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## Original Articles

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### A CLINICAL AND PATHOLOGICAL STUDY OF A CONDITION OCCURRING IN THE AGED USUALLY ATTRIBUTED TO CEREBRAL ARTERIOSCLEROSIS<sup>1</sup>

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Through the kindness of Dr. William G. Spiller an opportunity has been given me to study, clinically and pathologically, a type of nervous disorder frequently observed in the aged, which is often correctly diagnosticated as cerebral arteriosclerosis.

Vascular disturbances within the central nervous system present a varied clinical picture, depending upon the degree of sclerosis, its extent and distribution, and the development of such accidents as hemorrhage, thrombosis, or embolism. The symptoms, therefore, may be transient or permanent, localized or general, or there may be a combination of general and localizing features. These several types, particularly the diffuse variety described by Collins (1), are familiar disorders, and only the important symptoms will be abstracted from the records of the four patients who have furnished the material for this contribution.

Three of the patients were from the wards of the Philadelphia General Hospital and the notes upon a fourth case were given to me from the personal records of Dr. Spiller, who in each instance confirmed the diagnosis of cerebral arteriosclerosis.

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J. M., a male, past the age of seventy, was observed sitting in a chair apparently inattentive to his surroundings. The drooping shoulders and head, expressionless countenance, marked emotionalism, and the partly open mouth from which saliva was dribbling, contributed to the general picture of senility and impaired mentality. When attempting to arise from the chair all movements were slow and deliberate, and in walking the short quick step with the feet wide apart were quite characteristic. There were no evidences of ataxia, paralysis, sensory disturbances, or degenerative involvement of the pyramidal tracts. The peripheral arteries and retinal vessels were sclerotic and tortuous, and arcus senilis was marked.

F. S., a male, past middle life, experienced some difficulty in speech and unsteadiness in walking. All movements were slowly performed, but not so much so as in the previous case, and mental impairment was less pronounced. When walking, the feet were placed wide apart; the stride was short and quick; and when performing this movement with the eyes closed, there was some unsteadiness which was intensified when standing with the feet together. There was evidence of slight ataxia in the upper extremities in performing the finger-nose test, and in the lower extremities when performing the heel-tibial test. This condition was more pronounced upon the right side. No gross sensory disturbances were detected. The pupils were unequal, the right slightly larger than the left, and both reacted slowly to light and during accommodation. All deep reflexes were present and slightly exaggerated, but equally so upon the two sides. There was no ankle or patellar clonus and plantar stimulation produced a normal response. The peripheral vessels were markedly sclerotic.

E. M., a patient of Dr. Heubner, of Allentown, Pa., was referred on October 30, 1912, to Dr. Spiller, who has given me the following notes: The patient is a male, 66 years of age, and a carpenter by occupation. He complained of almost constant pain in the forehead, and stated that last June almost a quart of blood was removed in order to give him relief. For the past two years there has been some difficulty in walking. While walking, but only then, he has fallen about five times and has had occasional attacks of unconsciousness. These attacks sometimes last an hour, but have never been associated with convulsions. Upon arising, and also at other times, he has suffered from dizzy spells, and memory has failed, so that he does not comprehend quickly.

Examination shows that the patient's comprehension of questions is very slow. The pupils are equal and the irides respond freely to light and in convergence. The remaining cranial nerves appear to be normal. Arcus senilis is marked. The biceps reflex is feeble on each side, and there is a fine tremor of each hand, especially during motion. He arises from a chair and begins walking with extreme difficulty and takes very short steps. There is no paralysis or ataxia in any of the extremities. The patellar reflexes are about normal, and the Achilles reflexes probably are present, but were not obtained because of the difficulty in making the patient relax his muscles. There is no real spasticity of the extremities.

The kidneys are said to be in good condition. The radial arteries are not particularly rigid, and the heart sounds are clear. The blood pressure has not been determined.

J. W., a male, 76 years old, was admitted to the Philadelphia General Hospital October 3, 1907, where he died January 30, 1908. I did not have an opportunity to observe this patient during life, but the anatomical material was placed at my disposal. The clinical history and examination are abstracted from the hospital records.

The family history is unimportant. When a child he had measles but was otherwise healthy until the age of 61. He denied lues; there was no evidence of secondaries; and the marital history was insignificant. Alcohol and tobacco were used moderately.

Fifteen years ago, after suffering from headache and vertigo, he suddenly fell and lost consciousness. Upon regaining consciousness, the right side was paralyzed and speech was "peculiar." The duration of these symptoms is not known, but it is probable that in a short time recovery was complete, for he enjoyed good health for about ten years, when he again complained of headache and vertigo, which occurred at intervals for a period of five years and terminated in a second "stroke" described as follows:

After some slight exertion he tried to sit down, but suddenly fell to the floor and lost consciousness. This attack lasted only about three minutes, when he was able to get up and walk with assistance, but the right leg was weak and the right arm was paralyzed with the exception of slight movement in the fingers. The face was not affected and he could talk better immediately after the stroke than when admitted to the hospital. There was no difficulty in swallowing nor was he aware of any sensory disturbance upon the right side. During the following two months, he recovered some use of the right arm, but vision, which was good before the attack, has gradually failed so that he is now almost entirely blind. Sphincter control, which was lost at the time of the "stroke," has not been regained.

The patient talks monotonously and indistinctly and there is definite mental impairment. The muscles are poorly developed and the peripheral vessels are markedly sclerosed. There is evidence of slight paresis of the right side of the face and the tongue is deviated to this side, but is under good control. All movements can be performed with the arms, with some limitation upon the right side. He places this arm over the head with a peculiar jerky movement, but is finally successful. Ataxia is present in both arms. The right biceps jerk is not obtained but the muscle reflex is present. The triceps jerk is exaggerated. Both of these reflexes are hyperactive in the left arm. There are no contractures.

Both legs are moved normally in all directions, with some limitation upon the right side. Ataxia in both legs is extreme, and more pronounced in the right. Edema and scars of old ulcers are observed upon both legs. The deep reflexes at the knee and ankle are equally exaggerated upon the two sides, but there is no clonus, and plantar stimulation gives a normal response. The following additional note was made by Dr. Spiller: "Ataxia in both lower

extremities is extreme and the limbs are slightly flaccid. There is slight ataxia in the upper limbs." Examination of the blood showed marked anemia, and the urine contained albumen.

Twenty-eight hours after death an autopsy was performed by Dr. Sykes, who made the following notes: "Coronary arteries prominent and tortuous. The mitral and aortic leaflets are thick, rigid, markedly sclerosed, and covered with numerous calcified nodules. The aorta has numerous calcified, sclerotic areas throughout its entire length. The kidney shows evidence of chronic interstitial nephritis." Apparently, no note was made upon the gross appearance of the central nervous system when it was removed, and when examined by me it had been in formalin solution for several months. The cerebrospinal vessels were not sclerotic and there were no calcified areas or aneurysmal dilatations. The convolutions of the brain were of good size and shape and the pia was not adherent. Since no gross changes were observed upon sectioning the hemispheres, brain stem, and spinal cord, it was suspected that a microscopic study of the tissue would furnish valuable information.

Very minute lesions are sometimes responsible for quite a definite group of clinical symptoms, and in such cases the histological study, to be of any value, must be thorough. Accordingly, microscopic sections from the following cerebral areas were carefully examined: The right and left optic nerves, the optic chiasma, the inferior portion of the medulla through the twelfth nucleus, the right and left paracentral lobes, the anterior central convolution of each hemisphere, the left internal capsule, the left superior temporal convolution in the region of the operculum, the right and left cuneus about the calcarine fissure, and the superior vermis of the cerebellum.

Transverse sections from the first cervical, cervical enlargement, low cervical, mid-thoracic, twelfth thoracic, and lumbar segments of the spinal cord were also studied.

Cross-sections were made from the following cerebral arteries: The right and left anterior cerebral, the left middle cerebral within the Sylvian fissure, the intracranial portion of both internal carotids, the right and left posterior cerebral, and the basilar.

The nervous tissue was stained with hemalum and acid-fuchsin, Weigert's myelin stain, Bielschowsky's neurofibrillar method, and thionin. Hemalum and acid-fuchsin, and Mallory's elastic tissue stain were used for the arteries.

In all, fifty-four microscopic preparations were carefully examined by Dr. Spiller and myself and in none of them did we find any single lesion which we felt was sufficient to account for the symptoms in this case; nor were there sufficient evidences of thickening in the blood vessels to support a diagnosis of cerebral arteriosclerosis.

My desire for completeness would lead me to include a descriptive paragraph for each of the fifty-four sections, but consideration for those who may have occasion to refer to this study makes me feel that a general summary of the pathological changes is preferable.

In several parts of the brain and spinal cord there is considerable round-cell infiltration, which is particularly marked about the optic

chiasma (Fig. 1). This infiltration extends for a short distance along the sheath of each optic nerve, but does not show a perivascular arrangement. The fibers of the optic nerve are not degenerated, and the axis cylinders are healthy looking. The pial and intraneural vessels show slight thickening of the media but are nowhere occluded. Similar evidences of a moderate inflammatory reaction are found upon the surface of the right anterior central convolution, the left superior temporal convolution, the cortex of the superior vermis, and to a lesser degree upon the surface of the

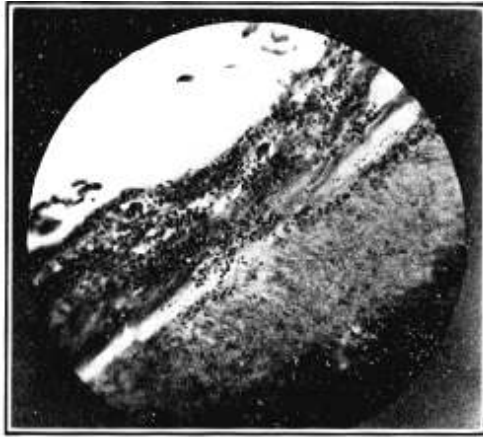


FIG. 1. Photomicrograph of a section of the optic chiasma, showing round-cell infiltration. Hemalum acid fuchsin stain.

pons and pyramids. Moderate infiltration is also observed in portions of the spinal meninges, particularly in the cervical and high dorsal regions, where it is most pronounced upon the posterior surface of the cord.

In the nervous tissue proper, there is no evidence of hemorrhage, softening, or degeneration in the internal capsule, and the pyramidal fibers of the pons appear to be normal. There are, however, variable degrees of cellular disintegration. The Betz cells show increased pigmentation and moderate chromatolysis. Similar changes are observed in the nucleus of the twelfth cranial nerve, in the Purkinje cells of the superior vermis, and in the anterior horn cells of the spinal cord. In many sections there is distinct shrinkage of the cerebellar cortex, and many of the Purkinje cells are completely disintegrated. Although the right and left halves of the brain-stem and spinal cord were not differentiated when the tissue was imbedded, it is quite obvious in the sections that cellular disintegration is more pronounced in one half than in the other, and further investigation has shown that the cellular alteration is greater in the right side of the cord. In the cervical region of the cord, where the cellular changes are more pronounced, it is found

that in one of the sections twenty-seven anterior horn cells can be counted in one half, while the opposite half contains only seven. This loss of cellular substance is probably not due to technical methods, since no cellular spaces were observed and one of the horns is slightly shrunken. In the middle thoracic cord, these cellular changes are confined mostly to the nucleus dorsalis, while the anterior horn cells are more nearly normal than elsewhere. The lumbar cord shows only slight cellular disintegration which, as in the cervical region, is more marked in the right half.

Weigert preparations from the upper cervical segment and the cervical swelling show moderate degeneration in each half of the posterior column. This degenerated area begins at the periphery in the region of the paramedian septum and extends ventro-medialward for about three fourths the depth of the posterior column, and is situated almost entirely in the fasciculus cuneatus in the region

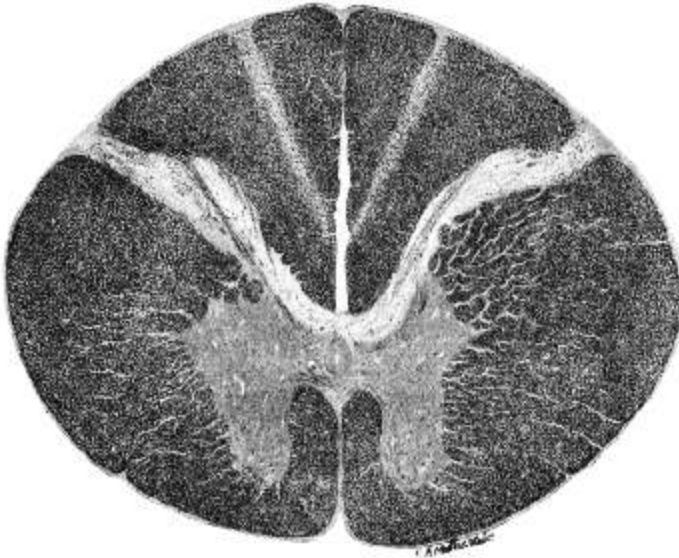


FIG. 2. Cross-section of the first cervical segment of the spinal cord, showing degeneration in each half of the posterior column. Weigert stain.

occupied by fibers arising from the lower cervical nerves. Under the microscope, this area shows definite absence of medullated fibers and has the appearance of a degenerated area which can be followed for a short distance into the lower part of the cervical swelling (Fig. 2). There is no degeneration elsewhere in the spinal cord, and the pyramidal fibers are normal throughout.

Microscopic examination of the cortical and intraspinal arteries shows no occlusion or marked thickening of the vessel wall, and considering the advanced age of the patient, the arteries at the base of the brain are surprisingly normal in appearance. The media is, in general, slightly thickened, and takes the stain poorly, and occa-

sionally there is moderate proliferation of the intima in the larger vessels, but in none of them is the lumen occluded or greatly reduced in size. There is no perivascular infiltration. The elastic tissue is, in general, diminished in amount, and slightly fragmented. Occasionally all three coats of an artery are reduced in thickness and slightly evaginated, but not to the extent of aneurysmal formation.

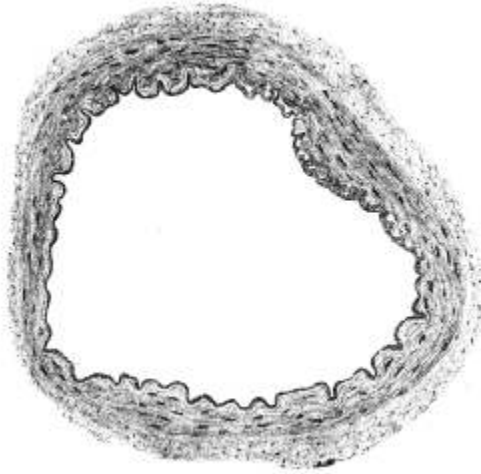


FIG. 3. Cross-section of the left middle cerebral artery, showing moderate sclerosis, which is more marked than in the other cerebral vessels. Hemalum acid fuchsin stain.

A cross-section of the left middle cerebral artery (Fig. 3) represents fairly accurately the more pronounced pathological changes which are present in the cerebral vessels.

Although the histological examination of the cerebral vessels does not confirm the clinical diagnosis of cerebral arteriosclerosis, there are other important pathological changes which may explain some of the symptoms. There were marked changes in the peripheral vessels, chronic interstitial nephritis, anemia, moderate local meningeal infiltration, and disintegration of the Purkinje cells, the cells of the nucleus dorsalis and the anterior horn cells of the spinal cord. In the absence, however, of a localizing cerebral lesion or cerebral arteriosclerosis, it is difficult to explain the two attacks of right hemiplegia with persisting hemiparesis, almost total blindness and mental impairment.

Conditions indicating localized organic lesions of the central nervous system without confirmatory pathological evidence have been recorded. Not infrequently, the pathological study in such cases has been incomplete, or when a more thorough search has

been made the presence of minute aneurysmal dilatations, microscopic areas of softening, or hemorrhage, have been demonstrated, and in the absence of these, the symptoms have been attributed to toxemia, pseudo-tumor, or arterial spasm. Chronic interstitial nephritis with defective elimination, anemia, and enfeebled circulation, offer suitable conditions for the production and accumulation of toxins, and it is not unlikely that some of the symptoms in the case which I have studied might be due to chronic renal or gastrointestinal intoxication. Although the clinical examination was made before the introduction of the Wassermann reaction, the presence of moderate round-cell infiltration in the meninges, particularly about the chiasma, together with evidences of old leg ulcers suggests the probability of a syphilitic toxemia.

That certain toxins exhibit a degree of selectivity for particular nervous structures, is an opinion supported not only by clinical observation, but also by experimental pharmacology and toxicology. The effect of strychnine upon the motor neurones, of cocaine upon the sensory system, and the localized paralyses of the infectious diseases and metallic poisons are familiar illustrations. Uremic or syphilitic toxemia, then, even in the absence of arteriosclerosis, might explain the cellular changes in the cerebral cortex, the lower motor neurone, and in the cerebellum with resulting mental impairment, flaccidity, sphincter paresis, and ataxia. It is also conceivable that such symptoms may be transitory or permanent, depending upon variations in the intensity of the toxemia and in the degree of cellular derangement. In spite of this apparently selective property of toxic substances it is difficult to imagine the cortical cells of the two hemispheres so unequally affected that hemiplegic symptoms are produced by a poison distributed through the general circulation. It is true, evidences of cellular disintegration may be present, and to all appearances of equal intensity in the two hemispheres; but, unfortunately, except in the presence of complete disintegration, cytology has not reached that degree of exactness which has enabled one to say when any particular cell has ceased to function or exceeds its limit of recuperative ability.

There is, however, some clinical evidence which suggests the occurrence of toxic paralyses of the central nervous system and toxic hemiplegias. Bornstein (2) records the case of an epileptic boy fourteen years of age, who for six years suffered from intermittent attacks of lameness, characterized by flaccid paralysis in certain muscles, ataxic gait, ankle clonus, reaction of degeneration, and absence of sensory changes. Recovery after each attack was complete.

The author is of the opinion that the condition was due to toxemia but does not suggest its probable source. Hochhaus (3) has reported interesting observations upon seven patients in whom there were evidences of localized disease of the brain for which no anatomical explanation could be determined. Six of his cases presented the clinical symptoms of cerebral hemorrhage or thrombosis, and although no gross lesions were found at autopsy, the pathological examination was not sufficiently thorough to permit of trustworthy conclusions. Arteriosclerosis was pronounced in three of the specimens, and in none of his cases was syphilis excluded. Hochhaus attributed the symptoms to pseudo-tumor, arteriosclerosis, localized cerebral congestion, and toxemia. He makes no suggestion as to the character of the toxine, but from a study of his cases I find that all but one patient had some nephritis; and one in particular showed a definite relationship between the severity of symptoms and the degree of albuminuria. The author refers to a case of toxic hemiplegia reported by Oppenheim in which the symptoms developed in a carcinomatous patient without anatomical changes in the brain substance; and a similar case by Finkelnburg occurring in a patient with carcinoma of the pancreas. A suggestive case of toxic periodic paralysis occurring in a boy seventeen years old is reported by Gardner (4). The attacks were characterized by complete loss of power in the head, arms, and legs, and had been preceded for several years by attacks of migraine, which ceased when the paralytic phenomena developed. There was no loss of consciousness or sensory disorder, but the deep reflexes were lost, and the muscles did not respond to electrical stimulation. A pathological study was not made, and, because of the marked indicanuria, the author is of the opinion that the condition was due to defective metabolism with liberation of toxic substances.

An interesting pathological study of seven cases of paralysis without gross anatomical changes in the brain has been made by Rhein (5). All of these cases had marked renal disturbance; in six, there were positive evidences of lues; and in the seventh, syphilis was suspected. Cerebral arteriosclerosis was pronounced in all but one of the specimens, and microscopic areas of softening were occasionally observed. Although these changes were probably sufficient to account for the symptoms, Rhein thinks the condition was due to uremic or syphilitic toxemia, and remarks that: "The diagnosis in old people is more difficult on account of the resemblance to symptoms following hemorrhage or softening." His belief in the toxic nature of the affection is encouraged by the experiments of

Castaigne, who injected the spinal fluid of uremic patients into the brains of guinea-pigs and produced marked convulsions, terminating fatally.

Cases of hemiplegia without discoverable anatomical lesion were observed by Andral and were thought to be due to cerebral congestion, and Sands (6), in 1856, made a study of two cases of fatal hemiplegia at Bellevue Hospital, in which the cerebral findings were entirely negative. Both occurred in young adults and in neither was there evidence of nephritis or arteriosclerosis. In one of the cases, a microscopic study was made of the cerebral hemispheres, corpora striata, optic thalami, crura, pons, and anterior columns of the spinal cord, and all were found to be "perfectly normal." There was, however, marked disease of the mitral leaflets. The probability of syphilis is not mentioned and the author offers no explanation.

A short time later, Draper (7) reported from the same hospital, the study of two more fatal cases of hemiplegia in which no gross lesion was found at autopsy. One occurred in a young adult who gave a positive history of lues and showed periosteal nodes upon the tibiae; and the second case had had syphilis "in all its forms." It was suggested by one of the attending physicians at Bellevue that the paralysis might have been due to the "syphilitic poison acting either by virtue of its toxic properties, or indirectly by its effect upon the nutrition of the brain."

Weisenburg (8) from a study of two cases of hemiplegia, with marked nephritis, in which no gross changes were found in the brain, concludes that the paralyzes were of uremic origin; and Warrington (9) contributes additional evidence in support of the toxic origin of cerebral or spinal lesions from an anatomical study of a case of carcinoma uteri, which had shown evidences of bulbar involvement, without demonstrable changes in the nervous system.

Although the selective action of a circulating toxine is a more or less speculative explanation for the development of localizing cerebral symptoms, convincing studies have been made by Rossi (10) and Fickler (11) upon toxic cerebellar disease in which the symptoms were not unlike those usually attributed to cerebral arteriosclerosis. The former studied the brain of a patient, 66 years old, who gave a history of severe diarrhea of six weeks' duration. As this condition improved, he noticed that he walked "like a drunken man," and had difficulty in speaking. These nervous symptoms were gradually progressive, and characterized by difficulty in walking, ataxia, disturbance in speech, exaggerated reflexes, sphincter weakness, and positive Babinski. There was no nystagmus or

strabismus, and the pupils reacted normally. No gross changes were found in the brain except slight atrophy of the superior vermis. Microscopically, the Purkinje cells and cortical layers of the vermis were definitely atrophic and there was some loss of fibers in the central portion of the dorsal columns of the spinal cord. The cerebral arteries were not thickened and the meninges appeared to be normal. The condition was regarded as a primary atrophy of the cerebellum beginning in the Purkinje cells, and probably dependent upon gastro-intestinal toxemia. Fickler concluded, from a review of the literature and his study of eight cases of cerebellar disease, that a condition exists in the aged which might be called senile cerebellar involution; and it is usually, but not invariably, associated with sclerotic changes in the cerebral vessels. Among other causes, he mentions acute and chronic cerebellar ataxia from the absorption of gastro-intestinal toxins, alcohol, syphilis, and other infectious diseases. In those cases of toxic origin, there is no arteriosclerosis and the most marked changes are confined to the cerebellar cortex, with only slight secondary degeneration. Similar observations have been made by Thomas (12), Dejerine and Thomas (13), and in a later study by Garbini and Rossi (14) of a patient fifty-five years old, who suffered from right hemiplegia, dysarthria, and dysphagia. The only changes found at autopsy were sclerosis and atrophy of the cerebellum, from which it was concluded that the cerebellum acts as an accessory coördinating speech center, and that the dysarthria and dysphagia were due to incoördinate movements of the primary speech mechanism. It is not unlikely that the speech defect in the case which I have studied may be of this origin.

Symptoms resembling those of cerebral arteriosclerosis have been observed in a case of chronic purulent meningitis studied by Schlesinger (15), although he does not compare the two conditions. The moderate meningeal infiltration observed in my sections was not sufficient, however, to account for the hemiplegic symptoms nor did it suggest a chronic purulent affection, and its pathological importance is due largely to the evidence it furnishes in favor of the syphilitic nature of the disease. It is interesting in this connection, that some time before the publication of Schlesinger's paper, Sir William Osler (16) reported a case without autopsy, in which ten attacks of transient mutism occurred, with numbness of the right side. The patient had previously consulted a well-known specialist, who made a diagnosis of "chronic meningitis," which was not concurred in by Dr. Osler, who attributed the condition to arteriosclerosis and vascular spasm.

Inability to explain satisfactorily the symptoms in my case entirely upon a theory of chronic intoxication or meningeal infiltration, and the presence of marked peripheral arteriosclerosis suggest the probability that such symptoms might be due to the changes in the peripheral vessels. Naturally, as the cranial cavity is approached, the pathological importance of a peripheral vascular lesion becomes more evident, and a recent thesis by Ferry (17) calls attention to the development of cerebral symptoms from occlusion of the extracranial vessels. Although his cases showed evidences of cerebral edema or areas of softening sufficient to account for the gradually progressive hemiplegia, there was no sclerosis of the cerebral vessels. A study of the extracranial and cavernous portions of the internal carotid arteries, however, showed marked thrombosis with almost complete occlusion, which was usually confined to one side, but occasionally involved both. Similar observations, he states, have been made by Lancereaux and Bristowe, and the condition is thought to be due to syphilitic arteritis and atheroma. The fact that surgical ligation of both carotid arteries has been practiced without the development of local cerebral symptoms discredits somewhat the pathological significance of Ferry's observations, but he attempts to meet this objection by quoting from Le Fort, who maintains, that in surgical ligation a thrombus is formed at the point of ligation which advances to the first bifurcation of the artery. If collateral circulation is established before the thrombus reaches the bifurcation of the common carotid artery, cerebral symptoms do not develop. If, however, the clot reaches the bifurcation and passes into the internal carotid branch, hemiplegic symptoms are likely to occur.

Unfortunately, I did not have an opportunity to examine the carotid arteries in my case, but with the marked peripheral sclerosis, it may be reasonably assumed that there was impairment of the general circulation and cerebral malnutrition. Under such conditions, even transitory disturbances in the general circulation might be sufficient to produce localizing symptoms from an already impoverished brain. An interesting study of the effects produced by interruption of cerebral circulation has been made by Sand (18), who examined the brain of a patient subjected to prolonged chloroform anesthesia during an operation for osteomyelitis. At the close of the operation syncope developed, the pulse could not be felt, and the patient was thought to be dead. After an hour he was partially resuscitated, so that he would answer questions vaguely, respond to a pin prick, and protrude the tongue when asked to do so. The pupils responded normally, and there was no paralysis, but he was

incontinent. Death occurred nine hours later, and the autopsy showed slight edema of the brain and cord, but no other gross lesion. Microscopically, the nerve cells were in various stages of disintegration and this change was especially pronounced in the cerebellum, where there was almost complete disappearance of the Purkinje cells. These cellular changes were thought to be due to the interruption of the circulation rather than to the direct action of chloroform, since the liver did not show changes characteristic of chloroform intoxication. This observation is interesting, when it is recalled that similar changes were found in the cerebellar cells of my specimens, and that both toxemia and circulatory disorders may have been contributing factors.

It is not improbable that sclerosis of vessels more distant than the carotid arteries might produce symptoms resembling those of a cerebral lesion. The observations of Boullay (19), in 1831, upon the cause of "string-halt" in the horse, and a later study by Charcot (20) upon a similar condition in man demonstrated the relation between these symptoms and changes in the arterial wall. Thrombosis and arteriosclerosis are usually present, but the symptoms of intermittent claudication may occur without thickening of the arterial wall, and the condition is generally confined to one or both lower extremities. The resemblance of this affection to an associated group of symptoms sometimes observed in Raynaud's disease, and the occasional absence of changes in the peripheral vessels have encouraged the belief that, in some cases, intermittent claudication is due to arterial spasm alone; hence, it has become known by some writers as *dysbasia intermittens angiospastica*. The disease is not always confined to the lower extremities; but occasionally one or both arms have been affected. Erb (21) and Determann (22) have recorded cases in which the leg, arm, and tongue, upon the same side, were involved. During the attack, the pulse in the lingual artery was obliterated.

Intermittent lameness, as originally described, showed no evidence of involvement of the spinal cord. Cases have been observed, however, in which symptoms indicating spinal involvement were present. Pathological examination revealed sclerosis of both the peripheral and intraspinal vessels, and a diagnosis of spinal intermittent claudication was made. It is only a step from these observations to imagine spasmodic closure of the cerebral vessels, and the term cerebral intermittent claudication has been adopted to account for a number of transitory cerebral symptoms of apparently vascular origin. Such a conception finds some support from a clinical and

pathological study of migraine, with its associated transitory paralytic phenomena.

The inability to demonstrate a nervous mechanism for the cerebral vessels and the general belief that they are therefore incapable of transitory constriction and dilatation have been the main support of those who oppose the theory of cerebral intermittent claudication. There is, however, clinical and experimental evidence, in favor of the independent irritability of the vessel wall, and the presence of vasoconstrictor fibers to the cerebral vessels has received some support from experimental physiology. Edgeworth (23) from a clinical study of four cases of transient hemiplegia attributes the condition to intermittent contraction of the cerebral arteries and is inclined to accept Wigger's experimental studies upon vasoconstrictor nerves to the cerebral vessels. In a later paper, Phillips (24) contends that it is not necessary to assume the presence of vasoconstrictor nerves to the cerebral vessels, since it is known that certain drugs when circulating through a vessel isolated from all nerve connections will produce temporary constriction; and it is therefore reasonable to assume that circulating toxins in the body may produce the same effect.

If the cerebral vessels possess independent contractility it is necessary to assume the presence of some irritating substance in the general circulation which stimulates the muscle coat directly. Arteriosclerosis, increased demands upon the circulation, and hyperexcitability, are regarded as essential conditions in the development of intermittent arterial spasm; while gouty and rheumatic states, metabolic disorders, and gastrointestinal toxemia are, according to Russell (25), predisposing factors. But a condition of general toxemia alone does not explain satisfactorily the spasm of a localized vascular area, which, of course, must be assumed if localizing cerebral symptoms are to be explained upon a theory of vascular spasm. Physiological experiments, however, seem to indicate that contraction of even a small portion of an artery does occur; but that some local condition, either within the arterial wall itself or from without, is essential. Hobhouse (2), in discussing Russell's paper, quotes from Sherrington as follows: "Local tonic spasm of short lengths of small arteries are seen in experiments. If the student touches the artery or if heat or cold is applied, a spasm occurs which may lead to almost complete closure." Sherrington further suggests that in diseased arteries unequal elasticity at a point of commencing change might be sufficient mechanical stimulus to produce contraction in the neighboring arterial wall. Parker (27) takes exception to the

theory of arterial spasm and would explain the symptoms of cerebral intermittent claudication upon the selective action of toxic substances for certain groups of nerve cells, and a similar opinion has been expressed by Heard (28). Herz (29), however, attributes the condition to extraventricular systole.

Two interesting clinical papers have been published by Langwill (30) and Edgeworth (31) in which transitory hemiplegia is attributed to the spasmodic closure of the cerebral vessels; which, in their opinion, may be caused by the toxemia of nephritis and occur independently of arteriosclerosis. In one of Allan's (32) four cases of transient paralysis, the probable toxic nature of the affection is strikingly illustrated. The patient, a young man, who gave a previous history of rheumatism, had suffered for three years from transient paralysis of the left side, of ten or twenty minutes' duration. During the interval between attacks the urine was quite normal, but following a seizure it almost invariably contained a heavy albuminous precipitate. Allan, however, is of the opinion that the symptoms were due to arterial spasm induced by circulating toxins absorbed from the gastrointestinal tract, and refers to the experiments of Dixon and Dale which showed that toxic substances derived from putrid meat, when injected into the circulation, produced arterial constriction. In two cases of Raynaud's disease, studied by Semon (33) and Fox (34), syphilitic toxemia was thought to be the cause of the arterial spasm.

Whatever view may be entertained concerning the occurrence of angiospastic phenomena and localizing cerebral symptoms in the absence of confirmatory pathological changes in the brain, it appears that any explanation must be more or less speculative; and while this study may not have contributed any positive information to the present conception of such conditions, it has, at least, been instructive through its negativeness.

That so striking a clinical picture of general and local cerebral arteriosclerosis can occur in the absence of sclerotic changes in the cerebral vessels is of interest. Although the histological examination furnishes no satisfactory explanation of the symptoms, it is not improbable that they may have been due to uremic or syphilitic toxemia, extracranial arteriosclerosis, or spasmodic constriction of the peripheral or cerebral vessels.

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