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Pathogenesis of apoplexy

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T H E P A T H O G E N E S I S

O F

A P O P L E X Y

by

PAUL V. BARTOS

Submitted to the Faculty in partial
fulfillment of requirements for the
Degree of Doctor of Medicine

University of Nebraska

College of Medicine

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THE PATHOGENESIS

OF

APOPLEXY

P R E F A C E

As great as the victories of medicine against disease have been, man continues to die before his time. Senility is eventual and cannot be conquered (as yet), but it may be forced to retreat, and many of its most dangerous divisions may be routed or even annihilated. If we should pay one-half the attention to old age as we do to infancy, many useful lives that are now blighted or lost would be prolonged into the vigor of full blown maturity.

Apoplexy, according to insurance statistics is the fourth cause of death in people past the age of forty, ranking after heart and kidney diseases. I am convinced that heredity is not without importance as a causative factor in apoplexy, for it is well exemplified in my family tree. My memory is still marred by the manner in which my paternal uncle suffered for five years in a hemiplegic state. Perhaps this

memory and the fact that several of my other relatives and ancestors died of apoplexy prompted me to choose apoplexy as my thesis subject.

I have confined myself to the discussion of the pathogenesis, for it is this phase in which I am particularly interested. My reading, however, has extended over the entire subject, and even though the symptoms of apoplexy suggest other conditions, such as, diabetic and uremic coma, epilepsy, hysteria, and alcoholism, all of which makes diagnosis difficult, little can be done in line of treatment since irreparable damage has been done. As far as treatment is concerned, prophylaxis is by far the most significant.

In the first section of this paper, a resume of the history and definition of the subject is included. The remaining sections are devoted to the discussion of the prevailing concepts of the pathogenesis of apoplexy.

I N T R O D U C T I O N

Few terms in medicine have caused more confusion than that of apoplexy. The word apoplexy is derived from the Greek's, who originally defined it as meaning, "to strike down, -- to stun". As originally defined and used, it was the name given simply to a certain complex of symptoms, and it brought into the minds the clinical picture of a man who suddenly falls to the ground with loss of consciousness, labored breathing, a tense slow pulse, flushed face, and some degree of paralysis upon one side of the body. In course of time, pathologists found that this condition was often associated with hemorrhage into the brain, and hence the terms apoplexy came to be used as identical with the pathological condition cerebral hemorrhage.

Later it was seen that the brain lesion was sometimes an acute softening, rather than a hemorrhage; and at times there was found perhaps only an intense hyperemia or an edema, hence the terms hemorrhagic apoplexy, serous apoplexy, nervous, congestive, and embolic apoplexy were employed. The use of the word was then still further extended and made to apply to all conditions in which hemorrhage occurred, so that authors began to speak of an apoplexy of the lungs, or of the kidney, or of the spleen, or of the liver. In effort to reduce the possibility of confusion, I shall use the term only to indicate that sudden loss of consciousness with usually more or less paralysis, that is produced by cerebral hemorrhage, or by acute cerebral softening due to an embolus or a thrombus.

Apoplexy has been observed since

the time of Hippocrates, (460 B.C.), and in those early days it was, as now, a striking and serious visitation. Hippocrates called apoplectics, "those who in health are taken with pains in the head, fall down, become suddenly deprived of speech, and have stertorous respiration. They die" he says, "in seven days or less if fever sets in." Galen (150-200 A.D.) gave a similar description, except that it did not include headache among the symptoms of attack. Paulus Aegineta, in the fourth century of the Christian Era, describes apoplexy as that condition in which all parts of the body have lost together sense and motion, and the victims "lie without voice, without motion, without sense, and without fever."

The Greek writers seem to have considered apoplexy and palsy as diseases of the same nature. Aretaeus, who lived in

the second century, A.D., says, "apoplexy, paraplegia, paresis, and paralysis, are all the same kind, and consist in a defect of sensation, or of motion, or of both." Apoplexy is a palsy of the whole system; of mind; of sense, and of motion. Galen says, "when all the nerves have lost sense and motion together, the disease is called apoplexy; when this happens to a part only, whether the right or the left, it is called palsy." This view was believed by Alexander Trallianus in 400 A. D. who stated that, "the disease paresis, commonly called paralysis, is no other than a loss of sensation and motion in the parts affected. It differs from apoplexy, in as much as this is a want of sensation and motion of the whole body, with injury of the governing energies, and death in some part; but paresis is a death of one part, or of half the body, or of

certain nervous parts, which have suffered obstruction without disease of the brain or spinal marrow." It may be inferred that Trallianus agreed with Aretaeus and Galen in the opinion, that apoplexy is general, and palsy a partial abolition of sense and motion.

In 1675 Wepfler showed that in apoplexy there was a hemorrhage in the brain, and Morgagni published many reports confirming this observation. The pathological anatomists of the eighteenth century devoted a great deal of study to this subject and did much to elucidate it. Up to the year 1820 according to Frank, the apoplectic stroke had been described by more than two hundred and fifty writers. Abercrombie in the last century, and Virchow in the present century, were among the first to show that apoplexies were dependent primarily upon diseases of the cerebral blood

vessels. This subject as later worked out in detail by Charcot and Bouchard. The symptoms of apoplexy were fully studied in the last century also by Boerhaave and his school in Holland; by Abercrombie and Todd in England, and by Richoux and Andral in France.

PATHOGENESIS OF APOPLEXY

The problem of apoplexy presents difficulties which are typical of those met in all investigations of pathology. While the problem itself is one of the most striking and dramatic events in clinical medicine, the pathologist must draw his conclusions from a static fixed picture, and then reconstruct the process in all its stages from the comparison of a great number of different final states. No wonder then that the interpretations are never conform-

able, and it is surprising that not only the interpretations, but even the facts of observation differ so largely with different investigators. This incongruity is to a certain extent caused by a confusion in terminology, for authors apply the same term for different things or different terms for the same thing. Therefore, it is necessary to summarize briefly what is generally accepted as the anatomical equivalent of apoplexy. Three different kinds of lesions can be classified: first; there is massive hemorrhagic apoplexy in which is found a massive haemorrhage in one or several areas of the brain. Often from the area in which the hemorrhage occurs a solid clot is easily separated and falls out on section, leaving behind a cavity with hemorrhagic walls. Secondly; there is softening, an area which does not show hemorrhage, but a diminished consistency

and slight or more pronounced shrinking or discoloration of the tissue. Thirdly; there is the hemorrhagic infarction, which presents a picture similar to the softening, and distinguished from it only by the extravasation of blood into the softened area, usually in innumerable small stipples. A great deal of confusion in the more recent literature is due to the fact that a distinction is not always clearly drawn between the apoplectic hemorrhage, and the hemorrhagic infarction. In a large number of cases, however, one finds other additional lesions, such as small foci of necrosis and scar formation in the basal ganglia and in the cortex. As these smaller areas of necrosis differ from the large areas of softening only in size, it seems to be obvious that they represent the anatomical equivalent of short transitory attacks of fainting, giddiness, aphasia, blindness, or

paresis which may occur in those patients.

In reading the description of cases, it is quite evident that most of the anatomical investigations on apoplexy deal with the type characterized by massive hemorrhage. Until a few decades ago the pathogenesis of this disturbance seemed to be clear. Charcot's view was more or less accepted. Charcot and Bouchard (1868) had reported seventy-seven cases of cerebral hemorrhage, in all of which they found circumscribed small swellings of the arterial branches within the brain. These they called miliary aneurysms. These miliary aneurysms were 0.2 to 1 millimeter in size and had a globular or fusiform shape. Their number varied from two to one hundred in each case, and were found not only inside, but also outside the actual focus. According to Charcot and Bouchard, the aneurysms were not caused by arteriosclerosis, but by a diffuse per-

arteritis, with thickening and proliferation of cells on the vascular adventitia and muscularis. As Charcot and Bouchard saw aneurysms in the wall of the hemorrhage, or in close relationship to the focus of the hemorrhage, it seemed probable that this hemorrhage was associated with these aneurysms. In order to prove that these aneurysms were really the source of hemorrhage, the actual rupture must be seen. It is, therefore, important to note that in only three of their cases did Charcot and Bouchard mention definite ruptures of aneurysms.

Lowenfeld (1886), alleged by Stern (in 1938), pointed out in a thorough investigation of seventeen cases of hemorrhagic apoplexy with recent and old areas of hemorrhage, that the hemorrhage did not necessarily arise from the miliary aneurysms.

He found severe changes, which he described as a "simple fatty and granular degeneration" in the walls of the cerebral vessels in such cases. He found that it was chiefly the media that was affected in the center of the apoplectic focus. He called this condition granular degeneration. The muscle fiber swells and becomes more refractive; the nuclei disappear, and the whole mass becomes finely granulated: these granules afterward conglomerate, the refractive power diminishes, and the whole muscular wall may disappear. The adventitia is least affected, but in this layer the nuclei are often increased in number. In the adventitia cells showing fatty degeneration are often found, as are also red and white blood cells, and occasionally dissecting aneurysms. Lowenfeld considered this a process of diapedesis, for he did not find a rupture of the inner vascular wall.

Pick and Ellis (1910), as cited by S. J. Webster (1929), made thorough and exact investigation into the nature of these aneurysmal formations. They showed that the brain substance and elements of the vessel wall were destroyed by either subadventitial hemorrhages or extramural hematomas surrounded by fibrin, and not by true aneurysms. These are formed by the rupture of a previously normal vessel, or of a vessel which has shown dissection of its layers. According to Pick and Ellis a fatal hemorrhage can never occur from these military aneurysms, and the aneurysms which actually are seen to be ruptured within the hemorrhagic area are of a larger size than the military aneurysms of Charcot and Bouchard. Pick also emphasized that the tissue surrounding the military aneurysms never showed a marked cellular reaction; thus it may be presumed that they did not arise a long time

before death. Shennan (1915) came to a similar conclusion, namely, that a local dilatation of the diseased vessel ruptures and produces the apoplectic hemorrhage. This local dilatation is not a pre-existent chronic change, but immediately precedes the rupture. It is also of a larger size than Charcot's military aneurysm. The hemorrhage may follow the formation of a dissecting aneurysm similar to the dissecting aneurysms of the large arterial trunks. In Shennan's study, he only found one case of a military aneurysm, which corresponded to Charcot's and Bouchard's description. As early as 1895, it was reported that in a series of thirty-four cases, none had shown any evidence of military aneurysms. In some cases however, the adventitial space was filled with blood. Thus, findings showed even more conclusively,

that the classical theory of causal significance of the military aneurysms in apoplectic hemorrhage was not entirely adequate.

This was the situation when the paper by Rosenblath (1918) appeared. His study, and resulting explanation (which was interpreted by G. B. Hassin, 1927) formed the basis of discussion in most of the succeeding investigations, just as Charcot's and Bouchard's work had done. Rosenblath had found in the earlier French literature an article by Rouchoux, who had given the following description: "a hemorrhage caused by rupture following alteration of the brain tissue." He considered this conception important. Too little notice had been taken of the numerous small hemorrhages so often found near the large lesions. There was not simple rupture of vessels causing small and infinitesimally small hemorrhages, but

these vessels had been subject to a process of necrosis. The tissue between such hemorrhage also shows signs of serious damage. Rosenblath found in macroscopical and histological study of eleven cases of two hours to fifteen days duration between apoplexy and death, that hemorrhage never occurred from one vessel alone, but from any vessels simultaneously; and that vessels and brain substance had both undergone acute necrosis in the area of the hemorrhage, and that the form of the lesion, and the mode of expansion of the hemorrhage could not be explained by the mechanical violence of the blood stream destroying the tissue. Hence, he concluded that the necrosis of the vessel and the brain tissue was the primary event, and that the hemorrhage followed into a previously necrotic area. What is the cause of this process of encephalomalacia? Rosenblath postulated an unknown toxin suddenly attacking a circumscribed cerebral area in which glia,

nerve fibers, ganglion cells, capillaries and veins are all destroyed in a diffuse manner or in patches which subsequently melt together. Some of the arteries escaped this process of necrosis, especially those of which the walls have become thickened, and resistant through arteriosclerotic changes. The blood that oozes through the vascular wall under very little pressure is derived chiefly from capillaries and veins. The arteries are often occluded by thrombi, and the blood cells do not suffer from this toxin. Rosenblath's hypothetical explanation of this process is unlikely. He postulated that a toxic ferment produced by the kidney caused the necrosis in the brain. This theory, which endeavored to explain the formation of the toxin was not accepted by succeeding investigators.

Although Rosenblath's conception

was a great stimulus to investigators which followed him, some of his results appear open to criticism. For instance, the presence of many punctate hemorrhages in the periphery is no evidence that the entire lesion must have been produced by the confluence of such small hemorrhages. The violence of a massive hemorrhage can undoubtedly produce small punctate hemorrhages in the neighborhood simply by the mechanical damage to the small vessels. Similar small hemorrhages may be found round a fresh bullet-hole in the brain. (Stammler 1927), or an experimentally injected chicken clot in a dog's brain, (Ruhl, 1927). But there seems to be a difference between these secondarily produced marginal small hemorrhages and the small foci of hemorrhage, which are to be seen in the peripheral zone of gross apoplectic lesions. This point requires

tissue and, as is well known, there are many cases in which the hemorrhage actually breaks through into the ventricle.

Several points in Rosenblath's theory have received ample proof. The source of hemorrhage is multiple in most cases. The vessels in the entire area of the hemorrhage undergo "arterio-necrosis". The expansion of the hemorrhage cannot be explained by rupture and mechanical violence only. Lastly, the small miliary dissecting aneurysms of Charcot and Bouchard are not the cause, but one of the accidental results of the process.

It seems to be an appropriate place to discuss the experiments of Lotmar, (1921) as described by L. Bowman (1931). He worked with dysentery toxins, and was able to cause, by a method of injection, a myelitis and an encephalitis, small hemorrhages and progressive and retrogressive changes of

of the vascular wall. In cases of nephritis, Lotmar also observed, that one often finds retinal hemorrhages and albuminuric retinitis, and it is this same characteristic changes one so often sees in apoplexy.

Lindemann(1924) as stated by Globus and Strauss (1927), confirms that there are always many vessels from which the hemorrhage occurs, and that hemorrhage is not so much produced by rupture as by diapedesis. Böhm (1927) compared the volume of both hemispheres, that is, the hemorrhagic and the normal hemispheres of the same brain. (Globus and Strauss 1927). The volume of the apoplectic hemisphere may be a quarter more than that of the healthy one. Thus there must be a considerable displacement of brain substance by the hemorrhage. This study caused Boehne to insist that the primary nature of the disease is in the brain tissue, and concluded that the vascular walls are only secondarily

affected. He could not accept the theory of an isolated spasm of the intracerebral vessels, because physiology teaches that one has always to do with the entire vascular areas, which contract or dilate under sympathetic or parasympathetic influence. He believed that the ischemia has a mechanical cause as exemplified: (1.) in the case of arteriosclerotic changes of intracerebral and extracerebral vessels; (2.) through spasm of cerebral arteries at the base of the pia. He also classifies two forms of hemorrhages characterized by: (1.) extravasation of erythrocytes into the perivascular sheaths and nearby cerebral tissue, and (2) large hemorrhages. Rosenblath had emphasized that in many cases one cannot judge by external appearance in which part of the brain the hemorrhage had occurred, and that the hemorrhage did not obviously displace a considerable amount of brain substance. On

the other hand Bohne's contrary statement is not against the presumption of a preceding necrosis.

Westphal and Bar (1926) studied the problem of apoplexy and obtained results similar to Rosenblath, however, they tried to replace his hypothesis of a chemical noxis destroying the brain tissue by another, which seemed more in accordance with clinical findings. Westphal's view is substantiated and built on certain facts. Spasm of the retinal vessels has been observed occasionally in patients with arterial hypertension, and in whom certain paradoxical micro-capillary reactions have been observed. There was no "reactive hyperemia", but rather angiospasm after arterial compression. Moreover, it is true that apoplexy is often preceded by minor fits, which obviously do not lead to a gross hemorrhage. From these facts, combined with the anatomical findings, Westphal draws the conclusion that in arterial hypertension, a

local arterial spasm producing ischemia and necrosis precedes the hemorrhage. This hypothesis necessitates the assumption that the cause of the necrosis of the artery is a preceding arteriospasm, and that hemorrhage follows the arterionecrosis with subsequent tissue necrosis. Westphal mentions cases in which the clinical picture was that of a typical stroke with following paralysis in a patient with arterial hypertension, and in which at post-mortem neither a lesion in the brain, nor an obstruction of the vessels was found. In such cases a transitory ischemia due to an arterial spasm may have produced the stroke. Jaffee (1927) studied the vessels in the case of a gross cerebral hemorrhage occurring in an eclamptic woman of thirty-three, who had high arterial pressure and no signs of arterio-sclerosis. He followed Westphal's theory. Globus and Strauss

We can only say that the same diseases which tend to produce softening and diffuse proliferative changes in interstitial tissue also leads to hemorrhages. The immediately causal connection between the two processes postulated by Westphal is not proved.

Westphal's view is fairly typical of current opinion regarding our present subject. While in the classical literature hemorrhage was almost identical with vessel rupture, and softening with thrombosis, the conception of transient "functional" vascular disturbances has dominated recent work.

It is, however, often very difficult to differentiate clearly between unfounded conjectures and fruitful theories. Therefore, it is necessary to inquire why the basis of a direct causal connection between a visible organic lesion of a vessel and the resulting brain lesion was aban-

done in favor of a much vaguer and less-defined conceptions. It is quite a common experience in morbid anatomy that there may be no immediate connection between the degree of arteriosclerosis on one side and the amount or number of hemorrhages and softening on the other. One may find on the one hand extensive and numerous lesions in a brain with only slight disease of the vessels, and on the other no gross lesions in a brain with severe arteriosclerosis (Neuburger 1926). If a comparison is made in arteriosclerotic brains between the extracerebral vessels in an area of high vulnerability, such as the pons, and those of a very resistant area near to it, as the hypothalamus, the degree of arteriosclerosis is found to be the same in both. Such observations deal only with a gross examination of extracerebral vessels. In regard to the intracerebral vessels, the

occurrence of cerebral necrosis in the absence of visible obstruction is reported by a number of different observers. Study and report^{of} cases of cerebral softening in which serial sections of the arteries to the softened areas^{were made,} did not reveal the presence of either thrombosis or obliteration. Unfortunately, these cases are only mentioned without details in a discussion. Spielmeyer (1924) as cited by Globus and Strauss (1927) reported cases of arteriosclerosis with necrotic areas of apparently the same age scattered all over the cortex in which the arteries supplying these areas showed no recognizable change. He speaks of "vasomotor" disturbances in cerebral arteriosclerosis. Neuburger (1930) reports an interesting case of a healthy man of 31 who, after a traumatic commotion with a lucid interval of one hour, developed a hemiplegia and died two days later. At post-mortem no lesion of the skull was found,

but there was a softening in the area of one of the branches of the middle cerebral artery though the vessels were healthy and patent. Neuburger draws a parallel to the post-traumatic segmental arterial spasm, which has been observed in a living patients by surgeons. In most of these surgical cases, however, a lesion of a neighboring vein seems to have preceded the spasm of the artery. A good example is the case in which the ligation of a jugular vein was followed by a hemorrhagic softening on the same side. In 1927 Rosenblath described twelve cases of arterial hypertension with cerebral softening in which he found vascular changes similar to the arterio-capillary fibrosis of Gull and Sutton (1872). But as these vascular changes were not merely confined to the area of softening, it is probable that such vascular changes were

not the immediate cause of the necrosis. No other obstruction of the arteries, embolic or thrombotic, was seen. H. Spatz (1935), as cited by Stern (1938), described a case of cerebral form of Buerger's disease in a man of forty-three years old. There were varying symptoms of speech disorder, mental disturbance, and transitory paresis throughout the seven years of illness. The anatomical examination finally revealed a proliferative endarteritis and organizing thrombosis of both carotid arteries and several of their branches, especially the left cerebral artery, which resulted in multiple diffuse lesions of the nervous tissue. There were similar changes in the coronary arteries. There was no evidence of arteriosclerosis. In the clinical history there was nothing suggestive of any gangrenous disease of the limbs, though there was considerable evidence of frequent vasomotor disturbance of the

extremities, such as paroxysms of coldness and lividity of hands and feet. The blood pressure was normal. From this and from the way in which the neurological and mental symptoms developed, Spatz concluded that cerebral angiospasm had preceded the organic disease of the vessels. If this is so we still do not know if the cerebral softenings did occur at a stage when the vascular disease was of a purely "functional" ~~in~~ character. A case was demonstrated with intact arteries in which there were symmetrical necrosis of long standing in the parietal and occipital lobes. In a case of cerebral softening, gelatine was injected into the arteries supplying the softened area. The arteries showed some small narrowings produced by arteriosclerotic plaques, but they were otherwise patent.

From all these facts it is quite evident that necrotic lesions of

the brain may occur without any associated visible obstruction (thrombosis, embolism) of the arteries. As the shape and distribution of such lesions suggest their arterial origin, they must have resulted from transient "functional" non-organic, or vasomotor disturbance. Thus for the pathogenesis of a great number of the cerebral softenings the function of the vessels becomes more important than their morphological picture. This view receives further support from those cases where completely obstructed arteries have not caused any necrosis; as is well known a slow development of the obliterative process may allow a sufficient anastomotic supply.

The next important problem is to determine if the same or similar transient "functional" disturbances of the vessels, the nature of which is not known, can produce not only softenings but also hemorrhages. Lampert and Muller (1925) as

cited by G.W. Robinson (1932), have carried out an interesting experiment regarding the question of rupture of vessels by an increase of intra-arterial pressure. In human bodies of subjects who died with cerebral arteriosclerosis they injected fluid under a high pressure into both carotids. Only by applying pressure of one to two and a half atmospheres for six minutes did they succeed in producing ruptures with destruction of brain substance by the leaking fluid. Such pressures never occur in human pathology. From the results of such experiments, and from the histological findings of Rosenblath (1918) and Lindemann (1924) it may be said that cerebral hemorrhage is not likely to be the result of rupture of one or a few rigid blood vessels from a sudden increase in blood pressure.

There is no supporting fact of observation, either in the brain or in

any other organ, for Westphal's theory of an angiospasm causing not only necrosis of the parenchyma, but also necrosis of the spastic vessel itself.

Let us eliminate the massive apoplectic hemorrhage and consider only the hemorrhagic infarction. By the latter is meant the necrobiotic change with intact continuity of tissue and numerous capillary hemorrhage within the damaged area. Ricker (1934), alleged by Meakins, (1934), has shown in experiments on the pancreas and the ear of the rabbit that necrosis does not actually occur during the period of angiospasm and ischemia. It occurs during the stage of spre-stasis, when the blood stream in the pre-capillary and capillary bed is extremely slowed or when the blood flow has stopped and the vessels are engorged. Ricker shows that if he applied to an artery a stimulus of varying character, the result to be observed in the pre-capillaries and capillaries

belonging to that artery was always the same. With a light stimulus angiospasm and ischemia occurred. If he increased the strength of the stimulus the arterioles and capillaries widened and the leucocytes took up a marginal position and emigrated into the tissues through the stomata of the capillary wall: erythrodiapedesis then took place. At this stage the earliest necrotic changes of the tissue were observed. If he increased the stimulus still further, stasis occurred with massive erythrodiapedesis. Ricker observed that these processes occurred constantly in the same order, and that there was no difference if he applied chemical, mechanical or thermal stimuli. He assumes that the mechanism producing these changes is nervous. It is not possible here to go into any further details of the physiology of the circulation, but even if Ricker's findings really represent an invariable

law, there are reasons enough to believe that these observations cannot immediately be applied to the human brain. With this reservation, it may nevertheless be said that Ricker's attempted explanation best meets the histological picture of ischemic and hemorrhagic infarction.

In infarction of the brain it is possible to see all the different stages described by Ricker in his experiments. The ganglion cells may have undergone necrotic changes, the capillaries being extremely engorged; or the ganglion cells and capillaries may show the same changes with the leucocytes scattered through the necrotic tissue; or the ganglion cells may be unstainable by basic aniline dyes and there may be massive erythrodiapedesis, or there may be erythro and leuco diapedesis in a tissue in which the damaged ganglion cells are still to be seen. In other words, all stages described by Ricker in the living

animal may be seen in one or other lesion found at post-mortem of the human.

The necrosis in typical infarctions may be confined to a certain part of the grey matter, namely, the cortex or only the lower layers of the cortex. This sharp limitation cannot be explained by the angio-architecture, because some of the pial arteries pass through the cortex into the deep parts of the white matter. It could be explained by the higher vulnerability of the nerve cells to the ischemic noxa, a point which is so often emphasized. But the fact that the hemorrhage in hemorrhagic infarction is almost exactly confined to the area where the necrosis occurs is hardly explained in this way. If Ricker is correct in stating that the disturbance in the terminal vascular area-----prethrosis, leucodiapedesis, erthrodiapedesis, stasis, necrosis----- is due to a stimulus to the arterial trunk, which is transmitted to the

periphery by a nervous mechanism it is necessary to prove that such a pathological stimulus to the arterial wall does occur.

Consideration of this leads to a discussion of Schwartz's (1930) theory of embolic lesions. Schwartz, as cited by Kreis, (1938), considers that the obstructive factor in embolism is not the deciding factor, because it does not explain the limitation of the small hemorrhages to certain parts of the grey matter such as are quite common in embolic infarction. He believes that the true cause is the trauma to the arterial wall by the sudden lodgement of the embolus. This lodgement brings about a functional disturbance in the distribution of the artery. This disturbance follows the same mechanism Ricker has described in his experiments. Schwartz's extensive monograph on the pathology of apoplexy is based on Ricker's theory. The result is that all lesions in

arteriosclerosis, embolism and arterial hypertension, with the exceptions of massive thrombotic obstructions in arteriosclerosis, are due to pathological stimuli to the arterial trunk, which cause by a nervous mechanism, circulatory disturbance in the terminal distribution. Against such an hypothesis it must once more be emphasized that the circulation in the brain is in many ways different from that in the organs Ricker has studied, and, moreover, the analogy to Ricker's different stages is only to be found in ischemic and hemorrhagic infarctions, and not in massive apoplectic hemorrhages such as are so common in the basal ganglia, and the white matter of the cerebrum, and in the pons. The material which Schwartz demonstrates, illustrates once more the inadequacy of the classical mechanical theories. His hypothesis, however, is insufficiently supported by physiological facts. The

bilateral and absolutely symmetrical softenings and small hemorrhages in the basal ganglia, which he shows may possibly be explained by a nervous impulse transmitted symmetrically along the arterial tree to its terminal branches on both sides. Physiological evidence in favor of this, is, however, wanting. Again, these findings are not frequent enough to give sufficient basis for such a general explanation. Schwarz[†] stresses the morphological similarity between embolic and hypertensive lesions to prove the similarity in pathogenesis,---namely, a **shock** to the arterial trunk producing functional disturbance in the terminal vessels. It is known that embolus is likely to pass along vessels which continue the most direct stream of blood. As the lenticulo-striate arteries come off the middle cerebral artery opposite the end of the internal carotid, emboli

passing up the carotid tend to lodge in the lenticulo-striate artery. This results in embolic lesions being found chiefly in the distribution of the lenticulo-striate arteries. As Schwartz found in arterial hypertension the site of hemorrhage or softening to be in the distribution of the lenticulo-striate artery, he postulated that a sudden rise in arterial pressure passed as a wave from the heart along the most direct route---namely, into the lenticulo-striate artery. If this hypothesis is correct, it would be expected that those branches of the basilar artery which come off in a most direct line with the stream of blood would be the site of hemorrhage and softening in cases of hypertension. The vessels so placed are those going to supply a part of the hypothalamus including the mamillary bodies. Vascular lesions in these areas are, however, extremely rare. In fact, it should be pointed out that the site of vascular lesions is com-

monly in the distribution of the pontine arteries, which come off the basilar artery at a right angle or even more acutely.

Another attempt to explain the multiple hemorrhages in areas of infarction has been made. This suggests that the hyperemia is reactive to the lack of oxygen in the ischemic area, and the diapedic hemorrhage only as a higher degree of this reactive hyperemia.

It is only to be expected that Westphal's and Schwartz's hypothetical conceptions are followed by investigators who either returned completely to the classical and purely mechanical view or at least restricted themselves more to the observation of visible changes and rejected all other hypotheses.

In 1928, F. H. Mackay listed the chief causes of apoplexy as being (1) arteriosclerosis, (2) bacterial infection, (3) toxic degenerative processes, notably chronic

alcoholism and syphilis. Fearnside (1918) has described aneurysmal formation and considered them to be sometimes due to an inherent weakness in the vessel wall, a local developmental defect. He speaks of congenital weakness of the arterial wall at junctional points. According to Turnshull (1929) this aneurysmal formation is not an essential factor as the inherent defect in the vessel wall may lead to a break in the media without intervention of an aneurysm. C. P. Symonds (1929) collected an imposing series of aneurysms in young people with no sign of cardiovascular disease, and states that they are not uncommon. Goldflom's hypothesis, as cited by Mackay (1928), that a functional vasomotor disturbance analogous to that of migraine may set up capillary oozing, which appeared to be based upon insecure evidence; as insecure as the evidence that links migraine with vasomotor instability. The sudden onset with rapidly

developing signs cannot be conceded to be the clinical counterpart of oozing, but rather that of frank rupture whether or not it be preceded by aneurysmal formation. Autopsy evidence proves that aneurysm formation is not an essential pre-cursor of rupture. Cone and Barrera (1931) pointed out that from a pathological standpoint acute destruction of the brain from outside noxious agents, as in that occurring within, a reaction takes place which in its early phase is exudative or inflammatory. This reaction is frequently so intense as to suggest that an infectious agent is operative. This fact has largely been disregarded. If it is kept in mind one will not be tempted to regard the changes in simple trauma as essentially different from those in infectious processes, a difference that is not necessarily one of degree, but rather of time. In the aseptic destruction the

the evidence of inflammation disappear early; in infectious processes they persist for a longer period. In 1935 Otto Saphir~~s~~ stated that anomalies of the Circle of Willis with resulting interruption of the circulation between the internal carotid and vertebral arteries may form the anatomical basis of cerebral vascular disturbances. The recognition of such anomalies is significant, because they aid in the explanation of cerebral hemorrhage and encephalomalacia on morphologically demonstrable grounds in the absence of occluding lesions of the supplying arteries. J. St. C. Elkington (1935) also draws attention to the occurrence of cerebral vascular accidents in healthy persons without cardiovascular disease. He, too, suggested that they are due to a pre-existing vascular anomaly. Storrington (1940) emphasizes particularly the fact that functional vascular spasms such as occurs

in migraine can be the cause of softening of the brain. J.C. Paterson (1940) noted that intimal hemorrhages in sclerotic cerebral arteries are similar in structure to those described previously in sclerotic coronary arteries. They result not from the backflow of blood through the defects produced by rupture of atheromatous abscesses as were previously thought, but rupture of capillaries derived from the main arterial lumens. From his observations it appeared that capillary rupture with intimal hemorrhage is intimately concerned with the mechanism of cerebral arterial thrombosis, and possibly in certain cases, with the causation of cerebral arteriospasm and rupture. He suggested that the factors responsible for the rupture of the intimal capillaries in the cerebral arteries are high intracapillary pressure from hypertension, progressive atheromatous degeneration of the

supporting tissues, and increased capillary fragility from a variety of causes. He observed that intimal hemorrhages were noted only in areas of atheromatous degeneration, so that it was reasonable to suppose that the two are related. Many of the hemorrhages lay at the outer borders of the atheromatous plaques in proximity to the media, and it is reasonable to suppose that the sudden disruption of tissues by the hemorrhages may have set up transient spasms of the muscle coat. The walls of the cerebral arteries are known to be supplied by vasomotor fibers, and local spasm due to local injuries or influences definitely occurs. It must be admitted, however, that attempts to demonstrate nerve fibers in the actual area of the intimal hemorrhage have as yet been unsuccessful. He also noted that coronary and cerebral intimal hemorrhages are not infrequently found

in the same patient, a fact which suggests a common etiologic agent.

This leads to the question of the frequency of hemorrhages and softenings in certain areas and their extreme rarity in others. If arterial hypertension affects the vessels of all parts of the central nervous system equally, why is it that the resulting lesions are not distributed according to mathematical probability? In a series of ninety-one cases studied, the site of the lesion was as follows: there were seven hemorrhages and six softenings in the area of the posterior cerebral artery, especially in the region of the thalamus; six pontine lesions in the distribution of the basilar; eight lesions in the area of distribution of the posterior communicating artery; three lesions in that part of the internal capsule supplied by the anterior choroidal arteries. All the remaining sixty-one

lesions were in the distribution of the striate arteries. Boyd (1938) in his textbook gives a somewhat different distribution. In the order of frequency they are: (1) the area of the lenticulo-striate artery; (2) the white matter of the frontal lobe (anterior cerebral artery); (3) the pons and the cerebellum. Schwartz (1930), as cited by Kreis (1938), emphasizes that the predilective areas are similar in apoplexy associated with arteriosclerosis, arterial hypertension, and embolism. There was only one exception among his observation; the cortex was more seldom affected in hypertension than in arteriosclerosis or embolism. The areas most affected are the middle of the third of the corpus striatum and the claustrum, then the thalamus and the pons. The globus pallidus and the medulla oblongata extremely rarely showed lesions.

The most common cortical lesions in arteriosclerosis and embolism were located in the insula, the operculum the supra-marginal gyrus and the superior temporal gyrus.

If it were possible to find a common feature in the vascular supply of all the vulnerable areas, or in that of the most resistant parts of the central nervous system, it would undoubtedly advance knowledge as to the pathogenesis of these lesions. As early as 1874, the importance of the presence of extracerebral arterial anastomosis was stressed in explaining the resistance of certain sites to vascular lesions. Kolisko (1891), as cited by Reilly (1925), thought that the comparatively rare occurrence of such lesions in the area of the anterior choroidal artery might be explained by the acute angle at which this vessel branches off the carotid.

artery. But as has already been mentioned that the pontine vessels branch acutely from the basilar artery and that hemorrhages frequently occur from these branches. It is therefore unlikely that the angle of the branching is closely associated with the cause of the lesions. The striate and pontine vessels have in common the fact that their diameters at their origin from the parent vessel and at their entrance into the brain substance are the same. These arteries have no extracerebral anastomosis. On the other hand the extracerebral anastomoses so much stressed by the early authors are probably of importance when the anastomoses occur between vessels of the right and left side. Areas receiving such a double supply are extremely resistant to circulatory disturbance. As examples may be cited the spinal cord, colliculi, hypothalamic nuclei, and cortical areas adjoining the corpus calosum. The

multiple ramifications of the cortical arteries, in contrast to the striate and pontine arteries, may cause the blood pressure to be "stepped down" gradually, as Boyd (1934) expresses it.

As our knowledge of the embryological development of the cerebral vessels is still rudimentary, it is not possible to decide if the areas of high vulnerability represent areas in which minute developmental anomalies ^{occur}. In discussing local vulnerability mention should be made of the developmental abnormalities in the walls of the cerebral vessels giving rise to congenital aneurysms. It is doubtful if the occurrence of congenital obliteration of the posterior communicating artery found in arteriosclerotic brains with softenings and hemorrhages are actually of as much pathogenetic importance as Saphir (1935) suggests. As

these anomalies may frequently be found in otherwise healthy brains the cases described by Saphir seem to represent a coincidence. In cases of hypertension occurring in acute, subacute, and chronic Bright's disease, the area of the basilar artery seems to be more often affected than other areas. This finding may be related to cerebral edema or rapid increase of intracranial pressure, for hemorrhages and softenings may be found in the branches of the basilar artery in the brain tumors, sunstroke, apoplectic ventricular hemorrhage, and cerebral injury. There are different theories to explain this, none of which is as yet sufficiently substantiated. It was thought that a sudden displacement of cerebrospinal fluid by increased intracranial pressure compresses the vicinity of the aqueduct. It was also pointed out that the basilar

artery as it lies parallel to a bony surface is more exposed to the mechanical effect of increased pressure than other basal arteries. An idea that there must be some mechanism regulating the flow of blood to the brain through the carotid and vertebral systems respectively was also considered. As the result of the massive ventricular hemorrhage the mechanism becomes disturbed, and as a result, a backflow of blood within the Circle of Willis may take place.

As our knowledge of the physiology of cerebral circulation is still incomplete the problem of local vulnerability must await advances in physiology.

S U M M A R Y

The exact method of the developement of cerebral hemorrhage is not clear. There are many different viewpoints, some of which are quite incompatible with one another, and others of which are variations of another. The various theories of the pathogenesis of cerebral hemorrhage may be listed as follows:

1) ARTERIOSCLEROSIS This regards the arteriosclerosis of the vessel as the fundamental cause of hemorrhage. The vessel disease leads to rupture, and hence to hemorrhage. Rupture is assumed to occur as the result of miliary aneurysms which develop along the course of the vessels (Charcot and Bouchard) Bleeding may occur either from one such aneurysm or it may be the result of several such aneurysms in adjacent areas. Charcot and Bouchard, who are

responsible for the theory of cerebral hemorrhage by miliary aneurysms, regard the fundamental vessel change as a "sclerosing periarteritis" which causes thickening of the adventitia, with later weakening and complete disappearance of the muscular coat of the artery, followed by an aneurysmal dilatation of the vessel with eventual rupture. This diffuse sclerosing perⁱarteritis has nothing to do with the arteriosclerosis, according to Charcot and Bouchard. There are many objections to the theory of miliary aneurysms. Chief among these is the fact that hemorrhage occur in cases which it has not been possible to discover aneurysms, even on the most careful dissection. Furthermore, what have been regarded as aneurysms by some are looked upon by others as merely manifestations of thickening in sclerotic vessels.

2) SOFTENING THEORY: According to this

concept, hemorrhage takes place in a region in which there has been previous destruction of brain tissue by softening. This so-called pre-hemorrhagic softening presumably is never a complete softening, but is a disintegration of the nervous tissue sufficient to cause a diminished resistance in the brain tissue near a disintegrating blood vessel. This, in the presence of a rise in blood pressure, and rupture of the vessel, explains the fact that the hemorrhage usually is confined to a certain circumscribed area. Why a previous incomplete softening should determine the exact locus and shape of a hemorrhage is difficult to understand. Brain tissue is so soft that a hemorrhage may easily destroy it even in its normal state, and there is no reason to suppose that if a hemorrhage occurs into a pre-existing area of softening it must necessarily be confined to this area. Furthermore, the theory does not explain why hemorrhage

occurs: it only tells where it occurs.

3) VASCULAR SPASM This theory was propounded by Westphal, who asserted that arteriosclerosis is not an important factor in the production of cerebral hemorrhage. The fundamental cause of the hemorrhage into the brain is vascular spasm, which leads to softening of the brain substance, and may cause a defect or even necrosis on the arterial wall. A rise of pressure in a vessel or vessels in the softened area leads to rupture of the vessel and hemorrhage, due to decreased resistance of the surrounding brain tissue.

4) FERMENT THEORY According to this concept, the primary process in the cerebral hemorrhage is softening of the brain tissue due to the action of a ferment or enzyme, which is probably the result of kidney disease. By means of this ferment the brain tissue is softened and becomes necrotic. The vessels are destroyed and

the parenchymatous tissue also, and hemorrhage results from the necrotic vessels in the destroyed area.

5) DIAPYCNOSIS THEORY This concept is advocated by Ricker and Schwartz. It assumes that, as a result of nervous impulses playing on the cerebral vessels, there follows ischemia or anemia and stasis, depending on the degree of severity of the reaction. In the stage of stasis, diapedesis of red cells takes place through the capillary walls. This leads to massive hemorrhage in the brain by confluence or by involvement of larger vessels.

Whatever the actual state of affairs in the production of cerebral hemorrhage, whether it be due to military aneurysms, pre-hemorrhagic softening, enzymes, or spasm, the fact remains that hemorrhage occurs in persons with normal as well as diseased blood vessels, under conditions which accompany a sudden rise

of pressure, which is too great for the vessels to bear, with rupture and hemorrhage resulting. Obviously, whatever the exact mechanism, hemorrhage cannot occur without rupture of the vessel. It is probable that not all hemorrhages have the same mechanism. In the hypertensive cases military aneurysms undoubtedly account for some of the cases; erosion of the vessel walls from other causes for others. In cases of embolism a rupture of a weakened vessel is at the bottom of the trouble. And in other cases a congenitally weak vessel is the cause.

C O N C L U S I O N

In looking over the subject of the pathogenesis of apoplexy, the impression is obtained that a limit has been reached which purely descriptive investigation cannot pass. It has been shown that the original mechanical theories of the

early authors had to be abandoned in view of more recent findings, and it now appears as if cerebral softenings are not necessarily the result of obstruction of the arteries, and the concept that cerebral hemorrhage is due to rupture of rigid or deformed vessels by internal strain is not sufficiently supported by facts.

The role of the veins in the pathogenesis of apoplexy has been much neglected, due to the fact that little is known about the normal anatomy of the intracerebral veins.

Since embryological defects offer an explanation for the pre-dilection of certain sites for hemorrhage, a more intimate embryological study may be undertaken with advantage. It appears probable that investigations directed to correlate the different clinical forms of hypertension and the pathology of the brain may be fruitful.

The existence of a large amount of theories merely proves that none of them is adequate to explain all the facts. When the knowledge of the physiology of intracranial circulation has proceeded further, a better explanation of events may be available.

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