland, Ohio). With this technique one can quickly scan the fundus and pick up minute lesions which might otherwsise escape observation by direct ophthalmoscopy. Once they are found, these small lesions should be studied by higher magnification with direct ophthalmoscopy or with the 20-diopter and 13-diopter indirect lens. In spite of the excellence of our instrumentation we must still have a routine method of viewing the fundus to avoid overlooking a lesion. Thus one may start at the disk and in turn cover the macula, vessels, midperiphery by tracing out the arteries and veins from the disk, the far periphery, and finally the region of the ora serrata with scleral depression. At each point along the way we should run through a mental checklist. For example, at the disk we notice its outline, color, cupping, etc. In other words, we must think when we look. The value of this method of examination is well illustrated by a case referred to me with a total detachment in the right eye. The patient had been examined by several ophthalmologists, some of whom felt that it was an inflammatory detachment. The left eye was said to be completely normal. When we examined the right eye there was a total detachment with considerable blood in the vitreous over the lower half of the fundus. In going through a mental checklist when we came to vessels, it was noted that the vessels coming off the disk inferiorly were greatly dilated. By careful scrutiny the hazy outlines of an angioma could be seen through the vitreous blood. With the realization of the diagnosis the left fundus was examined with indirect ophthalmoscopy and a "sensitized eye", and a small peripheral angioma was found (Figure 8). It seems obvious that it was because of examination technique that many of the small lesions reported in the literature by histological sections were not seen clinically.[4,83,84] We also have available now the technique of intravenous fluorescein which may be useful in observing small

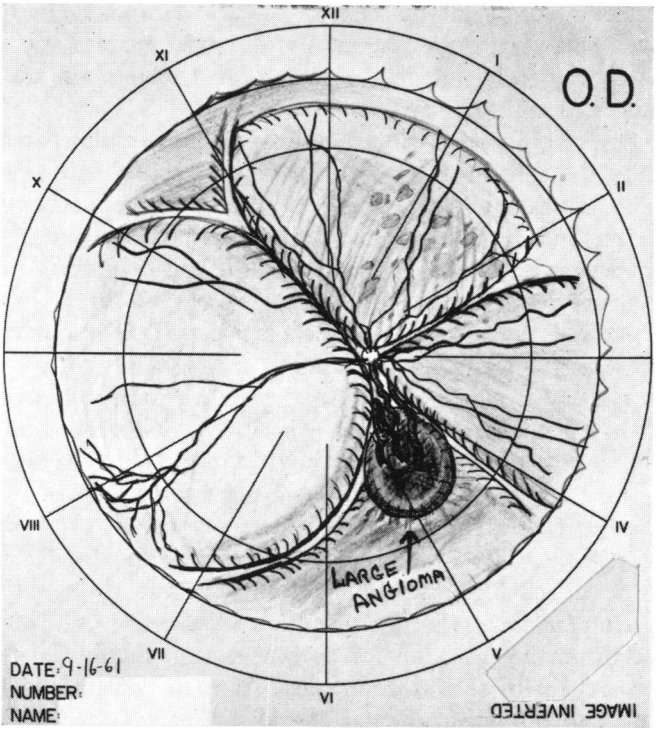

FIGURE 8A

Schematic retinal drawing of case with total detachment in the right eye. Previously undiagnosed, the retinal angioma was almost obscured by detachment and vitreous blood, but dilated vessels from the disk provided the clue.

lesions. With this technique the areas "light up" in the fundus, and also permit us to record them photographically.

CASE REPORTS

CASE IV-8. This 18-year-old brother of our initial case (IV-7) was seen in July 1966, because of the diagnosis of the disease in his sister. He had no ocular or systemic complaints. On examination his left eye showed a somewhat dilated artery and vein leading to a pair of upper temporal angiomata arranged in a channel or arcade fashion. The proximal lesion was a nodule but the peripheral one was still a cluster of capillary vessels. This channel system was similar in appearance to that described by Stern[78] and Ditro[79] (Figure 9). The patient's right eye however demonstrated two very early angiomatous lesions, one temporal and the other nasal. There was no enlargement of feeder vessels. Both lesions filled with

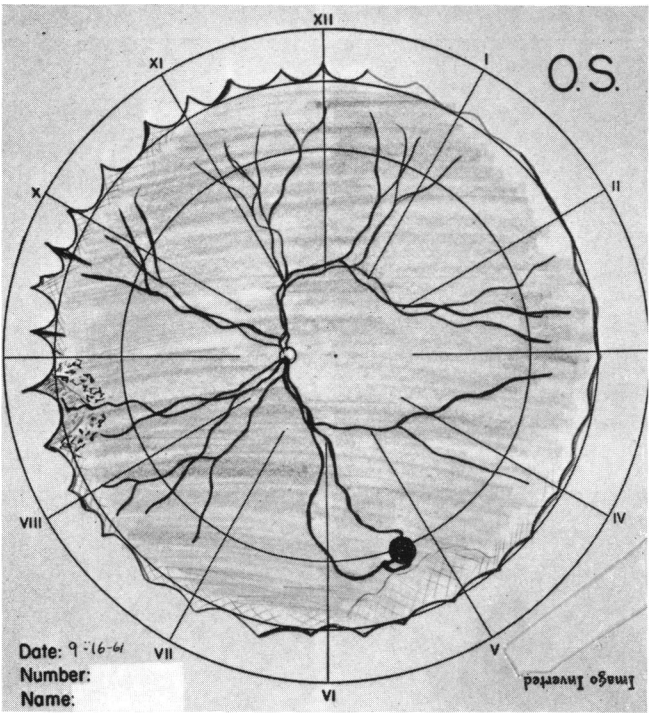

FIGURE 8B
Drawing of left eye previously reported as normal with small peripheral angioma.

fluorescein. These small capillary clusters might easily have been overlooked but for indirect ophthalmoscopy, for it would have required diligent coverage of the fundus with direct ophthalmoscopy (Figure 10) (see also under Treatment).

CASE IV-5. This 21-year-old brother of the previous patient was seen in March 1967. He was brought to the Retina Clinic on leave from the Navy and was found to have bilateral involvement. He had been admitted to the hospital six years previously for a muscle operation because of exotropia of the right eye. No fundus abnormalities were noted at this time nor had subsequent examinations reported any retinal lesions. On our examination the right eye was partially amblyopic with a vision of 20/50 while the left eye was 20/20. The left eye showed two angiomatous lesions arranged in arcade fashion in the temporal periphery. The proximal lesion was a cluster of dilated capillaries, and the peripheral one was a large pinkish white tumor. The right eye was the fascinating one. Here in the midperiphery at 8 o'clock was a small reddish nodule which almost blended into

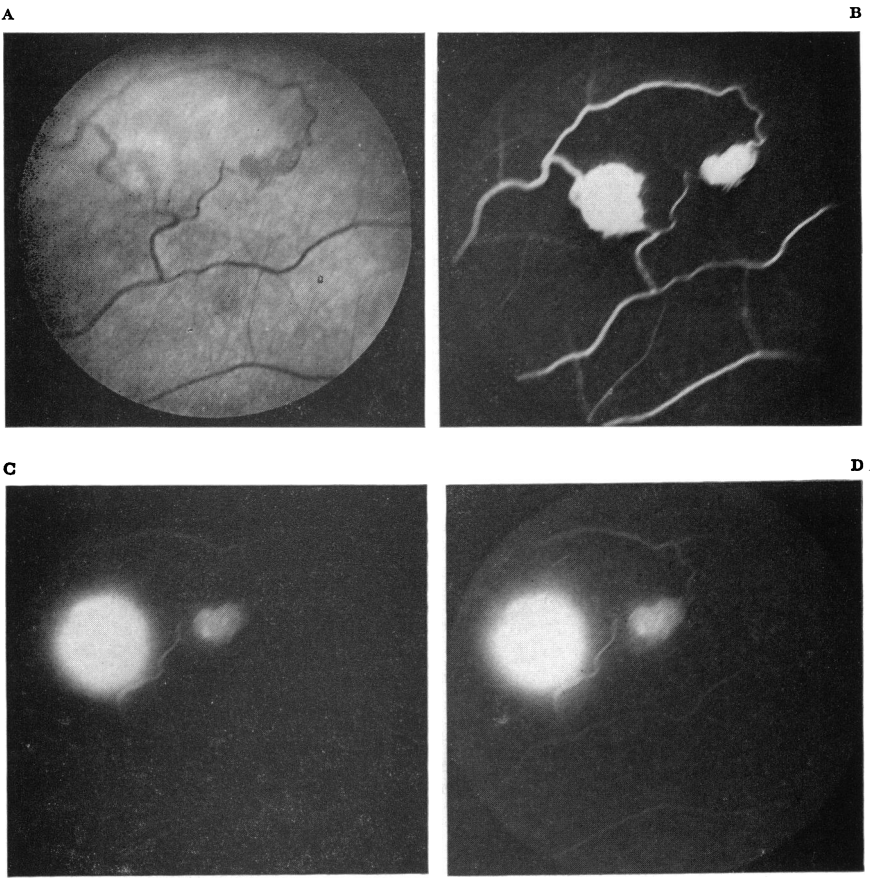

FIGURE 9

A: fundus photograph of angiomas in arcade arrangement in left eye of Case IV-8. B, C, D, are sequential fluorescein photographs. Note diffusion of fluorescein into the vitreous from the proximal tumor.

the pattern of the choroidal vascular channels. Intravenous fluorescein failed to show any fluorescence either by direct observation or photographically. Examination by direct ophthalmoscopy and contact lens failed to disclose any feeder vessels (Figure 11). The fact that it was of red color seemed to indicate that blood was entering into it, perhaps through adjacent capillaries, or that the hemangioblastoma cells were undergoing hemopoeisis as shown by Roussy and Oberling[85] in the central nervous system. The eye was followed and recently the area has developed fine feeder vessels and now fills with fluorescein (Figure 12). This case would therefore seem to indicate that there may not be a developmental aber-

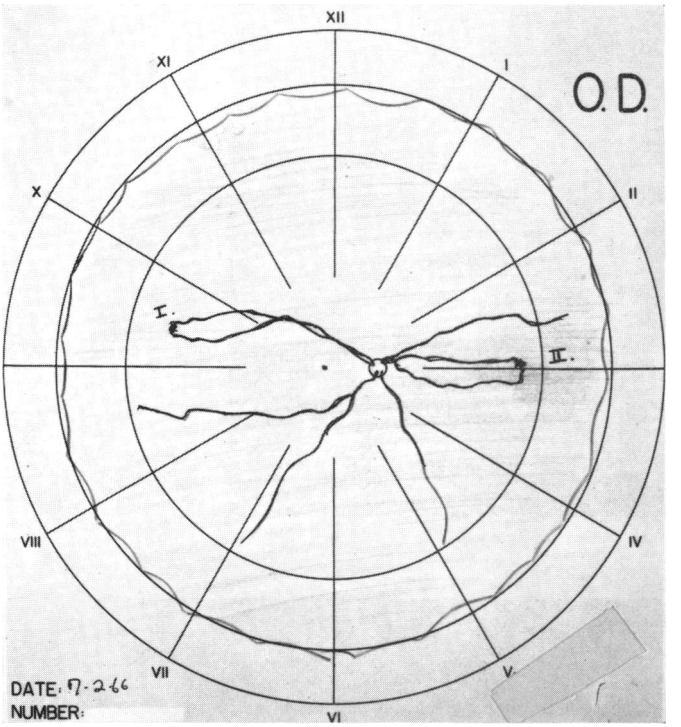

FIGURE 10
Schematic retinal drawing of right eye of Case IV-8 depicting very early angiomatosis retinae. The lesions (I and II) appeared as capillary clusters.

ration of entire vascular units as suggested by many authors,[67,78] but that the feeder vessels develop in response to growth of the angioma.

CASE IV-9. This 14-year-old sister, also without ocular complaint, showed in her right eye a lesion which without a family history of von Hippel-Lindau disease would be passed off as of no consequence. She has been seen in July 1966, and again in July 1968, without change. The lesion is a small greyish white retinal elevation in the midperiphery at 10:30 o'clock (Figure 13). There are no feeder vessels and the lesion does not fluoresce. One can only speculate as to the nature of this lesion, but follow up study may provide an answer.

CASE III-11. This 30-year-old sister of Case III-7, and aunt of the children in Generation IV, was the patient who had a complete ophthalmologic evalution at my insistance, as she resided out of state. In spite of the realization of a strong family history of von Hippel-Lindau disease and careful examination of the fundi through dilated pupils, the patient was

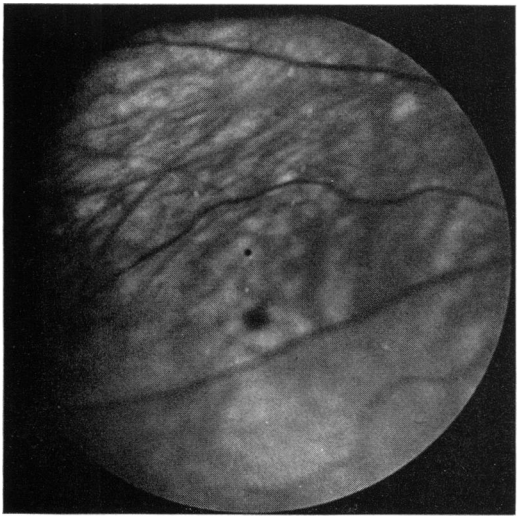

FIGURE 11A
Case IV-5, right eye, small reddish nodule in mid-periphery at 8 o'clock (small black dot is an artifact). No demonstrable feeder vessels.

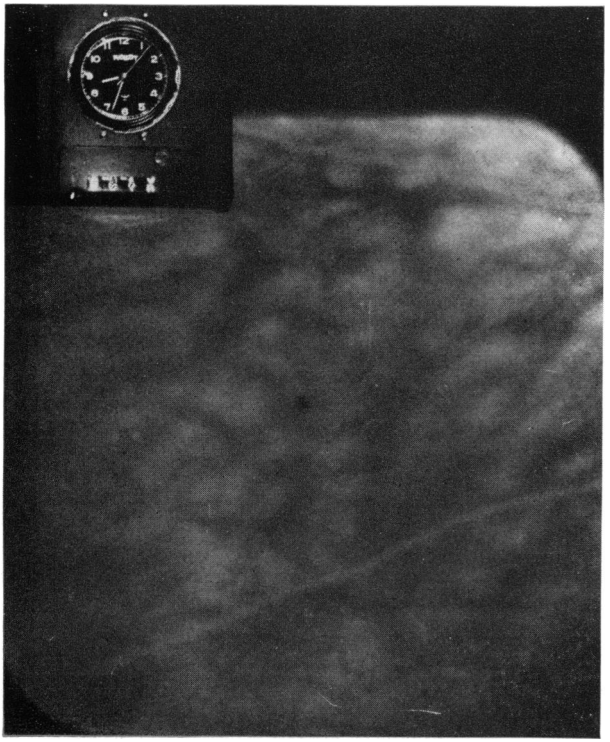

FIGURE 11B
Fluorescein photograph failed to reveal fluorescence in this area.

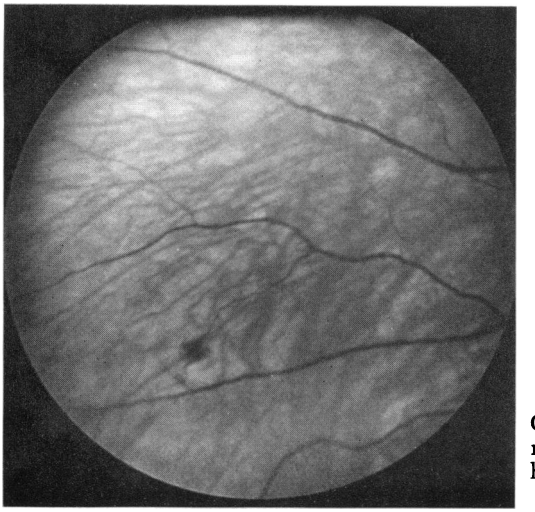

FIGURE 12A
Case IV-5, right eye, small reddish nodule one and one-half years later. Lesion now reveals fine feeder vessels.

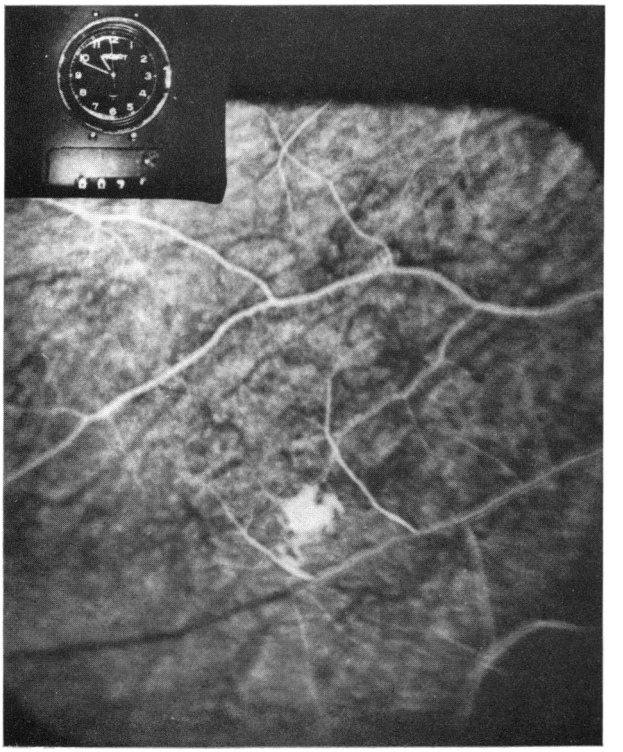

FIGURE 12B
Fluorescein angiography confirms arteriole and venule feeding small angiomatous lesion. Note vein peripheral to entrance of efferent feeder venule has not yet filled with fluorescein.

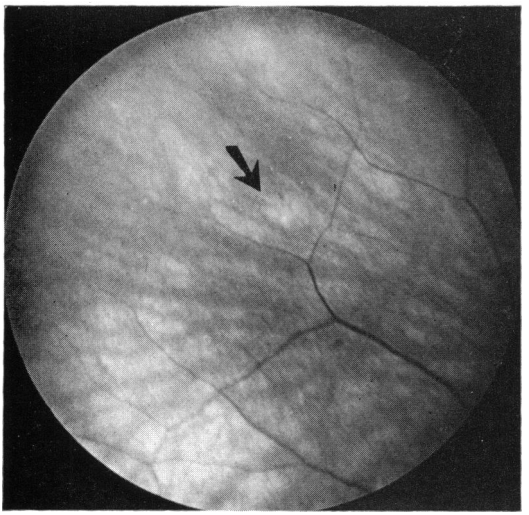

FIGURE 13

Case IV-9, right eye, small greyish white retinal elevation near equator at 10:30 o'clock. No feeder vessels and no fluorescence.

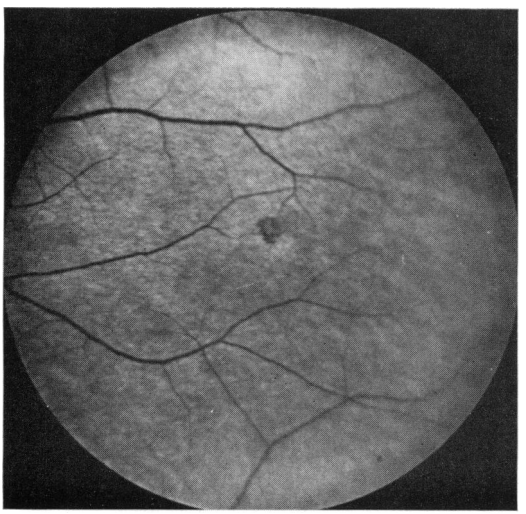

FIGURE 14A

Case III-11, right eye, very small angiomatous cluster in nasal mid periphery.

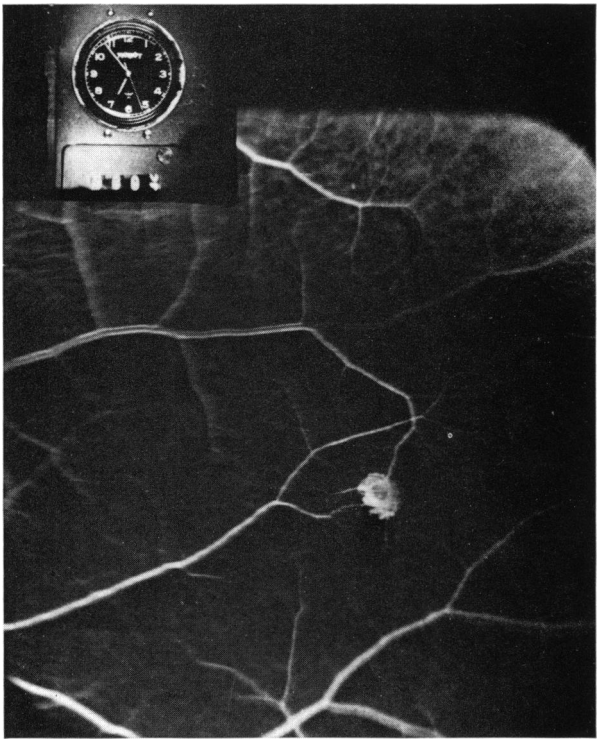

FIGURE 14B
Fluorescein photograph of above lesion.

told she had a negative examination. A few months later she came to Baltimore and was examined at the Retina Clinic by indirect ophthalmoscopy both before and after the injection of intravenous fluorescein. In the nasal midperiphery at 4 o'clock in the right eye there was a small angiomatous cluster between afferent and efferent vessels which were not enlarged (Figure 14). This case again stresses the importance of indirect ophthalmoscopy in the diagnosis of early lesions. Recently Jesberg et al.[86] have reported on incipient lesions and have demonstrated a small angioma in a flat mounted retina after trypsin digestion. This report lends further support to my emphasis on the importance of early diagnosis.

These examples of early lesions are important and would seem to justify a change in the clinical classification of Stage I in this disease. It would seem reasonable in light of our improved techniques of observation of the fundus to classify Stage I as small angiomatous capillary clusters or tumors with normal sized afferent and efferent vessels showing fluorescence following injection of intravenous fluorescein. Indeed, from Case IV-5 and perhaps Case IV-9, we may speak of preclinical lesions without feeder vessels or fluorescence demonstrated by fluorescein angiography.

TREATMENT

It is obvious from a review of the literature as well as a study of the patients in our own pedigree that a majority of eyes harbouring a capillary hemangioblastoma go on to blindness if left untreated. The question of treatment is of paramount importance in spite of the rare report of spontaneous regression.[87] (I have had the fortune of observing a 24-year-old patient at the Walter Reed Army Hospital with a positive family history of von Hippel-Lindau disease who shows the spontaneous regression and obliteration of angiomas in both fundi. These areas which are replaced or surrounded by circumscribed pigmented scars led me to inquire, when I first observed the patient, as to when he had been treated.)

In the early literature treatments were nondefinitive and of no benefit, but are of interest historically. Alperin,[88] in 1926, suggested foreign protein therapy while Armstrong,[89] in 1937, presented a case with bilateral ocular involvement that had been treated with "intravenous salvarsan, tuberculin calcium gluconate, and x-ray treatments to the head" six years previously. At the time of his report the patient was pregnant and underwent cesarean section on recommendation by the ophthalmologist who felt that the dilated and diseased vessels might not withstand the vascular strain of spontaneous labor. In recent years (1961) Thomas and Burnside[90] have reported the use of CVP or Duo-CVP (citrus bioflavonoid compound and ascorbic acid) in the treatment of five of their patients. They state that there was no increase in the activity of the lesions for three years.

Up to the present report there are five methods which have been advocated for the treatment of angiomatosis retinae: (1) roentgen (x-ray) irradiation, (2) radium (radon seeds) irradiation, (3) electrolysis, (4) diathermy, and (5) Zeiss photocoagulation.

ROENTGEN (X-RAY) IRRADIATION

In 1919, Houwer[91] reported x-ray therapy of an advanced case of angiomatosis without success. Similarly Erggelet,[92] in 1920, was unsuccessful, but again the case was advanced. In 1940, Cordes and Hogan[57] reported the treatment of a typical retinal angioma by x-ray therapy of 1202 r. At the end of seven months the tumor was reduced in size as were the exudates. The vessels remained the same. Three and one-half years following the irradiation[93] the vision remained good, the exudates were gone, and the vessels were somewhat re-

duced. In 1943, Cordes and Dickson[93] reported, in addition to the previous case, another case with bilateral involvement. The right eye showed advanced disease while in the left eye there was a peripheral angioma. Each eye received 1800 r over a three-week period in February and March 1941. Twenty-two months later the right eye showed more detachment while the lesion in the left was smaller. In July 1943, the right eye was the same while the left eye lesion seemed a little larger. Therefore an additional 2000 r were given to the left eye in August 1943. The patient was next seen in January 1952, or 11 years after the first x-ray treatment.[94] The right eye was blind while the left eye had normal vision. The fundus picture of the left eye was unchanged from the previous examination except that there was now a new lesion. In 1942, Ballantyne[49] reported a case which received 4750 r four months after he had used radon seeds with a total dose of 4000 to 5000 r. Two years later the eye was lost from hemorrhage and glaucoma. In 1943, McGovern[95] reported a 13-year-old girl with bilateral lesions. Each eye received 1500 r. Following x-ray therapy the right eye remained the same while vision in the left eye decreased, and the disease progressed. He concluded that the unfavorable results of x-ray therapy would suggest the use of surface diathermy and micropuncture or localized radium therapy.

RADIUM (RADON SEEDS) IRRADIATION

Holm,[96] in 1917, used radium on two cases and stated that the tumors regressed. In 1935, Foster Moore[97] presented two cases of angiomatosis retinae. Both cases were essentially one-eyed patients as their other eye was almost blind from the disease. The first case he treated in 1932, with three 5.1 mc seeds sutured to the sclera and left in place for ten days. Six months later there was no evidence of angioma and the vessels supplying the lesion were obliterated. The second case, in 1933, was treated with one seed of 2.5 mc over each of two angiomas and left in place four days. The upper lesion responded rapidly, but the lower required three months to show obliterative scarring. In 1931, Traquair[98] applied 80 mgm of radium to the orbital rim for twelve and one-half hours and two months later he inserted 15 mgm under the conjunctiva for seventy-two hours. One and one-half years later it was reported that the vessels were smaller and the tumor more fibrotic. Although the treatment of these patients was initially successful they later developed cataracts.[99] In 1938, McDonald and Lippincott[100] presented a case in which radium

was used to no avail, but again the eye had advanced disease with retinal detachment. In 1941, Staz[101] also reported unsuccessful treatment of a very advanced case by means of radium needles. He suggested treatment by diathermy according to the technique of Weve.

SUMMARY OF IRRADIATION FOR ANGIOMATOSIS RETINAE

To summarize the effects of irradiation as a form of treatment for angiomatosis retinae we may state that neither radium nor x-ray is effective in advanced cases. In early angiomas the use of radon seeds sutured over the lesion is effective in obliterating the lesion, but late complications of cataracts may be expected. X-ray treatment of early lesions may also regress the tumor although once again one risks the dangers of irradiation cataract and damage to retinal blood vessels leading to vitreous hemorrhage. It would appear that these techniques, although of some value at one time, have given way to methods such as diathermy and photocoagulation which directly attack the angiomatous tumors without causing remote or delayed damage to other portions of the eye.

ELECTROLYSIS

In 1928, Collins[102] speculated on the use of electrolysis as a possible form of therapy. He stated that an insulated electrolysis needle could be passed across the vitreous cavity under observation with the ophthalmoscope and inserted into the tumor. In 1930, he[103] again mentioned this treatment, but this time felt that one should insert the needle into the tumor through the sclera overlying it. He felt that the exact spot could be determined by "the ingenious technique devised by Gonin for ascertaining the position of a hole in a detached retina." In 1936, Neame[104] tried this method. He noted difficulty in perforating the sclera, but stated that an effect of treatment was obtained as mottled pigmentation near the tumor. In 1948, he[99] concluded his report and noted that treatment with electrolysis was unsuccessful. He too leaned toward diathermy as the treatment of choice.

DIATHERMY

In 1939, Weve[105] in presenting the Bowman lecture on diathermy in ophthalmic practice mentioned an important use of diathermy in treating angiomatosis retinae and was able to report a cure two and one-half years after operation. He mentioned that his colleague, Professor Rochat, had also treated a case. Weve felt that surface

diathermy would be effective in early cases while penetrating diathermy for advanced cases seemed advisable. In 1941, Kaye[106] reported two cases treated by Stallard by a combination of katholysis, surface, and penetrating diathermy. Katholysis had been used for localization and treatment of the large feeder vessels, and it is worthy of note that no hemorrhage occurred. In 1943, Lewis[107] reported a case successfully treated with diathermy punctures. In discussing this paper Fralick[108] reported a case of his own treated successfully by diathermy in April 1941, or seven months prior to Lewis' treatment. Guyton and McGovern[109] also reported a successfully treated case in 1943. In 1957, Vail[74,75] reported an interesting case which he had treated with diathermy punctures in June 1946. Eleven years later the patient had good vision and there was no recurrence of the angioma. It is important to note that no new lesions had occurred. In addition to the case report, Vail presented the results of his survey of the literature for cases treated with diathermy. He was able to assemble 47 eyes treated with diathermy either as an initial treatment or as a final form of therapy. Treatment was successful in 33 eyes or 70 per cent. In this group seventeen eyes showed postoperative hemorrhage and of these, five were failures. Transudative detachment of the retina was mentioned in eight eyes following treatment. Most of the cases reported received both surface and penetrating diathermy. Only the tumor was treated in the majority of cases, and when the feeder vessels were treated there was occasionally a severe intraocular hemorrhage.[99] Following successful treatment it was noted that the feeder vessels returned to normal size and lost their tortuosity while the lipid deposits which were present gradually disappeared. Vail pointed out the advantage of diathermy over radium, x-ray, or electrolysis to be (1) ease of use, (2) little or no damage to unaffected parts of the eye, (3) little delayed or remote damage to the eye, (4) familiarity on the part of the surgeon with instrumentation, (5) the ability to use surface as well as penetrating punctures, (6) the ability to observe the fundus during treatment, (7) no danger of producing cataract, and (8) a higher percentage of cures. Thus with the introduction by Weve in 1939, diathermy became the method of choice for the next twenty years. With the development of photocoagulation by Meyer-Schwickerath a new, and in many cases, improved form of therapy became available.

ZEISS PHOTOCOAGULATION

In 1949, Meyer-Schwickerath[110] developed the technique of photo-

coagulation. His early machines utilized a variety of light sources including the sun itself. When the Zeiss light coagulator was developed in the 1950s, with the Xenon tube as its source of energy, one now had an excellent method for treating a whole array of fundus lesions with a destructive chorioretinitis. In addition to fulfilling the eight points enumerated by Vail for diathermy, photocoagulation demonstrates certain advantages over diathermy which include (1) treatment without surgical intervention, (2) a safer procedure in many cases (eg. treatment of lesions lying along the long posterior ciliary nerve and artery, or over the region of a vortex ampulla), (3) ultra precise localization of treatment and the ability to control the treatment under direct observation, (4) the ability to perform repeated treatments without the problem of scleral necrosis, etc. (ideal for posterior pole lesions), and (5) a psychological advantage to the patient. Meyer-Schwickerath[111] pointed out three main complications in photocoagulation of these lesions, (1) ablatio fugax – a transudative detachment of the retina which comes on shortly after treatment and is related to the size of the tumor treated and the intensity of treatment (the detachment may be total – personal observation), (2) hemorrhage – hyperemia and small hemorrhages usually appear in and on the surface of the coagulated tumor whereas large hemorrhages are probably due to coagulation of a large vessel, (3) circulatory embarrassment – lipid deposits in the macula and around the angioma is a well known phenomenon; however, following therapy with photocoagulation lipid may appear in a previously unaffected part of the fundus such as the macula and lead to diminution of vision. These deposits gradually reabsorb as the angioma is destroyed. The angioma should be destroyed gradually, by treatments to the tumor only, to prevent "blow out necrosis" of the large feeder vessels. To reduce the complications from transudative detachments, hemorrhage, or lipid deposits in the macula one should always plan a multistage procedure and individual treatments should not be too intense.

Worthy of note is a case treated by photocoagulation by Dupont Guerry et al.[112] in 1957. This case is of interest in that it was a central lesion and was treated successfully by an experimental machine using a carbon arc source. It is also the first case treated in the United States. In 1961, Locke[113] also treated a central angioma and Baras et al.,[114] in 1964, were successful in treating multiple angiomas.

LASER PHOTOCOAGULATION

With the demonstration of laser action in 1960, the ruby laser was soon

developed as a clinical tool and received great notoriety in the press; however, because its source was a ruby crystal (694 mM – not absorbed by blood) and its lesion was produced by a pulse, its use for the treatment of vascular lesions was not as efficacious as for the treatment of retinal tears and other fundus lesions. L'Esperance[115] pointed out that angiomas were not effectively treated by the use of ruby laser coagulation. The argon ion laser, however, which is now in its developmental stage may prove to be an effective mode of therapy since it is a continuous wave emitter and its wave lengths are in the blue-green part of the spectrum (absorbed by hemoglobin).

SUMMARY OF TREATMENT BY ELECTROLYSIS, DIATHERMY, AND PHOTOCOAGULATION

When Gonin,[116] in 1919, demonstrated that the successful treatment of retinal detachment required incorporation of the retinal break into a chorioretinal scar, the search began for the best technique and instrumentation to produce this adhesive chorioretinitis. Thus ignipuncture, chemical cautery, electrolysis, and diathermy were develepod. Various investigators soon saw that these modalities could also be used to destroy certain fundus lesions. Collins, in 1930, suggested that electrolysis be used to treat angiomatosis retinae, which could be localized by the "ingenious technique of Gonin." Neame tried electrolysis in 1935, but it was not until Weve, in 1939, reported success with diathermy that an electrosurgical approach was deemed feasible and the treatment of choice for angiomatosis retinae. Over the next tweny years, great success was obtained with diathermy, and Vail found a figure of seventy per cent success on reviewing the literature. With the development of photocoagulation by Meyer-Schwickerath, an ideal form of treatment came into being which combined all the advantages of diathermy with the ability to treat without surgical intervention. Laser photocoagulation with all its publicity was not ideal for treatment because of its ruby source and pulsed lesion. Therefore, Zeiss photocoagulation became the treatment of choice with diathermy backing it up for use in advanced cases.

TREATMENT IN PRESENT STUDY

ZEISS PHOTOCOAGULATION

Experience had been obtained with the use of photocoagulation in several patients with moderate to large-sized angiomas prior to the present study. In November 1963, treatment was undertaken for a

large angioma in the right eye of a nineteen-year-old white male (Figure 15). This tumor required a series of three photocoagulations at six- to eight-week intervals to destroy the lesion, and graphically illustrates the complications referred to by Meyer-Schwickerath in the treatment of large tumors. Following the first treatment, in spite of only five applications of photocoagulation (regular load 1, image field 4.5 degrees) to the angioma, a total detachment (ablatio fugax) developed. This detachment gradually disappeared over the next ten days; however, following this there was a deposition of lipid material both around the shrinking tumor as well as the appearance of one exudate in the macula just above the fovea. The vision which was initially 20/20 fell to 20/40. Several weeks after the initial treatment the artery had almost returned to normal size, while the vein remained somewhat engorged. Following two subsequent treatments the area of angioma was reduced to a chorioretinal scar, and both the feeder vessels appeared of normal size. The lipid gradually reabsorbed and one year after initial treatment the vision had returned to 20/30+3. When the patients in our present pedigree were discovered with very early angiomatous lesions it was obvious that photocoagulation was the treatment of choice for the obliteration of this retainal disease with a minimal risk of complications.

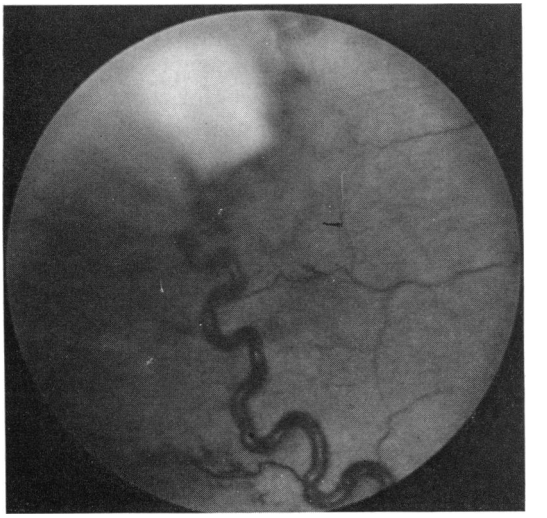

FIGURE 15

Classic ophthalmoscopic picture of angiomatosis retinae. Angioma in temporal periphery of the right eye of a 19-year-old white male.

CASE REPORTS

CASE IV-8. This is the 18-year-old brother of our initial case whose disease was picked up on routine examination (see also under section on Early Lesions). The right eye contained two very early lesions, one temporally and one nasally. On August 20, 1966, these lesions were treated with photocoagulation under local anesthesia. The Zeiss machine was set at regular load 1 and the image field diaphragm at 4.5 degrees. One photocoagulation spot was placed on the nasal lesion (Figure 16) and two on the temporal

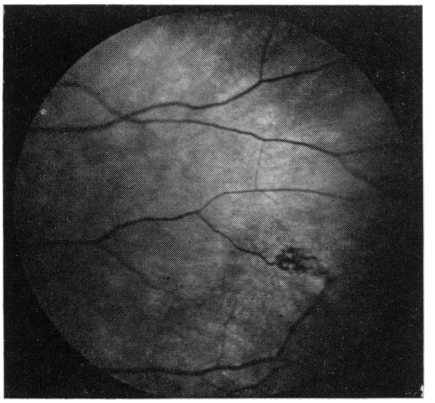

FIGURE 16A
Case IV-8, right eye, photograph of very early angiomatous lesion in nasal periphery.

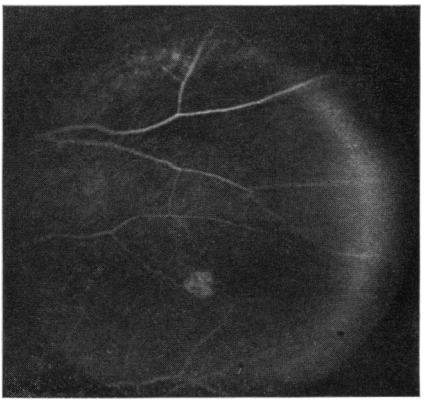

FIGURE 16B
Fluorescein photograph of same lesion.

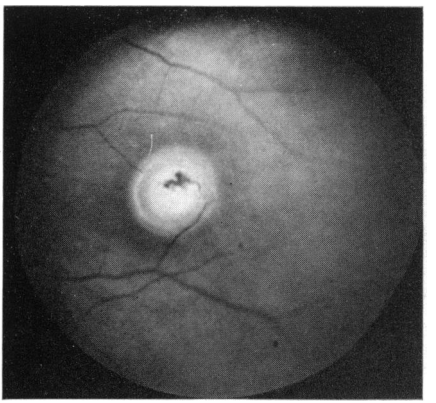

FIGURE 16C
Appearance of lesion following Zeiss photocoagulation.

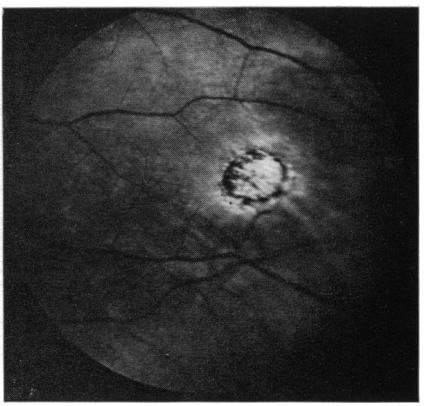

FIGURE 16D
Photocoagulation scar two years later; lesion is obliterated.

lesion (Figure 17). Both lesions healed without complication and in August 1968, there was no recurrence and the vision in the right eye was 20/15. The left eye showed a more advanced situation, but still quite early as far as standard classification is concerned. In this eye there was a double lesion in arcade arrangement, the proximal lesion forming a definite nodule while the distal lesion was still an angiomatous capillary cluster. This complex required a two-stage treatment. The first in July 1966, and the second in November 1966. Following the first treatment, there was a localized transudative detachment which appeared within the first hour after treatment and disappeared in three days. The distal lesion was completely eradicated

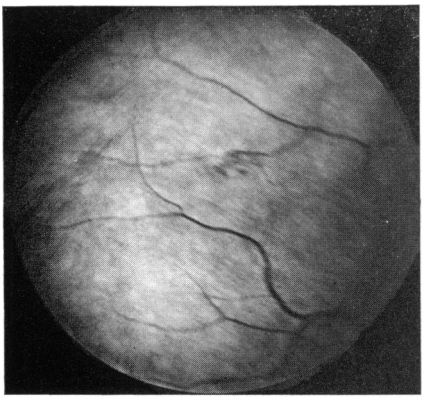

FIGURE 17A
Case IV-8, right eye, very early angiomatous lesion in temporal periphery.

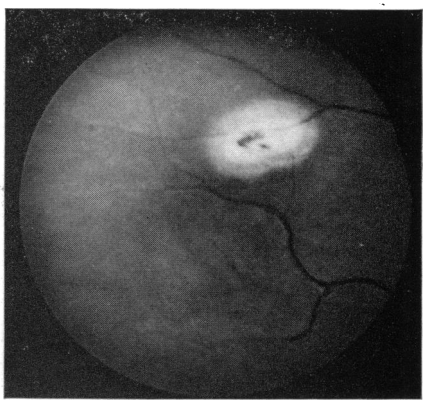

FIGURE 17B
Following two photocoagulation burns.

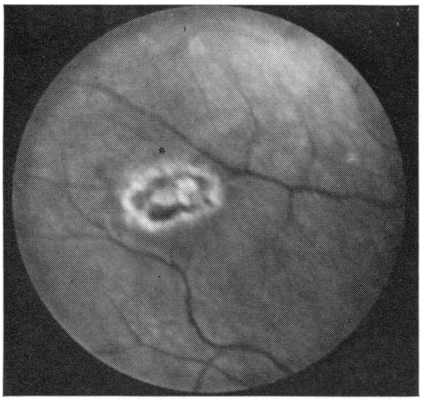

FIGURE 17C
Healed lesion.

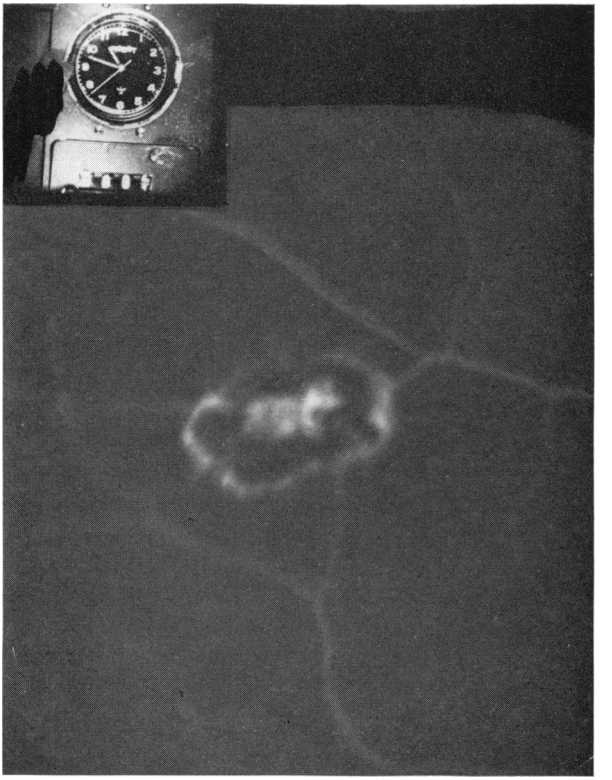

FIGURE 17D
Fluorescein photograph two years after treatment showing scar at site of previous angiomatous lesion.

after the first treatment. A two-year follow up shows obliteration of the lesions and a vision in the left eye of 20/15 (Figure 18).

CASE IV-5. The 21-year-old brother of the above case. The left eye showed a double lesion in arcade arrangement. The large distal tumor was treated by cryotherapy (see section on Cryotherapy). The proximal lesion was an angiomatous cluster lesion which was obliterated by one course of photocoagulation in March 1967.

CASE III-11. The 30-year-old aunt of the previous cases. The right eye showed a very early angiomatous cluster lesion. This was treated with photocoagulation in December 1967. Follow up examination in June 1968, showed no recurrence.

CASE IV-7. Our original case, this 15-year-old child with bilateral advanced disease had two small angiomas in the right eye treated with photocoagulation with obliteration after one treatment (see section on Cryotherapy).

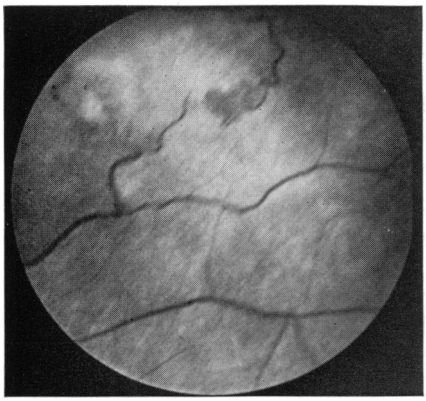

FIGURE 18A
Case IV-8, left eye, double lesion in arcade arrangement.

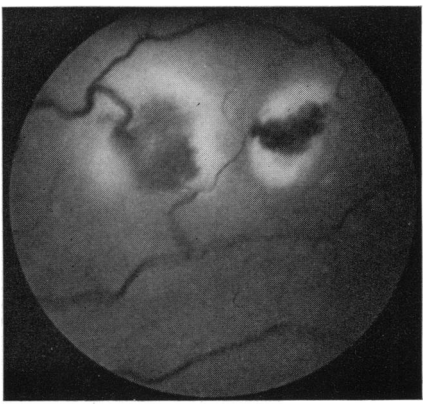

FIGURE 18B
A few hours after photocoagulation. Note localized transudative detachment (ablatio fugax).

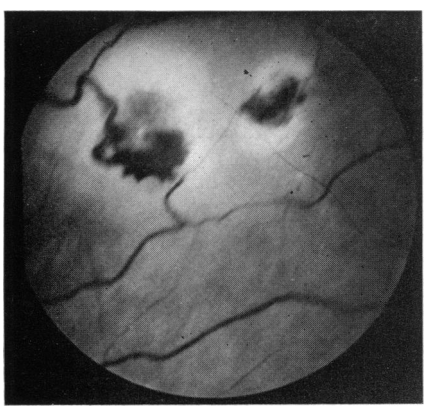

FIGURE 18C
Four days after photocoagulation. Transudative detachment gone.

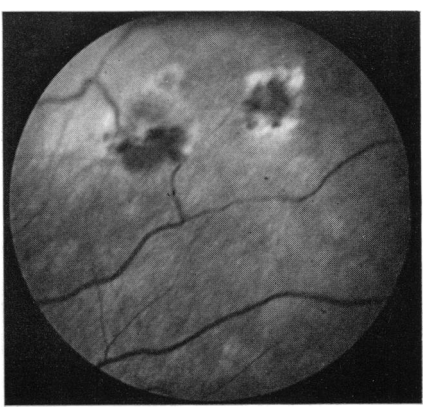

FIGURE 18D
Eight weeks after photocoagulation. Peripheral lesion obliterated. Residual angioma present in proximal lesion.

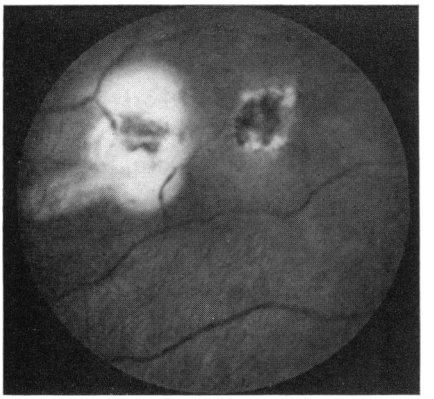

FIGURE 18E

Four months following initial photocoagulation. Proximal area retreated.

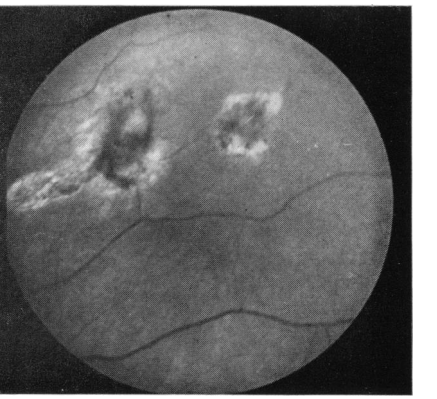

FIGURE 18F

Resultant scar one month following treatment.

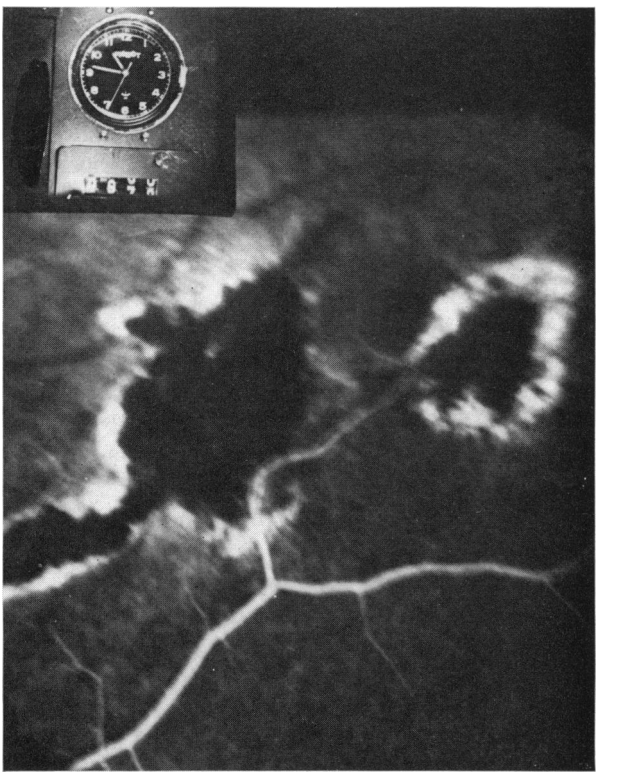

FIGURE 18G

Fluorescein photograph shows obliteration of angioma two years following treatment.

SUMMARY OF PHOTOCOAGULATION FOR EARLY LESIONS

Zeiss photocoagulation is the treatment of choice for very early angiomatous lesions. These areas may be easily eradicated by a single treatment with one or two photocoagulation burns, and there is little danger of complication from ablatio fugax (transudative detachment), hemorrhage, or lipid deposition. Slightly larger angiomatous lesions may develop a localized ablatio fugax following treatment, but this is of short duration. Additional photocoagulation may be necessary for the more advanced early lesions. Follow up examination with intravenous fluorescein enables one to follow the state of obliteration of the angioma and is helpful in decisions concerning retreatment.

CRYOTHERAPY FOR ANGIOMATOSIS RETINAE

BACKGROUND

In 1961, there was the rebirth of cryosurgery in ophthalmology when Krwawicz[117] described its use in cataract surgery. This technique, which was soon to revolutionize cataract surgery, stimulated an investigation of the literature. It was found that Scholer,[118] in 1918, had reported the experimental production of chorioretinitis with carbon dioxide snow. In 1933, both Deutschmann[119] and Bietti,[120–122] had successfully used carbon dioxide snow to produce adhesive chorioretinitis and cure retinal detachments. This was carried forth by others such as Cavara,[123] but soon fell into disuse when Weve popularized the technique of diathermy. Interest in cryogenics, however, was going on in different fields and in this country Fay,[124] in 1936, attempted to induce low temperature in the brain to destroy malignant tumors. When Cooper,[125] in 1961, reported successful cryogenic neurosurgical procedures an added impetus was given to the advocates of cryotherapy. Kelman and Cooper[126,127] further added interest in this new field with both ophthalmologic and neurosurgical articles. In 1962, Lincoff and McLean[128] began the use of cryotherapy for retinal detachment work and reported this in 1964. This set the trend of cryosurgery for retinal detachments and led Norton[129] to predict in 1965, that cryosurgery would replace diathermy in retinal surgery. Today his prediction has partially been fulfilled. What of its ability to destroy fundus lesions such as those treated by diathermy and photocoagulation? It has been demonstrated histologically[130] that the main effect of a "standard" cryo lesion used for retinal detachments (i.e. −40° C to −50° C) is on the retinal cells, secondarily on the choriocapillaris, and least of all on the large retinal and choroidal

vessels. The sclera as well as the conjunctiva and extraocular muscles (when treated transconjunctivally) are essentially undamaged by freezing. These facts permit a method of treatment without surgery (transconjunctival application) which makes its use similar to photocoagulation. It is of added interest that there is great similarity in the histopathology of two lesions. From the knowledge of histological aspects of the lesion, Lincoff[131] attempted cryosurgery for retinoblastoma and was successful. Rubin[132] also reported success in the treatment of patients with retinoblastoma. Lincoff,[133] however, was unsuccessful in the treatment of a von Hippel-Lindau angioma. When he applied very low temperatures (−90° C to −120° C) to metastatic carcinoma or malignant melanoma, the reaction to the cryo was so great that the eye was lost from vitreous retraction and retinal detachment. Shea[133] stated that cryotherapy "cannot be used to sclerose vascular lesions such as angiomatosis retinae." Jesberg,[86] in 1968, reported a large peripheral angioma which was initially treated with photocoagulation, but was unsuccessful because of the extreme peripheral location. He next performed cryotherapy, but this also had no significant effect on the tumor. These reports then were discouraging for the use of cryotherapy in the treatment of vascular abnormalities of the fundus.

PRESENT STUDY

Prior to seeing the initial case in this study, I had become interested in the use of transconjunctival cryotherapy for the treatment of various fundus lesions. The basis for this interest was the successful transconjunctival treatment of retinal tears without detachment. It was noted that the tear could be treated easily, often with only local anesthetic drops (Ophthaine). The cryoprobe acts as a scleral depressor and with indirect ophthalmoscopy was much easier to use than photocoagulation for tears anterior to the equator. The cryoprobe in fact could be used to treat areas at the level of the vortex ampullae without opening the conjunctiva. Thus in my hands cryotherapy gradually replaced photocoagulation in the treatment of retinal tears located at the equator or anteriorly. As in all new techniques, treatment was often excessive and it was noted that cases frozen and refrozen in the same area showed much more chorioretinal destruction than with a single freeze. In spite of these obviously overtreated areas there was no hemorrhage or vitreous contraction as had been observed by Lincoff with very low temperatures (−90° C to −120° C). We, of course, were utilizing considerably higher temperatures, in the range of

−60° C to −70° C. Cahan[134] has noted that repetition of the cycle of freezing and thawing is one of the criteria for producing cryonecrosis of tissues, and Chenoweth and Appleton[135] had observed that a preliminary freeze at a higher temperature (−50° C) may protect against hemorrhage from a subsequent low-temperature freeze (−80° C). Based on these observations various fundus lesions were treated at temperatures ranging from −60° C to −80° C using repetitive freeze and thaw cycles and repeated treatments.

PROCEDURE

Most of the treatments by cryotherapy were performed transconjunctivally. When the lesion was too far posterior to reach without opening the conjunctiva, photocoagulation was performed. As some patients complained of discomfort with only ophthaine drops, the majority of patients were given a local anesthetic of 2 per cent xylocaine by the technique of van Lint and by retrobulbar injection. Three types of cryosurgical units were used, (1) the Linde CE-3 (Linde Division, Union Carbide Corp, Indianapolis, Indiana) using liquid nitrogen as the source of freezing. This unit was necessary when we wished to deliver a probe-tip temperature of −80° C, and the unit also had the advantage of having a recorder for documentation of probe temperatures, (2) the Kelman Retinal Cryopexie Unit (Frigitronics, Inc, Bridgeport, Conn.) using liquid Freon with a probe-tip temperature of approximately −60° C and, (3) the Amoils Cryosurgical Unit (Keeler Optical Products – Dynatech Corp, Cambridge, Mass.) using carbon dioxide gas and having a probe-tip temperature of −70° C. All lesions were treated by repetitive freezing and thawing with the probe in the same position for at least two or three cycles.

All treatments were clinically monitored using indirect ophthalmoscopy and the lesions were noted to be within the resultant ice ball before thawing was begun. Most lesions were treated initially at higher temperatures (−60° C to −70° C) while subsequent treatments were as low as −80° C. The end point of treatment was based on the clinical appearance of the fundus lesion as well as its appearance following intravenous fluorescein. Various types of fundus lesions were treated including the vascular lesions of Eales's disease. Coats's disease, and Sickle Cell Hemoglobin C disease as well as certain inflammatory diseases (toxoplasmosis and "pars planitis"). With the appearance of patients with angiomatosis retinae, the repetitive freeze-thaw cycle technique was attempted to see if it would be effective in this disease.

CASE REPORTS

CASE IV-7. This 15-year-old white female was the initial case seen in the pedigree. In May 1966, the right eye showed a vitreous hemorrhage which partially obscured the fundus. It was noted that enlarged vessels led inferiorly to an indistinct angioma at 6:30 o'clock near the equator.

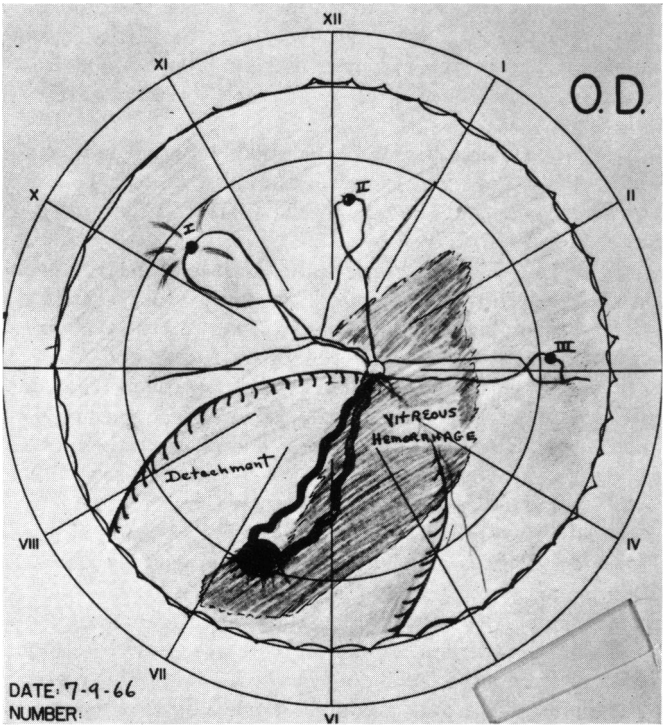

FIGURE 19
Schematic retinal drawing showing large inferior angioma with retinal detachment extending into the macula. Three small angiomas above.

There appeared to be some retinitis proliferans from the surface of the tumor and some retinal detachment surrounding the base of the angioma. The vision was 20/20 with difficulty. By July 1966, the detachment had extended into the macula and the vision was reduced to 12/200 (Figure 19). The patient was operated on for a detachment with repeated freeze and thaw cycles in the region of the tumor. A 5-mm silastic sponge exoplant was sutured in place from 5 to 8 o'clock and drainage was per-

formed at 8 o'clock. Following the procedure there was a good buckle and the retina was reattached. The vision returned at 20/40. Subsequently, three small angiomas were noted in the superior fundus. The more posterior were photocoagulated while a peripheral lesion, at 3 o'clock, was treated with cryotherapy. Because this tumor was very small an initial treatment of three freeze-thaw cycles was performed at –58°C with the Linde Unit. In spite of a good chorioretinal scar which almost obscured the tumor, fluorescein angiography clearly demonstrated that the tumor had been little affected (Figure 20). A subsequent freeze at –70°C showed marked reduction in the size of the angioma. Recent follow up of the right eye two and one-half years postoperatively reveals a vision of 20/40 and all lesions quiescent.

The left eye when examined in May 1966, revealed a vision of 4/200, showed four retinal angiomas, a swollen optic disk, and heavy deposition of lipid in the macula and throughout the fundus (Figure 21). Treatment was begun in June 1966.

10 o'clock lesion: This angioma, quite large and near the ora serrata, showed a classic picture with dilated tortuous feeder vessels going to a large well circumscribed tumor. On 18 June 1966, this angioma was treated transconjunctivally by the repetitive freeze and thaw technique for three cycles at –70°C. Immediately postoperatively the angioma became very hyperemic and there was only localized transudation of fluid around the tumor. The tumor gradually shrank and the vessels showed reduction in size. In August 1966, the lesion was refrozen with the Linde Unit at –80°C, and following this the angioma was replaced by a chorioretinal scar and the vessels appeared completely normal (Figure 22).

11 o'clock lesion: This small tumor was destroyed by photocoagulation in July 1966.

1 o'clock lesion: This large angioma with retinitis proliferans from its surface and some detachment around its base was treated on four occasions by cryotherapy from June 1966 to July 1967, using the repetitive freeze and thaw technique. The area gradually scarred down although the vessels have remained somewhat tortuous.

4 o'clock lesion: This large angioma was unusual in that it was not well outlined and appeared to be buried in the substance of the retina. Fluorescein angiography graphically illustrates the arterial and venous circulation (Figure 2). Since this lesion was posterior to the equator and difficult to reach with cryotherapy it was treated by photocoagulation on several occasions. Following each treatment ablatio fugax developed.

One year following therapy to these angiomas the lipid had disappeared from the macula and the vision was 20/100 (Figure 23). There was some persistent detachment around the 4 o'clock lesion. This increased in size by November 1967. Therefore, in February 1968, this area was treated with surface and penetrating diathermy. Following this the fluid disappeared and the lesion appeared well treated. Now, two and one-half years

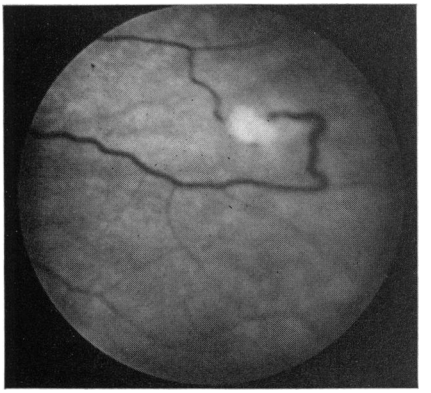

FIGURE 20A

Case IV-7, right eye, photograph of 3 o'clock lesion.

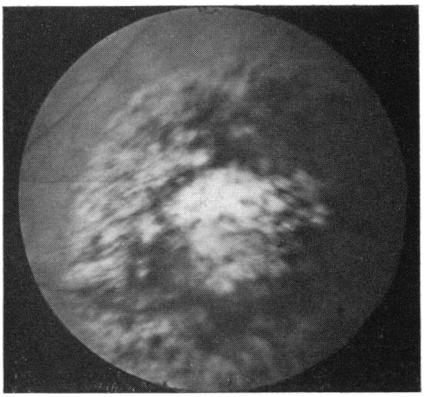

FIGURE 20B

Three o'clock lesion following three freeze-thaw cycles at −58° C.

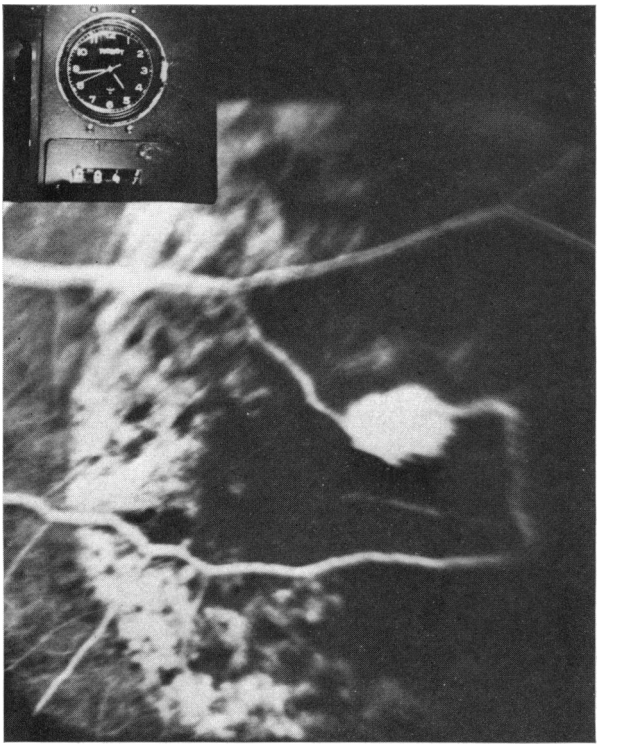

FIGURE 20C

Fluorescein photograph showing that lesion has been little affected by freezing.

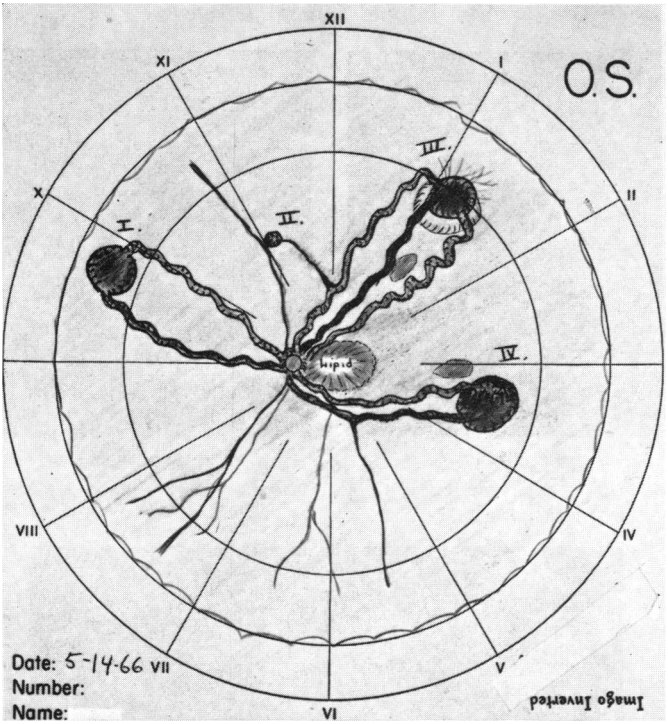

FIGURE 21

Case IV-7, left eye, schematic retinal drawing showing fundus with multiple angiomas, swelling of the disk and lipid in the macula.

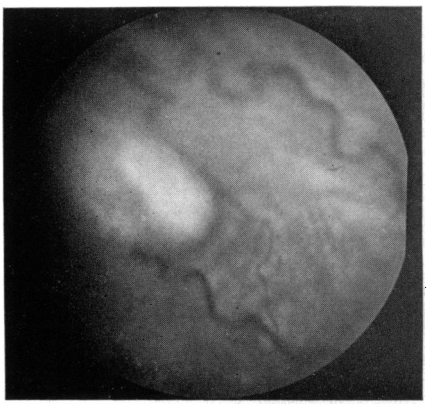

FIGURE 22A

Case IV-7, left eye, 10 o'clock angioma. Classic appearance with dilated and tortuous feeder vessels.

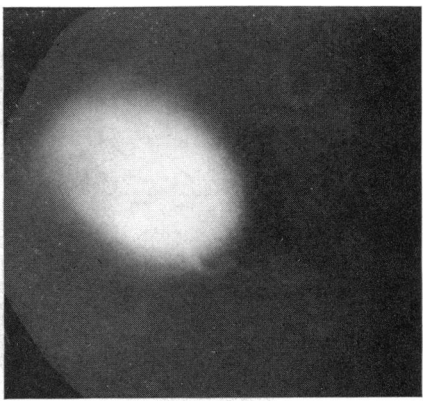

FIGURE 22B

Late fluorescein photograph showing diffusion of fluorescein into the vitreous.

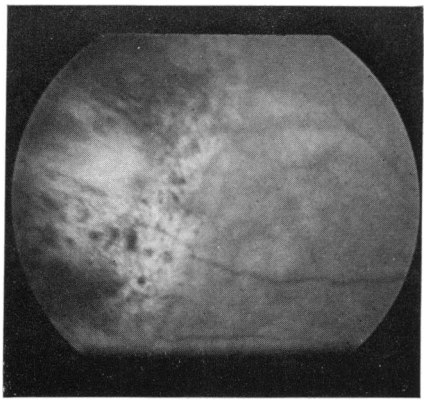

FIGURE 22C

Two years following cryotherapy by repetitive freeze-thaw method. Note tumor is reduced to gliotic area and vessels are of normal size.

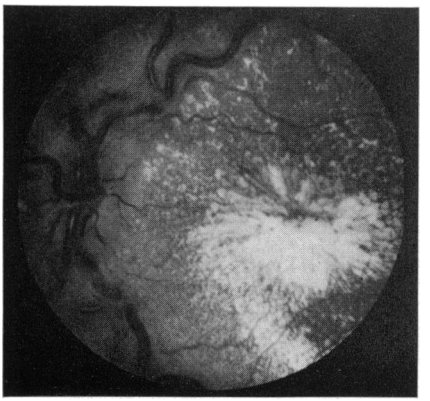

FIGURE 23A

Case IV-7, left eye. Heavy lipid deposition in the macula.

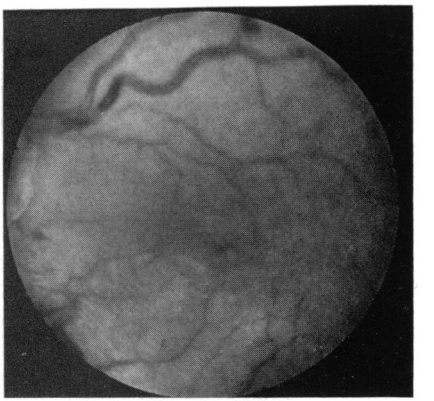

FIGURE 23B

Case IV-7, left eye. One year following therapy the lipid has completely disappeared.

following initial therapy, the left eye remains 20/100 with no lipid or fluid and all lesions quiescent.

CASE IV-5 was seen in March 1967, and as previously described, the left eye showed a double arcade lesion (Figure 24). The small proximal cluster was obliterated by photocoagulation. The large peripheral tumor seemed an ideal case for treatment with cryotherapy. First, it was near the ora serrata which would make photocoagulation very difficult. Second,

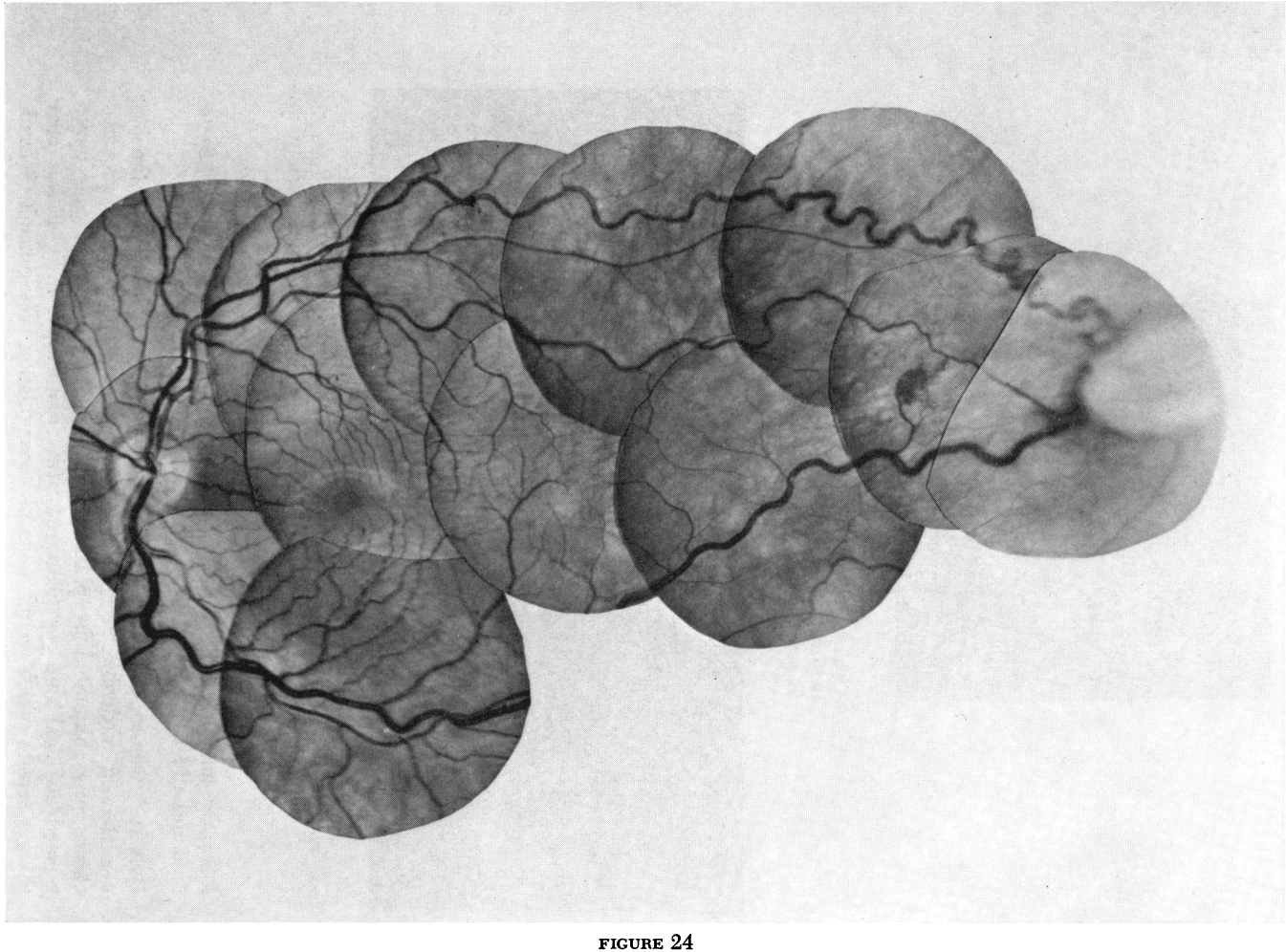

FIGURE 24

FIGURE 24

Case IV-5, left eye, photograph showing two peripheral angiomas arranged in channel or arcade fashion. Proximal lesion an angiomatous cluster and peripheral lesion a large tumor.

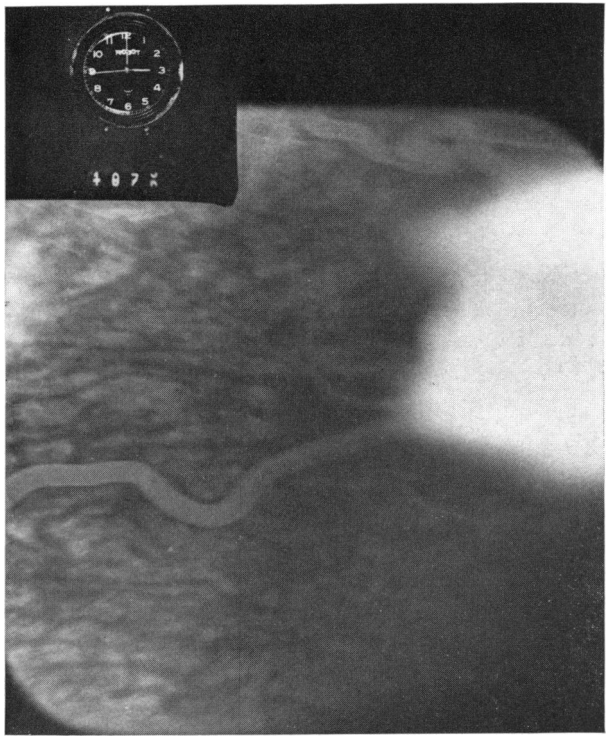

FIGURE 25A

Fluorescein photograph of large angioma in Case IV-5 prior to therapy.

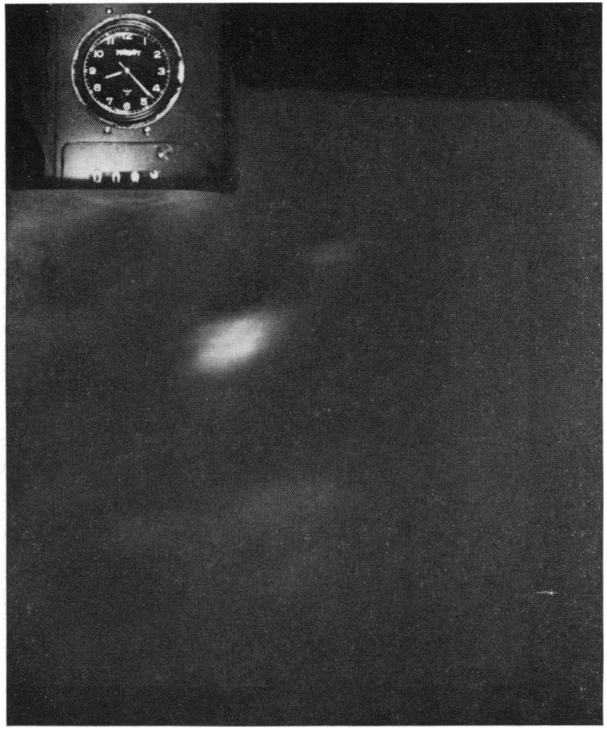

FIGURE 25B

Fluorescein photograph showing area of large angioma following cryotherapy.

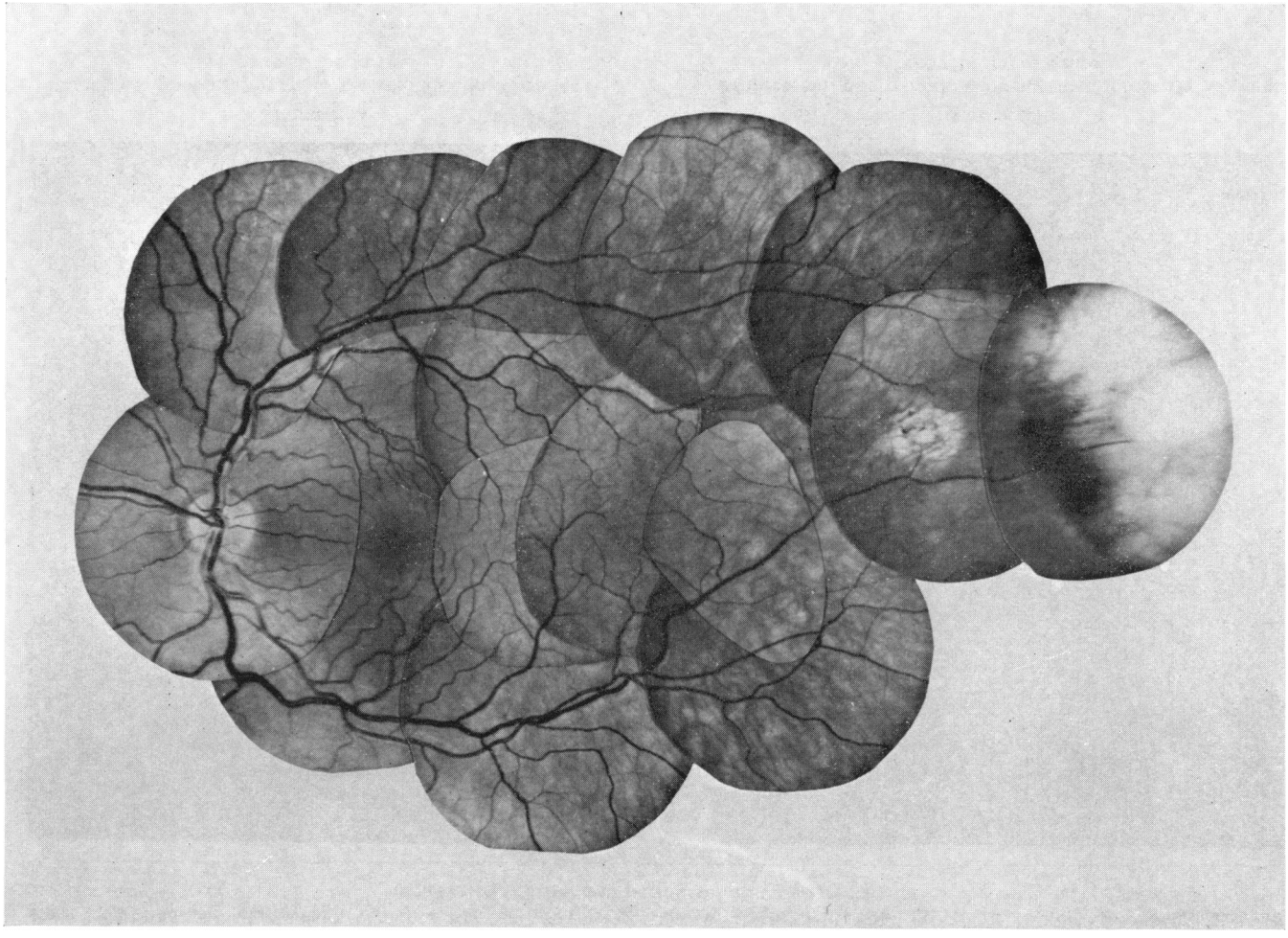

FIGURE 26

it was near the area of the long posterior ciliary nerve and artery which would make diathermy punctures hazardous both from the aspect of hemorrhage as well as the possibility of producing anterior segment atrophy on that side. Furthermore, diathermy treatment would require either removing or working under the lateral rectus muscle. The lesion was therefore treated with cryotherapy over the next year with three courses of treatment. Each treatment session consisted of 3–4 repetitive freezes and thaws at temperatures between –60°c to –80°c. Following the initial treatment there was only localized hyperemia and ablatio fugax. After the second freeze there was some hemorrhage on the surface of the tumor. The vision has remained 20/20 and no lipid was found throughout the course of treatment. In spite of the return of the vessels to normal size following the second treatment, a third course of freezing was given to the small nubbin of tissue which remained and which showed filling with fluorescein. Although there is still a small area in the scar which fluoresces (Figure 25) the lesion seems to be successfully treated (Figure 26).

From the previous cases it would seem that cryotherapy may be effective in the treatment of angiomatosis retinae if the areas are treated by the repetitive freeze-thaw technique, the temperature is cold enough, and if repeated treatments are carried out. We have been using temperatures as low as –80°c without any adverse reactions in the vitreous and without significant hemorrhage. Reaction in large tumors seems much less to cryo than to photocoagulation, thus reducing the danger from ablatio fugax and post treatment lipid deposition. This form of therapy seems ideal for peripheral angiomas which may be frozen through conjunctiva and muscle without damaging them. The response of the angioma to treatment may be relatively rapid as in the 10 o'clock lesion of Case IV-7 or more gradual as in the lesion in Case IV-5. This may depend on the cellular make up of the lesion and how much glial tissue is present. Even though small, angiomas do not respond to relatively high-temperature freezes (−58° c) after only one treatment (Case IV-7).

Because of my interest in this form of therapy I have suggested its use and technique to several of my colleagues. I am gratified to note that a recent article by Amoils and Smith[136] confirms my results on destruction of retinal angiomas by cryotherapy.

FIGURE 26

Case IV-5, left eye, one and a half years following therapy. The proximal lesion was treated with photocoagulation. The large peripheral angioma was treated on three occasions with cryotherapy using the repetitive freeze-thaw technique. Note return of vessels to normal size.

SUMMARY AND CONCLUSIONS

1. The fascinating syndrome of von Hippel-Lindau disease is reviewed and provides interest for those in almost every branch of medicine. It is a prime example of the all too infrequent but highly desirable union of the various medical specialties.
2. A large pedigree has been assembled from the chance referral of one patient with angiomatosis retinae. An insight into various genetic aspects of this hereditary disease is gained, and a graphic illustration of the phenomena of gene penetrance, expressivity, and specificity is provided.
3. The importance of improved techniques of examination in the recognition of retinal pathology is well exemplified by the use of indirect ophthalmoscopy and fluorescein angiography in the study and observations of early angiomatosis retinae.
4. Very early retinal angiomatous lesions are presented which appear as capillary clusters between normal sized retinal arteries and veins. It would seem warranted to reclassify Stage I to include these early lesions.
5. The evolution of an angiomatous lesion from an area of non-fluorescence without demonstrable feeder vessels to a classic early lesion with afferent and efferent vessels illuminated by fluorescein angiography is presented. This case would seem to support those who feel that the feeder vessels form in response to the growth of the hemangioblastoma.
6. Recognition of early lesions permits easy treatment with Zeiss photocoagulation with little danger of complication.
7. Cryotherapy may be effective in the treatment of angiomatosis retinae if the angiomas are treated by the repetitive freeze-thaw technique, the temperature is cold enough, and if repeated treatments are carried out.
8. Cryotherapy appears to be especially well suited for the treatment of peripheral angiomas by the transconjunctival approach.
9. The value of diathermy should not be forgotten and it should be kept in reserve for advanced disease and lesions which may not respond to photocoagulation and cryotherapy.

In conclusion it is worthy of note that although von Hippel-Lindau disease has been recognized as a clinical entity for almost half a century, its popularity as a subject for study continues unabated. We are continuing to discover new and interesting facets of this disease with our advances in both therapeutic and diagnostic instrumenta-

tion and technique. With a look at the past and a glance into the future, let us remember that technology is only as advanced as the mind that applies it.

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