CHAPTER XXVI.

THE INTERNAL SECRETIONS IN THEIR RELATIONS TO PATHOGENESIS AND THERAPEUTICS (*Continued*).

DISORDERS DUE TO HYPERACTIVITY OF THE ADRENAL SYSTEM.

Although the above heading would appear to incriminate the adrenal system as the source of the disorders considered in this chapter, the morbid effects its excessive functional activity engenders are, in truth, primarily due to the presence in the blood of one or more poisons which overstimulate the test-organ, and thus cause an excessive production of adrenoxidase. As I will show in the following pages, it is this agent which, by enhancing metabolism inordinately in the walls of the arterioles of the vasa vasorum, causes the lumen of these vessels to become obliterated. Atheromatous degeneration thus becomes but a normal result of the fact that the nutrition of the vascular tissues supplied by these minute vessels is prevented.

This points, however, to the adrenal system as the dominant factor of arteriosclerosis, a disease which, although as stated by Sir James Barr,[1] "kills more men in the prime of life and vigor of manhood than any other," is far from being understood. Indeed, Joseph Collins,[2] after a comprehensive study of the subject, was recently led to conclude that "there is no unanimity of opinion concerning the way in which the morbid condition constituting arteriosclerosis develops." The adrenal system fulfills quite as prominent a position in the pathogenesis of the two main results of arteriosclerosis, viz., angina pectoris and cerebral hæmorrhage, as we will presently see.

ARTERIOSCLEROSIS.

SYNONYMS.—*Atheroma; Arteriofibrosis; Endarteritis Chronica Deformans.*

Definition.—Arteriosclerosis is primarily due to the presence of endogenous or exogenous toxic substances in the blood,

[1] Sir James Barr: Brit. Med. Jour., Jan. 20, 1906.
[2] Collins: N. Y. Med. Jour., June 9, 1906.

in excess of the quantity which the auto-antitoxin of the latter can convert into benign and eliminable end-products. The adrenal system being kept overactive by these poisons, however, the proportion of adrenoxidase in the blood is excessive, and the walls of all vessels are the seat of inordinate metabolic activity. The arterioles of the vasa vasorum being similarly affected, their muscular coat finally becomes hypertrophied—sufficiently in many instances to obstruct or obliterate their lumen. The vascular tissues supplied by these obstructed vasa vasorum being no longer adequately nourished, they undergo necrosis and the necrosed areas become the seat of atheromatous or sclerotic patches.*

Symptoms.—Although arteriosclerosis gives rise to symptoms that vary according to the organ which is the seat of the most advanced lesions, there are certain phenomena that are common to all cases. Before the characteristic vascular lesions are discernible, these cases are apt to show evidences of general asthenia, being readily fatigued by exertion, and sweating readily without adequate cause. The face is pale, especially about the mouth, temple and eyes, and a tendency to giddiness and loss of intellectual acumen is occasionally observed.

When the disease is sufficiently advanced, the characteristic symptoms are eminently vascular. Prominent among these is the resistance of the vessels to pressure, especially discernible when the finger is applied over the arteries of the wrist and popliteal space. The resistance may be due to two factors: one of these, increase of tension of the vessel, is not always present, and often occurs in other diseases; while the other, thickening of the vessel-walls, is a characteristic sign when high tension is alone present, firm pressure arresting the pulsations beyond the seat of pressure. When the artery is sclerosed, however, this cannot be done, the vessel's pulsations being quite perceptible notwithstanding the compression; the pulsation is also prolonged owing to the narrowing of the vascular lumen. High tension and sclerosis are often present simultaneously; in that case, the signs of sclerosis prevail. Another sign is usually present to confirm the diagnosis: a tortuous, dilated, and pulsating appearance of the arteries of the temple. Sphygmographic

* *Author's definition.*

tracings show a short sloping upstroke, a wide top and a slow, gradual downstroke. The pulse is usually slow and retarded at the wrist when the narrowing of the artery is marked, and may differ on the two sides if the stenosis of one vessel is more marked than that of the other arm. Another confirmatory sign is often present, *i.e.*, the *arcus senilis*.

Early in the course of the disease the urine is apt to be more abundant and to show variations of specific gravity. Albuminuria may then appear intermittently, and finally contain casts. When these organs are seriously involved, anuria and the symptoms of chronic fibrous nephritis may appear and symptoms of uræmia likewise. Arteriosclerosis of the uterus is sometimes the cause of severe hæmorrhage at the menopause or in aged subjects. In the latter the bleeding is difficult to control, owing to the arterial fibrosis. The dislodgement of thrombi, due to endarteritis, or detached thrombi or widespread arteriosclerosis, sometimes gives rise to gangrene of the extremities.

An important feature of the whole problem is the asthenic character of the disease emphasized by many authors, whether met in a decrepit old subject or in an overfed gourmand. Thus Stengel[3] includes among the earlier symptoms "reduced vitality," and remarks that "many cases of neurasthenia are of cardiovascular origin," and characterizes as the "arteriosclerotic facies," "a peculiar pallor" specially conspicuous around the mouth, temples and eyes. Kisch[4] associates obesity with arteriosclerosis.

Bittdorf,[5] as shown farther on, associates marked pallor with aortic arteriosclerosis. As to the involvement of the uterus, Reinicke[6] observed four cases of this kind in which hysterectomy became necessary to avoid a fatal issue. The vessels of the organ showed typical lesions of the senile type. Similar instances have been reported by Cholmogoroff,[7] Grube[8] and others. Ergot invariably aggravates the bleeding.

The *heart* finally becomes hypertrophied, owing to the increased resistance of the blood-column. The left ventricle having to bear the brunt of the increased work, however, it is the one which undergoes hypertrophy first; the aortic second sound is therefore unusually accentuated, clear and ringing. This is best heard behind, over the angle of the left scapula on a level with the seventh dorsal spine. This unilateral enlargement and the unusual displacement the increased vigor of the left ventricle entails tend to displace the heart as a whole—the apex being sometimes over an inch or more nearer the sternum than usual. This hypertrophy is a desirable condition, and serves to overcome the obstruction to the blood-stream. The general health may not be impaired by its presence a number of years therefore, until the coronary arteries are markedly diseased and the nutrition of the myocardium is seriously compromised. When this occurs degeneration of the heart-muscle supervenes with its consequences: heart-failure, arhythmia, dyspnœa, pulmonary congestion, œdema, etc. Angina pectoris is a formidable complication of the lesions of the coronaries, though not due, as now believed, to obstruction of these vessels, but, as shown farther on, to their inability to control the volume of blood admitted into the pericardium.* Rupture of the heart-wall may occur, with hæmorrhage into the pericardium.

[3] Stengel: Amer. Medicine, Jan 2, 1904.
[4] Kisch: Wiener klin. Rundschau, Bd. ix, S. 371, 1895.
[5] Bittdorf: Deut. Archiv f. Med., Bd. lxxxi, S. 65, 1904.
[6] Reinicke: Archiv f. Gynaek., Bd. liii, S. 430, 1897.
[7] Cholmogoroff: Monats. f. Geb. u. Gynaek., Bd. xi, S. 692, 1900.
[8] Grube: *Ibid.*, Bd. xvi, S. 258, 1902.

Hasenfeld[9] found in the course of extensive pathological studies that arteriosclerosis only leads to hypertrophy of the left ventricle when the splanchnics or thoracic aorta are severely affected. Arteriosclerosis of the other vessels does not seem to have such an effect. Runsberg[10] holds, on good ground, that the cardiac symptoms are of dual origin, the one set arising from the sclerosis of the coronaries, the other due to impairment of the cardiac functions owing to the sclerosis of the vascular system at large. Stengel very appropriately states that arhythmia in persons near forty is too often attributed to gastric disturbances, tobacco, tea, coffee, etc.

The *aorta* is often involved, and tends greatly to aggravate the patient's general condition. The face is often very pale and there is a marked tendency to obesity. Abnormal pulsations in the subclavian and carotid arteries are usually marked, and dilation of the veins of the chest may sometimes be provoked by forced respiration; the tissues over the sternum will then appear œdematous as in aortic aneurism. The pupils may differ in size, though the reflexes remain normal, and the retinal vessels may be dilated and even hæmorrhagic. Respiratory phenomena are of frequent occurrence, there being a tendency to bronchitis, emphysema, bronchiectasis and hæmoptysis, with a marked susceptibility to tuberculosis. A prominent symptom is weakness of the arms. The resistance to the blood-stream being increased in the aorta, the cardiac hypertrophy attending the general disease is aggravated, and may even occur if the aorta

* *Author's conclusion.*
[9] Hasenfeld: Deut. Archiv f. klin. Med., Bd. lix, S. 193, 1897.
[10] Runsberg: Finska Lak. Handl., Bd. xliii, Nu. 8, 1900.

be alone the seat of the characteristic advanced lesions. While the first aortic sound is clear and distinct, the second sound is more or less accentuated. The peripheral vessels may show but slight arteriosclerosis. The pulses of both sides often differ, and the pulse is generally rapid, though the blood-pressure be increased. Palpitations, cardiac oppression and dyspnœa are caused by exertion, while vertigo, tinnitus and other symptoms of the general dyscrasia may appear.

The symptomatology of aortic arteriosclerosis has recently been carefully worked out by Bittdorf[11] in 54 cases not complicated by aortic stenosis, aneurism, coronary sclerosis or nephritis. The symptoms outlined in the general text are mainly those given by this investigator. William Welch[12] states that the aorta is a region of predilection for the cicatricial form of arteriosclerosis. It shows but little tendency to extend into the large branches of the aorta or into the abdominal aorta. The changes occur in the adventitia and media, and may consist of furrows and depressions, elevated plaques or fibrous scar-like patches.

Arteriosclerosis of the *brain* is a prominent feature of many cases. Vertigo is a salient symptom of this condition, especially in the aged. In these and younger subjects the early manifestations may assume the form of intellectual torpor with loss of memory for recent events, irritability and darting head-pains. Aphasia, somnolence, tinnitus aurium, inequality of the pupils and disorders of vision and sensation, *i.e.*, insecurity of gait or even numbness of one limb or one side of the body. Apoplectiform and epileptiform attacks, preceded by the characteristic prodromes, are sometimes witnessed in such subjects, and, in fact, may precede those just outlined. Senile dementia or general paralysis which occasionally occur are due, in keeping with the other phenomena, to degenerative changes.

In a study of 200 cases of apoplexy M. Allen Starr[13] found that 80 per cent. showed many of the above phenomena as prodromal signs. Hence the importance of recognizing them early so as to foretell, if possible, the apoplectic attack. Joseph Collins,[14] in an able article based on a study of 800 cases of arteriosclerosis, states that "the most striking feature of the disease is the alteration of the patient's appearance. The individual becomes transformed from a person expressing grace in movement and relaxation in repose, into an immobile, inanimate replica of the normal person" . . . . "the gait is perhaps the most remarkable feature of the patient. The stride is short, oftentimes only a few inches, the feet widely separated and not lifted from the ground, the rhythm of the movement often slow and rapid." In 15 advanced cases Zapin-

[11] Bittdorf: *Loc. cit.*
[12] William Welch: N. Y. Med. Jour., June 18, 1904.
[13] M. Allen Starr: Med. Record, July 4, 1903.
[14] Joseph Collins: N. Y. Med. Jour., June 9, 16, 23, 1906.

sky[15] found cortical vascular lesions in 14. Collins states that the most striking alterations are found in the middle cerebral arteries and the branches. In some instances the entire brain is shrunken. Bondurant,[16] after a study of 200 cases, concludes that "the characteristic and ever-present mental expression of arteriosclerosis is dementia of some kind or degree."

Arteriosclerosis of the *spinal cord* and *peripheral nerves* may act as the underlying cause of numerous diseases of these organs. Lesions of the lower half of the cord evoke morbid phenomena in the lower extremities; lesions of the upper half in the upper, or in both upper and lower. If the anterior horns are involved, motor symptoms appear; if the lesions are located in the posterior horns, the disorders are sensory. Besides these territorial effects, however, the specific symptomatology of arteriosclerosis asserts itself. Thus, besides gradual development of paralysis of the lower extremities, preceded by stiffness, muscular cramps, etc., the arteries show the typical signs; the blood-pressure is high and the characteristic heart-sounds are present.

The spinal type of neurasthenia, pain in the back, numbness of the legs, irregular twitchings of the muscles and weakness, irregularity in urination, and constipation and various forms of neuralgia are also witnessed.

Joseph Collins, referring to the symptomatology given in outline in the first paragraph, and illustrated by a typical case seen with Zabriskie, states that when advanced, such cases are often diagnosticated as transverse myelitis or chronic myelitis. He refers to an instance in which the symptoms came on so abruptly that the diagnosis of Landry's paralysis was made. He states also that it was well described by von Leyden (1875), who looked upon it as a senile process in the spinal cord. The neurasthenic type outlined in the second paragraph is regarded by M. Allen Starr[17] as due to malnutrition of the cord.

Pathogenesis and Pathology.—In the majority of cases of arteriosclerosis, the disease is preceded by a general adynamia due to functional torpor or hypoactivity of either of the organs of the adrenal system, or all of them, *i.e.*, the adrenal center, the adrenals or the thyroid.* This may be the result of normal or premature senility, starvation, or of diseases such as syphilis and influenza, which depress markedly the functional activity of the adrenal center;* or of poisons such as alcohol, phosphorus

* *Author's conclusion.*
[15] Zapinsky: Wratch, No. 4, p. 95, 1896.
[16] Bondurant: Intern. Med. Mag., July, 1896.
[17] M. Allen Starr: *Loc. cit.*

—that of the endotoxin of tuberculosis, for example—which deoxidize the blood and thus render all the organs of the adrenal system hypoactive;* or of inherited functional debility of this system.*

Old age is not a cause of arteriosclerosis. The organs of the adrenal system becoming senile with the rest of the organism, the process of life which they govern, *i.e.*, tissue metabolism, is inhibited in proportion. The other etiological factors are generally recognized as such. Moritz,[18] in a study of 100 cases of arteriosclerosis under 60 years of age (Russians), found that 47 gave a history of syphilis acquired from eight to thirty years before the date of examination, and that all but four were immoderate or moderate consumers of alcohol. Though this applies to Russian lower classes and cannot be taken as standard for people of other countries, the potent influence of syphilis and alcohol is, nevertheless, illustrated. Sir J. Barr[19] regards syphilis as the most potent factor in the production of arteriosclerosis, and holds that typhoid fever plays a considerable part in its induction. Excessive smoking is also believed to be pathogenic. Boveri[20] produced atheroma of the aorta in the rabbit by the administration per ora of an infusion of tobacco. Nammack[21] attaches great importance to heredity as an etiological factor. Bock[22] attributes a certain proportion of cases to insufficient food.

In this group of cases the exciting causes of arteriosclerosis are toxic products of hypocatabolism, including xanthin and hypoxanthin, which are present more or less continuously in the blood, owing to the functional torpor of the adrenal system.* Hence* the fact that the gouty diathesis is generally included among the causes of arteriosclerosis.

The poisonous properties of xanthin, hypoxanthin and other toxic wastes of the purin group were first shown, we have seen, under Gout, by Grancher and fully confirmed by Kolisch, Tandler Paltauf and Albrecht. Croftan,[23] moreover, showed that they produced granular degeneration of the epithelium of the convoluted tubules and proliferation of the endothelium of the intertubular epithelium. The corresponding lesions in the smaller vessels in arteriosclerosis, in the familiar "endarteritis obliterans," the "arteriolitis" of Letulle, etc., correspond with these processes,—all inflammatory in nature, as pointed out by Virchow in 1856, precisely as the lesion in the kidneys, the interstitial nephritis leading to contraction, is inflammatory.

Gout is now generally considered as a cause of arteriosclerosis, whereas, as interpreted from my standpoint, the etiology of gout and that of arteriosclerosis are—as far as the xanthin group is concerned—similar, *i.e.*, adrenal insufficiency leading to the formation of toxic wastes as a preliminary feature. Rachford,[24] nearly ten years ago,

* *Author's conclusion.*
[18] Moritz: Med. Examiner, Oct., 1904.
[19] Sir J. Barr: *Loc. cit.*
[20] Boveri: Clinica medica, No. 6, 1905; Gazz. d. Osped. e delle Clin., vol. xxv, pt. i, p. 666, 1905.
[21] Nammack: Med. Record, Oct. 26, 1901.
[22] Bock: Zeit. f. diat. u. physik. Ther., Bd. ii, S, 33, 1898.
[23] Croftan: Jour. Amer. Med. Assoc., July 8, 1899.
[24] Rachford: Phila. Med. Jour., Apr. 16, 1898.

emphasized this kinship and attributed the main phenomena witnessed in arteriosclerosis to xanthin and other purin bodies. "We can well imagine," says this author, "that this condition of the arteries might result from their long-continued irritation by the presence of an excess of the alloxuric bodies in the blood," several cases being adduced in support of this view. If the multiplicity of conditions with which arteriosclerosis is associated, migraine, neuralgia, neuritis, asthma, etc., are compared to those associated with the gouty diathesis, the strength of this interpretation will appear. Again, we have seen in the article on Gout that, as first shown by Levison, the kidneys are profoundly diseased in gout. The similarity of the lesions in both diseases, however, may be illustrated by Osler's statements that in gout[25] there is "an interstitial nephritis, either the ordinary 'contracted kidney' or the arteriosclerotic form," and that in arteriosclerosis,[26] "the condition is practically that of contracted kidney."

Arteriosclerosis differs from gout and the diseases that are provoked by the gouty diathesis in that it may be caused (indirectly) by poisons other than the purin bases. Thus it may be caused by products of tissue catabolism, such as those derived from the muscles during violent exertion or physical labor, or from the brain tissues during excessive mental strain, or from the combination of these two factors which constitutes "strenuous life." The disease may also be provoked by the pathogenic elements of many infectious diseases, typhoid fever, variola, erysipelas, pneumonia, measles, scarlatina, acute rheumatism, septicæmia, etc., and various poisons such as lead.

Excessive muscular exertion is regarded as a prominent predisposing factor. Thayer and Brush,[27] in an analysis of nearly 4000 patients suffering from various diseases, found the percentage of palpable radial arteries materially higher among individuals in whom there was a history of heavy physical labor. Collins[28] states that "within the present generation arteriosclerosis has advanced from the position of a senile manifestation and a necessary accompaniment of old age, which our predecessors had given it, to one of the commonest sequences of the strenuous, disordered life."

The toxic origin of arteriosclerosis has been pointed out by Traube, Rokitanski and many others. Both Huchard and Runeberg ascribed endarteritis to a toxin in the blood. Thérèse[29] was able to prove this fact experimentally. Gilbert and Lion,[30] Boinet and Romary[31] and others produced atheroma of the aorta by injecting various pathogenic bacteria. A comprehensive study of the question also led Russell[32] to conclude that the disease is due to the presence of deleterious substances in the blood. Again, Flexner[33] observed a case in which the aorta had

[25] Osler: "Principles and Practice of Medicine," third edition, p. 411, 1893.
[26] Osler: *Ibid.*, p. 775.
[27] Thayer and Brush: Jour. Amer. Med. Assoc., Sept. 10, 1904.
[28] Collins: N. Y. Med. Jour., June 9, 1906.
[29] Thérèse: Thèse de Paris, 1891.
[30] Gilbert and Lion: C. r. de la Soc. de biol., 9 série, vol. i, p. 583, 1889; Arch. de méd exper., vol. xvi, p. 73, 1904.
[31] Boinet and Romary: *Ibid.*, vol. ix, p. 902, 1897.
[32] Russell: Lancet, June 1, 1901; Feb. 7, 21, 1903; and Brit. Med. Jour., June 4, 1904.
[33] Flexner: Johns Hopkins Hosp. Bull., Aug., 1891.

apparently been rendered tuberculous through infection of the intima by the blood-stream—a legitimate conclusion in view of my contention that the endotoxin of tubercle bacilli acts through the phosphorus it contains. Thayer and Brush,[34] in 21 out of 52 autopsies in typhoid fever, found fresh patches in the aorta, and in 13 out of 62 autopsies, similar patches on the coronary arteries.

These poisons provoke arteriosclerosis by causing an excessive or too prolonged defensive reaction of the adrenal system.* The blood being supplied with an excess of adrenoxidase, the muscular coats of all vessels, including those of the nutrient arteries of the latter, the vasa vasorum, are subjected to excessive metabolism, which causes them to remain more or less permanently constricted, and finally to hypertrophy, thus obliterating the vessel.*

The marked vascular tension observed in many cases of arteriosclerosis—which constitutes one of its most dangerous phases, owing to the danger of arterial rupture, cerebral hæmorrhage, aneurism, etc., it entails—is the subjective manifestation of this condition.* The arterioles which supply the vasa vasorum being primarily affected in this manner, owing to their diminutive size, the areas of the vascular coats to which they are distributed are no longer adequately nourished; they finally become necrotic, therefore, and are then transformed into atheromatous or sclerotic patches.*

Russell[35] has urged the existence of a close connection between arteriosclerosis and vasoconstriction, the latter being attributed by him to the presence of poisons in the body, *i.e.*, to autointoxication.

The vasa vasorum have long been known to play an important rôle in the process. Cowan[36] states, in fact, that the "vasal changes may, in some cases, be the only visible lesion," and refers to cases in which "the interference with the vascular supply from the vasal vessels produced medial and intimal necrosis." Osler, referring to Councilman's study of 41 autopsies, states that "in the circumscribed or nodular arteriosclerosis the primary alteration consists in a degeneration or a local infiltration in the media and adventitia, chiefly about the vasa vasorum." All this applies to the large vessels as well as to the aorta. Cowan states that he has witnessed obliterating lesions in the aortic vasa after acute rheumatism.

Interesting experiments have shown recently that injections of a solution of adrenalin during a prolonged period produced typical atheromatous lesions. This fact, first observed by Josué, has been confirmed by Gouget,[37] R. M. Pearce and E. MacD. Stanton[38] and L. Braun.[39] The latter observer, however, injected amyl nitrite simultaneously to counteract the vasoconstrictor action of the adrenalin. As the arterial sclerosis followed nevertheless, he concluded that its action was similar to that of other toxics. This view is in accord with my interpretation of the mode of action of the adrenal secretion: By injecting persistently adrenalin (the active principle of this secretion) into the blood, they produced excessive intracellular metabolism, constriction and obstruction of these vessels in the experimental animals.

* *Author's conclusion.*
[34] Thayer and Brush: *Loc. cit.*
[35] Russell: *Loc. cit.*
[36] Cowan: Practitioner, Mar., 1906.
[37] Gouget: Presse méd., vol x, p. 898, 1903.
[38] R. M. Pearce and E. MacD. Stanton: Albany Med. Annals, Feb., 1906.
[39] L. Braun: Wiener klin. Woch., Bd. xviii, S. 150, 1905.

The fact that the adrenal extractives raise the arterial tension has long been known. M. Allen Starr[40] suggested that in some cases of arteriosclerosis, the high tension was due to *lack of activity* of the thyroid gland. On giving thyroid extract, he observed considerable improvement and *lowering* of tension. The manner in which this beneficial effect was produced is plain, in view of the rôle of thyroidase. Not only did the latter sensitize (as opsonin) the poisons in the blood, but by increasing the sensibility of the depressor nerve, it reduced the functional activity of the adrenals and thyroid[41] and produced general vasodilation. It could not stimulate the adrenal system here, since it was already overactive.

That the adrenals are powerfully stimulated by waste-products and disease toxins we have seen in the first volume and in this. Vaquez[42] reported "a case of persistently high tension which at autopsy showed an adenoma of the adrenal." The same observer suggests that "an adrenal irritation is responsible for the change in tension and the tendency to arteriosclerosis." Coplin writes in this connection: "In the discussion, Josué referred to his experimental studies and stated that, with Bernard, he was at present studying the adrenals from cases of atheroma; they have reached the conclusion that in such cases the glands show evidences of increased activity." Coplin,[43] who refers to these observations as "highly suggestive" and demanding "careful clinical and experimental study and further observation," refers to histological sections of the adrenals of 22 cases of arteriosclerosis in which only 5 were found by him not markedly altered, the only cases departing from conditions which I ascribe to excessive stimulation being 3 of tuberculosis and 1 of secondary neoplasm. A large number of investigators have confirmed the observations of Josué. Lissauer[44] and others, having studied the lesions histologically, hold that they differ from those of true arteriosclerosis. That an experimental condition brought on acutely, as it were, should differ somewhat from a corresponding disorder gradually developed in human beings; is self-evident. Again, as observed by Josué, Loeb and Githens, and others, various drugs which raise the blood-pressure do not produce atheroma. This only proves that, in accord with my conception of the process, it is not the rise of blood-pressure which causes the disease—since any agent capable of exciting the vasomotor and sympathetic would do so—but excessive metabolic activity in the vascular elements and hypertrophy, which in such minute vessels as the vasa vasorum—arterioles—means obliteration.

That we cannot ascribe the elevation of pressure to a direct action of the poisons upon the adrenals is shown by the fact that *destructive* metamorphosis does not enhance the functional activity of these organs; it reduces it. We have proof of this fact in the course of events in Addison's disease. Moreover, we have conclusive evidence to the effect that the antitoxic properties of the blood are increased in the observation of Sir James Barr[45] that the blood of arteriosclerosis in 55 per

[40] M. Allen Starr: *Loc. cit.*
[41] *Cf.* this volume, p. 1087.
[42] Vaquez: Presse méd., vol. xi, p. 102, 1904.
[43] Coplin: Medicine, Aug., 1904.
[44] Lissauer: Berl. klin. Woch., May 22, 1905.
[45] Sir James Barr: *Loc. cit.*

cent. of the cases gave complete agglutination with the colon bacillus, as compared with only 20 per cent. with the blood of persons free from arteriosclerosis. I have shown that agglutination indicated an increase of proteolytic activity.

The fact that the administration of thyroid extract reduces the vascular tension, as stated by Allen Starr, Osborne[47] and others, indicates, moreover, that the high blood-pressure is often but a temporary condition, and not, therefore, an inherent factor of the morbid process. This accounts for the lack of accord as to presence of this symptom. Thus, while Cowan states that "the essential cause of arterial sclerosis is an increase of arterial tension," implying therefore that it is present in every case, Dunin[48] found it normal or reduced in 80 out of 440 instances, after excluding all cases in which there was loss of cardiac compensation. Keigi Sawada,[49] in a series of 98 cases, found an increase of blood-pressure in only 12.3 per cent., the accentuation of the second aortic sound being often present without such a rise. Romberg's[50] investigations showed even a smaller proportion, *i.e.*, a rise of pressure in only 10 per cent. Allbutt,[51] who contends that the rise is not due to arteriosclerosis, but to some alteration of the blood or some "perversion of metabolism" (a prominent factor, in the light of my views), states that in the senile form, the blood-pressure is not usually elevated.

In some cases a high vascular tension is maintained through the resistance offered by the kidneys when these organs are considerably inflamed or when they are contracted. Under these conditions, the toxic wastes accumulate in great quantities in the blood and the two morbid conditions operating simultaneously,* a very high and dangerous rise of the blood-pressure may occur—which may be reduced by appropriate measures.

In accord with the experience of other clinicians Groedel[52] states that the blood-pressure is invariably increased when contracted kidney exists simultaneously. Both Hasenfeld[53] and Hirsch[54] found that both ventricles of the heart, and not the left alone, were hypertrophied when the kidneys were diseased.

Arteriosclerosis may be circumscribed into patches, the so-called "nodular" plates commonly found in the larger vessels, especially the aorta, where they often occur in great numbers, the coronaries, the carotids, etc., and which vary in size from that of a pin-head to that of a dime. At first they are smooth, grayish and translucent, the endothelium being unaltered (a fact which shows that the lesion is not caused by the blood circulating in the artery itself) and project from the surface—usually about one millimeter. Later, however, they degenerate and become opaque and yellowish-white. At this stage they may either break down, forming a ragged necrotic ulcer, the atheromatous ulcer, over which thrombi may be formed and carried to other parts by the circulating blood; or they may at once undergo a process of repair—if replacing of destroyed tissue by a lime mortar may be thus called—and the hard, calcareous atheromatous plate is formed. In this form the elastic portion of the media is the seat of the most marked lesions, being more or less atrophied owing to degeneration. As a result, the vessel loses its elasticity, and its walls being calcareous give rise to the resistance felt at the pulse.

* *Author's conclusion.*
[47] Osborne: N. Y. Med. Jour., Aug. 20, 1904.
[48] Dunin: Zeit. f. klin. Med., Bd. liv, 353, 1904.
[49] Keigi Sawada: Deut. med. Woch., Bd. xxx, S. 425, 1904.
[50] Romberg: Verhand. Congress f. inn. Med., Bd. xxi, S. 60, 1904.
[51] Allbutt: Lancet, Mar. 7, 1903.
[52] Groedel: *Ibid.*, Apr. 17, 1897.
[53] Hasenfeld: *Loc. cit.*
[54] Hirsch: Deut. Archiv f. klin. Med., Bd. lix, S. 193, 1897.

The diffuse form of arteriosclerosis is mainly found in the smaller vessels, the walls of which consist mainly of the circular muscular layer of the media. As a result it is this layer which bears the brunt of the morbid process, but instead of becoming atrophied as does the elastica, it becomes, as a rule, as is the case with the heart-muscle, hypertrophied. Nor is the process of repair the same: the calcareous deposits of atheroma are seldom observed and an overgrowth of fibrous tissue is the main resource to compensate for the loss of contractile elements.

The circumscribed and diffuse forms may, however, occur concomitantly and the processes of repair likewise. In both forms narrowing of the caliber of the vessel, or even complete obliteration of the lumen, may occur when the vessel is sufficiently small. In both forms also this is mainly due to hyperplasia of the tissues of the intima underlying the endothelium, most marked during the earliest stages of the morbid process, and followed by the formation of dense sclerotic tissue.

T. D. Savill[55] considers atheroma as a patchy fibrocellular infiltration of the intima, and distinct from intimal sclerosis. From a study of 400 bodies of persons who had died at the age of 60 or upward, he concluded that extensive patchy atheroma was consistent with extreme longevity and with a total absence of symptoms or vascular complications. Conversely, he considers moderate disease of the *musclar coat* a serious potential evil. Atrophy of this coat may occur in association with some wasting disease, but hypertrophy is more common, especially after middle life; and may be succeeded by cloudy swelling, with which granular degeneration is frequently associated; necrosis and calcification occurring in spots or foci of varied size. Savill holds that the combination of hypertrophy of the muscular coat and focal necrosis of the media is a most deadly one, and may produce death by hæmorrhage at an early age.

[55] T. D. Savill: Lancet, Sept. 24, 1904.

As to the obstruction of the vascular lumen, Thoma[56] holds that when the blood-stream is slowed from any cause, the intima, by a process of hypertrophy, reduces the lumen of the vessels to restore the normal rate of flow—an explanation which Councilman,[57] Gibson[58] and others have criticized. That we are dealing with a morbid phenomenon due to inflammation, devoid of any physiological purpose, coincides more accurately with the teachings of clinical experience. Obliterating endarteritis may be marked in syphilis, but Cowan[59] states that he has seen it "in the *aortic vasa* after acute rheumatism," and that it has been found in cases of diphtheria, scarlatina, smallpox and typhoid fever. Barié[60] also found that small arteries and veins were not infrequently blocked by inflammation in typhoid fever.

Treatment.—In the treatment of this disease its two pathological stages must be clearly differentiated, since measures indicated during the second stage may prove harmful in the first.*

The *first stage* corresponds with the development of the lesions and includes (in the group of cases, by far the largest met with, due to toxic waste-products of catabolism) three definite, though concurrent, morbid conditions: (1) general adynamia, which entails (2) hypocatabolism, and, therefore, an accumulation of toxic wastes in the blood, the cause in turn of (3) the vascular lesions.

The first indication is to reduce the volume of the patient's waste-products.* The *diet* requires the greatest attention, the prime requisite being a reduction of the daily aggregate of food. This applies particularly to meats, which contribute, owing to their wealth in nucleins, the bulk of the pathogenic xanthin and hypoxanthin. The total omission of meat—fowl being allowed—and of alcohol from the diet, with reduction of the other foods generally partaken of at regular meal hours, is sometimes sufficient, when persevered in, to arrest the morbid process and initiate convalescence. In severe, though not advanced, cases, a milk-diet, at least one quart being taken daily during a couple of weeks to rid the blood of accumulated poisons, is necessary, before the preceding diet is begun.

Sir James Barr[61] contends that so far as arteriosclerosis is concerned, the excessive use of nitrogenous food kills more adult men than alcohol. After witnessing one of the great temperance advocates of the last century dine, he predicted that he would not live three years; the intemperate eater was dead within two.

* *Author's conclusion.*
[56] Thoma: "Blood Pressure in Surgery," 1903.
[57] Councilman: Trans. Assoc. Amer. Phys., vol. vi, p. 179, 1891.
[58] Gibson: Lancet, Sept. 19, 1896.
[59] Cowan: Practitioner, Aug., 1905.
[60] Barié: Rev. de méd., T. iv, pp. 1, 124, 1884.
[61] Sir James Barr: *Loc. cit.*

Of material assistance in the curative process is the abstention from the use of beverages which stimulate the vasomotor center, coffee and tea. Pure water in large quantities and diuretic drinks, such as milk and mineral waters, favor materially the elimination of toxic wastes. A pinch of common salt in a glass of milk increases its digestibility and diuretic action.

Important in this connection is the use of saline beverages, the destruction of toxic wastes by the blood's endogeneous antitoxin being greatly enhanced when the blood's alkalinity and therefore its osmotic properties are adequate. The bi-weekly use of a rectal injection of one quart of saline solution at 110° F. (43.3° C.) is very beneficial.*

Sodium chloride, we have seen,[62] enhances greatly the osmotic properties of the blood and other body fluids. Allbutt[63] attributes to "increased viscosity" and the interference with the capillary circulation which this entails, the degenerative processes of arteriosclerosis.

The abstention from undue physical exertion is a necessary feature of the treatment, to prevent the excess of tissue wastes and the rise of blood-pressure it entails.* Occupations which involve physical and mental strain, simultaneously, especially if attended with worry, are particularly pernicious.

Shattuck[64] states that men carrying great responsibilities, such as the captains of industry, show a high arterial tension. Bock[65] holds that men who speculate, brokers, bankers and those of similar occupation are predisposed to the disease.

Various clinicians recommend systematic muscular exercise, regulated gymnastics, resisted movements, etc. I can discern no scientific reason for such measures, and am inclined to believe that what benefit is apparently derived from them is, in reality, due to the hygienic or medicinal treatment resorted to concomitantly. Huchard[66] recommends massage on the plea that it enhances the elimination of waste-products. It becomes a question whether this excess is not a product of the manipulations.

Tepid baths should alone be recommended, as cold or warm baths increase subcutaneous metabolism, and therefore the formation of waste-products. Cold baths are particularly dangerous when there is a tendency to cerebral hæmorrhage—a comp'ication which threatens any case of arteriosclerosis and which can but seldom be foreseen. Lukewarm sea-water baths are beneficial in all stages of the disease.*

* *Author's conclusion.*
[62] *Cf.* this volume, p. 1368.
[63] Allbutt: Lancet, Jan. 17, 1903; and Trans. Pathol. Soc., vol. lv, p. 438, 1904.
[64] Shattuck: N. Y. Med. Jour., June 25, 1904.
[65] Bock: *Loc. cit.*
[66] Huchard: Jour. des praticiens, Dec. 23, 1899.