Abstract:
Metabolic Changes in Response to Acute Cerebral Ischemia Following Unilateral Carotid Artery Ligation in Arteriosclerotic Versus Nonarteriosclerotic Rats

The left carotid artery of arteriosclerotic and nonarteriosclerotic male and female rats was surgically ligated to induce a state of cerebral ischemia. The animals promptly developed signs of cerebral impairment and were sacrificed 2, 4, 6, 8, 10, 12, 24, and 48 hours later to determine what dynamic pathophysiological changes attend acute cerebral ischemia.

Several of the arteriosclerotic animals developed myocardial infarcts concomitant with the cerebral edema, hemorrhage, necrosis, and leptomeningitis observed in general. All of the experimental animals manifested necrosis and fatty infiltration of the liver, and their adrenal glands were hypertrophied, hemorrhagic, and depleted of lipid.

Serum creatine phosphokinase and glutamic oxalacetic transaminase rose abruptly after 24 hours of cerebral ischemia. Triglycerides, free fatty acids, and cholesterol alterations were in keeping with intense lipid mobilization, dissolution of peripheral adipose tissue sites, and fatty metamorphosis of the liver. The animals also showed marked hyperglycemia and increased secretion of corticosterone. These investigations indicate that acute cerebral ischemia is a severe stress and will elicit dynamic alterations in serum parameters such as enzymes, lipids, glucose, and the adrenocortical stress hormones. Animals with pre-existing arteriosclerosis manifest more untoward effects and greater excursion in serum metabolic parameters than nonarteriosclerotic subjects.

ADDITIONAL KEY WORDS
- arteriosclerotic breeder rats
- carotid artery ligation
- cerebral ischemia
- fatty liver
- myocardial infarction
- hepatic necrosis
- free fatty acids
- triglycerides
- total cholesterol
- glucose
- Cmpd. B

An unusual spectrum of degenerative changes has been found to develop spontaneously in repeatedly bred male and female rats (1-13). These animals develop hyperlipidemia (5), hyperglycemia (6, 7), and hyperadrenocorticism (8-10) in concert with a fatty liver (5), diabetes (6, 7), hypertension, arteriosclerosis (1-4), accelerated aging, cerebrovascular complications (2, 11), myocardial infarction (12, 13), and premature death.

The pathogenesis of the naturally occurring arteriosclerosis is particularly intriguing for...
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many reasons. Morphologically, the lesions consist of arterial ground substance alterations, e.g., mucopolysaccharides, fibrosis, elastic tissue degenerative changes, and, in advanced cases of arteriosclerosis, calcification and even bone formation (1–4). Although the breeder rats are fed a regular (low fat) diet, they develop marked hyperlipidemia and fatty metamorphosis of the liver (5). Nonetheless, the arterial lesions contain very little lipid. The hyperlipidemia, therefore, is believed to be due to the lipid-mobilizing effects of the extra circulating levels of adrenocorticoids associated with repeated breedings. The arterial lesions first appear in the abdominal aorta, but with progression of the arterial disease concomitant with repeated breedings, the arterial lesions spread to the aortic arch and thoracic aorta (1). In time the lesions also appear in the coronary (3), carotid (2), mesenteric, renal, and peripheral arteries (4). A unique feature of this naturally occurring arterial disease is that although male breeder rats develop microscopic arterial lesions in their aortae and grossly visible, calcific arterial plaques in their iliac arteries, they succumb significantly earlier than female breeders. The earlier demise of the male breeders is due to myocardial infarction or vascular complications associated with diabetes and hypertension. Somewhat paradoxically, although the female breeders develop severe, lurid-appearing, grossly visible, calcific arterial plaques in their aortae, they can withstand more stress and survive longer than their male breeder counterparts. A particularly provocative feature of this spontaneously occurring arterial disease is that the arterial lesions insinuate themselves into the carotid and cerebral arteries. Also, the carotid arteries and the arch of the aorta are especially prone to calcification and are often kinked and tortuous. The appearance of arterial lesions in the arteries of the head and neck is seldom encountered in experimental animals.

We have taken advantage of this unusual experimental model of naturally occurring vascular disease by using it to investigate those metabolic and morphological interrelationships which are most apposite to problems related to human vascular disease, e.g., diabetes, hypertension, myocardial infarction, and cerebrovascular disease. For example, we have found that ligation of the carotid artery of a repeatedly bred female rat having pre-existing, severe, carotid artery disease would result in unusual endothelial hyperplasia, ground substance alterations, fibrosis, and complete arterial occlusion, often due to massive and extensive thrombosis. By direct contrast virgin or nonarteriosclerotic subjects free of pre-existing carotid artery disease subjected to the same regimen of carotid artery ligation manifest only a mild reaction, i.e., some endothelial proliferation but no thrombosis. In addition, we have found that breeder rats with pre-existing carotid artery disease were especially prone to the untoward effects of such experimental maneuvers as the production of hypertension with desoxycorticosterone, or alloxan-induced diabetes, or the induction of myocardial infarction with isoproterenol. During the course of these experiments, we also observed that there were profound metabolic alterations which could be related to the presence of carotid artery disease and cerebral ischemia. Therefore, a special series of investigations was designed to observe the metabolic effects of acute, unilateral carotid artery ligation—and partial cerebral ischemia—in animals free of arterial disease (virgins) in contrast to those having known, pre-existing, carotid artery lesions (breeders). The results of these exploratory investigations are reported here.

Methods

A total of 1,000 male and female, virgin and breeder Sprague-Dawley rats were used in these experiments. The nonarteriosclerotic subjects were male and female virgin rats which were comparable in age to the arteriosclerosis-prone breeder rats, i.e., eight to nine months old. The nonarteriosclerotic male virgin rats (group I) were compared with the arteriosclerotic male breeders (group II) which had sired at least four to five litters during active stud service. These male breeders develop microscopic aortic lesions but grossly visible calcific plaques in their common iliac arteries. The nonarteriosclerotic female virgin rats (group III) were compared with arteriosclerotic female breeder rats (group IV) which had completed four to five pregnancies. These female breeder rats develop grossly visible aortic arteriosclerosis ranging from minimal to severe degree after they have completed four to five pregnancies.

Twenty-four animals of each of the four groups described above were sacrificed at the outset of the experiment to provide baseline levels for the parameters being measured, i.e., male vs. female,
arteriosclerotic vs. nonarteriosclerotic subjects. The remaining 904 animals, 226 in each group described above, were subjected to unilateral carotid artery ligation. Although many animals died shortly after this surgical maneuver, the extra large number of animals provided at the outset resulted in the availability of no less than 24 surviving animals in each of the sequential time intervals described below. (Previous experience demonstrated that sham carotid artery manipulations do not cause any significant changes in the serum parameters measured. For this reason all of the animals prepared surgically were incorporated into this experiment as experimental subjects.)

The animals were anesthetized with secobarbital (Seconal). A longitudinal incision (2 cm) was made lateral to the midline over the hyoid muscles. Fascia and muscles were displaced to expose the triad of carotid artery, jugular vein, and vagus nerve. The carotid artery was carefully separated from this complex, and a single ligature placed about the common carotid artery 2 cm below the bifurcation of the carotid artery into the external and internal carotid arteries. The ligature was tied snugly to occlude but not damage the vessel. Muscle and skin were closed as separate layers. The animals recovered promptly from their light secobarbital anesthesia, were returned to their cages, and were allowed to have food and water on an ad libitum basis.

The animals were sacrificed by decapitation to avoid the stress of anesthesia, and blood was collected from the severed neck vessels. Each of the four groups of animals was sacrificed, sequentially, 2, 4, 6, 8, 10, 12, 24, and 48 hours after unilateral carotid artery occlusion. The blood of each animal was spun in a refrigerated centrifuge and the serum frozen and stored until time of analysis. The following serum parameters were measured by means of automated techniques (Auto-Analyzer, Technicon): glutamic oxaloacetic transaminase (SGOT), creatine phosphokinase (CPK), triglycerides, total cholesterol, free fatty acids, and glucose. In addition, serum corticosterone (Cmpd. B) levels, the main adrenocortical steroid in the rat, was also measured (14).

At autopsy each animal was carefully examined for any evidence of cerebral or cardiovascular disease. In addition, the site of ligation was carefully checked; animals showing questionable ligation were discarded. Pertinent tissues, such as brain, heart, aorta, carotid arteries, thymus, adrenal, liver, and kidney, were weighed and fixed in 10% neutral formalin (Lillie) for histopathological examination. Tissues were embedded in paraffin and sectioned at 3μ. Frozen sections for demonstration of lipids were cut at 10μ. Adjacent sections were stained with hematoxylin and eosin for routine analysis, alcian blue and toluidine blue for metachromasia, the Hale stain for mucopolysaccharides, the von Kossa method to demonstrate calcium, oil red O and Sudan black B for lipids, and the Klüver-Barrera stain for brain tissue.

Results

A. GENERAL OBSERVATIONS

Within minutes after occlusion of the carotid artery, the animals manifested complete blanching of the eye of the same side and signs similar to Horner's syndrome. A few animals promptly developed convulsions and died; some became paraplegic, and the majority showed marked extensor rigidity.

At autopsy all of the animals sacrificed 4 to 12 hours after carotid artery ligation exhibited fatty metamorphosis of the liver. Fifteen percent of the arteriosclerotic breeder males manifested grossly visible myocardial damage, i.e., ischemia, blanching, or hemorrhage. None of the male breeders had grossly visible arteriosclerosis. Eighty percent of the female breeders were found to have grossly visible aortic sclerosis ranging from minimal to severe degree. None of the virgin control rats showed any signs of cardiovascular disease. All of the experimental animals manifested progressively increasing cerebral edema after carotid artery ligation. However, the incidence of grossly visible, advanced cerebral ischemia, hemorrhage, or necrosis was scant, occurring only on an erratic basis in all of the groups investigated and without any apparent temporal pattern of development.

B. MICROSCOPIC OBSERVATIONS

The nonarteriosclerotic virgin control rats were free of any vascular disease even under histopathological scrutiny. However, the male breeder rats which ordinarily do not display any grossly visible aortic or carotid plaques did have well-defined intimal lesions containing accumulations of deeply staining mucopolysaccharide. These intimal lesions were capped over by collagenous material and were often invaded by large, deeply basophilic, rounded cells which were believed to be chondrocytes. The more obviously arteriosclerotic female breeder rats had advanced aortic and carotid artery arterial disease ranging from intimal ground substance degenerative changes to medial elastolytic, calcific, and even cartilaginous and osseous metaplasia. The morphologi-
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Cross section of a carotid artery of a nonarteriosclerotic female virgin rat taken 48 hours after surgical ligation and a few sections proximal to the site of ligature. There is no evidence of inflammation. A relatively mild, eccentric intimal reaction, consisting of edema, some fibrosis, and endothelial proliferation, is present. H&E, X 75.

Details of these aortic and carotid artery lesions have been described (1, 2).

Histological examination of the carotid artery proximal and distal to the ligature site demonstrated that within the 48-hour time period of this experiment, the nonarteriosclerotic subjects responded to the injury of carotid artery ligation by a relatively moderate endothelial cell proliferation just above and below the site of ligature (fig. 1). The arteriosclerotic animals showed a similar response, but superimposed on the endothelial reactivity in practically every subject was some degree of occlusive thrombosis ranging from moderate to severe degree (fig. 2). However, this was a localized phenomenon confined to the immediate vicinity of the ligature injury. Therefore, the cerebral ischemia and the serum metabolic changes described below are believed to be due to the effects of carotid artery occlusion following acute ligation. Details of the response to ligation injury of carotid arteries of arteriosclerotic and nonarteriosclerotic rats have also been described (11).

The arteriosclerotic male breeders which developed myocardial infarction during the 48-hour period of partial cerebral ischemia showed scattered, splotchy areas of necrosis of the myocardium and consistently showed endocardial necrosis and round cell infiltration (fig. 3). The livers of all of the animals contained diffuse areas of focal necrosis (fig. 4) and beginning fatty infiltration (fig. 4). Also, concomitant with severe thymus gland involution, the adrenal glands of the experimental animals were hypertrophied, the zona fasciculata greatly depleted of lipid, and the zona glomerulosa completely devoid of lipid (fig. 5). The kidneys showed no evidence of damage except for occasional tubular casts and protein and some glomerulo- and arteriolesclerosis in the case of the arteriosclerosis-prone breeder rats. However, no renal pathology could be related to the acute unilateral
FIGURE 2
Cross section of a carotid artery similar to the one shown in figure 1 but taken from an arteriosclerotic female breeder rat. The ectasia and extensive, focal, elastolytic damage were present prior to the 48-hour period of carotid artery ligation. The entire lumen is occluded by an early thrombus which is beginning to show evidence of organization and fibrosis. H&E, × 75.

carotid artery ligation procedure. In addition to generalized cerebral edema, these animals also displayed extensive marginal cerebral necrosis, superficial hemorrhage, and leptomeningitis (fig. 6).

C. PATHOPHYSIOLOGICAL CHANGES IN THE SERUM

Enzymes
Creatine Phosphokinase (CPK). There was no increase in serum CPK levels during the first 12 hours of partial cerebral ischemia. However, there was a real increase 24 hours after ligation, subsiding and returning to normal levels 48 hours later (fig. 7). All of the animals, arteriosclerotic and nonarteriosclerotic, showed this same pattern of response (fig. 7).

Glutamic Oxalacetic Transaminase (SGOT). As in the case of CPK levels, all of the animals showed a peak increase in SGOT levels after 24 hours of partial cerebral ischemia (fig. 8). However, the SGOT levels manifested a pattern of progressive increases with each interval of time after carotid artery ligation (fig. 8).

Lipids
Triglycerides. Two hours after carotid artery ligation, there was an acute rise in serum triglycerides, increasing progressively in male rats but falling precipitously in female rats (fig. 9). By the close of the experimental period, the triglyceride levels of the majority of animals had returned to near normal levels.

Free Fatty Acids. All of the animals manifested an acute increase in free fatty acids in response to the partial cerebral ischemia. This was most marked in the arteriosclerotic animals. By the close of the experiment the free fatty acid levels were close to normal (fig. 10).

Total Cholesterol. All of the animals showed a prompt and progressive increase in total cholesterol. Again the arteriosclerotic rats
manifested the most marked hypercholesteremic response. Unlike the other lipid modalities the serum cholesterol levels remained elevated throughout the 48-hour test period (fig. 11).

**Carbohydrate**

**Glucose.** There was a definite hyperglycemic response during the acute stages of cerebral ischemia, i.e., two to six hours after carotid artery ligation. The arteriosclerotic female breeders showed the most intense hyperglycemia. Again, the serum glucose levels gradually fell toward normal by the close of the 48-hour test period (fig. 12).

**Adrenol Steroids**

**Corticosterone (Cmpd. B).** Male rats showed a very prompt increase in Cmpd. B levels, peaking two hours after ligation and returning gradually to near normal levels. The female rats showed a similar acute response, particularly in the case of the arteriosclerotic rats which have decreased steroidogenic capacity as a concomitant of their arteriosclerosis (8–10). The nonarteriosclerotic females, which normally have higher Cmpd. B levels than males, also showed a progressive increase in Cmpd. B which did not reach a peak until the tenth hour after the induction of cerebral ischemia. By the forty-eighth hour of the experimental period, the Cmpd. B levels of most of the animals had fallen to below normal, with the notable exception of the arteriosclerotic female breeders (fig. 13).

**Discussion**

The essence of these experimental findings is that partial cerebral ischemia induced in the rat by unilateral carotid artery ligation will elicit definite pathophysiological responses similar to those observed following myocardial ischemia. Further, the prior existence of arteriosclerotic disease greatly aggravates the pathophysiological sequelae of cerebral ischemia. This exacerbation of the untoward effects of cerebral ischemia is manifested not so much in increased cerebral damage but in pathologi-
Liver of a nonarteriosclerotic male virgin rat 24 hours after unilateral carotid artery ligation. Note the foci of extensive necrosis (labeled A in photo) and the irregular-sized droplets of lipid, in keeping with the fatty infiltration observed in all animals following carotid artery ligation. H&E, ×120.

Some question may be raised as to whether the experimental maneuver of unilateral carotid artery ligation will indeed induce a state of partial or meaningful cerebral ischemia. However, the signs of Horner's syndrome, convulsions, extensor rigidity, paraplegia, cerebral necrosis, and high morbidity attest to the effectiveness of this procedure. Other investigators have also found that the cerebrovascular system of the rat is particularly responsive to the cerebral ischemia-inducing effects of carotid artery ligation, e.g., the rat does not have the well-defined circle of Willis that man has (15).

The prompt development of fatty metamorphosis of the liver in these animals after acute cerebral ischemia also attests to the stressful nature of carotid artery ligation. In these animals and in animals in which we have induced massive myocardial infarction, there is extensive dissolution of peripheral adipose tissue sites, hyperlipidemia, and fatty infiltration of the liver (12, 13, 16). It would appear that this intensive lipid mobilization is meditated by the adrenocorticoids released during the stress of acute cerebral ischemia. In connection with the above, it is of interest that the male breeder rats should be most prone to develop myocardial infarction during the acute induction of cerebral ischemia. Although male breeder rats do not develop grossly visible aortic sclerosis, their less dramatic-appearing microscopic lesions do occur in such vital places as the ostia of the renal, mesenteric, and coronary arteries (1–13). Further, male breeder rats develop hypertension, diabetes, hyperlipidemia, and other degenerative changes which disposes them to the development of cardiovascular disease and premature aging. Patients often suffer cerebrovascular impairment concomitant with an episode of myocardial infarction and vice versa (17). Burch et al. have shown that there are definite
myocardial alterations in animals (18) and EKG changes in humans (19) in association with cerebrovascular accidents. The special susceptibility of male breeder rats with pre-existing coronary artery disease to acute cerebral ischemia is another illustration of the closely integrated hemodynamic vectors between the cerebral and myocardial vascular systems.

The lack of grossly detectable cerebral damage in these unilaterally ligated rats is not too surprising in view of the rich collateral circulation to the head of rodents. Also, our own experience demonstrates that severe cerebral ischemia produced by bilateral carotid artery occlusion is required to induce grossly detectable cerebral damage in the rat. It is of interest, however, that our unilaterally ligated animals developed cerebral edema and hemorrhage comparable in severity to the bilaterally ligated rats described by Levine and Klein. That is, our animals and theirs developed cortical damage of similar severity and in similar anatomical foci, e.g., cerebral cortex and corpus striatum (20). These latter areas of the brain are purported to be particularly susceptible to anoxia because of their high metabolic rate (21, 22). We agree with Levine and Klein that the disparate susceptibility of various strains of rats to cerebral ischemia is probably due to the differences in cerebral collateral circulation between strains. However, it should be pointed out that in our experimental protocol breeder rats with pre-existing, advanced arteriosclerosis, with particularly severe carotid artery disease in female breeder rats, did not evince any greater cerebral damage following unilateral ligation than animals with healthy arteries. The assumption is that animals with pre-existing, severe, generalized arteriosclerosis would have reduced collateral cerebral blood flow through their remaining carotid and vertebral arteries because of their arterial disease. It is pertinent...
to add that in our investigation of the experimental induction of myocardial infarction in arteriosclerotic breeder rats, we have observed better survival in arteriosclerotic vs. nonarteriosclerotic subjects. We believe that, paradoxically, the subjects with pre-existing arteriosclerosis survive better because they have a better collateral coronary circulation as a result of their long-standing myocardial ischemia in direct relationship to the progression and severity of their coronary artery disease. Perhaps a similar protective mechanism is operative in the case of the arteriosclerotic rats subjected to partial cerebral ischemia.

One of the outstanding features of these experimental studies is the fact that the induced cerebral ischemia did elicit definite changes in various blood enzymes and other metabolic parameters. Progress in the clinical investigation and development of diagnostic procedures pertinent to cerebrovascular disease has been hampered by the lack of clear-cut evidence that cerebral anoxia or ischemia will lead to changes in serum lipids, enzymes, and other metabolic parameters which have been so amply demonstrated after myocardial anoxia and ischemia. The enzyme creatine phosphokinase is an ideal diagnostic agent for the detection of early myocardial infarction because, unlike the other enzymes currently in use, e.g., SGOT, SGPT, LDH, etc., CPK is rather specifically found in skeletal and myocardial muscle. It is also found in relative abundance in the cells of the central nervous system. However, patients with acute episodes of cerebral damage do not show any consistent or dramatic increase in serum CPK levels, as they do following acute myocardial ischemia or severe exhaustion of skeletal muscle (23). In our experiments the delayed rise in CPK levels 24 hours after carotid artery ligation followed by the abrupt increase in activity may be a reflection of the slow but undeniably detrimental effects of the induced cerebral ischemia. The similar pattern exhibited by the enzyme SGOT would also support this interpretation. The fact that the level of SGOT
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Changes in serum creatine phosphokinase levels in nonarteriosclerotic male and female virgin rats compared with arteriosclerotic male and female breeder rats during 2 to 48 hours of acute cerebral ischemia induced by unilateral carotid artery ligation. Intact arteriosclerotic breeder and nonarteriosclerotic virgin rats served as "controls" to provide baseline levels for reference purposes. Each point consists of a minimum of 24 determinations (n = 24), the mean and standard error are also indicated. Figures 8 to 13 are based on the same protocol.

As indicated previously, the lipid mobilization and fatty liver, which appeared during the period of cerebral ischemia, certainly was accompanied by dramatic alterations in circulating lipid patterns. It is difficult to explain why male rats should show a prompt increase in serum triglycerides and females such a prompt and precipitous decrease. The prompt increase in free fatty acids in all subjects would be in keeping with the typical response of animals or man to stress, myocardial infarction, or hormonal agents such as the adrenal steroids or catecholamines. The fact that the arteriosclerotic subjects showed the greatest increase of serum free fatty acids is probably a reflection of the pre-existing hyperlipidemia and hyperglycemia which accompany their arteriosclerosis (5-7). The prompt and persistent increase in serum cholesterol is rather surprising to us since in all of our other experimental investigations, we have found that serum cholesterol levels remain relatively unaltered or unresponsive to stressful maneuvers, e.g., myocardial infarction (12, 13).

In connection with the lipid changes discussed above, the dramatic hyperglycemic response of these animals also attests to the stressful nature and metabolic response elicited by cerebral ischemia. It is well known that patients in the acute stages of myocardial infarction will become temporarily diabetic. Perhaps a similar mechanism is operative in the case of these animals. As with serum lipids the greater degree of hyperglycemia in the arteriosclerotic animals probably is a reflection of their diabetes, which existed prior to acute cerebral ischemia (6, 7).
Finally, the pattern of increase and subsequent decrease to below normal levels of circulating corticosterone in these animals can be interpreted as an adrenocortical response to a stress of unusual degree. That is, the pattern of the Cmpd. B increase is too intense to be due to the surgical manipulation and anesthesia involved in ligating the carotid artery. Rather, we would interpret this response to be more characteristic of an unusually severe stress, one which borders on the fatal, since the adrenal cortex will produce unusually great quantities of steroids during life-or-death situations. In the case of these animals this response is exemplified in (a) the high mortality rate, (b) the greatly hypertrophied and lipid-depleted hemorrhagic adrenal glands, (c) thymus gland involution, and (d) depletion of adrenal steroid reserve, as evidenced by below normal serum Cmpd. B levels 48 hours after the acute onset of cerebral ischemia. Of particular significance is the fact that arteriosclerotic female breeders whose carotid arteries are often kinked and tortuous and calcified, in distinct contrast to the other animals whose carotid arteries are free of such complications. Some investigators have also encountered great increases in adrenal steroid production in patients with cerebral vascular accidents and consider cerebral ischemia to be a most stressful event (24). Those patients showing the greatest elevation of adrenal steroids were (8–10).
those with the poorest prognosis and who attained the highest levels just prior to death (24). It is especially pertinent to note that the depletion of lipid observed in the zona glomerulosa of the adrenal glands of these animals is indicative of increased aldosterone production and secretion. Recently, experimental evidence has indicated that manipulation of the carotid artery or carotid artery occlusion or partial ligation will elicit specific adrenocortical vascular and hormonal changes. For example, Sapirstein and Goldman have found that unilateral carotid artery ligation will cause an 80% increase in adrenal blood flow, whereas an injection of ACTH will cause 114% increase in adrenal blood flow (25). In connection with our observation of lipid depletion from the zona glomerulosa, Hodge et al. (26) have shown that carotid artery occlusion in the dog will cause increased renin and angiotensin formation. Similarly, Bartter et al. (27) found that bilateral carotid artery constriction in dogs caused increased aldosterone production. This response is believed to be mediated by baroreceptor mechanisms,
reflexogenic responses in the cardiovascular system, central nervous system receptors, the hypothalamus, a neurohumor or ACTH, and it is felt that the trauma of carotid artery ligation is not responsible for the intense adrenocortical stimulation which ensues (26-30).

In conclusion, these experimental studies indicate that cerebral ischemia induced by carotid artery occlusion will cause specific and intense adrenocortical stimulation accompanied by definite pathophysiological responses evidenced by alterations in serum enzymes, lipids, and glucose. Further, the presence of arteriosclerosis prior to and during the induction of cerebral ischemia is associated with intensification of these pathophysiological changes as well as exacerbation of the potential for development of cardiovascular defects in such subjects, e.g., appearance of myocardial infarction.

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References

21. Himwich HE: Brain Metabolism and Cerebral Disorders. Baltimore, Williams & Wilkins Co., 1951
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