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and
Minnesota Medical Foundation

The Retina in Systemic Hypertension

Volume XIX | Friday, April 9, 1948 | Number 21

BULLETIN OF THE
UNIVERSITY OF MINNESOTA HOSPITALS
and
MINNESOTA MEDICAL FOUNDATION

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UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
CALENDAR OF EVENTS

Visitors Welcome

April 12 - April 17, 1948

No. 198

Monday, April 12

9:00 - 9:50 Roentgenology-Medicine Conference; L. G. Rigler, C. J. Watson and Staff; Todd Amphitheater, U. H.

9:00 - 10:50 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff; Interns' Quarters, U. H.

9:15 - Fracture Rounds; A. A. Zierold and Staff; Ward A, Minneapolis General Hospital.

10:00 - 12:00 Neurology Ward Rounds; A. B. Baker and Staff; Station 50, U. H.

11:00 - 11:50 Physical Medicine Conference; Conduction Pathways in the Central Nervous System; Berry Campbell; E-101, U. H.

11:00 - 11:50 Roentgenology-Medicine Conference; Staff; Veterans' Hospital.

11:00 - 12:00 Cancer Clinic; K. Stenstrom and D. State; Eustis Amphitheater, U. H.

12:15 - 1:20 Obstetrics and Gynecology Journal Club; M-435, U. H.

12:50 - 1:20 Pathology Seminar; Multiple Myelomas; Robert Brietenbacher; 104 I. A.

12:30 - 1:30 Physiology Seminar; Chronic Hyperventilation in Normal Human Subjects; E. B. Brown, Jr., 214 M. H.

12:30 - 1:50 Surgery Grand Rounds; A. A. Zierold, Clarence Dennis and Staff; Minneapolis General Hospital.

1:30 - 2:30 Pediatric-Neurological Rounds; R. Jensen, A. B. Baker and Staff; U.H.

2:00 - 3:00 Surgery Problem Case Conference; C. Dennis and Staff; Small Class Room, General Hospital.

4:00 - 5:00 Pediatric Seminar; The Congenital Heart; T. Hall; 6th Floor Seminar Room, U. H.

4:00 - 5:00 School of Public Health Seminar; Subject to be announced; Dr. Wilson G. Smillie, Cornell University; 113 MeS.

5:00 - 6:00 Urology-Roentgenology Conference; D. Creevy and H. M. Stauffer and Staffs; M-515, U. H.

Tuesday, April 13

8:30 - 10:20 Surgery Seminar; Lyle Hay; Small Conference Room, Bldg. I, Veterans' Hospital.

9:00 - 9:50 Roentgenology Pediatrics Conference; L. G. Rigler, I. McQuarrie and Staff; Eustis Amphitheater, U. H.

10:30 - 11:50 Surgical Pathological Conference; Lyle Hay and Robert Hebbel; Veterans' Hospital.

12:30 - 1:20 Pathology Conference; Autopsies; Pathology Staff; 102 I. A.

2:00 - 2:50 Dermatology and Syphilology Conference; H. E. Michelson and Staff; Bldg. III, Veterans' Hospital.

3:15 - 4:20 Gynecology Chart Conference; J. L. McKelvey and Staff; Station 54, U. H.

3:30 - 4:20 Clinical Pathological Conference; Staff; Veterans' Hospital.

4:00 - 5:30 Surgery-Physiology Conference; O. H. Wangensteen and M. L. Visscher; Eustis Amphitheater, U. H.

4:00 - 5:00 Pediatric Rounds on Wards; I. McQuarrie and Staff; U. H.

5:00 - 5:50 Roentgenology Diagnosis Conference; J. Richards Aurelius and Staff of Ancker Hospital; M-515, U. H.

8:00 - P.M. Clinical Research Club; Pulmonary Hypertension in Cardiac Disease; Results of Right Heart Catheterization, Craig Borden; Treatment of Leukemia with Urethane, Howard L. Horns; Eustis Amphitheater, U. H.

Wednesday, April 14

8:00 - 8:50 Surgery Journal Club; O. H. Wangensteen and Staff; M-515, U. H.

8:30 - 12:00 Neurology Rehabilitation and Case Conference; A. B. Baker and Joe R. Brown; Veterans' Hospital.

11:00 - 11:50 Pathology-Medicine-Surgery Conference; Chronic Myelogenous Leukemia; O. H. Wangensteen, C. J. Watson and Staff; Todd Amphitheater, U. H.

4:00 - 5:00 Infectious Disease Rounds; Todd Amphitheater, General Hospital, Veterans' Hospital.

Thursday, April 15

8:15 - 9:00 Roentgenology-Surgical-Pathology Conference; Walter Walker and H. M. Stauffer; M-515, U. H.

8:30 - 10:20 Surgery Grand Rounds; Lyle Hay and Staff; Veterans' Hospital.

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; Todd Amphitheater, U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:30 - 11:50 Surgery-Radiology Conference; Daniel Fink and Lyle Hay; Veterans' Hospital.

11:00 - 12:00 Cancer Clinic; K. Stenstrom and D. State; Eustis Amphitheater, U. H.

11:30 - 12:30 Clinical Pathology Conference; Steven Barron, C. Dennis, George Fahr, A. V. Stoesser and Staffs; Large Class Room, General Hospital.

12:00 - 12:50 Physiological Chemistry Seminar; Antinvasin in the Development of Malignant Diseases; Erick Hakanson; 214 M. H.

1:00 - 1:50 Fracture Conference; A. A. Zierold and Staff; Minneapolis General Hospital.

4:00 - 4:50 Bacteriology Seminar; Subject to be announced; 129 M.H.

4:30 - 5:20 Ophthalmology Ward Rounds; Erling W. Hansen and Staff; E-534, U. H.

5:00 - 5:50 Roentgenology Seminar; Parotid Tumors: A Review of 93 Cases; M. J. Smith; M-515, U. H.

Friday, April 16

8:30 - 10:00 Neurology Grand Rounds; A. B. Baker and Staff; Station 50, U. H.

9:00 - 9:50 Medicine Grand Rounds; C. J. Watson and Staff; Todd Amphitheater, U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:30 - 11:20 Medicine Grand Rounds; Staff; Veterans' Hospital.

10:30 - 11:50 Otolaryngology Case Studies; L. R. Boies and Staff; Out-Patient Department, U. H.

11:00 - 12:00 Surgery-Pediatric Conference; C. Dennis, A. V. Stoesser and Staffs; Minneapolis General Hospital.

11:30 - 12:50 University of Minnesota Hospitals General Staff Meeting; Ewing's Bone Sarcoma; David Nelson; New Powell Hall Amphitheater.

12:00 - 1:00 Surgery Literature Conference; Clarence Dennis and Staff; Minneapolis General Hospital, Small Class Room.

1:00 - 1:50 Dermatology and Syphilology; Presentation of Selected Cases of the Week; H. E. Michelson and Staff; W-312, U. H.

1:00 - 2:50 Neurosurgery-Roentgenology Conference; W. T. Peyton, Harold O. Peterson and Staff; Todd Amphitheater, U. H.

Saturday, April 17

7:45 - 8:50 Orthopedics Conference; Wallace H. Cole and Staff; Station 21, U. H.

8:00 - 9:00 Pediatric Psychiatric Rounds; Reynold Jensen; 6th Floor West Wing, U. H.

8:00 - 9:30 Psychiatry and Neurology Grand Rounds; Staff; University Hospitals.

9:00 - 10:30 Pediatric Grand Rounds; I. McQuarrie and Staff; Eustis Amphitheater, U. H.

9:00 - 9:50 Surgery-Roentgenology Conference; O. H. Wangensteen, L. G. Rigler, and Staff; Todd Amphitheater, U. H.

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; M-515, U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; M-515, U. H.

10:00 - 12:50 Obstetrics and Gynecology Grand Rounds; J. L. McKelvey and Staff; Station 44, U. H.

11:00 - 12:20 Anatomy Seminar; The Use of Vital Staining in the Study of Liver Injury; W. Lane Williams: Alteration of the Glucose Tolerance Curve in White Rats Receiving Sub-diabetogenic Doses of Alloxan; David Molander; 226 I. A.

II. THE RETINA IN SYSTEMIC HYPERTENSION

John P. Wendland

Introduction

For almost a century ophthalmologists have been peering into the fundus in cases of hypertension for the express purpose of analysing the changes observed. The subject has been of interest not only to ophthalmologists but also to physicians in almost every specialty. In spite of tremendous strides in the knowledge of the fundus changes in hypertension, certain key links in the pathogenesis of the subject are yet unsolved and because of this, differences of opinion have arisen. The interpretation of the fundus changes will be presented from the standpoint of opthalmology. A consideration of the changes in the uniquely accessible retinal blood vessels in vascular disease leads to conclusions and suggestions which may be of importance in the interpretation of vascular disease in general. Naturally such conclusions based on the study of a single organ are tentative and at all times they should be weighed in with the overall picture.

It should be stated at the outset that it is now felt the elevation of systemic blood pressure is the most important factor concerned in the production of retinal alterations in all of the various classified hypertensive diseases[1,2]. Thus, the same retinal picture may be present in primary and secondary hypertension. For this reason, the rare forms of secondary hypertensive disease will not be discussed as they give no distinctive picture. However, since much can be learned concerning the duration, severity and prognosis of the condition in the more common hypertensive states, namely, primary hypertension, glomerulonephritis and toxemia of pregnancy, these will be dealt with separately in a later section of the paper. In these conditions the fundus examination will at times be helpful also in the diagnosis. When such is the case, however, it is not because of the presence of distinctive lesions but because of the distinctive grouping of the lesions present. In other words, it is not because of characteristic lesions but because of the combination and special configuration of lesions, that the diagnosis may be made.

Ophthalmoscopically Visible Lesions Occurring in the Retina in Systemic Hypertension.

Before taking up the more complicated features of retinal arteriolar disease such as appearance of the retina in the various types of hypertension, let us simply list the various lesions occurring in the retina in hypertension without regard to their sequence of occurrence or significance.

1. Generalized narrowing of arterioles with or without sclerosis. If there is no sclerosis there is simply a diminution in caliber with a slight reduction in the light reflex. Grading of the degree of constriction is essential for proper following of the case. The grading to be suggested for this lesion and others to follow is that recommended in 1946 by the Committee on Classification of Hypertensive Disease of the Retina of the American Ophthalmological Society[2]. In Grade 1 generalized narrowing, the arterioles are reduced to 1/2 the caliber of the veins. In Grade 2, the caliber of the arterioles is 1/3 the caliber of the veins. In Grade 3, the caliber of the arterioles is 1/4 the caliber of the veins and in Grade 4, the arterioles are thread-like or invisible (Table I). In generalized sclerosis, the grading is as follows: Grade I sclerosis shows widening and increased brightness of the light reflex, slight depression of veins at arteriolovenous crossings with reduction in visibility of the underlying veins. Grade 2 sclerosis shows a coppery color to the arterioles, definite depression of the underlying veins at arteriolovenous crossings, widening of the arteriolovenous crossing spaces and almost complete invisibility of the veins where they lie beneath the arterioles. Grade 3 sclerosis shows a silver color to the arterioles, depression of veins at arteriolovenous crossings and distal dilatation of the veins, widening of arteriolovenous crossings, right angled arteriolovenous crossings and complete invisibility of those portions of the veins which underlie the crossing arter-

Table I

GRADING OF GENERALIZED NARROWING OF ARTERIOLES

Grade 1 -- arterioles reduced to 1/2 the caliber of the veins
Grade 2 -- arterioles reduced to 1/3 the caliber of the veins
Grade 3 -- arterioles reduced to 1/4 the caliber of the veins
Grade 4 - arterioles thread-like or invisible

Recommended by the Committee on the Classification of Hypertensive Disease of the Retina of the American Ophthalmological Society, 1946.

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ioles. Grade 4 sclerosis shows the arterioles visible only as white fibrous cords, without blood stream (Table II).

Table II

GRADING OF GENERALIZED SCLEROSIS OF ARTERIOLES

Grade 1 -- widening and increased brightness of the light reflex, slight depression of the veins at a-v crossings, with reduction in visibility of the underlying veins.

Grade 2 -- copper color to arterioles, definite depression of veins at a-v crossings, widening of a-v crossings, and almost complete invisibility of the veins where they lie beneath the arterioles.

Grade 3 -- silver color to arterioles, depression of veins at a-v crossings and distal dilatation of the veins, widening of a-v crossings, right angled a-v crossings and complete invisibility of those portions of the veins which underlie the crossing arterioles.

Grade 4 -- arterioles visible only as white fibrous cords without blood column.

Recommended by the Committee on the Classification of Hypertensive Disease of the Retina of the American Ophthalmological Society, 1946.

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2. Focal constriction with or without focal sclerosis.

This term refers to the localized constrictions of the retinal arterioles seen so frequently especially in severe hypertensive disease. The grading of areas of focal constriction is on the basis of the ratio of the diameter of the focal area to the proximal segment of the arteriole. Grade I localised narrowing is narrowing to 2/3 caliber of proximal segment of arteriole. Grade 2 is 1/2 the caliber of proximal segment of arteriole. Grade 3 is 1/3 the caliber of proximal segment of arteriole. Grade 4 is a localized area of narrowing of such degree that the arteriole is invisible (Table III). There is no satisfactory grading for focal sclerosis as yet. Focal sclerosis is felt to be present when there is marked increase of the light reflex and the vessel appears opaque[3] in the area of focal constriction. It is, however, difficult to recognize and must be surmised some-

Table III

GRADING OF FOCAL CONSTRICTION OF ARTERIOLES

Grade 1 -- narrowing to 2/3 the caliber of proximal segment.
Grade 2 -- narrowing to 1/2 the caliber of proximal segment.
Grade 3 -- narrowing to 1/3 the caliber of proximal segment.
Grade 4 -- narrowing of such extent that the narrowed area is invisible.

Recommended by the Committee on the Classification of Hypertensive Disease of the Retina of the American Ophthalmological Society, 1946.

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times from the presence of generalized retinal arteriolosclerosis.

3. Focal sclerosis of veins.

This occurs only at the arteriolovenous crossings and constitutes part of the arteriolovenous crossing phenomena. Generalized venous sclerosis does not occur in hypertension and when present means diabetes mellitus.

4. Arteriolar or venous occlusion.

5. Sheathing of retinal vessels.

6. Cotton wool patches.

7. Snow bank exudates around the disc.

8. Hard exudates.

9. Retinal and vitreous hemorrhages.

10. Retinitis proliferans.

11. Flat detachment of the retina.

12. Papilledema.

Correlation of the Ophthalmoscopic Picture Present with the Character of the Hypertension

The retinal picture observed varies with the acuteness of onset of the hypertensive process, its duration and its severity. The age of the patient and other unknown factors also contribute to the type of lesions found. Unfortunately, there is no standard terminology applied to the retinal picture. However, the old term "albuminuric retinitis", which was introduced at a time when it was felt the albuminuria and retention of nitrogenous waste products was necessary for the production of the retinal lesions, has been replaced by terms more descriptive of present day ophthalmological thought, such as angiospastic retinitis (Volhard[4]), (Wagener[5]), arteriospastic retinitis (Elwyn[6]) and hypertensive retinopathy (Gifford[7]).

Normal retinal arterioles are found in hypertension which is mild in degree, of fairly recent onset, and of great lability[8]. This type of hypertension is exemplified by the early stages of essential hypertension. Mild generalized narrowing of the arterioles (Grade 1 or 2) is seen in moderate hypertension of gradual onset and of relatively non-progressive character. No focal constrictions are present. If the hypertension is of some duration mild generalized retinal arteriolosclerosis (Grade 1 or 2) is present. Only rarely is any type of retinopathy present such as hard exudates and hemorrhages. If the hypertension is progressive in character, moderate to severe and of some duration, there will be in addition to generalized narrowing and sclerosis of the arterioles, focal constrictions. Hemorrhages and exudates are quite common in this type of hypertension. If the hypertension is of sudden onset and severe, we find no sclerosis but generalized narrowing, focal constrictions and usually cotton wool patches, hemorrhages and edema of the retina. This type of hypertensive retinopathy

is illustrated by the severe toxemias of pregnancy but may also be seen in glomerulonephritis in which a sudden elevation of blood pressure has occurred and in primary hypertension of abrupt onset. This form of retinopathy has been called by Wagener, "acute angiospastic retinitis without sclerosis"[5]. When the retinal picture has in addition generalized arteriolosclerosis and papilledema, the hypertension is in the terminal malignant phase from the clinical standpoint. A macular star, snowbank exudate around the disc, cotton wool patches, retinal hemorrhages, retinitis proliferans, and venous and arterial occlusions may all be present though they need not be.

It should be emphasized that although the retinopathy present is of considerable value in determining the type of hypertension present, the changes in the arterioles are of perhaps even greater significance. Narrowed vessels with no generalized arteriolosclerosis means hypertension of recent onset. Generalized arteriolosclerosis means hypertension of some duration. The presence of both focal constrictions and generalized narrowing means a progressive hypertension. The degree of narrowing of the retinal vessels parallels fairly well the height of the blood pressure[9,10,11]. There are two exceptions to this last statement which should be borne in mind, however, in judging the systemic blood pressure from the appearance of the retinal vessels. In young people the degree of constriction lags behind the height of the blood pressure[3] and in elderly people slight narrowing of the retinal arterioles may be present with no elevation of blood pressure[12]. The reasons for these discrepancies are not definitely known. Possibly in young persons the more labile pressures frequently found may account for the difference. In elderly persons Wagener[12] believes that senescent changes in the arteriolar walls lead to decreased transparency and apparent narrowing of the blood column. Friedenwald[13] believes that in elderly persons atherosclerotic lesions occurring in the central retinal artery partially obstruct the circulation in the retinal vessels leading to a reduction in their pressure and consequent narrowing. A word of caution is also necessary in interpreting areas of focal sclerosis. These areas in elderly people, say past the age of 60, may be occasionally caused by atherosclerosis. When such is the case, they are not indicative of past or present hypertension but rather represent the visible outposts of a more advanced atherosclerotic process occurring in the central retinal artery. These atherosclerotic lesions likewise usually occur right around the disc and never beyond the tertiary branches of the retinal arterioles[13]. In the majority of instances, however, an area of focal sclerosis in the retina in which there is no generalized narrowing of the vessels means a previous episode of hypertension.

The presence of cotton wool spots means an acute process. Hard exudates mean a process of some duration as they do not occur at the onset of a hypertension and one may be superimposed upon the other. The significance of papilledema is well known to all.

Table IV, following the Committee's classification, presents in brief form the correlation of the retinal picture with the character of the hypertension. As in all clinical classifications the more sharply the dividing lines are drawn, the more exceptions to the classification that will be found. This fault does not mean classifications are to be condemned for they are certainly necessary in understanding the overall picture; it should, however, be borne in mind in examining the table.

Pathology of the Lesions

The pathology of the retinal lesions occurring in hypertension has been quite well determined. The degree of sclerosis seen ophthalmoscopically, whether it be general or focal, parallels quite closely the degree of medial hypertrophy and hyalinization seen pathologically[13,14,15]. A copper wire vessel pathologically does not show as advanced sclerosis as a silver wire vessel nor as high a lipoid content[16]. That a few areas of focal sclerosis in the aged may represent an atheromatous process rather than an arteriosclerotic lesion has been mentioned. When such is

Table IV

CORRELATION OF RETINAL PICTURE WITH CHARACTER OF THE HYPERTENSION PRESENT

Retinal Picture	Character of Hypertension	Examples of Clinical Conditions in which Found
Normal or mild generalized narrowing of arterioles (Grade 1).	Markedly labile, mild.	Early essential hypertension.
Generalized narrowing of arterioles (Grades 1 or 2) Mild generalized arteriolosclerosis (Grades 1 or 2). No focal constrictions or sclerosis. Only occasionally any retinopathy.	Chronic and relatively non-progressive. Moderate.	Established "benign" essential hypertension
Generalized narrowing of arterioles of any grade. Generalized arteriolosclerosis of any grade. Focal constrictions and focal sclerosis (of any grade). Frequently cotton wool patches, hard exudates and hemorrhages.	Chronic and progressive. Generally higher than class above.	Some cases of essential hypertension. Many cases considered for sympathectomy fall in this class. Some cases of hypertension secondary to glomerulonephritis or other kidney disease. A few cases of toxemias of pregnancy.
Generalized narrowing of arterioles (of any grade). No generalized or focal sclerosis. Focal constrictions (of any grade). Usually edema of retina, cotton wool patches, hemorrhages.	Acute hypertension of recent onset. Progressive unless cause is removed.	Most toxemias of pregnancy fall in this class. Some cases of hypertension secondary to glomerulonephritis or other kidney disease. A few cases of essential hypertension.
Generalized narrowing of arterioles (usually grades 3 or 4). Generalized arteriolosclerosis (of any grade). Focal constrictions and sclerosis. Always papilledema. Usually edema of retina, snowbank exudate, cotton wool patches, hard exudates, hemorrhages.	Terminal "malignant" hypertension.	End stages of either primary or secondary hypertension.

the case, these areas show deposits of lipoid in the intima beneath the endothelium. Invariably there is found a much more advanced similar process in the central retinal artery. Such people are of course prone to develop central retinal artery occlusion. The arteriolovenous crossing phenomena depends on a peculiar anatomical configuration. When a vein and artery cross, the two are surrounded by a single adventitial sheath[17] and their media are in contact. Arteriolosclerosis occurring at this point affects both the arteriole and vein resulting in narrowing of the lumen of the vein. The ophthalmoscopic appearance of compression of the vein is not so much true compression of the vein by the artery as it is actual constriction of the vein by the sclerotic process involving the common artery vein coat.

The cotton wool patches generally represent edema fluid which is rich in fibrin. Edema of the retina tends to accumulate in the outer plexiform layer in the form of cystic spaces as here the supporting structure of the retina is weak. Some cotton wool patches represent ischemic infarctions of the retina brought on by occlusion of a small arteriolar branch[13]. These often though are surrounded by a zone of hemorrhages and then are spoken of ophthalmoscopically as white centered hemorrhages. Similar appearing white centered hemorrhages may be seen in subacute bacterial endocarditis, leukemias and in pernicious anemia. They have, however, a different pathologic picture in these latter diseases. Ophthalmoscopically white centered hemorrhages are not pathognomonic of any particular condition but when studied in conjunction with associated retinal lesions will assist in making a diagnosis.

The snowbank exudate is due to massive edema fluid in the outer plexiform layer or sub-retinally.

Hard exudates represent really fatty degeneration and infiltration of the retina and consist either of lipoidal deposits in the outer plexiform layer of the retina or of lipoidal histiocytes, the so-called fat granule cells. These cells are large, fat containing cells which are derived probably from the pigment epithelium of the retina, from the histiocytes in the adventitia of the vessel walls and from the glial cells[18]. The radiating appearance of hard exudates in the macular region forming the macular star is of course due to the radial arrangement of the outer plexiform layer of the retina in this location being called here Henle's outer fiber layer. Occasionally, a hard exudate may be represented by the so-called cytoid body. These appear microscopically as ganglioform like enlargements of the nerve fiber layer. However, according to McLean[19] they probably represent "regressive products sequestered in the same manner and circumstance as in other tissues throughout the body". Friedenwald[20] believes the cytoid bodies are large, swollen, necrotic, mononuclear cells.

The flame shaped retinal hemorrhages are located in the nerve fiber layer; the round smaller hemorrhages in the deeper layers, principally in the outer plexiform layer.

Retinitis proliferans when it occurs in hypertension is generally located in the region of the disc and is seen to consist of new formed vessels suspended in a fairly firm connective tissue. It is found typically in hypertension following vitreous hemorrhages.

Papilledema microscopically is found to be both an inter- and intra-cellular edema of the nerve fibers and interstitial tissue at the nerve head[21]. The outer retinal layers are but little affected although they are pushed away by the swollen nerve head accounting for the enlargement of the blind spot seen in papilledema. Congestion of the retinal veins accompanies the papilledema of hypertension and disappears with its subsidence.

Sheathing of the retinal vessels, recognized ophthalmoscopically by the presence of white streaks along side the vessel walls, is seen microscopically to consist of an accumulation of mononuclear cells in the perivascular spaces engaged in removing lipoid and cellular debris from the injured retina. It

occurs in hypertension only after edema of the retina, but may be seen along the veins in about one-fifth of the cases of multiple sclerosis according to Rucker[11]. Its pathology in this latter situation is not determined.

Pathologically, microcystic edema of the retina and flat detachment of the retina may be found when often not recognizable ophthalmoscopically.

Mechanism of Production of the Lesions

It is under this heading that the greatest diversity of opinion is found. A great deal of what is to follow must be regarded as plain theory and as such modified or rejected as new facts become available.

The original view that the retinopathy of glomerulonephritis was due to nitrogenous waste products[22,23,24] has been abandoned as cases are seen in which there is an elevation of these products in the blood stream with no retinopathy and other cases are seen with retinopathy in which no elevation of these products is present[9]. However, that some toxic element may be a factor not only in the production of the retinopathy in glomerulonephritis, but in other forms of hypertension, must still be admitted although present day ophthalmological thought stemming from work beginning in the latter part of the Nineteenth Century[25,26,27] regards the retinopathy as principally secondary to retinal arteriolar disease. Impaired nutrition of the capillaries and retinal tissue, brought about by altered retinal hemodynamics, leads to weakening of the capillary wall with passage of fluid and red cells into the surrounding retina giving rise to the familiar retinal edema, cotton wool patches and retinal hemorrhages. If the circulatory decompensation persists, a state of chronic sub-oxidation and sub-nutrition of the tissues exist[28]. The removal of acid tissue metabolites is interfered with, the pH tends to shift to the acid side, the isoelectric point is approached and activation of proteolytic enzymes occurs. Breakdown of surface tension lowering proteins consequently results. Breakdown of these proteins renders the colloidal system unstable and the dispersed phase which is composed primarily of fats and fat like substances tends to separate out giving rise to what we call fatty degeneration. Meanwhile, incoming fats are not metabolized properly and fatty infiltration results. Invasion of the damaged retina by phagocytes which engulf the lipoid substances follows and we have our so-called hard exudates formed. Ricker[29] has coined the terms peristasis, prestasis and stasis to indicate progressive impairment of the circulation.

Papilledema in hypertension is usually associated with an increase in intracranial pressure and therefore in discussion its pathogeneiss we are entitled to examine all of the theories claiming to explain the etiology of papilledema in general and choose the one which suits our fancy best. It again is probably mainly circulatory in origin, the retinal circulation being further impeded by the raised intracranial pressure. It should be metnioned that papilledema in hypertension can occur without an elevated intracranial pressure although in these cases it is usually minimal in amount.

In explaining the reason for retinal arteriolar constriction, we are confronted with the problem of the etiology of systemic hypertension in general. Study of retinal vascular physiology unfortunately contributes little or nothing to the understanding of the etiology of systemic hypertension. The behavior of the rest of the peripheral circulation in hypertension is none too clear either. Prinzmetal and Wilson[30] feel that the hypertonus is not confined to the splanchnic area alone but is present throughout the systemic circulation including the extremities. Abramson and Fierst[31], however, concluded from their observations on peripheral blood flow, that the arm and leg did not participate in the arteriolar constriction. Elwyn[32] believes that in early essential hypertension, there is no constriction anywhere except in the splanchnic region, but that in hypertension accompanying glomerulonephritis and toxemias of preg-

nancy, there is constriction in all the arterioles of the body. When the retinal vessels do constrict it is not known whether they constrict as a portion of a larger constricted vascular bed, causing the hypertension, or whether their constriction is a defense reaction against an elevated blood pressure aimed at maintaining normal retinal hemodynamics. In favor of this latter view is the observation that retinal vessels sometimes dilate following therapeutic sympathectomy for hypertension[33,34,35]. This observation would also make it appear that constriction of the retinal arterioles in essential hypertension was not due to excessive sympathetic stimulation as the sympathetic supply to the eye is not denervated in the usual sympathectomy for hypertension. This statement does not mean to imply that the retinal arterioles may not be influenced by the sympathetic supply they possess, for Wagener[36] has found dilatation of the retinal vessels following stellate ganglionectomy and Cusick[37] found in people with an idiosyncrasy to tobacco a constriction of the retinal vessels which he interpreted as being due to sympathetic stimulation. Others[38,39], however, have had negative results after stimulation or section of the sympathetic supply to the eye. The effect of the sympathetic system on the retinal vessels is thus not clear[40].

Concerning the etiology of the sclerotic changes in the retinal vessels, although we do not know the exact cause, we do know that arteriolosclerotic changes in the retinal vessels are usually preceded by hypertension[13]. Anoxemia of the retinal tissue from the circulatory disturbance may cause liberation of a local tissue toxin which secondarily affects the vessel walls causing sclerosis[13].

The earliest ophthalmoscopic sign of sclerosis is widening and increased brilliance of the light reflex from the vessel. To understand the mechanism of this change, we should briefly review the principles governing production of the normal vessel reflex. The bright streaks and glistening areas seen on the normal vessels and retina represent nothing more than reflections. Reflection of light in transparent media can occur only at surfaces separating media of different refractive index. In the normal retinal arterioles a change of refractive index occurs at the media of the vessel wall and at the endothelium. The endothelium probably contributes primarily to the normal reflex[44]. Now, when sclerosis of the arteriolar wall begins, the wall becomes of greater refractive index and consequently contributes more to the reflex[45]. The reflex thus becomes brighter because of greater refractive index change between retina and vessel wall and wider because the curvature of the surface of the arteriolar wall is less than that of the endothelium where the normal reflex primarily originates. Increasing optical heterogeneity of the vessel wall leads to its increasing visibility as sclerosis progresses. The overlay of the heightened reflex and decreased transparency of the vessel wall on the blood column give rise to the familiar copper and silver wire arterioles.

In summarizing the pathogenesis of the retinal lesions in hypertension, we may say that with the knowledge available at the present time that as the systemic blood pressure rises, retinal arteriolar constriction proceeds "pari passu",[9,10,11,46] probably not as a part of the constriction of the vascular bed causing the hypertension but as a defense mechanism designed to maintain normal retinal hemodynamics[33,47]. When normal relationships can no longer be maintained, decompensation of the retinal circulation ensues and retinopathy results. It is probable that some toxic factor enters into the production of the retinal lesions in some cases.

Characteristics and Significance of the Retinal Picture in Various Clinical Disease States

We shall discuss under this section essential hypertension, the toxemias of pregnancy and glomerulonephritis. We shall contrast briefly diabetic retinal changes with those in hypertension.

Essential hypertension represents the typical picture of the hypertensive retinopathy we have been discussing and its characteristics need not be repeated

here. It is important to remember that the presence of focal constrictions renders the prognosis more serious although as long as edema of the disc is not observed the prognosis is somewhat better. Focal constrictions are rarely seen unless the diastolic pressure is over one hundred. When edema of the disc is present, death usually occurs within thirteen months.

Hypertensive Toxemias of Pregnancy. In the toxemias of pregnancy, the outstanding changes are functional narrowing of the vessels, both general and focal[48]. Retinal edema, hemorrhages and cotton wool patches appear later if the toxemia progresses. The severity of the ocular lesions parallel most closely the height of the blood pressure. If there is retinopathy, the chance that the patient will have a permanent hypertension is good[10,49]. Visual impairment results from macular edema or retinal detachment, although it may also come from cerebral involvement. Retinal detachment occurs in about 2% of cases of hypertensive toxemias of pregnancy[49]. The prognosis as to reattachment and return of vision is good in practically all cases. Hallum[49] in an extensive study of 300 toxemias of pregnancy found that if retinopathy occurred before the 28th week, there was only a 25% chance of having a live baby and almost 100% chance of a permanent high blood pressure in the mother.

Glomerulonephritis. The ophthalmologist is often asked to look at the fundus of a patient with retinopathy and state whether the patient has essential hypertension or glomerulonephritis. In the majority of instances, the distinction cannot be made; in some the distinction may be suspected, and in a few cases the distinction can be made with certainty. The reason for this is that either acute or chronic glomerulonephritis may present two distinct forms of retinopathy which may exist individually or together in the same patient. The one form of retinopathy is identical with what we have been discussing, i.e., hypertensive retinopathy. It is seen only in glomerulonephritis with hypertension and may be present with or without sclerosis of the arterioles. There is always narrowing of the arterioles and if the hypertension is acute and/or progressive in character, there are focal constrictions also. This form of retinopathy is the same as that seen in primary hypertension. The other form of retinopathy, which when present renders the differential diagnosis of essential hypertension and glomerulonephritis possible from the ophthalmological standpoint, is what may be called the retinopathy of anemia[50]. It is characterized by normal vessels, pallor of the disc, cotton wool patches and hemorrhages. There is no proof that it is due to the anemia but according to Wagener[9] it most closely parallels the degree of anemia present in the patient. It may be a retinopathy of toxemia although considerable retention of nitrogenous waste products may be present in the blood with no retinopathy. Either form of retinopathy may occur in both acute and chronic glomerulonephritis but it is very rare to find the retinopathy of anemia in acute glomerulonephritis. In chronic glomerulonephritis, Graham[50], in a series of 63 cases with retinopathy found only 11 with the retinopathy of anemia. The remainder were classed as having hypertensive retinopathy.

In acute glomerulonephritis, although the occurrence of retinopathy is rare, when present it is usually severe and of the acute hypertensive type. However, the onset of retinopathy in acute glomerulonephritis in no way seems to influence the prognosis. The retinopathy usually subsides and the patient recovers[5]. On the other hand, in chronic glomerulonephritis, the onset of retinopathy signifies a very grave prognosis. It is usually associated with a sudden rise of blood pressure and is also of the acute hypertensive type. Patients with chronic glomerulonephritis and with acute hypertensive (angiospastic) retinopathy live on an average of four months. If the retinopathy improves after its onset, the prognosis is only slightly better, the patients living an average of twelve months. The retinopathy may even disappear before death.

Diabetic Retinopathy. We shall briefly contrast diabetic retinopathy

with the forms of hypertensive retinopathy discussed in this paper. Diabetic manifestations in their uncomplicated form present a picture entirely different from that of hypertension. The changes in uncomplicated diabetes are in the capillaries, venules and veins[51,52]; in hypertension they are in the arterioles. When arteriosclerosis complicates diabetes, changes are of course then seen in the arterioles also. The earliest signs to appear in diabetes are usually small, round red spots in the posterior pole of the eye. These for many years have been called hemorrhages but many of them have now been shown to be small saccular like aneurysms of capillaries. Whether the capillary wall first ruptures allowing a true hemorrhage and then grows out around the hemorrhage is not known with certainty. These spots persist for months although they do sometimes disappear after a prolonged period of time. Somewhat later the small, hard, waxy exudates of diabetes appear. They are similar in nature to those seen in hypertensive disease although usually have a slightly more yellow cast to them. They are not derived from hemorrhages[53]. When retinopathy consisting of persistent, punctate red spots and small waxy exudates is seen in the fundus in the presence of normal arterioles, diabetes is almost certainly the diagnosis. Another change characteristic of diabetes is the proliferation of new formed small veins in a plexus like configuration in preretinal and retinal locations. There may be in some cases no connective tissue accompanying the new vessels. In others, very fine gossamer like connective tissue strands accompany the vessels. This form of retinitis proliferans seems to occur in diabetes without preceding vitreous hemorrhages. Still another change which may occur which is practically diagnostic of diabetes is a generalized, irregular sclerosis of the retinal veins resulting in dilated segments alternating with constricted segments giving the veins a beaded, kinked appearance. Cotton wool patches are not seen in uncomplicated diabetic retinopathy[52]. When hypertension and arteriolosclerosis complicate the diabetic process then a mixed form of retinopathy is present which renders the retinal picture more difficult to interpret. The underlying diabetes is usually discernible, however, The lesions of diabetes in the retina are more in proportion to the duration of the disease than to the severity. Control of the diabetes may help prevent progress of the retinopathy hut will not improve that already present[52].

Summary

We have discussed the various lesions which may occur in the retina in systemic hypertension along with their pathology and significance in the common diseases in which hypertension is a prominent sign.

It would seem that most of the retinal changes can be explained on the basis of the hypertension, the hypertension causing complex circulatory adjustments to be made as evidenced by arteriolar constriction. When relatively normal hemodynamics of the finer vessels cannot be maintained, nutrition of the capillary walls suffers and retinopathy results. Alternative explanations of the constriction of the retinal vessels are possible, however, and some cases are seen with retinopathy (notably in glomerulonephritis) in which it is impossible to substantiate the assumption that the hypertension and arteriolar constriction are responsible for the retinopathy seen. In these, an additional toxic factor must be assumed. However, regardless of what the mechanism of production of the lesions may be, the changes observed in the retina give us an indication of the severity of the hypertension, its duration and its prognosis.

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III. MEDICAL SCHOOL NEWS

Cancer Detection Center

A Cancer Detection Center recently was opened on the medical campus of the University. The Center is directed by Dr. David State, Assistant Professor of Surgery. At present it is housed in a temporary building located just south of the Botany building. The Cancer Detection Center does not examine patients who already have symptoms suspicious of cancer or any other disease. It is intended to provide a complete physical examination for those who are in apparent good health in order that the earliest possible lesions may be detected. Therefore, patients who already have symptoms are referred to their own physician without an examination. Patients in whom the examination at the Center reveals a cancerous lesion or one suspicious of being cancerous are referred to their physician for further study and therapy. The Center does not provide treatment for cancerous lesions which are found. A registration fee of $5.00 is charged for the complete examination. The Center operates two days a week and examines women on Tuesdays and men on Thursdays. The hours are from 8:00 a.m. to 5:00 p.m. It is being financed by the Minnesota Division of the American Cancer Society, the National Cancer Institute of the U. S. Public Health Service and the University's Malignant Disease Research Fund.

Metabolic Conference

The Conference on Metabolic Aspects of Convalescence was recently held in New York City and was attended by Dr. Wallace Armstrong and Dr. Saul Cohen of the Department of Physiological Chemistry. Dr. Armstrong was named Chairman of the conference for the coming year. The work of this conference is sponsored by the Josiah Macy, Jr. Foundation.

Federated Societies

An idea as to the amount and quality of the research being conducted in the University may be gained by reviewing the proceedings of the Federation of the American Society for Experimental Biology. The abstracted papers presented before the various societies makes up a book of 312 pages of fine print.

Dr. Visscher Honored

The American Physiological Society, one of the federated societies, elected Dr. Maurice Visscher to its presidency at its recent meeting in Atlantic City.

Judd Lectureship

The 15th E. Starr Judd Lecture will be given in the auditorium of the Museum of Natural History at 8:00 p.m. April 29th. Dr. Alfred W. Adson, Professor of Neurosurgery of the Mayo Foundation will speak on the subject, "The Evolution of Neurosurgery".

Cardiovascular Diseases

The Center for Continuation Study is presenting a course in Cardiovascular Diseases for physicians of this area on April 15-16-17.

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