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VESSELS OF THE OCULAR FUNDUS AS A GUIDE TO PROGNOSIS*

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In 1913 Sir James Mackenzie protested that our profession did not sufficiently recognize its responsibility concerning prognosis; but the two great wars waged since then have helped to show that a forecast about future fitness is of the utmost importance to patients. Medical boards have committed themselves to a prognosis in many thousands of Service cases. Such panels are not of course exclusively concerned with prognosis; there are many other questions they must settle, such as whether disability is attributable to Service conditions, and, if so, the amount of compensation due. Some of these problems admit of no immediate solution. There may be so many uncertain factors and so much chance of individual variation that often a temporary disposal is suggested. The very fact of postponing a decision is, however, a form of prognosis.

One reason why medical men are reluctant to give a prognosis is that they are for ever meeting things outside their previous experience and remote from what they learned in textbooks. From time to time the apparently hopeless case will recover, or a patient hitherto in perfect health succumbs to some ailment usually dismissed as trivial. Moreover, patients and their relatives are not always aware that probability is a matter of degree. Far too often they will interpret the physician's encouraging remark as a guarantee of recovery, or else will read a death sentence into words which were spoken only to emphasize the importance of treatment. Amid so much uncertainty and scope for misunderstanding many doctors prefer to concentrate upon diagnosis and treatment, and when they are driven to make a prognosis will try to be non-committal. Prognosis remains, however, one of our most important duties; and now that medical practice has become more specialized it is more than ever necessary to try to collate all facts which have a bearing upon the patient's future capacity. Admittedly a forecast can seldom be precise, but most patients can recognize that an approximate but realistic prognosis is infinitely more helpful than the "cure guaranteed" of Bernard Shaw's (1906) rascally Dr. Schutzmacher.

Three Categories of Retinal Vascular Signs

Certain changes in the vessels of an ocular fundus are significant only so far as that particular eye is concerned.

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Other changes can foreshadow similar disease in the second eye without permitting special conclusions about the rest of the body. Most important, however, are those retinal vascular phenomena which throw light upon the condition of other organs and systems. If we take these three categories in order, Coats's disease (massive retinal haemorrhage with exudation) will serve as an example of profound disturbance implicating the vessels of one retina in an otherwise healthy boy. Confronted with a typical instance of this disease, we can almost promise that the second eye will escape. Eales's disease (recurrent juvenile haemorrhage into the vitreous), on the other hand, nearly always becomes bilateral, even if no signs are evident in the second eye at the original examination. The third category is exemplified by arteriosclerotic retinopathy, in which the ophthalmoscopic appearances can facilitate diagnosis and prognosis concerning the general cardiovascular state. There is no sharp dividing-line between the signs of local and of general significance. One of the most disquieting of retinal vascular manifestations is shrinkage associated with irregularity of calibre. This beading of the vessels usually heralds the approach of visual failure, as well as indicating that the cardiovascular system is much deranged. Until recently this sign was regarded as irreversible.

Examination of the Fundus Oculi

The fundus may be defined as a picture resting upon the dome-shaped concavity of the scleral coat. Red coloration is due to a vascular membrane, the choroid, because the retina itself, which lies anterior to the choroid, is almost invisible except for the vessels which ramify upon its surface after emerging from the optic disk. Between the choroid and the percipient layers of the retina is the retinal pigment epithelium, which normally conceals the choroidal system of blood vessels, though the latter may be exposed by retinal atrophy or hypoplasia. Their flattened, ribbon-like disposition is conspicuous in the fundus of an albino. In interpreting fundus signs it must be remembered that the vessels of the retina nourish only its anterior percipient cells. The choroidal vessels nourish the posterior half, and indeed all the percipient layers at and immediately around the fovea centralis. Another important consideration is that the ophthalmoscopic picture is often modified by erratic proliferation of the retinal pigment cells and adjacent layer of the choroid (Bruch's membrane) owing to trauma, neoplasm, degeneration, or inflammation. Thirdly, the vessels may vary widely within normal limits. Just as the healthy optic disk can vary greatly in colour, size, marginal distinctness, and size of physiological cup, so do the retinal arteries emerge in many modes of branching, and a wide range of colour may be seen in both arteries and veins.

Direct ophthalmoscopy provides a simple method of inspecting the vessels of the retina magnified about 15 times. Considering the great variety of ophthalmoscopic signs bearing upon the function of the cardiovascular system, kidneys, haematopoietic organs, and many other parts of the body, including the central nervous system, it is not surprising that so many doctors utilize this method of investigation. Allbutt (1871) spoke of the wealth of material awaiting physicians at an eye hospital. He well knew that retinal venous pulsation is not a sign of disease, that vascular kinks can simulate haemorrhage, and that the retinae of some healthy subjects possess unusually tortuous vessels.

The medical implication of data derived from ophthalmoscopy has been reiterated by many authorities since the time of Allbutt; and Rosenheim (1954) and Bourne (1955) have recently testified to the value of fundus examination in hypertensive disease, in assessing not only the prognosis but also the efficacy of treatment. Ophthalmoscopic findings must be carefully collated with the clinical history and with the results of other methods of examination. Therefore no ophthalmologist can afford to ignore a patient's medical background, even if he is already aware of the main diagnosis. Often, however, the first symptom of systemic disease will be disturbed vision. Patients with hypertensive disease, diabetes, or maladies of the blood-forming organs, to mention only a few, may all present themselves for eye tests without having recently had a medical examination; therefore glasses should never be prescribed until the fundi have been thoroughly surveyed. A refractive error amenable to correction by trial lenses does not preclude grave disorder in the ocular fundi. Patients with bilateral disk oedema or advanced chronic glaucoma may for a time be able to see the 6/6 line of test-type with each eye, and so indeed may those whose retinal arteries show advanced obliterative change.

A Systematic Plan

Although this paper is mainly concerned with the vessels, other features of the fundus picture require mention. Most vascular abnormalities are not pathognomonic of one particular condition, so that other signs—for example, exudates, pigmentary degeneration, or localized atrophy—will often supply aetiological clues. Examination of a fundus should follow a systematic plan, starting at the optic disk, proceeding towards the periphery of each quadrant along the course of the main retinal vessels, and finally embracing the macula lutea. If the pupils are small or the fundus view is obscured by haze in the axial part of the eye media, detailed examination will be aided by the instillation of 1% "paredrine" (hydroxyamphetamine hydrobromide), which adequately enlarges the pupils in 25–40 minutes without paralysing the muscle of accommodation. Paredrine has the additional advantage that it need not afterwards be counteracted by physostigmine unless glaucoma is suspected. The mydriatic effect normally wears off within an hour or two.

Each main retinal artery ramifies in the corresponding quadrant of the fundus, and there are no visible anastomoses between the terminal branches of the different arteries, though some collateral circulation can be contrived if blockage is not too sudden. The transverse diameter of an artery is about two-thirds that of the corresponding vein, and the veins are darker than the arteries because the walls of both are normally transparent. A common adventitious sheath anchors arteries and veins together at the points where they cross. At these crossings the artery usually lies anterior to the vein, but the opposite is by no means exceptional.

Although it is common to speak of the retinal "arteries," structurally and functionally these vessels fall into the category of arterioles. To what extent their state indicates that of the rest of the arterial tree is not yet precisely known, but it is at least certain that retinal arteriosclerosis is often associated with sclerosis of other arteries, and particularly of those supplying the brain. The behaviour of the choroidal arteries, on the other hand, is commonly

different from that of other parts of the arterial tree. Bearing always in mind that the retina derives half its blood supply from the vascular network of the choroid, and that premature choroidal sclerosis can beset otherwise healthy young people, we shall expect occasionally to see a retina ravaged by ischaemia, even if the ophthalmoscope reveals no abnormality in the retinal vessels themselves.

Coats's Disease

No sure explanation has ever been advanced for these cases of massive retinal haemorrhage with exudation. Some authorities have denied that Coats's disease can be a clinical entity, but in practice the disease picture is characteristic. The typical victim is a healthy boy with no signs of disease in the other eye. At first the affected eye may show nothing worse than a few small haemorrhages and exudates, but sooner or later huge plaques of coagulation-necrosis splashed with blood are seen. Venous engorgement will by now have become conspicuous, and the next stage is progressive enlargement of the retinal arteries. This vascular distension, which first becomes evident near the largest exudates, tends to spread over the fundus, and ultimately the retina may be pulled from its bed by organized connective-tissue strands growing forward into the vitreous. Although the state of the fundus vessels in Coats's disease prognosticates destruction of the affected eye, the outlook for the other is good. I have never seen a bilateral case.

Eales's Disease

Like many other ocular maladies of unknown origin, Eales's disease has often been labelled tuberculous, but neither Hutchinson (1932) nor Juler (1942) found evidence to incriminate the tubercle bacillus. The cases originally described by Eales (1880) were in males aged 14–29 years suffering from recurrent retinal haemorrhage, epistaxis, and constipation. Eales's view that the menstrual cycle rendered females immune was probably linked with the concept of vicarious menstruation, which was at that time adduced to explain various haemorrhagic effusions in the eyes and their adnexa. It is interesting to recall that von Graefe (1855) had previously described recurrent intraocular haemorrhages in young people subject to epistaxis. Purists have objected to the use of the term "Eales's disease" unless the extraocular features described by Eales were present, but the label has nevertheless passed into current usage. Probably epistaxis and constipation were fortuitous in Eales's cases, because it is certain that these young people with recurrent haemorrhage from the retina into the vitreous make a clinical pattern as definite as that of Coats's disease, and of this pattern the state of the retinal vessels gives the main clue to prognosis.

Sudden blurring of vision in one eye is the characteristic mode of onset of Eales's disease. At this stage there may be no pathological signs in the second eye, and a clear view of fundus details in the affected eye may be unobtainable because of blood in its vitreous. Rapid clearing of this initial haemorrhage is the rule, and within a few weeks vascular changes will be found in the periphery of the fundus. Some of the smaller arterioles display pale-grey sheaths and there is opalescence of the adjacent retina. Sooner or later fine adventitious vessels ramifying in the affected areas will be seen. Similar twigs may be found sprouting in the periphery of the second eye before it has yet sustained a haemorrhage, and thereafter there is progressive bilateral deterioration of vision, though the progress is not regular. After clearance of the original attack there may be weeks or months of intermission, and the same encouraging sequel may be noted after subsequent haemorrhages, but later these effusions become too copious to be absorbed. Retinitis proliferans will by now have begun to develop. The new-formed vessels with their framework of connective tissue bud forward in the vitreous and ultimately drag the retina from its bed. Similar changes implicate the second eye, although there may be a lag of months or years,

The retinal vessels in Eales's disease appear to slip into purposeless multiplication in the manner of a malignant neoplasm, so that many desperate attempts have been made to stem the process. Sheathing of these vessels has been supposed to represent a tuberculous periphlebitis, and claims have been made for tuberculin treatment, but these have not been substantiated. Remissions and even intermissions are a well-known feature in the early stages, which may last several years, but in every instance observed over a long period I have seen relentless deterioration until both vitreous chambers are full of entangled curds. Good results have recently been reported from the application of diathermy to the abnormal vessels, but it is hard to imagine any lasting benefit, because in Eales's disease, as in that of Coats, we are confronted with a vascular change which spreads to involve the whole fundus. It is too much to expect that this vicious vascular circle can be reversed by infliction of a localized burn. Eales's disease will continue to menace the sight of its victims until some new wonder-drug can be found to control the as yet unidentified agent which brings such havoc to the retinal blood vessels.

Hypertensive Disease

The story of hypertensive disease is one of the most fascinating in the history of medicine, but the final chapters have yet to be written, although many advances have been recorded in the last few years. In this subject ophthalmology and general medicine are inextricably interwoven, especially as regards prognosis. Allbutt (1895) stressed that hypertension was not always due to nephritis, and that it might exist in a relatively benign form which he called hyperpiesia, as distinct from hyperpiesis—the latter being commonly an effect of kidney disease. Many years previously Bright (1836) had described visual failure in terminal nephritis. Naturally he made no distinction between uraemic amaurosis and loss of vision from retinopathy, because Türck (1850) was the first to describe the retinal changes; and then von Graefe (1855) was able to observe them with the ophthalmoscope four years after its discovery by Helmholtz. Liebrich (1859) elaborated von Graefe's description.

Bright's successors at Guy's carried his work further. The clinical implications of the large white kidney were clearly differentiated from those of the small red by Wilks (1852), and then Gull and Sutton (1872) conclusively showed that cardiovascular hypertrophy could be a general disease in which the kidney participates ("red granular" kidney). They suggested the term "arterio-capillary fibrosis" for this condition and they emphasized that, even in late cases, the renal damage may be inconspicuous. Mahomed (1874, 1879, 1881) has described the disease afterwards known as hyperpiesia, and he was one of the earliest to stress the importance of blood-pressure observations in disease. Although the sphygmomanometer had not yet been evolved, his predictions have been proved remarkably accurate.

When Nettleship (1903) reported retinopathy in two of three children suffering from pyelonephritis he aroused less interest than he might have done a few decades later, when Goldblatt *et al.* (1934) published their memorable experiments. Since that time Boyd and Lewis (1938), Platt (1942), and many others have recorded authentic cures of hypertensive retinopathy by the removal of a diseased kidney. Goldblatt (1947) gave a further detailed account of his experimental work, and later (1951) reviewed the problem of hypertension in simple terms. More recently Wilson (1953) has authoritatively reviewed renal factors in the production of hypertension. Pickering *et al.* (1952) have described three cases of pyelonephritis associated with bilateral oedema of the optic disks and gross retinopathy—all in young people, two of them under 14. Resolution of the retinopathy was noted after operation, and all three were alive and well five years later.

It is very encouraging that retinal changes formerly regarded as presaging early death have now been proved reversible. One of the most striking instances is the first

one in Rosenheim's (1954) well-illustrated paper. At the age of 20 this patient was found to be hyperpieptic, and was invalided out of the Forces because already she showed retinopathy and bilateral oedema of the optic disks. She then married, but within five years had four stillbirths and became desperately ill. At this stage (1949) she consented to the removal of a kidney which had been recognized as abnormal five years previously. Examination of the organ showed chronic pyelonephritis. The patient made a complete recovery and has since kept perfectly well; her blood pressure has remained normal and she has had three healthy children.

Until recent years retinopathy associated with swollen optic disks was interpreted as the harbinger of death. Wagener and Keith (1939) calculated that only 50% of patients survived longer than five months. A prognostic index by Keith *et al.* (1928, 1939) divided patients into four groups, according to the severity of fundus lesions. Those suffering from disk oedema with retinopathy were relegated to Group 4, and 90% of them died within 18 months—an observation in accord with Ellis's (1938) report. He found that in patients with malignant hypertension the average duration from early symptoms until death was only a year.

To-day it is easier than ever before to arrive at a reasoned differential prognosis in malignant hypertension. It would appear that over 80%, and perhaps over 90%, of patients with high blood pressure are suffering from Allbutt's hyperpiesia or essential hypertension. Most of these have the disease in a mild form, but some are severely affected from the onset, and a few pass suddenly from the benign to the malignant phase. Disease of one or both kidneys is responsible for some of the remainder, and ophthalmologists no less than general physicians should bear this possibility in mind when they discover hypertensive retinopathy in a young subject, especially if he gives no family history of hyperpiesis. Hyperpiesis may also be secondary to a number of comparatively rare conditions, such as congenital cardiovascular deformities, basophil pituitary adenoma, and phaeochromocytoma.

General Factors in Prognosis

Before considering the signs and prognostic significance of hypertensive disease in the retina it might be as well to recall the other main factors in prognosis. (1) Heredity is universally agreed to be important in hyperpiesia. Among those who have stressed this are Ryle (1948), Rosenheim (1954), and Bourne (1955); and Horace Evans (1950) quoted the remark that "the best way to avoid high blood pressure is to choose your parents." Osler (1912) long ago recognized the desirability of inheriting good arterial tissue. (2) The size of the heart and the efficiency of its musculature, especially that of the left ventricle. (3) The diastolic blood pressure; a sustained high reading bodes ill. (4) Age; in hyperpiesia the earlier age groups suffer more severely, but in hyperpiesis secondary to some remediable cause—notably a single diseased kidney which can be removed—the younger the patient the better his chances. (5) Renal function, though this is seldom much impaired, except in hyperpiesis secondary to nephritis. (6) Sex; other things being equal, women are more resistant than men to the ill effects of raised pressure. (7) Weight; Osler commented upon the high proportion of hearty, overeating business men among the victims of hyperpiesis, and he has been supported by many physicians in recent years. (8) Mode of life; obviously the prognosis must be improved if the patient's mode of life can be regulated to avoid stress and he conscientiously follows the regimen prescribed by his doctor. (9) General attitude. Worry predisposes to high blood pressure and can precipitate cardiac and encephalopathic crises. The influence of mental agitation was strikingly illustrated by Bourne's (1955) patient, who, when admitted for preliminary investigation, had a blood-pressure reading of 260/170 mm. Hg, but a week's rest in bed without other therapy reduced this to 146/104 mm. (10) Response to special treatment. The prestige of surgical measures for

essential hypertension has waned in the last few years, and it has been suggested that many of the benefits which seemed to accrue from operation were really due to rest in bed. Encouraging results have recently been claimed from the use of hypotensive drugs which act by blocking the sympathetic ganglia. That they also block parasympathetic ganglia has produced some disquieting side-effects, but the risk is minimized if patients enter hospital for regulation of dosage. Various methonium compounds have been used, and methods and results are described by Doyle and Smirk (1955), Harington and Rosenheim (1954), Platt (1954), and Smith and Fowler (1955).

When all these factors, together with the state of the fundi, are taken into account, a reasoned prognosis can be built up. Some unfavourable features almost certainly point to death within a few months, but even in their absence no one can state with certainty that a given patient will go on for years without some fatal cardiovascular attack, because changes impending in the cerebral and coronary arteries are not always self-evident. Subject to this reservation, however, a reasoned forecast is more attainable than ever before, so long as the factors mentioned are weighed.

Ophthalmoscopic Signs

The ophthalmoscopic signs of hypertensive disease have been described by numerous clinicians, including Gunn (1892, 1898), Moore (1916), and Salus (1929), and closely correlated with histological findings by Coats (1904, 1906, 1913), H. Friedenwald (1891, 1925, 1930), Sallmann (1937, 1938), Ballantyne (1945, 1946), Ashton (1951), and others. Inevitably identical phenomena have been interpreted differently and various schemes of classification have been put forward. It is proposed here to enumerate the vascular changes, giving some indication of their separate significance, although the final assessment of a fundus picture must take all the phenomena into account.

1. *Tortuosity of Arteries*.—This varies considerably among healthy people, and is not in itself unfavourable, unless it is well marked in those small branches of the temporal arteries which supply the macula.

2. *Intensification of the Arterial Light Streak*.—The wall of a normal retinal artery is invisible, but the contained blood column acts as a cylindrical convex mirror. Thus a light reflex can be seen occupying approximately one-third of the width of the larger branches. Broadening and intensification of this reflex produce a gleam which Gunn (1892) likened to copper wire, and he attributed it to hyaline degeneration of the vessel wall. Coats (1904) regarded it as a thickening of the middle coat.

3. *Indentation of Veins Where Crossed by Arteries*.—So long as the arterial calibre is not reduced, marked venous indentation is not incompatible with years of good health and excellent vision. On the other hand, indentations are potentially dangerous, because thrombosis of a main retinal vein or large tributary often originates at the site of flattening.

4. *Angular Deviation of a Vein Where Crossed by an Artery*.—Normally the artery and vein describe an acute angle as they cross. Arteriosclerosis may cause the angle to widen until it actually becomes obtuse. This deflection of the veins was first described by Salus (1929); it appears to depend upon (a) straightening and narrowing of the arteries concerned; and (b) intermingling and, according to Sallmann (1937, 1938), proliferation of the venous and arterial sheaths at the point of crossing. This angular deviation presumably goes with venous indentation to increase the risk of thrombosis.

5. *Forward Thrusting of a Vein Where it Crosses in Front of a Sclerosed Artery*.—This is an interesting sign if the convexity is well marked, but has no special significance.

6. *Obscuration of Veins Where Arteries Cross in Front*.—This lessening of translucency is one of several signs which indicate thickening of the arterial walls.

7. *"Silver-wire" Arteries*.—These are vessels with a grossly thickened wall. This appearance, according to Ballantyne (1938), is due to the presence of hyaline beneath the endothelium. It indicates an advanced stage of sclerosis, and therefore worsens the general and local prognosis.

8. *Narrowing of Arterial Calibre*.—Although the calibre of healthy retinal arteries varies from patient to patient, there is nearly always generalized shrinkage of these vessels in arteriosclerotic retinopathy. In some cases, and especially those with renal failure, certain branches may be reduced to the finest strands, which are impermeable to the blood flow.

9. *Irregularity of Arterial Calibre*.—Marked irregularity is nearly always associated with generalized shrinkage, and according to Coats (1913) is the result of erratic proliferation of endothelium. It gives rise to "beading" of the arteries. Geoffrey Evans (1944) among others regards it as a serious sign indicating obliterative changes. Although arterial "beading" is a sign of severe retinopathy, it need no longer be regarded as completely irreversible, normal and regular calibre having been restored in hyperpiesis secondary to some remediable condition, such as unilateral pyelonephritis. The possible role of spasm in producing changes in arterial calibre will be considered later.

10. *Arterial Sheathing*.—Attenuated connective-tissue sheaths enwrapping the main retinal arteries in the region of the disk can be dismissed as physiological, but pathological sheathing is of serious import. It is essentially due to thickening of the arterial coats, and is at first revealed as a whitish line on each side of the blood column. Later the blood column is entirely hidden and the artery resembles narrow clay-piping. Sheathing is for some time compatible with permeability, but sooner or later these branches may become blocked. In severe retinopathy it may be possible to see sclerosed arteries, pipe-stem branches, and fine strands representing obliterated arteries, branching over the same fundus. Venous sheathing is seldom found in arteriosclerotic retinopathy unless diabetes is also present.

11. *Micro-aneurysms*.—These will later be referred to as the earliest ophthalmoscopic sign in diabetes, but it has now been shown that they are not pathognomonic of that disease. Ashton (1951) and Syis (1951) have demonstrated them in a number of other pathological states, including hypertensive disease. The prognosis in this latter condition would not be seriously affected by a few small scattered micro-aneurysms, but it would certainly be worsened by larger buds, especially if their number were increasing.

12. *Engorgement of Veins*.—As already stated, the average artery has a transverse diameter about two-thirds that of the corresponding vein. Slight increase in this discrepancy is not necessarily pathological, but any large variation indicates abnormality in the arteries or the veins, or in both. Slight bulging of a vein immediately distal to where it is flattened by an overlying artery is not particularly serious, but gross turgidity of all the veins calls for special scrutiny of the optic disk. Disk oedema is almost invariably associated with distension of the retinal veins, and here the clinical history may furnish a clue. Schottstaedt and Sokolow (1953) having found that, of 104 patients suffering from hypertension with oedema of the optic disks, 78 initially complained of visual impairment.

The Question of Spasm

It is hardly feasible to place these twelve vascular changes in order of severity, as some observers have tried to do. They have to be collectively considered, interpreted in relation to other fundus abnormality, and correlated with the rest of the clinical facts. If one of them were to be singled out as the most important, it should probably be the ninth. Sudden intense narrowing of the arterial calibre repeatedly discernible across the fundus is an important danger signal and has been commonly supposed to mean spasm. J. S. Friedenwald (1935) went so far as to maintain that arteriolar spasm is the first link in the chain of fundus changes from

retinal arteriosclerosis, and Ayoub (1950) classified the retinal vascular changes of prolonged hypertension into two groups, spastic and sclerotic.

These assumptions with regard to spasm have been powerfully criticized by Pickering (1951). Pickering is well aware that arteries and arterioles can contract and expand according to the needs of various organs and tissues, and that certain stimuli, especially cold and trauma, can send these vessels into violent spasm. On the other hand, it is far-fetched, he says, to assume that spasm will suddenly fasten upon one small branch of the arterial tree in the absence of any ascertainable stimulus. Some observers profess to have watched while a length of retinal artery first became bloodless and later resumed its flow, but Pickering has often looked in vain for this dramatic sequence. On examining at intervals many hypertensive patients whose retinal arteries showed irregular calibre he has been impressed with the constant location of any particular point of stenosis, even after several weeks. He did see two apparent exceptions, but in each the obstruction was embolic, not spastic, one patient having subacute bacterial endocarditis, the other mitral stenosis. Temporary amelioration of blood supply by amyl nitrite is no proof, Pickering argues, that preceding ischaemia was due to spasm, because amyl nitrite will dilate normal vessels and increase the amount of their blood flow. He also points out that organized thrombi may subsequently be canalized, and that the so-called end-arteries of the retina, brain, and heart wall can fashion considerable anastomoses so long as they are not too suddenly blocked. Then again he is sceptical that spasm of the cerebral arteries causes transient paralysis in hypertension, these arteries being thin-walled and possessing scanty muscle in their media. Nevertheless Byrom (1954) has directly observed spasm of these vessels in rats after the onset of experimental hypertension, and has been able to correlate such spasm with acute cerebral symptoms. He maintains that high blood pressure provokes focal arterial spasm which, in proportion to its intensity, duration, and distribution, will bring about: (a) damage to capillary endothelium, leading to focal oedema; (b) tissue damage, entailing disorder of function; and (c) damage to the arteriolar wall, followed by necrosis of the vessel wall or of the tissue supplied, or both.

This question of the part played by arterial spasm in producing fundus change is most complicated, and many problems have still to be solved, but Pickering is probably correct in his main contention that spasm has been too freely adduced as a reason for changes which can more logically be explained by organic vascular stenosis. Volhard and Fahr (1914) clearly differentiated the two main clinical types of hypertension, and some authorities have interpreted the division as absolute, but it is now recognized that no sharp dividing-line separates them. In some cases the disease is fulminating from the beginning; others may suddenly enter the malignant phase after being almost stationary for years. Pickering (1952) insists that difference in the intensity of hypertension amply accounts for the benign and malignant courses.

Finally attention may be drawn to one fallacy which may render prognosis difficult: reliance on the patient's account of his symptoms. Ryle (1948) pointed out that in his experience the commonest symptoms detailed by hypertensive patients were headaches, dizziness, dyspnoea, and nervousness, all of which are common in many other diseases and may arise in the absence of an organic lesion. Others have remarked that freedom from symptoms is quite compatible with advanced hyperpiesis, and that symptoms often date from the time a patient was first told about his raised blood pressure. It is interesting to note that only 6% of Ryle's patients complained of ocular symptoms.

Diabetic Retinopathy

Small dark retinal aneurysms are the earliest sign of diabetic retinopathy. Some of these simulate the round haemorrhages which later emerge. Unless the circumfoveal portion of the macula is involved early, months or even

years may elapse before the patient notices any disturbance of vision. Ashton (1949) has histologically demonstrated leaking micro-aneurysms in specimens of unstained diabetic retinae, and these globular swellings are undoubtedly the origin of the characteristic rounded haemorrhages within the retinal substance. Small, clear-cut yellow exudates arise, chiefly near the posterior pole, but meanwhile the veins undergo marked distension, and later may display sheathing. Adventitious vascular radicles develop in some cases, especially if there is much arteriosclerosis. These new vessels, if profusely budding, worsen the prognosis, as they may be precursors of retinitis proliferans.

It was in 1856 that Jaeger first described fundus changes in diabetes, but many aspects of diabetic retinopathy remain a mystery. One thing is certain: the severity of the retinal changes does not correspond with the amount of metabolic disturbance, and it is not uncommon to find advanced retinopathy in a patient who is otherwise well and has closely observed all therapeutic instructions. Indeed Lawrence (1946) has suggested that retinopathy is particularly prevalent in mild diabetes. It now seems clear, however, that duration of disease is the most important factor in producing diabetic retinopathy. In its milder forms diabetes may remain unrecognized for years, but all the time fundus disturbance is drawing nearer. The literature on this subject is already enormous, and numerous statistical surveys have been made by Howells (1953) and others. Without quoting details, it is reasonable to say that retinopathy is unusual in the first few years of diabetes, but will be found in a growing minority between the tenth and fifteenth years of the disease. Fundus changes are evident in most patients after fifteen years, and it is exceptional to remain unaffected at the end of twenty years. No hard-and-fast limit can be laid down, because diabetics with unaffected retinae are occasionally seen 25 years or more after onset of the disease. It must therefore be concluded that vascular changes in the diabetic fundus afford little or no clue to a general prognosis, except in so far as there may be other changes, such as advanced sclerosis, in addition to those characteristic of diabetes. The ultimate prognosis for vision is poor once even the earliest changes of diabetic retinopathy are evident. Some observers have claimed retrogression of diabetic retinopathy under treatment, but I have not been so fortunate. Individual haemorrhages may sometimes absorb, though slowly, but fresh lesions will appear at other sites. The rate of visual deterioration varies from patient to patient, and of course the retinal state is not the only factor to consider in prognosis. Some diabetics are afflicted with cataract, and in these cases the general disease makes operation more hazardous. Iritis and retrobulbar neuritis are other possible sources of impaired vision in diabetics, and the clinical picture may be confused by associated hypertensive disease with hyaline degeneration of the kidneys, as described by Kimmelstiel and Wilson (1936). Lipaemia retinalis has seldom been noted since insulin has become widely available. It used to occur in uncontrolled young diabetics suffering from acidosis and with over 4% of fat in their circulating blood. The resulting yellow tinge of the arteries and violet coloration of the veins can be quickly corrected with insulin.

Renal Retinopathy

Now that renal disease and hyperpiesia have been proved to be closely related it seems clear that most cases formerly labelled albuminuric retinitis were in reality instances of severe arteriosclerotic retinopathy. Long-continued hyperpiesis and renal insufficiency are viciously interrelated, and the fundus picture is greatly modified by the speed of the systemic changes. Other things being equal, the quicker the constitutional deterioration, the more rapidly will the retinal arteries become stenosed, and in such circumstances oedema will be prominent. Thus there will be swelling of the disks, "cotton-wool" patches and "snow-bank" exudates of the retinae, folds radiating from the centre of

the maculae to describe a whitish fan or star, and possibly exudative retinal detachment in both eyes. The most fulminating of all renal-hypertensive retinopathies occurs with severe pre-eclamptic toxæmia, in which within a few hours both retinae may billow forward like sails. Prompt termination of pregnancy has often been followed by total resolution of the fundus damage and full visual recovery.

Obstruction of the Central Vessels

Sudden obstruction of the central retinal artery may arise from an impacted embolus, especially in mitral disease, but in many cases blockage is due to thrombosis occurring as a culmination of long-standing obliterative changes. Sudden painless loss of sight in one eye is the characteristic symptom, and the ophthalmoscope reveals pallor of the optic disk with marked narrowing of the retinal arteries. Spasmodic segmental shunting of the blood column in some of the larger vessels may be visible, and soon the macula goes temporarily white from coagulation-necrosis, except in its thinnest part around the fovea centralis. Usually the prognosis for recovery of vision in that eye is hopeless. Very rarely partial or complete restoration, either spontaneous or after administration of amyl nitrite or other vasodilator, has been reported; but the chances are remote, and presumably any improvement is explicable by fragmentation of the impacted plug, unless there is an accessory blood supply in the form of an aberrant cilio-retinal twig.

Thrombosis of the central retinal vein is in most cases a complication of retinal arteriosclerosis, but it may follow orbital cellulitis, which in its turn may be due to facial erysipelas. In describing the ophthalmoscopic signs Anderson (1952) speaks of enormously dilated veins writhing in massive haemorrhages, like "purple maggots in a squashed tomato." Any severe debilitating disease can precipitate thrombosis in the central vein or one of its tributaries, but occasionally the origin of the trouble remains obscure. In arteriosclerotic cases a tributary thrombosis often starts where the vein has been compressed by an artery, but further thromboses are not inevitable even if similar venous compression is visible at other points in each fundus. The general prognosis is not much worsened by either tributary or central retinal venous thrombosis. Visual disturbance from tributary thrombosis may completely resolve, but some obscuration as a rule persists if the upper temporal trunk is implicated, because the resulting exudate tends to seep downwards and plough up the macula. Detailed sight is rarely restored after central venous thrombosis, although many methods of therapy have been tried.

Retinal Angiomatosis

Angiomatosis, or the von Hippel-Lindau syndrome, often remains latent until adult life. Vascular neoplastic masses may be found in the abdominal viscera or within the skull, especially in the cerebellum. Partial calcification reveals them to x rays. Affected areas of the fundus show groups of engorged vessels among which arteries and veins are often indistinguishable. As the vascular distension increases, massive haemorrhages and exudates may become evident, as in Coats's disease. The prognosis for the affected eye is unfavourable; retinal detachment is the usual outcome, and secondary glaucoma may supervene. Attempts to limit the ravages of angiomata by diathermy have seldom if ever succeeded. Ballantyne (1941) reports the unsuccessful use of radiotherapy in a youth of 19, whose eye had to be removed because of raised tension from intraocular haemorrhage.

Miscellaneous Diseases Implicating the Fundus Vessels

Subacute bacterial endocarditis may lead to blockage of the central artery or its tributaries, and sometimes single or multiple abscesses or aneurysmal dilatations occur at the site of impacted particles, but these are not a reliable guide to the severity of the main disease.

Pernicious anaemia and advanced secondary anaemia give rise to flattening and pallor of the vessels, with loss of differentiation between arteries and veins. Haemorrhages in the form of a halo, showing a red rim around the central whitish core, can occur in any severe anaemia, primary or secondary. The various types of leukaemia can cause prodigious distension of the retinal veins, and leucocytic perivascular sheaths may later develop. Engorgement and duskiness of the retinal arteries and veins is a notable feature in cyanosis due to certain forms of congenital heart disease. Although fundus changes are usually visible in the haematopoietic diseases, they are not of primary importance in prognosis, although they sometimes facilitate diagnosis in early or obscure cases.

Among the rare but interesting diseases which may be associated with hypertensive retinopathy are disseminated lupus erythematosus and periarteritis nodosa; and severe obliterative changes in the retinal arteries leading to optic atrophy and carrying a bad prognosis for vision are usual in temporal arteritis. The retinal vessels may leak after blood transfusion; and secondary optic atrophy with marked attenuation of the retinal arteries may suddenly arise after severe repeated haemorrhage, especially from the gastro-intestinal tract or uterus. Among other conditions characterized by extreme arterial shrinkage is retinitis pigmentosa, a familial disease which slowly advances to blindness. Certain poisons, especially methyl alcohol, can also shrivel up the retinal arteries and permanently reduce visual acuity.

Senile massive exudate at the macula is a lesion of the central part of the fundus mainly confined to the elderly. The prognosis is bad not only for the affected eye but ultimately for the other eye, the condition being nearly always bilateral, although it may be months or years before the second eye is involved. After the haemorrhagic exudate has cleared, which may take several months, a large irregular area of atrophy and pigmentary degeneration remains at and near the macula. Many of the victims have relatively healthy retinal arteries, but the explanation for this apparent anomaly lies in the choroidal vessels, which may be in a state of degeneration far beyond that of the retinal arteries. Generally speaking, choroidal haemorrhages are more immediately destructive and more enduringly harmful than those from the retinal vessels.

Fundus Changes Associated with Disease of the Vessels

Defective oxygenation through the retinal vessels impairs the transparency of the anterior layers. This may create a diffuse milkiness, as in neuroretinitis, but more commonly the distribution is patchy. In severe retinopathy widespread shrinkage of the retinal arteries is usually linked with "beading," so that we should naturally expect irregular interference with the nutrition of the membrane. Such inconsistency is reflected in the "cotton-wool" patches and "snow-banks" disposed irregularly over each fundus. When the acute swelling subsides there remain a number of hard-looking whitish dots and irregular pigmented deposits, together with partial optic atrophy. Similar whitish dots may form even in the absence of oedema, and in some elderly arteriosclerotic patients they are disposed in circinate fashion like a great horseshoe incompletely enveloping the macula.

The late Treacher Collins and Malcolm Hepburn fought many a friendly battle over the part played by disease of the retinal and choroidal vessels in producing fundus lesions. Much still remains to be elucidated, but it seems clear that, though one or other of the two systems may be chiefly concerned in a given lesion—for example, the choroidal vessels in senile massive exudate—both can be simultaneously involved. Except in albinism or other abnormal circumstances, the choroidal vessels cannot be seen by ophthalmoscopy, but as it is known that they can be extensively diseased in an otherwise healthy young subject it is often reasonable to suspect choroidal sclerosis before signs of atrophy are visible. In familial choroidal sclerosis the

function of each retina is slowly destroyed, whether the process begins diffusely or first attacks one special region, as the juxtapapillary zone or the macula. The final outcome, if the patient survives long enough, is complete atrophic pallor throughout the fundi—a condition sometimes misinterpreted as congenital choroideremia. Choroidal haemorrhages are more rapidly destructive than sclerosis, but the two are not mutually exclusive; they can occur side by side in high myopia and in Dooyne's "honeycomb" familial choroiditis. Finally, another latent source of retinal anoxia should be borne in mind to account for defective vision, and that is atheromatous change in the central retinal artery immediately behind the optic disk, outside the range of the ophthalmoscope.

General Conclusions and Summary

In proportion to its size the ocular fundus has perhaps been more minutely surveyed than any part of the human frame, not even excepting the lens and cornea. Repeated ophthalmoscopic observations fortified by histological study and correlated with the rest of the clinical background make a foundation upon which the prognosis may be built. Complete certainty is seldom attainable, but marshalling of all the evidence does at least permit an approximate forecast. Although prognosis must be to a large extent based upon work done in the past, it is nevertheless essential to link up the facts with recent advances. New methods of therapy together with changing aetiological situations have within living memory altered the outlook in many important diseases, notably hyperpiesis and diabetes. The state of the fundus vessels will probably for a long time continue to be one of the more important considerations for all who seek to assess the cardiovascular system.

Changes in the ophthalmoscopic appearances of vessels in the fundus may supply guidance about the future prospects of (a) one eye, (b) both eyes, and (c) the other organs and tissues of the body. Thus it is possible to say, when confronted with a typical instance of Coats's disease, that the affected eye is likely to deteriorate, but the second eye will probably escape. In Eales's disease, on the other hand, the chances are that the fellow-eye will be implicated, even if it betrays no pathological signs long after the disease has become manifest in the first eye. Characteristic alterations in the fundus vessels may also be evident in hyperpiesia, hyperpiesis secondary to non-cardiovascular disease, diabetes, haematopoietic maladies, and many other abnormal states.

The prognostic implications of retinal vascular phenomena are not always self-evident. Legitimate conclusions from them can only be achieved by careful weighing of the ophthalmic and systemic evidence. The role of spasm in the production of arteriosclerotic retinopathy is not yet settled, but it does seem probable that spasm has been too readily assumed as an explanation for events that are probably due to obliterative changes in the vessel walls.

REFERENCES

- Allbutt, T. C. (1871). *On the Use of the Ophthalmoscope*. London.
 — (1895). *Abstr. Trans. Hunter. Soc.*, 11, 38.
 — (1898). *System of Medicine*, vol. 5. London.
 Anderson, A. S. (1952). *Med. J. Aust.*, 2, 170.
 Ashton, N. (1949). *Brit. J. Ophthalm.*, 33, 407.
 — (1951). *Ibid.*, 35, 189.
 Ayoub, J. E. M. (1950). *Ophthalm. Lit. (Lond.)*, 4, 233.
 Ballantyne, A. J. (1938). *Trans. ophthalm. Soc. U.K.*, 58, 255.
 — (1941). *Proc. roy. Soc. Med.*, 35, 345.
 — (1945). *Arch. Ophthalm. (Chicago)*, 33, 97.
 — (1946). *Trans. ophthalm. Soc. U.K.*, 66, 503.
 Bourne, G. (1955). *Practitioner*, 174, 129.
 Boyd, C. H., and Lewis, L. G. (1938). *J. Urol.*, 39, 627.
 Bright, R. (1836). *Guy's Hosp. Rep.*, 1, 396.

- Byrom, F. B. (1954). *Lancet*, 2, 201.
 Coats, G. (1904). *Trans. ophthalm. Soc. U.K.*, 24, 161.
 — (1906). *Ophthalmoscope*, 4, 605.
 — (1913). *Trans. ophthalm. Soc. U.K.*, 33, 37.
 Doyle, A. E., and Smirk, F. H. (1955). *Practitioner*, 174, 135.
 Eales, H. (1880). *Bgham med. Rev.*, 3, 262.
 Ellis, A. (1938). *Lancet*, 1, 977.
 Evans, G. (1944). *Practitioner*, 153, 129.
 Evans, H. (1950). *Ann. roy. Coll. Surg. Engl.*, 6, 143.
 Friedenwald, H. (1891). *J. Amer. med. Ass.*, 16, 622.
 — (1925). *Ibid.*, 85, 428.
 — (1930). *Trans. ophthalm. Soc. U.K.*, 50, 452.
 Friedenwald, J. S. (1935). In Berglund, H., and Medes, G., *The Kidney in Health and Disease*. Philadelphia.
 Goldblatt, H. (1947). *Physiol. Rev.*, 27, 120.
 — (1951). *Practitioner*, 166, 531.
 — Lynch, J., Hanzal, R. F., and Summerville, W. W. (1934). *J. exp. Med.*, 59, 347.
 von Graefe, A. (1855). *v. Graefes Arch. Ophthalm.*, Abt. 1, 2, 214.
 Gull, W. W., and Sutton, H. G. (1872). *Med.-Chir. Trans.*, 55, 273.
 Gunn, R. M. (1892). *Trans. ophthalm. Soc. U.K.*, 12, 124.
 — (1898). *Ibid.*, 18, 356.
 Harington, M., and Rosenheim, M. L. (1954). *Lancet*, 1, 7.
 Howells, L. F. (1953). *Brit. J. Ophthalm.*, 37, 716.
 Hutchinson, H. P. (1932). *Ibid.*, 16, 513.
 Jaeger, E. (1856). *Beiträge zur Pathologie des Auges*, p. 133. Vienna.
 Juler, F. A. (1942). *Proc. roy. Soc. Med.*, 36, 11.
 Keith, N. M., Wagener, H. P., and Kernohan, J. W. (1928). *Arch. intern. Med.*, 41, 141.
 — and Barker, N. W. (1939). *Amer. J. med. Sci.*, 197, 332.
 Kimmelstiel, P., and Wilson, C. (1936). *Amer. J. Path.*, 12, 83.
 Lawrence, R. D. (1946). *Lancet*, 1, 724, 773.
 Liebrich, R. (1859). *v. Graefes Arch. Ophthalm.*, 5, 265.
 Mackenzie, J. (1913). *Diseases of the Heart*, 3rd ed. London.
 Mahomed, F. A. (1874). *British Medical Journal*, 1, 585.
 — (1879). *Guy's Hosp. Rep.*, 24, 363.
 — (1881). *Ibid.*, 25, 295.
 Moore, R. F. (1916). *Trans. ophthalm. Soc. U.K.*, 36, 319.
 Nettleship, E. (1903). *Ophthalm. Hosp. Rep. (Lond.)*, 15, 320.
 Osler, W., and Macrae, T. (1912). *Principles and Practice of Medicine*, 8th ed., pp. 842-3. New York and London.
 Pickering, G. W. (1951). *Lancet*, 2, 845.
 — (1952). *Brit. med. Bull.*, 8, 305.
 — Wright, A. D., and Heptinstall, R. H. (1952). *Lancet*, 2, 952.
 Platt, R. (1942). *Proc. roy. Soc. Med.*, 35, 317.
 — (1954). *Quart. J. Med.*, 23, 441.
 Rosenheim, M. L. (1954). *British Medical Journal*, 2, 1181.
 Ryle, J. A. (1948). *Natural History of Disease*, 2nd ed., pp. 304-22. London.
 Sallmann, L. von (1937). *v. Graefes Arch. Ophthalm.*, 137, 619.
 — (1938). *Ibid.*, 138, 412.
 Salus, R. (1929). *Klin. Mbl. Augenheilk.*, 82, 471.
 Schottstaedt, M. F., and Sokolow, M. (1953). *Amer. Heart J.*, 45, 331.
 Shaw, B. (1906). *The Doctor's Dilemma*. London.
 Smith, K. S., and Fowler, P. B. S. (1955). *Lancet*, 1, 417.
 Syse, R. (1951). *Brit. J. Ophthalm.*, 35, 560.
 Türk, L. (1850). *Z.k.k. Ges. Ärzte Wien*, 6, 45.
 Volhard, F., and Fahr, T. (1914). *Die Brightsche Nierenkrankheit*. Berlin.
 Wagener, H. P., and Keith, N. M. (1939). *Medicine (Baltimore)*, 18, 317.
 Wilks, S. (1852). *Guy's Hosp. Rep.*, 8, 232.
 Wilson, C. (1953). *Lancet*, 2, 579, 632.

RECENT RESEARCH IN PHYSIOLOGY OF BREAST APPLIED TO MAMMARY CANCER

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It may be salutary to doubt but it is impossible to deny that approximately 50% of human breast cancers are hormone-dependent and do not possess the gloomy and mysterious attribute of "autonomy" so often regarded as the essential biological characteristic of all malignant tumours. A breast cancer is said to be hormone-dependent if progressive proliferation of its infiltrating and metastasizing cells is conditioned by an adequate supply of the specific mammatrophic hormones which are responsible for physiological mammogenesis whereby the mammary rudiments of the weanling reach the structural complexity of sexual maturity and the functional maturity of lactation. It is clear, therefore, that our control of hormone-dependent breast cancer primarily depends on our knowledge of mammary physiology.

Hormonal Control of the Normal Breast

Five years ago it was generally believed that the proliferation of the hormone-dependent epithelium of the normal