Original Articles.

CIRCULATORY FAILURE IN THE ACUTE INFECTIONS OF CHILDREN. CAUSES AND TREATMENT.*

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THE majority of physicians are not therapeutic nihilists, and most of us believe that much good can be accomplished by the proper administration of drugs. Were we asked if it were possible for us to influence favorably a failing circulation, we would unanimously give an affirmative answer. With this unanimity of opinion it therefore seems strange that to accomplish the same end such a variety of measures are employed by different men, and by them extolled as the most trustworthy and efficient. As a specific example: In the treatment of pneumonia it will be found that alcohol, strychnine, nitroglycerine, digitalis, caffeine, camphor, etc., each have their adherents as agents in resisting circulatory failure, and all are used with thorough reliance upon their virtues. It is most unlikely that all these drugs are similar in action and of equal efficiency; far more probable is it that there is lack of agreement as to the cause of the conditions which these drugs are used to combat and as to the action of the drugs themselves. And yet it seems to me there is sufficient experimental and clinical observation to warrant almost complete agreement as to conceptions and treatment. For this reason, and on account of the importance of circulatory failure, I ask your attention to a review of the opinions that have been held as to the cause of this failure in infectious processes, of the experimental work that has been done in an effort to explain their production, and finally to a consideration of those measures and drugs that theoretically would seem and experimentally have proved to be of value.

The subject of circulatory failure was first touched upon by the great clinicians of the early part of the last century. Fever was looked upon by all of them as the cause of the disturbance.

Stokes investigated with great care clinical symptoms and physical signs and came to the conclusion that the disturbance was due to cardiac weakness.

Laennec and Louis studied symptoms and physical signs occurring during fever, and they also recognized the softness of the heart wall, its friability and brownish color after febrile death, but they did not connect the pathological findings with the circulatory failure. Stokes was the first to do this, and he wrote and taught that the symptoms of circulatory failure were to be referred to the condition of the heart. Nevertheless, he admitted that in all cases the clinical and pathological evidences did not agree. The discoveries made by Virchow in regard to the parenchymatous inflammation in muscle, with their confirmation and extension by other pathologists, apparently lent great support to Stokes' belief in the dependence of circulatory disturbances in febrile condi-

tions upon anatomical injuries to the cardiac muscle.

Hayem just found interstitial changes in the heart in typhoid fever and Birch-Hirschfeld and Leyden, independently of one another, described interstitial changes in diphtheria. Romberg studied typhoid, scarlet fever and diphtheria hearts and showed that a certain number of days, roughly seven to ten, is necessary for the production of the interstitial changes which develop without reference to the early parenchymatous changes and continue after the infection is no longer apparent. During the early acute period, of which I wish especially to speak, the parenchymatous lesions are the only ones present, but these were considered sufficient to account for circulatory failure. Other constant anatomical changes in the circulatory apparatus that might be held responsible have not been found. Death was, therefore, regarded by the majority of clinicians and pathologists as due to failure of the heart which depended directly upon the anatomical changes in its structure.

There were, however, certain clinical observers who would not subscribe to these ideas. Dieulafoy, as long ago as 1869, thought that the majority of deaths in typhoid should be referred to what he called a neuro-paralytic reflex.

Naunyn carefully studied circulatory failure in fever from the clinical standpoint. He was impressed with the similarity of symptoms in febrile animals and those whose vessels had been paralyzed by a section of the spinal cord. He says that, according to his ideas, arrived at from the observation of animals in febrile collapse, it is absolutely impossible to say that the collapse in febrile conditions is due to heart weakness. Direct evidences of this entirely fail. In the majority of cases the heart remains regular and the pulse may be palpable until shortly before death. The heart sounds remain clear to the very end. Nor can the increased frequency be looked upon as a sign of cardiac weakness, because with extensive cardiac disease, as in the late stages of diphtheria, the heart may be slow.

The pulse curve with the sphygmograph shows also diminished tension, as Marey, Landois, Wolff, Riegel and others had found, and Riegel obtained the same curves in fever as after the use of amyl nitrite, which so markedly reduces tension. Naunyn also regarded as especially important Quincke's observation that the arm veins in fever may pulsate, a phenomenon which indicates with the greatest certainty (when it is not due to tricuspid regurgitation) that a diminished tension of the vessel wall with a dilatation of the capillaries and a lowering of the arterial pressure is present. Riegel came to the same conclusions as Naunyn.

Rosenbach, in 1881, wrote against heart weakness as a cause of death in infectious conditions in no uncertain terms. He said: "I believe that I have every ground for asserting that the belief that the heart is the earliest and most severely affected organ has nothing to sustain it. This belief has its practical expression in our fever therapy, and the results of it are the exaggerated

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stimulating and antipyretic treatment. Certainly, of the organs necessary to sustain life, that which shows the most important changes in its texture is to be regarded as the cause of death, but our methods are not fine enough rightly to judge of the grade of severity of the lesions in the separate organs. Severe molecular disturbances, important tissue changes in the brain, escape notice on account of the paucity and uncertainty of our methods, while, on the other hand, comparatively moderate disturbances, such as cloudy swelling of the heart muscle and slight grades of infiltration, are easy to observe."

Thus good clinicians have failed to accept the view that the heart is the cause of circulatory collapse. Opposed to them were those who believed the heart to be the sole cause. But there was still a third party.

It has been stated before that Stokes admitted that in certain instances no gross lesions could be found in the heart, and later observers had the same experience. To explain this small proportion of fatal instances without apparent lesions, those believers in heart failure found it very easy after the advent of bacteriology and the introduction of the study of bacterial toxins to explain the circulatory failure on the basis of a functional interference with the cardiac muscle caused by the metabolic products of various bacteria. This hypothesis was also extended to those hearts with pathological as well as without pathological findings. Hesse was, I believe, the first one to suggest such a functional disturbance, and he did it in regard to diphtheria. Griesinger followed suit in regard to typhoid fever and other diseases. Good clinicians, as, for instance, Krehl, believe in a certain amount of this influence, and it will be seen later that, vague though it is, this view receives experimental support in tests with the products of certain bacteria.

Thus there were three classes: First, and by far the largest in number, were those who believed in the anatomically diseased heart as responsible for circulatory failure; second, those who believed in a functional disability due to toxins with or without anatomical change; and third, those who exonerated the heart entirely or chiefly and held to a paralysis of the vessels from central influences.

This is a convenient point to refer to three pieces of work, two of which were done more or less recently, since the deciding experiments of Romberg and Pässler and Pässler and Rolly, which bear upon the view held by the first of these classes, viz., that the heart anatomically affected is responsible for death, and which, had they been known at that time, would have tended seriously to undermine this view. The first of these was the work of Krehl on hearts with fatty changes as the result of disease. Quantitative chemical examination showed there to be such a very slight increase in the fat content that it could hardly be sufficient to affect seriously the cardiac activity. Krehl came to the conclusion that the fat content of the heart muscle bore no relationship to its capacity for work.

The second was the painstaking pathological

study of Aschoff and Tawara. These investigators cut hundreds of sections from various parts of different hearts and decided that many of the changes frequently described as pathological were in reality artifacts, and the third was the experiment of Hasenfeld and Fenevessy. Hasenfeld and Fenevessy studied the capacity for work of fatty degenerated hearts. Phosphorus was used to bring about fatty changes and was given by mouth in doses sufficient to cause an enormous fatty transformation. Then, according to the methods of Romberg and Pässler, hereafter to be described, tests were made of the capacity of the heart to work against greatly increased resistance. The startling fact was disclosed that a heart degenerated by phosphorus even to the most extreme degree was able to respond to tests almost as well as a normal heart. From such an experiment one obtains an idea of the enormous factor of safety with which the heart is endowed. All these three investigations, however, are negative in their results. They point away from the heart as the direct cause of death, but they do not show what is responsible. Romberg, Pässler, Müller and Bruns attempted to show this, and their results are so important and convincing that I beg your indulgence if I describe their methods and results in considerable detail and in almost their own words.

They made their tests with reliance upon the following facts: By strong stroking of the abdomen from below upwards, a considerable quantity of blood is driven out of the abdominal vessels into the heart. At the same time the flow from the left heart into the abdominal aorta is impeded. The heart is filled to a greater extent, it drives the increased amount of blood into the aorta against an increased resistance, and the blood pressure rises. The increased pressure, however, only occurs when the heart is strong enough to satisfy the increased demands made upon it. If its capacity is diminished, the increase in pressure is less than normal or does not occur at all. The increase of pressure as a result of abdominal massage is then a test of the heart's power. The same is true of temporary compression of the descending aorta above the diaphragm. The blood pressure likewise rises in this case, provided the heart is capable, chiefly because it is compelled to work against an increased resistance. Abdominal massage and temporary compression of the aorta are, therefore, excellent means of deciding whether, and to how great an extent, the heart is capable of acting against increasing odds.

Certain sensory irritations of the skin or mucous membranes, such as cold to the skin, or faradization of the nose, call forth a reflex excitement of the vasomotor center in the medulla. A contraction follows in the vessels, chiefly of the splanchnic region, and the blood pressure rises. In order that an increase of pressure may take place, the sensory paths, the vasomotor center and the vasomotor nerves must be capable of stimulation and action. But besides this a capable heart is necessary for the production of increased pressure, for a weak heart would be as unable to

overcome the resistance afforded by arterial contraction as it would the overfilling caused by abdominal massage. In a similar way asphyxia for about thirty seconds causes an increase in blood pressure by a stimulation of the medullary vasomotor center.

By the use of these various manipulations, abdominal massage, compression of the aorta and stimulation by sensory stimuli and by asphyxia, it is possible to judge whether a circulatory disturbance accompanied by lowering of the blood pressure, such as occurs at the height of acute infections, is caused by an injury to the heart or to the vasomotor center or nerves.

It was necessary to follow the progress of the infection in all its stages, and for this reason tests were made during the early febrile period, at the height of the fever and during the stage of circulatory collapse. Rabbits were used. They were injected with living organisms in relatively enormous doses for the reason that in this way circulatory collapse was caused much more promptly and regularly, and the time of its onset could be prognosticated with great accuracy, a point of much importance when it is necessary to observe such animals almost constantly and to be ready to carry out experiments at the different desired stages.

The organisms used were the diphtheria bacillus, which remains localized in the tissues and injures the whole organism through its toxins; the pneumococcus, which causes in rabbits a general septicemia, and the bacillus pyocyaneus, which occupies an intermediate position between the other two organisms and sometimes remains localized and at other times causes pyemia. The blood-pressure tests were made in the carotid artery under morphine narcosis.

In the first stage of the disease, that is, in the early febrile period, all the infected animals reacted normally to abdominal massage, to compression of the aorta, to faradization of the nasal mucous membrane, and to temporary asphyxia. Their hearts and vasomotor systems were, therefore, normal.

In the second stage, or that of threatened collapse, the general condition of the animal indicated an unfavorable outcome. In this stage the pressure showed a decided tendency to fall. Abdominal massage, however, caused throughout a great rise in pressure exactly as in animals in the first stage. The hearts were, therefore, as capable as ever of driving the increased amount of blood. But, on the other hand, stimulation of the vasomotor center showed that in all cases its function had suffered some damage. The increased pressure after sensory irritation and asphyxia was plainly less than after abdominal massage, whereas normally it is as great or even greater. That the blood vessels themselves were unaffected was demonstrated by the intravenous injection of barium chloride, which caused, as it normally does, a marked constriction of the vessels, accompanied by a rise in blood pressure.

In the third stage, when the life of the animal was momentarily threatened, the blood pressure

sank to about 25 mm. of mercury, as opposed to the normal of 80-90 mm., but the tests showed plainly what part of the circulation was at fault. Abdominal massage and aortic compression caused a great rise in pressure. The reaction to nasal faradization was absolutely nil, and to asphyxia greatly decreased. The difficulty was, therefore, with the vasomotor apparatus, and that the failure was not in the vessels was shown by the effect of the injection of barium chloride when a marked vascular contraction with prompt blood-pressure rise occurred. The cause of such collapse must, therefore, lie in the center.

We have, then, throughout a practically competent heart and peripheral vascular apparatus, but a medullary center that at first shows signs of failure and then suddenly gives way. In almost all instances the blood pressure fell almost to zero, but respiration ceased before the heart.

It would take too long to enumerate the various criticisms raised against these experiments. They were not numerous or important save the one of Von Stejskal. His criticisms were on purely technical grounds, but they impelled Pässler and Rolly, with new methods, to repeat the experiments. Their results were much the same, absolutely so as far as pneumococcus and pyocyaneus infections were concerned, but they found a marked diminution of the capacity of the diphtheria heart to work against increased resistance or to withstand the effect of asphyxia.

These experiments, first of Romberg and Pässler and then of Pässler and Rolly, have been universally accepted as proving that paralysis of the vasomotor center is the chief cause of death in the circulatory collapse during acute infections due to these three organisms at least, and by analogy to many others.

Our knowledge in regard to other infections has been further increased by the experiments of Raczyński and Heineke. The former of these, Raczyński, investigated the influence of the streptococcus pyogenes upon animals, and his experiments were conducted exactly as were those of Romberg and Pässler. He obtained results exactly similar to those that had been obtained with the pneumococcus. The animals went into collapse and died with paralysis of the vasomotor center. The hearts were capable of responding to increased demands made upon them up to the end, and the blood vessels contracted after injection of barium chloride.

Heineke investigated the cause of death in rabbits with perforation peritonitis. Tests were made by the method of Romberg and Pässler. They showed that the heart responded admirably to abdominal massage, compression of the aorta and to the injection of barium chloride, and that the vasomotor center showed no response to any of the stimuli.

Their conclusions, which might stand for the conclusions of any of the experiments quoted, were as follows: That the cause of death is a paralysis of the centers in the medulla; that this is confined primarily to the vasomotor center and secondarily to the respiratory center; that the

circulation shows striking symptoms earlier than does respiration, but that respiration ceases first; that paralysis of the vasomotor center is the cause of the circulatory symptoms and that the heart is comparatively unaffected.

We have seen that these conclusions are applicable to infection with the diphtheria bacillus, the pneumococcus, the bacillus pyocyaneus and the streptococcus, which organisms play a most important part in infections, medical and surgical. These conclusions are also applicable to some forms of experimental peritonitis. There is, so far as I have been able to find, only one piece of work that shows any exception to the rule that experimental infections kill chiefly by vasomotor paralysis. That was done by Raczyński with the colon bacillus. He had previously experimented with the streptococcus, so there is no reason to question his methods or results, which were quite at variance with those obtained with any other organisms. Instead of finding at autopsy the abdominal veins engorged with blood, he found them empty and a marked degeneration of the liver, kidney and heart. The tests showed normal response to all stimuli in the early stages of the infection, but in the stage of collapse the heart was arrhythmic and failed to react to abdominal massage or aortic compression, and death apparently took place before a condition of vascular paralysis had resulted. No one is on record as having repeated or confirmed these experiments, and they stand as an exception to the rule that the other experiments established.

There has been almost no opposition to the utilization of the results obtained on animals to explain the cause of the sudden circulatory disturbances in human beings that occur in acute infections with many different organisms. The symptoms, their progression and the post-mortem findings are too strikingly similar. Many clinicians, notably among them Krehl, have been loathe to discard entirely the idea of cardiac weakness and have contended that the heart is still to be considered, and that just as in the diphtheria experiments it shows a certain degree of failure, so actually in other infections it may be weakened; but they ascribe to the heart weakness only a secondary rôle. There is thus practical agreement that the chief cause of death is to be found in paralysis of the vasomotor center.

The comparison between the animal experiments and human patients has been made with adults. The similarity is as great with children. In them the circulatory failure comes on rapidly or slowly, but when fully developed causes pallor, cold extremities, a rapid, soft pulse or its almost complete absence, with a heart whose sounds are usually clear, endeavoring by its over-activity to compensate for the emptiness of the arterial system. I have seen the heart of a child who was pulseless beating so tumultuously as to shake the whole precordium. The heart, too, continues to beat after the anemia of the respiratory center has caused the respirations to become shallow and irregular, and finally to cease altogether. The evidences of true cardiac failure, such as intense

cyanosis and venous engorgement and stasis with dilatation of the heart, especially the right ventricle, are only exceptionally met with in children; they are not the rule in fatal infections.

A knowledge of the pathological physiology is a *sine qua non* of intelligent treatment and we receive incalculable assistance from this source. The condition clinically is so severe and so frequently fatal that one is unable to judge accurately of the effects of any given treatment, and thus it comes about that opinions as to the value of different drugs vary widely. We have three methods of choosing a drug. First, by its known effect upon healthy animals; second, by its effect upon diseased animals, and third, by the results of clinical observation of diseased human beings during its use. Unfortunately these methods often do not agree, and two of them may be diametrically opposed to each other. Pässler supplied the second of these methods, the effects of drugs upon diseased animals, by numerous experiments which seem to point to a therapy more rational than could be indicated in any other way.

To consider first the drug around which most active warfare has been waged, alcohol.

By experiments on healthy animals, it is impossible to obtain any evidence that, after intravenous injection, it is a cardiac or vasomotor stimulant. When given in large enough doses to produce any effect on the heart it causes a lessened efficiency and a weakness of the contractions, and it also causes an inhibitory effect and finally a paralysis of the vasomotor center, exactly what we wish to avoid. On animals with acute infections, before the stage of collapse, Pässler found that alcohol in moderate quantities was without constant influence; it had no beneficial effect. Crile found that in shock, a condition much like that of circulatory collapse, alcohol in small doses had no effect and in large doses increased the danger. The experience of practitioners that alcohol in septic processes is beneficial and can to a certain extent be utilized as a food is entirely beside the question of circulatory collapse. From theoretical considerations and from experience with diseased animals and I also believe from clinical observation, one can expect no beneficial effects from its use.

The use of ether as a stimulant in severe collapse is widespread. Many regard it as the strongest stimulant we possess, while others consider it practically useless. On healthy animals no favorable influence either on the heart or vasomotor center can be demonstrated. Pässler's results on diseased animals entirely coincide with those on healthy animals. A favorable effect on the blood pressure was not observed, rather the contrary, and when the circulation began to be affected, ether caused an immediate drop in pressure. The capacity of the heart itself to overcome increased resistance remained unchanged, the excitability of the vasomotor center was diminished. In a condition accompanied by a rapid fall of blood pressure one can only foresee danger from the exhibition of ether, and its use is absolutely contra-indicated. The same may be

said of the other drugs that dilate the blood vessels and lower blood pressure; nitroglycerine and the nitrites in quantities large enough to produce any results can only do harm.

With regard to strychnine, what we should expect from experiments on healthy animals fails entirely to be realized on diseased animals. Strychnine, according to Mayer and Denys, causes a rise in blood pressure by stimulation of the vasomotor center, but Pässler found it without effect in circulatory collapse unless sufficient were given to cause convulsions, and Crile denies it any value in the treatment of the low blood pressure of shock. We can, therefore, not hope for much from strychnine; whatever beneficial effect it may have must be slight. It will, however, not act unfavorably.

Digitalis shows its chief effect in normal animals upon the heart and blood vessels and has only slight influence on the medullary center. According to Böhm and Görz, digitalis induces a decided rise in blood pressure after section of the cervical cord, that is, when paralysis of the peripheral vessels has occurred. The heart, by acting more powerfully, can make up for a time at least for the injurious influence upon the blood pressure. From a prior reasoning, then, one would expect a beneficial effect only in the stage when the heart is struggling by its over-exertions to compensate for the gradually widening vessels, and indeed Pässler found such to be the case. The blood pressure rose, but the rise was of only short duration and in the most favorable cases lasted hardly half an hour. Repeated injections had a lessened effect or none at all. Digitalis had no effect on the vasomotor center. For use on human beings in circulatory failure digitalis has the great disadvantage of slowness in action. It takes hours to manifest its effects after its exhibitions by mouth, and we have no thoroughly reliable preparation for hypodermic use. If the failure is gradual in onset and we are far-sighted enough to realize that the action of digitalis will be required in the not too immediate future, it may assist us, but for acute collapse digitalis by mouth is valueless. It is to be considered an aid in reinforcing the action of other drugs, those that are theoretically indicated and practically of most value, the drugs that stimulate the vasomotor center.

Of the central vasomotor stimulants at present used in medicine, caffeine is probably the best. The use of coffee in severe collapse has long been advocated, but its active principle has never received the appreciation in acute infections to which it is entitled. It has a marked, prolonged and constant effect in constricting vessels by central action, and it is readily soluble. Moreover it is a cardiac as well as a vasomotor stimulant. Pässler found that by its use slight degrees of vasomotor paralysis could be overcome for a considerable length of time and that centers incapable of stimulation by other methods responded readily to caffeine. He considers its effect more certain and more prolonged and the remedy is much more readily administered than

camphor, the other vasomotor stimulant most commonly employed.

In addition to stimulating the vasomotor center by caffeine and camphor, there is another method of raising blood pressure, namely, by increasing peripheral resistance, and for this are chiefly employed infusion of salt solution and the injection of adrenalin. Infusion will act only so long as the increased amount of fluid is contained in the arteries, and the blood pressure sinks when the abdominal veins still further dilate. Experimentally it is of value for only a short time.

The extraordinary influence of adrenalin on the heart and peripheral vessels is well known. It would seem a drug of great usefulness and, indeed, undoubtedly is, in such conditions as collapse from chloroform, surgical shock and in infections when the heart is entirely sound, but with diseased hearts, even those that respond favorably for long periods of time to other drugs, the use of adrenalin is attended with danger. Heinz found that with animals poisoned with diphtheria toxin and with phosphorus, adrenalin caused a marked rise in blood pressure, but that the heart was so gravely affected by the increased demands made upon it that it eventually failed and the animals died before the control animals who received no adrenalin.

For many years there was no effort made to confirm the results of experiments on animals by observations on human beings. Last year, however, appeared a valuable piece of work by Sonnenkalb. He used a Von Recklinghausen tonometer according to the method of v. d. Velden for estimating the functional activity of the circulation. He employed various drugs in health and disease and confirmed all of Pässler's results in acute infections. Caffeine was the most valuable drug; it worked certainly, promptly, and its effects were lasting (one to three hours). Camphor was also exceedingly valuable and was prompt but somewhat uncertain, and its effect was evanescent and was over in less than two hours. The bromin acted like caffeine, but was less powerful and had less influence on the vessels. The nitrites and nitroglycerine had always a bad effect.

Dr. Hoobler and I have made a series of observations on children in the wards of Bellevue on the effects of drugs on the blood pressure in pneumonia. We realize, of course, that blood-pressure readings do not give complete information as to the condition of the circulation, but it is the only method clinically available. We used caffeine, camphor and adrenalin intramuscularly. All three raised the pressure, adrenalin more promptly than the others, but its effect was evanescent, was over in less than half an hour, and in a few instances the subsequent fall was to a point below where the pressure had been before its use. Caffeine preparations were uncertain, but with a good one the best results were obtained. The increase in pressure began in five or ten minutes, reached its maximum in the neighborhood of half an hour and was manifest for two hours or more. Camphor also worked satisfactorily, but was not quite so certain or prolonged as caffeine.

That which raised the blood pressure more

certainly, constantly and satisfactorily than any drug was cold air. We noticed that when patients were brought in from the balcony, where many are kept constantly day and night, that their blood pressure fell progressively during the course of the next hour and then remained at a constant level, and indefinitely until they were put out into the cold again, when the rise again occurred. The difference between the pressure indoors and out of doors was 10 to 15 mm. of mercury, and the change always occurred. It was more marked the lower the pressure when indoors, and the sicker children responded better. This cannot be the effect of more oxygen; it must be the reflex stimulation of the center due to the cold on the skin of the face and the nasal mucous membrane, and this view is further strengthened by the observation that cases of pneumonia treated out-of-doors do better in the cold months than in the warm. The importance of cold air as a tonic to the vasomotor apparatus can hardly be over-emphasized, and as I said before, its effect is certain and constant and soothing.

We see, then, that critical clinical observation and animal experimentation are in accord in referring the cause of circulatory disturbance in acute infections to a failure and final collapse of the vasomotor center. There is also almost complete agreement obtained by animal experiments and by modern methods of determining the human circulatory capacity as to the drugs and methods most useful in this circulatory disturbance.

Let me repeat in conclusion that from the knowledge at present available it seems that the continuous use of cold air, the use of caffeine and camphor reinforced by digitalis, with infusions of salt solution and the careful administration, not too often repeated, of adrenalin, are our best methods to combat this dangerous condition.

THE INTERPRETATION OF CERTAIN CEREBRAL SYMPTOMS WITH REFERENCE TO v. MONAKOW'S THEORY OF DIASCHISIS.*

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It is perhaps presumptuous before this audience to revert to a theory by no means new, the worth of which you have no doubt considered and estimated. The justification lies in the fact that much of the recent writing on cerebral localization takes no adequate account of its significance in spite of the reasonable explanation it appears to offer of many of the contradictions of the commonly accepted teachings. Regarded from a purely practical clinical standpoint, the uncertainties of localization of symptomatic conditions in defined cortical or subcortical areas appear often to be out of proportion to our supposed knowledge. As experience grows, even the most firmly established cortical representations are found to be of doubtful validity, demanding a re-organization of our theories on the basis of a more comprehensive study of cerebral activities, con-

sidered alike from anatomical, physiological and psychological standpoints. During the fifty years (1861) which have passed since Broca's original observation, progress toward a satisfying conception of the intricate mechanism underlying brain function has been uninterrupted. The history of this movement, significant not only for practical medicine, but also in the solution of ultimate biological problems, does not now concern us. It is rather to the contradictions and inconsistencies of certain supposed facts to which I wish to call attention on the basis of v. Monakow's searching criticism.

For some ten years past this gifted investigator has been subjecting to analysis, on the ground of his own experience and that of others, the clinical, anatomical and experimental evidence underlying the general theory of localization.¹ Admitting at the outset that localization of some sort exists throughout the nervous system, and that it reaches its highest development in the brain, it is nevertheless apparent that even in what have been regarded as elementary matters there are noteworthy contradictions. Cases are multiplying in which, for example, lesions in the cortex of presumed focal significance may lead to no symptoms, and, on the other hand, that symptoms may occur of definite character for which no adequate lesion is to be discovered post-mortem. Again it has been recognized that under apparently identical pathological processes, the symptoms in different cases may vary widely. In man at least we are not able to say with definiteness what the minimal result must be of a given localized lesion. In other words, what must inevitably follow a focal destructive lesion has been very imperfectly determined; we are not able to predict with anything like exactness the necessary results even of those lesions which lie in areas long recognized as having special functions. Such uncertainty exists, for example, in the various forms of aphasia, notably in the motor type, in hemianopsia, hemi-ataxia or hemi-anesthesia and to less degree even in the disturbances of the much studied motor cortex. It not infrequently happens that on the one hand the localization of a defined cortical lesion may be accurately determined from the symptoms and that on the other there may be great difficulty in arriving at a diagnosis in spite of extensive focal lesions. It was such contradictory evidence that led Goltz, Loeb, Brown-Séquard and others to deny the localization of function in the cerebral cortex. (Goltz' decerebrate dogs, it will be remembered, by no means lost the power of movement though their motor activities were circumscribed and lacked purposiveness.)

It may at this point be said with slight probability of contradiction that sharply circumscribed cortical areas, so-called "centers," may no longer be considered to represent the facts of localization and this in spite of Flechsig's vigorous recent attempt on the basis of myelinization to localize the higher cerebral activities, and of the striking testimony of local irritative and paralytic effects

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¹ v. Monakow: Ueber den gegenwärtigen Stand der Frage nach der Localization im Grosshirn. *Erg. der Physiologie*, 1902, 1904, 1907, 2, 274 references. *Idem.*: *Aphasie und Diaschisis*, 1906, xxv, 1026.