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Cerebrospinal fluid pressure in the arterial hypertensive states

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THE CEREBROSPINAL FLUID PRESSURE IN THE ARTERIAL HYPERTENSIVE STATES

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INTRODUCTION

It is the purpose of this paper to review the literature and try to correlate the symptom of increased cerebrospinal fluid pressure with the other signs and symptoms of the areterial hypertensive states, as well as attempt to theorize the most plausible explanation why cerebrospinal fluid pressure is so commonly elevated in cases of arterial hypertension. Four principal types of high blood pressure will be considered in this paper; these are the types caused by essential hypertension, lead poisoning, eclampsia gravidarum and glomerulonephritis. The effect on cerebrospinal fluid pressure, as well as some effects elsewhere in the body, does not differ markedly in these conditions.

The consequences of cerebral vascular disease are relatively common, and they constitute an especially significant class of complications of the vascular hypertensive state. The term "hypertensive encephalopathy" has been used by many to indicate those particular disturbances of cerebral function that occur, such as convulsions, various types of paralyses, coma, blindness, and the like. Since this disturbance is but the expressed manifestation of several probable influences, the exact clinical interpretation

of the various factors at play often becomes difficult. It is the desire of the author to clarify the clinical syndrome, especially as it is related to increased intracranial pressure. It seems that exact diagnosis of hypertensive encephalopathy is often difficult and therefore is slighted; yet such a diagnosis is extremely important for the sake of correct therapeusis and sound prognostic evaluation.

It was recognized early that intracranial pressure is often markedly elevated in cases presenting arterial hypertension, but this was all classed as a part of the syndrome of "uremia", as stated by Cushing and Bordley (12) in 1908. It was not until 1925 that Blackfan and Hamilton (3) discovered that renal insufficiency was not present in all patients suffering from this "uremia", though they retained the old term and divided their cases into two groups, i.e. (1) Those with renal insufficiency, and (2) Those primarily vascular. They also noted that intracranial pressure was not elevated in all cases of arterial hypertension, and hypothesized that in cases without the intracranial pressure increase as measured by spinal tap, the foramina between the cerebral and the spinal subarachnoid systems had been compressed by cerebral edema to prevent communication, thus allowing

spinal fluid manometry to remain normal. These and other contradictory points are to be discussed more in detail below.

CASE STUDIES

As has been stated, it was known early that many cases presenting a picture of arterial hypertension also presented an increase in cerebrospinal fluid pressure. Beginning with this fact alone, many workers have made attempts to find, without doing lumbar puncture, which cases were elegible for this procedure and which should be omitted on the basis of extreme elevation of cerebrospinal fluid pressure and possible herniation of the cerebellum into the foramen magnum. The conclusions reached by many authors on this subject are far from uniform.

In 1918 Lyttkins (26) suggested that a rise in blood pressure is followed by elevation of cerebrospinal fluid pressure, but his evidence was scant and he made no attempt to explain the cases of moderate to severe arterial hypertension which fail to show increased tension on lumbar puncture.

In 1924 a series of experiments were carried out by Block and Oppenheimer (5) in which subjects with both normal and elevated arterial and cerebrospinal pressures were used in a comparative study of cerebrospinal fluid pressure, blood pressure, and intraocular tension. Normal subjects were used for artificial elevation of one pressure system with subsequent deter-

minations of the pressure effects which this had on the other two systems. They concluded that no strict individual parallelism exists between the three pressure systems, but that usually a prolonged high or low pressure of one system is associated with corresponding pressure changes in the other two systems. They also found that many local disease states produced isolated pressure changes without constant effect upon the other two systems.

Shelbourne, Blaine and O'Hare (39) in 1932 made a comprehensive study of fifty cases of known arterial hypertension without regard to cause. Their main attempt was to determine what percentage of their cases presented cerebrospinal pressure elevation, and the possible correlation of this elevation with other signs and symptoms presented by the patients. Of these fifty cases, they found twenty-two to have either elevated cerebrospinal fluid pressure (above 200mm. water) or papilledema, or both. Of these twenty-two cases, all but one had mild to severe papilledema and only two with papilledema failed to have elevated cerebrospinal fluid pressure. It was therefore assumed that the papilledema resulted from the increased cerebrospinal tension and not from the arterial hypertension primarily. Other significant findings are discussed under the section on hypertensive neuroretinopathy.

The above workers also found papilledema and increased intracranial pressure to occur more frequently with renal failure, but also were found where renal function was normal. They found increased intracranial pressure more often was associated with high diastolic blood pressure, but believed that both were due to some common factor and neither due to the other.

In a series of experiments performed both on humans and on dogs, Browder and Meyers (6) in 1940 attempted to postulate that the arterial hypertension may result secondarily from the increase in intracranial tension, though this hardly seems tenable since in most cases the arterial hypertension is progressive and known to exist prior to the intracranial hypertension. Their results failed when they found that no peripheral effects were attained until spinal fluid pressure was increased to 750 mm. of water or over, a leval comparable to diastolic blood pressure in most cases, and higher than usually seen in clinical cases. Up to the point of 750 mm. of water pressure, the cerebral venous circulation time slowed from three seconds to six seconds; however, the vessels increased in size, allowing more blood to flow through and thus be a compensatory mechanism to prevent anoxia. But this compensatory mechanism failed after diastolic

pressure was superceded in the subarachnoid system, and the immediate result was elevated blood pressure, decreased pulse rate, and slow irregular respirations; when this pressure was maintained, the final results were decreased blood pressure, increased pulse rate, and rapid respirations with cyanosis.

Yet the above results of vascular reactivity cannot be conclusive, as proved by Cameron and Rosen (8) in 1941. They tested vascular reactivity by blood pressure response to intravenous histamine injection in three classes of patients. These classes were the middle age, senile, and alcoholic groups. The average responses of blood pressure rises in these groups may be tabulated as follows:

1. Senile . . . . . 34 mm. Hg.
2. Alcoholics . . . . . 86 mm. Hg.
3. Middle age . . . . . 70 mm. Hg.

From this it may be postulated that the alcoholics have the best vascular reactivity to histamine injection, and possibly to other stimuli as well.

Burch and Neumann (7) found that the sympathetic activity in resting patients with hypertension is no greater than that in normal subjects. This was determined after a study of the rate of water loss from the surfaces of the finger tips and toe tips of normal and

senile subjects and patients with arterial hypertension.

Within the past decade there has been increasing interest in the relationship which exists between the cerebrospinal and blood pressure systems, which has stimulated much experimental work on the subject. In 1940, Edholm (14) in his experiments performed on cats found that bradycardia associated with increased intracranial pressure is independent of the rise of blood pressure, as shown by prevention of the rise in blood pressure associated with increased intracranial pressure and showing that the bradycardia still exists.

Forbes, Cobb, and Fremont-Smith (18), Michelson and Thompson (31), and Maurer (29) have worked independently on the relationship of carbon monoxide poisoning and of low oxygen tension upon cerebrospinal fluid pressure. Their results uniformly showed an increase in intractanial tension after both, with return to nearly normal in either case after administration of 100% oxygen.

In many cases the differential diagnosis of hypertensive encephalopathy, brain tumor, and epilepsy may become difficult. In this light, the work of Forster and Nims (20) in 1942 is significant. They found that

electroencephalographic changes do not occur due to rise of intracranial pressure alone, until such pressure is sufficient to impede cerebral blood flow, and this is a pressure which supercedes that of clinical experience, i.e. usually 750 mm. of water or over.

HYPERTENSIVE ENCEPHALOPATHY

Hypertensive encephalopathy is a cerebral symptom complex which may occur in diffuse glomerulonephritis, essential hypertension, eclampsia gravidarum and lead poisoning or in fact in any condition where hypertension is found. These episodes were formerly termed "acute uremia" because they were considered uremic in nature. Work of recent investigators has proved these attacks to be non-uremic in nature; this was particularly corroborated by the work of Oppenheimer and Fishberg (33) in 1928, who first proposed the very apt term of hypertensive encephalopathy to cover the conditions under consideration. Some include under this syndrome those cerebral episodes occurring in hypertensive individuals that are never local in their manifestations. Some of these are homonymous hemianopsia, which may last for several hours and disappear as quickly as it started. Various transient motor disturbances may develop, as monoplegias and hemiplegias. Transient sensory changes may occur, last for several hours and leave no remnant of the crisis. Numbness and tingling in one part or on one whole side are relatively common. Other focal neurological symptons such as aphasia, ataxia and chorea occur. It is the general opinion that these effects are due to generalized angiospastic phenomena associated with increased intracranial tension.

These hypertensive crises are usually preceded by or are concomitant with many other signs, such as various psychic disturbances, headache (which is often occipital), and occasionally stiff neck and positive Kernig's sign.

As summarized by Reed (36), the whole symptomatology of these cerebral episodes is similar to that seen in lead encephalopathy and the eclamptic seizures. Fishberg (16) reminds us that the cerebral manifestations of the hypertensive states, as essential hypertension, eclampsia, lead poisoning, and golmerular nephritis, are quite similar and engulfed into the term hypertensive encephalopathy. The classic form closely resembles the epileptiform seizure, consisting of prodromes, followed by tonic and clonic convulsions, with coma continuing afterward. These seizures, however, vary directly in severity and proportion to the severity of the hypertensive state. The important factor to be noted is the resemblance to epileptiform seizures, even to the aura.

Hypertensive encephalopathy is most commonly observed during the course of active cases of acute glomerular nephritis, or in cases of an acute exacerbation of a latent or chronic nephritis, and in some cases of nephrosis of pregnancy. Cases of acute glomerular

nephritis may be ushered in by a severe convulsive seizure. And this episode takes place with no elevation of the non-protein nitrogen of the blood and also before impairment of renal function can be demonstrated. This syndrome occurs less often and takes on a slightly different character in some cases of essential hypertension and arteriosclerosis with hypertension. The constant finding in these various cases developing the cerebral symptom-complex is an elevated blood pressure, and it is generally true that there is correlation between the rapidity of rise of the blood pressure and the severity of the symptoms. Fishberg (15) points out that the blood flow through the vital centers of the brain must be diminished due to the end-arterial spasm which must be concomitant with the elevated blood pressure. And as most of these patients have a markedly elevated cerebrospinal fluid pressure, usually on the basis of cerebral edema, this further limits the blood supply to the vital centers, and the symptoms are thus intensified. This probably accounts for the paroxysmal dyspnea, or even Cheyne-Stokes respiration, which may occur with the attacks.

As has been discussed, studies of kidney function show that the most severe form of hypertensive encephalopathy may occur without impairment of renal

function. More important, there may be no demonstrable deviation from normal in the blood chemistry picture. But what would be the result of addition of renal insufficiency and uremia to the picture of hypertensive encephalopathy? Fishberg (15) states that sudden changes in renal function and blood chemistry merely serve to intensify the symptoms already present, and explains this on the basis of water retention leading to cerebral edema, resulting in further increase in cerebrospinal fluid pressure, further ischemia to the vital centers, and finally intensified symptoms. Even before the significant variation between uremia and hypertensive encephalopathy was recognized, Blackfan and Hamilton (3) became cognizant that renal insufficiency was not present in all their "uremic" patients, so they divided them into two groups:

1. Those with renal insufficiency.
2. Those primarily vascular.

In essence, this corresponds to our present day classification into uremia and hypertensive encephalopathy respectively.

Theories concerning the direct etiology of the symptom-complex of hypertensive encephalopathy have been discussed in detail by many authors, and with

some difference of opinion. Blackfan and Hamilton (3) attributed the entire symptom-complex to cerebral edema, but did not propose a cause for the edema. They also proposed the idea that the arterial hypertension is due secondarily to increased intracranial pressure, since they found that the blood pressure was reduced and the cerebral symptoms abated after reduction of cerebral edema by one per cent magnesium sulfate therapy. Yet it was known that some patients presenting the symptom-complex failed to show elevation of cerebrospinal fluid pressure by spinal tap. In explanation of this fact, they found cases at necropsy with pale, edematous brains and compressed medullary cones who had not shown an increase in intracranial pressure premortem. They hypothesized that increased intracranial pressure was present in all cases, but that it sometimes compressed the foramina between the cerebral and spinal subarachnoid systems, thus obliterating communication and allowing spinal fluid pressure to be normal while intracranial pressure was greatly increased.

Fishberg (15) attributed the cerebral manifestations of the hypertensive states to cerebral ischemia resulting from end-arteriolar constriction and intensified by the cerebral edema, which he thought was not present in all cases. Workers before him had proved

experimentally that tonic and clonic convulsions can be experimentally produced by ligation of the arterial tree to the head in rabbits and terminated quickly on release of the ligatures. He presented a series of facts which proved to the satisfaction of many that the basic cause of the symptoms was cerebral vasoconstriction, aided in most cases by cerebral edema:

1. Hypertension present in all cases, indicating at least scattered end-arterial spasm.
2. Sharp rise in blood pressure, especially the diastolic, usually just precedes the seizure.
3. Brains pale and bloodless at necropsy.
4. Decrease in blood pressure (especially diastolic) and cerebral symptoms on administration of amyl nitrite.
5. Observed spasm of retinal arterioles.

In a later discussion we will consider the correlation of cerebral angiospasm and cerebral edema, when the most tenable theories as to the cause of the edema are presented.

Rosenberg (37) in 1940 conducted a series of studies on the autopsy findings in the brains of patients in whom the cause of death had been malignant hypertension. In his series of cases nearly all had

increased cerebrospinal fluid pressure premortem, but he, like Blackfan and Hamilton (3), proposed that in those who failed to show increased tension on lumbar puncture, there had been compression of the foramina and segregation of the cerebral from the spinal subarachnoid spaces. Otherwise, he stated, how can we account for papilledema being present without increase in intracranial tension?

Yet Rosenberg (37) was not in agreement with previous authors as to the cause of the cerebral manifestations of the arterial hypertensive states. In his series of necropsies he found vascular lesions to account for all the seizures and focal signs present in his patients premortem. Such lesions he described and illustrated as hemorrhage, thrombosis, infarction and multiple petechiae. On this basis he divided the cerebral symptoms of malignant essential hypertension into three groups:

1. Symptoms of increased intracranial pressure, as headache, nausea and vomiting, mental dullness and drowsiness.
2. Symptoms of multiple miliary cerebral lesions, as vertigo, equilibratory loss, olfactory hallucinations, transient hemiplegias and aphasias, and personality changes.

3. Symptoms of large cerebral vascular accidents.

His advice is to not rely passively on angiospasm as the explanation, but to attempt to classify the patient as to which of these three groups he belongs, for the sake of logical therapeusis and sound prognostic evaluation.

Diagnosis of hypertensive encephalopathy, as outlined by McNitt (30), is not difficult when associated with chronic glomerulonephritis. The fact that this condition may occur in correlation with uremia should not be overlooked. Generalized epileptiform convulsions are rarely seen in uremia except preterminally. Amaurosis is not of uremic origin. Epilepsy which is closely simulated by the seizures can be excluded by the history, blood pressure determinations, and examination of the urine and eye grounds. Biting of the tongue is unusual in hypertensive seizures. Meningitis and subarachnoid hemorrhage can be ruled out by spinal tap. Brain tumor may present the most difficult differential diagnosis. The ophthalmoscopic picture of brain tumor may closely resemble hypertensive neuroretinopathy when areas of degeneration are present. However, one important point is that pronounced vascular hypertension is rare in brain tumor.

Prognosis is always serious and only a small number of patients with hypertensive encephalopathy recover. Death may occur during a convulsion from circulatory failure. A fatal outcome may be precipitated by intercurrent infection.

CEREBRAL EDEMA, THEORIES AS TO CAUSES

All but a few workers have attributed the increase in cerebrospinal fluid pressure in hypertension to cerebral edema, and this has repeatedly been proved on the operating table and post mortem. Rosenberg (37) is fully in agreement with this, but suggested the possibility that artefacts might be produced in some cases due to post mortem handling of the delicate tissues and to staining techniques. Though it is agreed that edema is present, no one has proved a constant reason why the brain should become waterlogged, often in the absence of any edema elsewhere in the body. It is the main purpose of this discussion to review the proposed theories as to the cause of cerebral edema in arterial hypertensive states, and attempt to conclude which theory or theories are most tenable, and to try to decide whether the same cause is likely for the cerebral edema in all the hypertensive states.

Yet the fact remains that all patients who present the picture of hypertensive encephalopathy do not show cerebral edema, either upon trephining or at autopsy. This fact led Pickering (35) to make a very comprehensive study of a series of patients who had persistently high blood pressures, regardless of

the cause. He based much of his study on the relationship of systolic and diastolic blood pressures to the cerebrospinal fluid pressure. Still his main objective was to determine if any change occurs in the absorption or formation rates of cerebrospinal fluid. He found that, although other factors must be concerned, the diastolic arterial pressure is the only one actually to show a close relationship to the cerebrospinal fluid pressure, and this relationship might result in one of two ways. In the first place, a raised cerebrospinal fluid pressure might produce a raised blood pressure. Dixon and Heller (13) have shown in the dog that when the absorption of cerebrospinal fluid is hindered by intracisternal injection of kaolin, the resultant raised intracranial pressure is accompanied by a rise in blood pressure. They postulated that the mechanism might be similar in cases of human hypertension, and supported this view by statements of previous authors that in some cases of hypertension, removal of cerebrospinal fluid produces a fall of blood pressure. Pickering (35), however, found this not to be true in his series of cases, as had Shelbourne, Blaine, and O'Hare (39). Pickering stated the second possibility that the cerebrospinal fluid pressure is determined by the diastolic arterial

pressure, or more probably by the mean arterial pressure to which the diastolic approximates more closely than does the systolic value. Such a relationship was explained by him as follows. Available evidence suggests that high blood pressure is due to an increased peripheral resistence resulting from arteriolar constriction. It is, however, unlikely that this constriction affects the cerebral vessels to any extent, since in animals they react very weakly to such agents as sympathetic stimulation and adrenalin and do not participate in the generalized vasoconstrictor response to the carotid sinus and depressor reflexes. The cerebral capillary pressure, and therefore the pressure in the choroid plexus which largely determines the rate of formation of cerebrospinal fluid, may thus be proportional to the mean arterial pressure. He admits, however, that evidence for this conclusion is not decisive, and final proof must wait until we have more precise knowledge of the mechanism of hypertension. Fishberg (15) later presented a series of cases on which he had made repeated Ayala Index determinations in an attempt to disprove that the elevation of cerebrospinal fluid pressure which occurs in hypertension is on the basis of increased spinal fluid formation. He found no constant rela-

tionship between the volume and the pressure of the cerebrospinal fluid. After the work of Fishberg, strength was lent to the views of Pickering concerning increased spinal fluid formation in hypertension by Griffith, Fry, and Roberts (22), who studied the interrelationships of increased intracranial pressure, papilledema, minute vessel pressure, cutaneous lymphatic flow, and blood volume. They found that increased intracranial pressure and papilledema occur in hypertension only when minute vessel pressure cutaneous lymphatic flow and blood volume are increased. In certain cases the increased blood volume is associated with an antidiuretic factor in the blood, possibly derived from the pituitary, and in other cases there is renal disease to account for fluid retention. His evidence, then, supports the theory that the increase in intracranial tension is due to increased spinal fluid formation. He, and Pickering, say that the papilledema is caused by fluid dissecting its way along the perineural sheath of the optic nerve, and thus infiltrating to the retinal area. However, they make no mention as to why generalized anasarca, or at least ascites, does not occur from the same source as the cerebrospinal fluid increase.

Blackfan and McKhann (4) remind us that in some cases of hypertensive encephalopathy the cerebral edema may be very marked, as shown at necropsy by flattening of convolutions, ventricles reduced to the size of slits, and a "medullary cone" due to compression of the brain stem into the foramen magnum. Also the pia may be edematous. Many have believed the edema due to ischemic injury of the brain capillaries due to arteriolar constriction, which would coincide well with the theory that the attacks of hypertensive encephalopathy are due to cerebral arteriolar spasm and resultant ischemia. However Fishberg (15) believes the opposite, i.e. that as generalized arteriolar constriction occurs, the constriction in the cerebral vessels is not so marked as that of other small arterioles throughout the body, and the added pressure in the cerebral capillaries increases the filtration of fluid into the perivascular tissue. This is in agreement with Cobb's (9) experiments, in which he found that the constriction of cerebral arteries which follows stimulation of cerebral vasoconstrictor nerves is only about one-tenth as great as the constriction of arteries of the same size in the skin and extracranial organs. So the cerebral arteriolar constriction is unable to keep pace with arteriolar

constriction elsewhere and transudation is augmented in the cerebral vessels. When cerebral edema is pronounced, the classic signs of increased intracranial tension are presented, as severe continous headache, projectile vomiting, epileptiform seizures, amaurosis, coma, and slow pulse. Palilledema appears shortly. Fishberg further states that individual cerebral arterioles or arteries may react to the rise in arterial pressure by intense spasm with ischemia of the part of the brain supplied and focal cerebral symptoms result. This would be most likely to occur in the presence of marked cerebral arteriosclerosis, for observations in peripheral arteriosclerosis indicate that diseased arterioles are prone to spasm.

In comparison of this theory to that of hyperhydration as set forth by Pickering (35) and by Griffith, Fry, and Roberts (22), let us consider the response of the patient to venesection. The latter authors argued, due to the well known response to venesection of decreased blood pressure and consequent decrease in cerebrospinal fluid pressure, that an increase of blood volume must have been present to have produced this response. But when we consider one of the original mechanisms known to be at fault in production of the arterial hypertension, which is

arteriolar constriction, we must admit that venesection merely "shrinks the foot to adapt it to the size of the already shrunken shoe", so it could apply equally to either of the theories.

It appears that the effect of the cerebral ischemia and anoxia, as reported by Blackfan and McKhann (4), should not be taken lightly. It seems that even if, as Fishberg (15) says, the cerebral intracapillary pressure is increased by greater peripheral than cerebral vasoconstriction, cerebral ischemia and anoxia must be present and must play an important part in the physiopathology of the process, the anoxic damage to the capillary walls resulting in increased transudation of fluid. As has previously been stated, Browder and Meyers (6) found that the minute blood volume is decreased in patients who have elevation of the cerebrospinal fluid pressure. Also, the findings of Michelson and Thompson (31), Forbes, Cobb, and Fremont-Smith (18), and of Maurer (29) lend support to the theory of Blackfan and McKhann, that anoxia may produce a reversible damage to the cerebral capillaries to allow for transudation of fluid, with a return to normal when the anoxia is corrected. The above authors all found that administration of carbon monoxide gas and of gas containing only six per cent

oxygen to animals and to human subjects causes an increase in the cerebrospinal fluid pressure with a return to normal in all cases after administration of one hundred per cent oxygen. On the other hand, O'Connell (32) states that maintenance of normal cerebrospinal fluid pressure depends on the filling of the cerebral vessels, as shown by the fact that almost immediately after death the cerebrospinal fluid pressure is reduced to atmospheric pressure, probably due to cerebral vascular collapse. This again adds weight to Fishberg's (15) theory of hydrostatic transudation of fluid to produce the edema.

Other interesting studies include those of Pickering (35) and of Cope (10), who attempted to prove or to disprove any possible relationship of the osmotic pressure of the blood and spinal fluid proteins to the cerebral edema which is found in arterial hypertensive states. Cope found that in cases of nephritis with generalized anasarca, there is definite reduction of the protein osmotic pressure of the blood, which disappears coincidently with subsidence of the edema. But in his cases of of non-edematous nephritis, some of which showed hypertensive encephalopathy and increased intracranial tension, he uniformly found no reduction of

of blood protein osmotic pressure, except slightly just before death in a few cases; conversely, he found the blood osmotic pressure to be higher than normal in a few cases. Pickering carried his work further and made comparative studies of the colloidal osmotic differences in the blood and the cerebrospinal fluid. He found no constant relationship to account for the cerebral edema proved to be present either on trephine or at post mortem. However, he did find that in cases with spinal fluid pressures exceeding 250 mm. of water, there was slight elevation of spinal fluid protein levels above the normal, which he attributed to increased permeability of the cerebral capillaries; this, of course, would be expected on the basis of the findings of Blackfan and Hamilton (3), as presented above.

Repeated studies of the relation of retention of chemical substances by the kidneys to the cerebral edema of the nephritides have shown the two processes to be independent, and neither the result of the other. This was first recognized by Oppenheimer and Fishberg (33) in 1928, who found that hypertensive encephalopathy and increased intracranial tension are independent of the blood urea and non protein nitrogen levels, and that either may be altered with-

out changes in the other. Almost all workers in this field have since corroborated this observation.

HYPERTENSIVE NEURO-RETINOPATHY

Hypertensive neuro-retinopathy is a term applied to the eye signs characteristic of the afore-mentioned hypertensive states, i.e., acute glomerular nephritis, essential hypertension, lead poisoning, and eclampsia gravidarum. In production of the eye signs and symptoms, there are three mechanisms involved:

1. Constriction of the retinal arterioles.
2. Lesions of the retinal arterioles.
3. Increased intracranial pressure.

As we are here primarily interested in increased intracranial tension in hypertensive neuro-retinopathy, this discussion will be partially limited to the role of the increased intracranial tension in production of the ophthalmologic signs and symptoms.

The classic ophthalmoscopic signs of hypertensive neuro-retinopathy are, in the usual order of their occurrence:

1. Contraction of the arterioles; silver wire arteries.
2. Progressive papilledema, with some swelling of the adjacent retina. Papilla also is reddened due to venous congestion.
3. Late, grayish clouding of the retina, first peripapillary.

4. Cotton-wool exudates in the retina, due to fatty degeneration and edema.

5. Occasionally, flame-shaped hemorrhages.

Concerning the pathogenesis, it appears that ischemia resulting from angiospasm is an important factor. Active, rather peristaltic spasticity has often been observed in the retinal arterioles with eclampsia gravidarum.

However, patients with brain tumor often present a rather typical picture of hypertensive neuro-retinopathy, the obvious cause being increased intracranial pressure. Cushing and Bordley (12) in 1908 noticed disappearance of retinal lesions following subtemporal cecompression in cases of chronic glomerular nephritis with increased intracranial pressure. Later, many others made similar observations.

Shelbourne, Blaine, and O'Hare (39) observed that nineteen of twenty hypertensive patients with a cerebrospinal fluid pressure of over 200 mm. of water had papilledema, while the latter was present in only two of thirty patients with lower tension of the liquor. Pickering (35) later found hypertensive neuro-retinopathy in all his hypertensive patients with a cerebrospinal fluid pressure over 250 mm. of water, while this lesion was present in only one of

twenty-one patients with lower cerebrospinal fluid tension. Well marked papilledema in hypertensive neuro-retinopathy is evidently a manifestation of increased intracranial pressure. The same is true of pronounced distention of the retinal veins, which often precedes manifest edema of the disc.

In summary, it may be assumed that where marked papilledema and venous destention are present, there is increased intracranial tension. Where the retinal picture is more markedly that of arteriolar manifestations, angiospasm is a pertinent factor. In all cases, these two factors coincide and overlap to produce the ophthalmoscopic picture, but the variations in the retinal pictures of various patients is probably due to differences in proportion between angiospasm and increased intracranial pressure.

Concerning the prognostic significance, it was stated by Fishberg (15) that 90% of patients with hypertensive neuro-retinopathy die within two years. In cases of acute glomerular nephritis, if the renal picture is cleared, the retinal signs will also regress, sometimes to complete healing. This also is the case in eclampsia gravidarum where pregnancy is interrupted early enough.

HYPERTENSIVE HEADACHE

The symptom of headache has always been a vague and mysterious one of which the etiologic factors have been the source of much mythology, as well as scientific research, for centuries. The term "hypertensive headache" was initiated many years ago due to the incidence of headache in patients with high blood pressure. Since this time, many varied research problems have been undertaken in attempt to find some significant relationship between the two. As this topic is not of particular significance to the problem at hand, it will be given only a brief resume.

In 1913, Janeway (23) described the typical features of the hypertensive headache, which observations are strikingly similar to those described by present day authors. The headache is one which appears on awakening, or which wakes the patient in the early morning hours. It has its greatest intensity before arising and passes away either immediately after breakfast or during the course of the morning, only to reappear in the same manner day after day for considerable periods of time. The intensity and location of the pain are somewhat varied, the most severe being similar to rather intense migraine, and in a few cases attended by nausea and vomiting.

Janeway also observed that a surprising number of the hypertensives with headache have been subject to what had been termed migraine headache throughout their lives.

Sutherland and Wolff (40) remind us that the term "hypertensive headache" merely implies severe and incapacitating headache associated with high blood pressure and does not necessarily imply hypertensive encephalopathy or hypertensive crisis. The term, they state, is misleading since it implies headache proportional in severity to the degree of elevation of the blood pressure, which he has found not to be true in many cases in which bed rest afforded relief of the headache without depression of the blood pressure.

Whereas many have attributed the headache of hypertension to either vascular contraction or dilatation or both, this appears to be a difficult problem to either prove or disprove. The work of Schumacher and Wolff (38) and of Wolff, Kunkle, and Ray (44) and (24) indicates that increased intracranial pressure per se plays no important role in headache, at least in some cases. They assumed this after increasing the cerebrospinal fluid pressure in a series of subjects to as high as 850 mm. of water for as long as two minutes without production of headache. How-

ever, other workers have reported severe headache on increasing spinal fluid pressure to 450 mm. of water, and also by withdrawal of as little as 12 cc. of spinal fluid.

Since the headache which occurs with brain tumor often simulates closely the hypertensive headache, many authors, including those above, attribute the headache to traction on pain-sensitive structures within the calavarium, and state that increase or decrease of the cerebrospinal fluid pressure is only a contributory rather than an essential or sole factor.

THERAPEUTIC MEASURES IN HYPERTENSIVE ENCEPHALOPATHY

The care of this condition is extremely variable, according to the particular needs of the individual patient, but there are many obligatory therapeutic measures which almost universally apply. For the sake of this discussion, the treatment may be divided into two phases, i.e., the general treatment and the treatment aimed at lowering the cerebrospinal fluid pressure.

Of the general measures in therapy, Fishberg (15) places venesection first on the list, and states that it should be done in all patients except those who show signs of an anemia. This procedure gives quickest amelioration of the acute symptoms, and if performed during the prodromal period, may prevent the active attack of hypertensive encephalopathy. Reed (36), however, states that venesection is not indicated in all cases, but should be carried out in the face of increased headache, increasing eye signs, and rising blood pressure. Also, he states, this treatment is especially valuable in patients with essential hypertension and in those showing signs of left-sided heart failure.

The use of sedatives is of great importance in prevention of convulsive attacks, control of the at-

tacks, and in treatment of the post-convulsive patient. The choice of sedatives is open to much discussion. Reed (36) recommends the use of sodium luminal, grains three, during the prodromal period for prevention of convulsive attacks, this therapy to be repeated every two hours until improvement is noted in the patient's condition. This should be followed by 20 to 40 grains of chloral hydrate in four ounces of water per rectum. In the convulsive type, almost all authors agree to the use of either morphine sulfate intramuscularly or sodium amytal intravenously, the latter especially if the seizures are frequent and prolonged. If these measures fail to control the seizures, chloroform anesthesia is very good and effective therapy. After control of the convulsion the patient must be kept quiet; chloral hydrate per rectum is again recommended for this.

Care of the general condition also includes comfortable bed rest, exclusion of tedious examinations, and prohibition of visitors. Oxygen in the form of fresh air is helpful. A warm soapsuds enema seems to bring some relief and it prepares the bowel for medication that is usually necessary. The convulsive type requires protection from injury, but should not be actively restrained. The tongue should be watched

and mucus removed as it collects. This is best accomplished by lowering the head of the bed and using suction apparatus. The patient must be watched constantly for signs of impending cardiac failure.

When one considers the lowering of cerebrospinal fluid pressure, the first measure which comes to mind is lumbar drainage; this treatment, however, must be done with extreme caution and only in selected cases. It should not be performed until the program of treatment is well under way and there has been a lull in the convulsive storm. Then it should be done slowly, the fluid being allowed to escape drop by drop, and only a small amount at any one time. It should be kept in mind that too active drainage may cause untoward effects, and occasionally the most dreaded of all, the herniation of the edematous brain into the foramen magnum.

The use of various types of hypertonic solutions for reduction of the cerebral edema in these cases has proved of great value. The use of magnesium sulfate solutions, as advocated by Blackfan and Hamilton (3) in 1925, has repeatedly proved to be a very valuable measure. Blackfan and Hamilton, in treating nephritic children with cerebral edema, used 30 to 60 cc. of 50 per cent magnesium sulfate solution orally every

four hours if before the convulsive attack; during the convulsive attack, he administered a two per cent solution intravenously in dosage of 10 cc. per kilogram of body weight. Approximately the same regimen is used today. It is thought that the action of magnesium salts is to relax smooth muscle, and thus relieve the arteriolar spasm of the cerebral vessels. This improves cerebral circulation and allows the excess fluid to be carried from the tissues. Respiratory depression may result from the magnesium therapy, but is readily relieved by intravenous administration of five per cent calcium chloride solution.

The use of hypertonic sugar solutions, especially in conjunction with magnesium sulfate therapy, is a valuable aid in reduction of cerebral edema. In 1921 Weed and Hughson (41) and (42) experimented with injection of solutions of various concentrations, with special interest in the cerebrospinal hydrodynamic effects. They found that intravenous injection of relatively large amounts of Ringer's solution causes temporary rise in cerebrospinal fluid pressure, with a quick restoration to normal; distilled water administered intravenously produced prolonged rise in pressure; intravenous injection of both hypertonic glucose and hypertonic sucrose produced initially a

rise of cerebrospinal fluid pressure, followed by a prolonged depression. It was later recognized that the use of 50 per cent glucose produces a secondary rise in pressure due to diffusion of glucose into the cerebrospinal fluid, and that this effect was not true of 50 per cent sucrose solution. Bedford (1) has confirmed this in his experiments on dogs, and pointed out that hypertonic saline solutions have an effect comparable to that of glucose. Consequently, many authors advocate sucrose as the hypertonic solution of choice. The adult dosage is 200 cc. of 50 per cent sucrose solution given slowly intravenously, followed by 100 cc. in twenty-four hours.

Subtemporal decompression, as indicated by Cushing and Bordley (12) in 1908, is a valuable procedure in cases with chronically elevated cerebrospinal fluid pressure or when hypertensive neuro-retinopathy threatens to go on to total blindness. Results may be disheartening, but often there may be regression of the papilledema and relief of the headache. There may also result a fall of the systemic blood pressure due to relief of the intracranial tension and improvement of the circulation to the vasomotor center of the brain.

CONCLUSIONS

1. A review has been made of the cerebral effects of the arterial hypertensive states, with special reference to hypertensive encephalopathy and to the cerebrospinal hydrodynamic effects.

2. An attempt has been made to determine why the cerebrospinal fluid pressure is so commonly elevated in the arterial hypertensive states. It appears that the cause is, in most cases at least, cerebral edema which results from diffusion of fluid from the cerebral capillaries into the brain tissues. It is recognized that there is generalized arteriolar constriction in the arterial hypertensive states, and is further known that the cerebral arterioles possess less contractile ability than do arterioles elsewhere; this inequality of constriction would allow cerebral capillary pressure to be greater than capillary pressure elsewhere and fluid could literally be pushed into the surrounding cerebral tissues. This would be enhanced by the anoxic effect upon the capillaries resulting from reduced

blood flow.

3. The general therapeutic regimen has been presented, and may be outlined as follows:

   A. General therapeutic measures.

      a. Venesection.

      b. Sedation.

      c. Supportive treatment.

   B. Treatment aimed at lowering cerebrospinal fluid pressure.

      a. Lumbar puncture and drainage.

      b. Magnesium sulfate solution.

      c. Hypertonic sugar solution.

      d. Subtemporal decompression.

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