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THE TRIPLE ALLIANCE: HEART, KIDNEY, AND ARTERIAL DISEASE*

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THE simultaneous presence of chronic heart, kidney, and arterial disease is not so uncommon in individuals above middle age. It does not make its appearance in the same characters in the different cases, but when more closely analyzed clinically or studied pathologically, we find similar earmarks of disease in each of the three organs. At times the condition of the heart, at others the finding of Bright's disease, or it may be the sudden development of cerebral conditions, calls our attention to the particular system, suffering the greatest strain, and we are apt, erroneously, to refer to that organ as the sole region of disease. These combinations of heart, kidney, and arterial disease, or any two of them, are most commonly brought to our attention when the process, from a pathological point of view, has become chronic. In no way do we face an acute lesion of an organ, but only the manifestations of a process insidiously progressive, and clinically recognizable late in its development. A correlation of the many facts bearing upon the condition which I have termed the triple alliance, is, I believe, possible.

A physiological alliance has been recognized as existing between the heart, arteries, and the kidneys. The proper function of each is, to some extent, dependent upon the healthy activities of the others. The relationship is perhaps more prominently brought out in the dependence of the function of the kidney as related to the

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heart, while a similar relationship also exists between the heart and the circulation in the arteries. To a great extent this relationship centres around the question of blood pressure within the arteries. It is realized, too, that this blood pressure is normally altered with great ease and that the alteration is observed by a greater or less response in all of these organs. From the recognition of the physiological interdependence of the activities of this group, have proceeded the theories that many of the pathological processes arising in any one, have their explanation in changes occurring in one or both of the other organs.

The lesions which we recognize in heart, kidney, and arterial disease, are of the character of sclerosis in each. The heart is hypertrophied, mainly in its left ventricle, and shows areas of scleroses throughout its musculature. The arteries are thickened with more or less distortion of their lumina, although the altered calibre may not be referable to intimal sclerosis. The kidneys are small and fibrosed, showing characters that we readily classify as chronic interstitial nephritis. In the fully developed cases of heart, kidney, and arterial disease, the fibroses of these organs are marked, though the relative extent of the cirrhotic change differs in each case, sometimes being most marked in the heart, at other times showing an unusual arterial sclerosis or, again, having marked chronic interstitial reactions in the kidneys. Because of the variation in the quantitative deposition of fibrous tissue there has been much speculation in suggesting the disease or the organ which was primariiy at fault.

Bright and subsequent pathologists recognized the association of the contracted kidney with morbid changes in other parts of the body, particularly in the presence of hypertrophy of the heart. It was generally believed that the kidney was the organ primarily affected and that other bodily conditions were secondary.

The hypertrophy of the heart has been explained on a purely mechanical basis as due to the difficulty of the circulation in the cirrhotic kidneys. Ewald and, later, Loeb have suggested that the heart lesions were the result of increased work brought about by the greater viscosity of the blood. Others (Hasenfeld and Hirsch) have found that the cardiac hypertrophy was associated particularly with a sclerosis of the splanchnic vessels while scleroses in the remaining portion of the peripheral tree, they believed, had less effect.

In the belief that the kidney was primarily involved in disease and was followed by the retention of a variety of products of meta-

bolism, it was held by some that both the heart and arterial lesions were the result of a chemical irritation. The retained substances, it was claimed, had a direct effect upon the musculature of the heart as well as upon the arteries. It was also suggested that besides this the direct toxic effect of the retained excretions caused a persistent high blood pressure induced by arterial spasm. More recently it has been suggested that chronic kidney disease is accomplished by an abnormal function of the adrenal glands, associated with a greater production of adrenalin. This, it is claimed, leads to a tonic spasm, or contraction of the arterial walls, materially raising the blood pressure to which the cardiac hypertrophy is a response. Thus a variety of factors have been suggested as initiating the hypertrophy of the heart secondary to other diseases.

Even under the circumstances where cardiac hypertrophy is recognized clinically, the heart condition may not have reached the final stage of the process. Insufficiency of the myocardium may yet develop, particularly in the presence of a subsequent disease, as myocarditis, or with a progressive sclerosis of the coronary arteries. These changes, however, are rather to be viewed as complications and sequelæ which do not assist in clearing up the nature and process of the primary disease causing the hypertrophy.

Undoubtedly, when a definite sclerosis of the large and small arteries has occurred, the increased resistance rapidly leads to an alteration in the circulation. The maintainance of an equal supply of blood in the peripheral arterioles demands greater activities on the part of the heart, and whether the heart may properly compensate for this increased demand depends, in the individual case, upon the reserve activities of the musculature. An adequate nutrition, using the term in its broadest sense, will permit the myocardium to compensate by hypertrophy. It may be, as suggested by some, that prior to the arteriosclerosis, the heart may show no evidence of enlargement, but it would be going too far to say that in the absence of recognizable hypertrophic changes, the heart had not previously suffered myocardial lesions. It may be, as some have indicated (Hasenfeld, Romberg), that though the heart be damaged by degeneration, the hypertrophy does not arise until the musculature is given the stimulus for growth by suffering undue stretching.

Hirsch examined a series of cases with cardiac hypertrophy and found that where this hypertrophy was associated with arteriosclerosis, the left ventricle was mainly or alone involved. He also observed that when diseases of the lung and pleura had an effect

upon the pulmonary circulation, the hypertrophy of the heart was mainly on the right side. In a third group of cases those having chronic nephritis, a few showed hypertrophy of the left ventricle alone, but the majority showed that the hypertrophy involved both right and left heart, though the increase was greater upon the left side than the right. It was assumed by Stewart that this latter condition arose from an increased peripheral resistance in an increased viscosity of the blood acting primarily upon the arterioles and then upon the left ventricle. It is also indicated that the cardiac hypertrophy without valvular disease, associated with arteriosclerosis, while more especially affecting the left ventricle, is also present in the auricles (Hirsch). These authors claim that no pathological factor other than that mentioned is available for explanation. In his experimental work Stewart has been able to show that a hypertrophy may be induced by the production of aortic insufficiency and is the result of increased work.

The spirit has gone abroad that wherever arteriosclerosis is present in the body, there must be some increase in the blood pressure. Yet, when this is put to test, it is found that there is no uniform relation between them. Sawada found that in only about 12 per cent. of arteriosclerotics was there a heightened pressure. Romberg noted that in some districts arteriosclerosis was unaccompanied by increased pressure while in others it was the common manifestation. He points out, however, that in the latter chronic interstitial nephritis was a complication. Thus he indicated that arteriosclerosis with nephritis and arteriosclerosis without nephritis may occur in unequal proportion among different people.

There are so many factors which appear to influence the development of chronic disease of the heart, kidney, or arteries, that much speculation has been indulged in respecting the importance of each. Richard Bright, who was among the first to give definite recognition to these associated processes, looked upon the kidney disease as the prime causative factor for hypertrophy of heart. These contentions of Bright were opposed by Rayer, who denied the common association of heart and kidney diseases. Even Frerichs opposed Bright's view and claimed that cardiac hypertrophy preceded the nephritis. Up to this time much confusion existed in the classification of Bright's disease and difficulty was expressed in segregating the types, so that a proper comparison could not be made of the relationship of the diseased process to that in other organs. Traube, in 1845, divided Bright's disease into several groups, in one of which he found heart disease was particu-

larly prone to occur. He believed that some cardiac affections could lead to kidney disease, other than infarction, and eventually to chronic changes. Cardiac hypertrophy, he observed, occurred mainly with the contracted kidney and the left ventricle responded most promptly. This exposition by Traube was favourably received and indicated progress in the recognition of a variety of lesions in the kidney. Johnson, in 1852, noted the association of thickened arteries with chronic Bright's disease. The arterial change he viewed as hypertrophy of the media resulting from an impure blood containing urinary excreta. The minute arteries, it was thought, resisted the passage of this abnormal blood and the heart putting forth an increased effort developed a hypertrophy of the left ventricle.

In 1872 Gull and Sutton again attracted attention to the association of cardiac hypertrophy with chronic nephritis and arterial disease. They were, however, insistent that the cardiac condition was not secondary to the disease in the kidney, but resulted from a general arterio-capillary fibrosis. This vascular lesion they believed was not isolated to any part of the body, but was generalized, involving all the small arterioles. The vascular changes were present in the heart muscle as well as the kidney and other parenchymatous organs. It was claimed that this widespread arterial disease bore the same relationship to the interstitial myocarditis, as did the acute softening of the heart muscle to the embolic process of the coronary arteries as described by Virchow. These contentions of Gull and Sutton were substantiated by Buhl, Koester, Huber, Sternberg, and others. The cardiac disease was looked upon as resulting from an altered nutrition consequent to the coronary sclerosis. Previous to these observations much stress has been laid upon so-called idiopathic hypertrophy of the heart.

Gull and Sutton showed that the vascular lesions were independent of renal disease and that the kidney condition was a manifestation of a more general systemic process. Furthermore, they indicated that in other kidney diseases where much destruction of renal substance had taken place, with the probable retention of excreta, no cardiac hypertrophy was found. That cardiac hypertrophy was not the result of renal disease was illustrated in the fact that it might occur without the presence of kidney involvement, as well as preceding chronic Bright's disease. The authors observed a hyaline fibrous change about the vessels of the heart similar to that which they had found in the kidney. This they considered

was, in part at least, the cause of the hypertrophy. Gull and Sutton observed that the arteries in the pia mater in chronic interstitial nephritis sometimes showed a thickening of the intima, sometimes a hypertrophy of the media, but more commonly a fibrosis surrounding the vessel. The media sometimes was atrophied. These same changes were further found in the skin, stomach, spleen, lungs, heart, and kidneys. In a table of ages of patients examined, the authors have found that granular conditions of the kidney belong to a period of life at or over forty years of age. However, in the few cases in which the condition was found before the age of forty, the general disease process simulated those at more advanced ages. Here, too, there was observed the periarterial thickening accompanied by hypertrophy of the heart. They pointed out that clinically the manifestations of this general disease might be such that no attention is attracted to the heart, kidney, or arteries, but only after other progressive changes have damaged one of these systems may we recognize the presence of chronic Bright's disease with its accompanying manifestations. In the early stages the symptoms depending upon the intensity of the vascular involvement may be more evident in diverse parts of the body. In conclusion they recognized a systemic disease of the arterioles and capillaries which, as a periarterial fibrosis, may begin in the kidney, but which also has its pathological changes in other organs.

Our attention must not be too closely centred upon the conditions arising in any one organ. A general perspective of the lesions throughout the body is essential, and for this purpose nothing short of a combined study of many regions will allow us a proper interpretation of the diseased processes in question. It is furthermore necessary to study the disease in its various stages of development. Too much stress has been laid upon the importance of the pathological changes in the heart, kidney, or the arteries after one or other of them has suffered severely. To indicate that the heart and arteries are subject to a sclerosis in chronic interstitial nephritis is simply a statement of the gross pathological features observed in an individual after he has passed through consecutive stages of a disease and arrived at a point where the functional activities of several organs are so impaired that a continuance of healthy life is impossible.

Thus the observations upon the clinical pathology of these associated diseases are far from clearing up the moot points concerning the importance of common processes. Difficulty is experienced in indicating the beginning of a sequence of changes whose

manifestations are not the same, and whose recognition is only late in the progress of those changes. Some of the clinical features have been explained upon pathological findings. But here again much difficulty has been experienced in indicating the order in which the lesions have occurred. Conclusions have been drawn from studies made upon fully developed cases alone. In respect to these, the observers do not differ so much in the recognition of the lesions, but in the importance of each as dominating the presence and progress of others.

Senator points out that while there are a great number of factors which, upon purely theoretical grounds, may be suggested as the causative factor leading to cardiac hypertrophy, it is probable that no single cause may be found to account for all, as the individual conditions differ considerably in each case. Thus he believes that the increased viscosity of the blood, the narrowing of the capillary bed, the thickening of the muscular coat of the arterioles, the resistance of the blood stream displayed by the visceral arteries, as well as other factors, might be important causes for some cases, yet each will not act with equal intensity in the different individuals. He has further observed that the molecular concentration of the blood differs in the different forms of nephritis. The blood contains substances which are toxic for various tissue and the character and concentration of the albumens are altered. These changes have a direct effect on the heart muscle as well as an irritating action on the vessel walls, stimulating them to contraction.

He points out that chronic interstitial nephritis is a slowly progressive disease in which the changes do not occur suddenly. The altered blood content gradually acts upon the vessel walls, leading to histological changes as well as functional incapacity of their tissues. The circulatory change as well as the direct effect of the altered blood upon the heart is, he believes, the main cause for cardiac hypertrophy. He further suggests, however, that it is quite possible for the true causative factor to exist outside of the heart and kidney and to attack these organs simultaneously.

Although fibrous myocarditis was noted by Veniviene (1529) and later discussed by Morgagni, its nature was not appreciated until 1806, when Corvisart recognized it as an inflammatory process and believed that it was always associated with a pericarditis or an endocarditis.

Pathologically the chronic fibrous myocarditis indicates a replacement of the muscular tissue of the heart by connective tissue. The left ventricle is mostly involved. Commonly when

small patches of fibroses are observed in the heart it is found that they had given no clinical evidence of their presence. It has, however, been demonstrated that the presence of connective tissue greatly interferes with the function of the heart by reducing its elasticity as well as its contractile power. Its association with cardiac hypertrophy has been commented upon, while Rigal and Juhel-Renoy have applied the term "*myocardite-sclêreuse hypertrophique*," to this association. Leyden called attention to the several forms of cardiac sclerosis, sometimes observed in a diffuse and scattered manner while in other individuals isolated plaques are found. Koester drew attention to the frequency of the process and indicated the more important pathological characteristics of the disease. The fibrous areas appear as parallel tendinous streaks following the direction of the muscle cells. The distribution of these areas is not uniform. They are commonly present at the apex while the posterior and upper portion of the left ventricle may also show much involvement. They are prone to lie quite superficially either directly beneath the pericardium or close to the endocardium. The papillary muscles of the left ventricle are also structures showing a predilection for this process. Koester was able to observe that this development of connective tissue in the heart resulted from two different causes, on the one hand associated with inflammation with secondary destruction of the muscle fibres, or otherwise as a degenerative process without inflammatory change and associated with disturbance of the coronary arterioles. The former type is the one which is particularly associated with kidney and arterial disease. The distribution of the lesions in the heart muscle is quite characteristic, and may be observed in different stages of development. Inflammation precedes the development of the connective tissue in all. Koester believed that this myocarditis had its origin in infection, while Ruehle observed that it was most commonly associated with rheumatism. It was likewise pointed out by others that myocarditis as it occurs in rheumatism and its allied diseases was associated with endocarditis and pericarditis.

Aschoff and others have described an acute non-suppurative lesion of the myocardium occurring during an attack of acute rheumatic fever, acute articular rheumatism, muscular rheumatism, and rheumatoid affections. This heart lesion is quite distinctive and differs from that observed in infections by pyogenic organisms as well as by a variety of specific organisms. The lesions in the heart are focal and develop in the vicinity of the nutrient vessels

of the myocardium. Isolated areas of inflammatory exudate surround the small arterioles leading to greater or less degeneration of the musculature in the vicinity. The greatest amount of damage by these foci is produced in the outermost coat of these vessels and in the tissues immediately surrounding them. The small arterioles are in themselves not extensively involved during the acute stage. Gradually, however, as the process enters upon a chronic stage there is a thickening of the vessel wall, partly due to an hypertrophy, but mainly due to a fibrosis occurring in the adventitia with some thickening of the media. The total bulk of heart that is affected by this perivascular inflammation, is considerable, and the myocardial weakening observed in these affections is the result of the degeneration of the heart muscle occurring immediately about the nutrient vessels.

These observations by Aschoff and Tawara were confirmed in experimental studies by Waechter and others. It was shown that when organisms (streptococci) isolated from cases of acute rheumatic fever and the milder allied diseases, were inoculated into susceptible animals, tissue disturbances simulating the original disease in man could be readily induced. Not alone were the clinical manifestations reproduced but lesions occurred in the myocardium of a nature similar to those noted in the human heart. The lesions have been found so characteristic that from the myocardial picture alone the diagnosis of a rheumatic affection could be made. In a series of experiments to which we will refer again we have been able to confirm the findings of Waechter.

In an individual study reported upon during the past year we have made observations upon the various arteries of the body during acute rheumatic fever. It was observed that the larger vessels, and more particularly the arch of the aorta, which are supplied by nutrient vessels advancing into the outer and middle coat, suffered a non-suppurative inflammatory reaction similar to that found in the heart. This reaction was of the same character as that in the myocardium and was disposed in a perivascular manner. The vasa vasorum of the arteries take the place of the small divisions of the coronary arteries of the heart. These vasa vasorum carry the burden of the reaction in the vessel wall. Accompanying the reaction there is a certain destruction of the essential elements of the arterial coat, leaving the vessel weaker and subject to subsequent fibrous replacement of its own tissue. In our earlier studies it appeared to us that the peripheral arteries did not become involved. This conclusion was mainly drawn from a study of arteries

of intermediate size which passed to the limbs and to the main viscera. It is true that in the majority of cases these moderate sized arteries of the muscular type show no evidence of inflammatory invasion. Nevertheless, as we then indicated, an irregular distribution of the inflammatory reaction may be observed in some of the arterioles when the larger visceral arteries are not involved.

In the cases which we have examined, the simultaneous occurrence of lesions in the myocardium and the arteries has been very constant. The intensity of the reaction in each or both has been varied; at times that in the heart being greater and out of proportion to that in the arteries, at other times again, the reverse was observed. Moreover, we have been able to follow the processes during the various stages of development. From the acute non-suppurative variety with extensive perivascular infiltration of the small arterioles all gradations of chronicity with progressive fibrosis have been found. The amount of fibrosis occurring in the vicinity of the arterioles was dependent upon the intensity of the reaction, and the extent to which the neighboring parenchymatous tissue was affected. From the minute, microscopic fibrous tissue masses to the larger fibrous streaks, such as are observed in the heart and large vessels, all degrees and stages were demonstrated.

It is in association with these particular arterial lesions that hypertrophy of the heart is prone to develop. This hypertrophy, however, does not begin to show itself until the reparative processes about the minute vascular channels become evident. In many cases the heart suffers some dilatation of its cavities during the acute stages, but though the heart at this time is receiving the stimulus for growth through stretching, it is unable to compensate so early by hypertrophy on account of the systemic illness, which offers the explanation in an inadequate nutrition. Hypertrophy does not begin until recovery from the effects of the immediate acute involvement has passed over. Repair of the inflammatory focus does not begin until, in part, at least, the infection is overcome. From this time on not alone is there a repair of the lesion induced during the inflammatory reaction, but also opportunity is given for the compensation of the weakened myocardium sustained in muscular degeneration.

When, now, we suggest a type of kidney lesion ending in chronic interstitial nephritis as commonly associated with this combination of acute and subacute myocarditis and arteritis, we will receive considerable opposition from clinical observers. The constancy of association of myocarditis and mesarterial diseases has

gradually impressed itself upon us so that we view this occurrence as the usual lesion in certain forms of infection. We have hardly reached the time when all are willing to place definite forms of kidney disease in the same group. Nevertheless, an examination of human material as well as experimental studies force us to accept this view. As is true with so many forms of non-suppurative infections in which a bacteriæmia is temporarily and periodically present, many of the organs suffer unequally. The bacterial attack upon various tissues is only an incident in the disease, and it would be impossible to designate the lesion in each organ as a common or constant manifestation.

With the type of infection which dominates acute and subacute cardiac disease, we recognize organisms which are not constant in their virulence, which are sporadic in their systemic distribution and which are very uncertain in their localization in the tissues of the body. At times, during a given illness a dissemination of bacteria occurs in the blood stream for short periods of time, then the circulation is rapidly freed from the meteor-like distribution, only to be involved in a subsequent and similar reinfection from a local focus. The disease does not carry with it a constant bacteriæmia.

As, then, the hæmatogenic infection of different organs is so uncertain and unequal, the lesions arising in different cases are difficult of comparison. We have, however, found that inflammatory changes arising in the interstitial tissue of the kidney were not so uncommon in these infections. In the milder forms where the kidney was least involved and where clinical evidence of a nephritis was wanting, the lesion consisted of a lymphocytic and plasma cell infiltration in the interstitial tissue close to the interlobular arterioles. This subacute inflammatory reaction was distributed mainly about the arterioles and began in about the middle of the medulla. The inner coats of these arteries were not appreciably altered but the adventitia was quite loose and œdematous with an infiltration of lymphocytes. From the perivascular lesion the inflammatory exudate spread along the course of the vessel into the cortex, so that streaks of infiltration could be followed from the medulla to the surface of the organ. Primarily, this perivascular non-suppurative inflammation with its œdema gave a more bulky appearance to the involved areas. The tubules of the vicinity were surrounded by the exudate of cells while but little change occurred in the epithelial lining. Similarly, the capsules of the neighbouring glomeruli were not uncommonly surrounded by a similar infiltration.

For the most part the inflammatory reaction was present in radiating zones, leaving intervening patches of kidney tissue uninvolved. The larger vessels near the base of the pyramids also showed a perivascular reaction, but the main artery to the kidney was, in itself, devoid of inflammatory change.

This non-suppurative inflammatory reaction beginning in the vicinity of the interlobular vessels and extending through the cortex appears to be a typical lesion associated with the common subacute inflammation of the myocardium. In the human organs, however, it is usually associated with other lesions which tend to obliterate the character here described. Individuals dying during the first attack of acute infective myocarditial disease have commonly extensive endocardial vegetations. The presence of embolic masses of small or large size is apt to involve the kidney in a well marked infarct or lead to the occlusion of the vessels to the glomeruli with subsequent changes in these structures, not definitely to be viewed as the typical lesion of the disease.

We must, however, recognize a form of acute glomerulonephritis with the local exudate, and occasionally showing a proliferative reaction within the glomerulus or its capsule, as a common reaction of the kidney. The presence of an acute glomerulonephritis in a number of bacterial diseases is now well recognized, particularly through the work of Councilman and Loehlein.

The observations upon the various types of acute non-suppurative nephritis, indicate the close relation of the lesion to the circulatory apparatus. That at times the lesion is greater in the glomerulus while at others the perivascular reaction appears more intense, is not to be wondered at, when we remember the unequal reaction in tissues by many varieties of bacteria. Moreover, the different forms of reaction occurring within the glomeruli may well be variations in the intensity of reaction to a single strain of organism. Thus, as has been amply illustrated in late years, a single irritating agent such as uranium nitrate may give rise to tubular, glomerular, and even vascular lesions in the kidney. We have repeatedly observed a variety of pathological processes in different glomeruli brought about by the same bacterial agent.

These inflammatory disturbances of the kidney, showing their main reaction about the blood vessels and their associated parts, were observed in the early stages of heart and arterial disease. When closely analyzed it will be observed that the reaction in each of these tissues, heart, kidney, and arteries is very similar. There is a type of subacute inflammation particularly distributed in the

vicinity of the small nutrient vessels, disturbing the parenchymatous tissue in the immediate vicinity. We have indicated the late effect of this inflammation upon the heart muscle as well as the disturbance of the media of the arteries. We now call attention to the effect of the inflammatory reaction upon kidney tissue.

In the milder conditions the reaction remains localized in the vicinity of the vessels, causing but little disturbance of the tubules or glomeruli. An œdema pervades the intertubular connective tissue in the interlobular zone. Relatively little kidney tissue is involved by this localized inflammation, although streaks of reaction follow many of the small cortical arterioles. Where the reaction is more intense the infiltration spreads for some distance into the cortex involving considerable areas in an irritative process. More or less tubular degeneration may be present and granular debris appears within the secreting structures. The glomeruli may be involved in congestion with proliferation or show the presence of a lymphocytic infiltration amidst the capillary loops. Some of the glomeruli may become occluded and undergo hyaline change. Crescentic spaces between the glomerulus and its capsule show the presence of debris and hyaline masses. Occasionally hyaline and granular casts are found within the tubules.

As these inflammatory lesions progress to the chronic stages, the perivascular areas of infiltration become replaced by connective tissue. There appears to be a large gap in the observations, both clinical and pathological, between the acute and chronic stages of the disease. Many individuals die during the height of the disease when the acute reaction is well evident in the kidney. Otherwise death does not overtake them, save through intercurrent accident, until the late sequelæ bring about these changes in the heart, kidneys, or arteries, which have been so thoroughly observed and studied. The intermediate stages of repair are infrequently seen. Nevertheless, one may observe combinations of the acute and chronic lesions in those cases where the disease has been of a recurrent nature. This is not so uncommon, and we have observed a number of instances where perivascular fibrosis was accompanied by an acute lymphocytic infiltration. The acute lesions of the heart were a further evidence that the inflammatory infiltration was a recurrent one and not that of a progressive disease.

The healing of the acute inflammatory exudate takes place by a fibrosis which is observed in radiating streaks advancing from the base of the pyramids through the cortex. The small arterioles which ramify from the interlobular vessels carry with them an

excess of connective tissue. This fibrosis develops through the increase of connective tissue around the small vessels and becomes attached to the fibrous capsule of the organ. The radiating character of this fibrosis is quite distinct. Only secondarily does it involve the tubules and glomeruli which lie in its path in the cortex. The structures intervening between these lines of fibrosis are uninvolved in the cirrhotic change so that many glomeruli throughout the cortex have normal characters and the tubules lying outside of the zone of fibrosis are unchanged. With the shrinkage which accompanies all forms of inflammatory fibrosis, the involved areas tend to narrow the cortex by drawing the surface closer to the outer border of the medulla. The unequal distribution of the fibrous tissue leads to an irregular amount of contraction producing a very granular kidney. Naturally the amount of shrinkage is dependent upon the state of the disease as well as the intensity of the primary inflammatory process. This final stage is known to us as the granular kidney, the genuine contracted kidney, or true chronic interstitial nephritis.

In our discussion we have suggested a bacterial irritant underlying the inflammatory reactions in each of the involved organs. The same organism appears capable of producing inflammatory lesions simultaneously in many tissues and owes its distribution to the blood stream.

In recent years much has been done to indicate the importance of definite streptococcal infections in the inflammatory lesions of the heart and circulatory organs. Although all are not agreed upon the particular type of organism which is mainly at fault, yet it is important that various observers have had their attention attracted to an organism or group of organisms which induce a subinfection, having more severe focal processes in one or other organ. Though we believe that these focal depositions of bacterial infection may involve many different organs and bring about various grades of inflammatory reaction, our chief attention has centred about the infective heart disease. Nevertheless, the arteries, meninges, kidneys, joints, and liver have been shown to be variously involved in different cases. A study of the organisms associated with such lesions has called forth a nomenclature greatly confusing the subject.

The important bacteria belong to the group of streptococci, and may be recognized by their biological characters and separated from the pus-producing streptococcus, as well as from the pneumococcus. By Schottmuller this variety of streptococcus was

named the streptococcus viridans. In the further investigations it was shown that streptococcus viridans represented a group of organisms which, although having some common characteristics separating them from other members of the streptococcus group, had further points of differentiation which divided the group into a number of types, whose characteristics were fixed and whose habitat was more or less defined. To this group belong the streptococcus fecalis, streptococcus salivarius, streptococcus equinus, streptococcus mitis, and several unnamed forms. The group in itself is quite distinct and by proper means can be readily recognized.

The organisms which have been isolated by different observers from acute and subacute endocarditis belong to the streptococcus viridans group as described by Schottmuller. Such organisms as were described by Poynton and Paine as the streptococcus rheumaticus, the endocarditis coccus of Libman, and the organisms described by Rosenow must be considered as members of this group. It has been pointed out by Gordon and others, including my colleague, Dr. Holman, that the organisms found in connexion with heart lesions do not represent an individual type or a specific variety, but recognizing that they belong to the streptococcus viridans group, they may be represented in a variety of types. Of five organisms obtained from different cases of heart disease, three were shown by Gordon to simulate the streptococcus mitis, while two had characters similar to streptococcus salivarius. Dr. Holman has likewise demonstrated the type of streptococcus salivarius in the blood of patients with vegetative endocarditis, while in three other instances he isolated a form simulating the streptococcus fecalis and in another the streptococcus equinus. Andrewes and Horder in an extensive study upon streptococci found the presence of the streptococcus viridans in fifteen out of twenty-three cases of malignant endocarditis. Of these, eleven belong to the group of streptococcus salivarius; and four to streptococcus fecalis.

In five of our cases having acute non-suppurative processes in the heart, arteries, and kidneys, there was isolated a type of the streptococcus viridans from the blood at autopsy.

The association of these organisms with the occurrence of inflammatory processes in each of the three organs under discussion, led us to test our results upon animals. Through the kindness of Dr. Holman, I had the opportunity of obtaining a number of types of the streptococcus viridans for the tests. Rabbits were used, and living cultures in different amounts were inoculated intravenously. Nine cultures giving the reaction of the streptococcus fecalis,

seven streptococcus mitis, four streptococcus salivarius, one streptococcus equinus, and four other unnamed types of the streptococcus viridans were used. None of these inoculations gave rise to pus formation (one recently isolated strain of streptococcus salivarius was found to be highly virulent for rabbits, death being produced in forty-eight to seventy-two hours). The inoculated animals were killed at different intervals, and the lesions were studied both macroscopically and microscopically. In the majority of instances only one inoculation was given.

In brief, we were able to demonstrate pathological processes in the majority of animals surviving beyond the forth day. The variation in the pathogenicity was quite evident even among the organisms of the same strain. Some of the older cultures proved to be of low pathogenicity so that, although a slight non-suppurative reaction appeared at the end of the first week, complete resolution occurred within a month. On the other hand, the more virulent forms showed quite intense reactions by the end of the first week which persisted for varying periods of time up to six weeks. When, however, the inoculations were repeated at intervals of three weeks, a progressive inflammation with productive fibrosis was observed over a period of seven months.

In our experiments we were unable to indicate definitely the type of organism which appeared to give the greatest tissue reaction. The variation in the length of time in which the different organisms had been cultivated on artificial media had greatly altered their pathogenic qualities.

The particular point, however, in which we were interested was the simultaneous occurrence of lesions in the heart, arteries, and kidney. The affection of the heart was mainly to be observed in the myocarditis which simulated that described for the human heart. An interstitial infiltration of lymphocytes and plasma cells was the usual observation, and this infiltration was mainly in the vicinity of the small arteries. We failed to demonstrate the uniform periarteritis and mesarteritis of the ascending aorta, as we have on a previous occasion indicated for the human vessel. In two instances a slight grade of periaortitis was present. Otherwise, however, we found an irregular and inconstant periarteritis of the arteries of the liver, diaphragm, mesentery, and kidney. In the latter organ upon which our attention was concentrated, some remarkable results were obtained.

The kidney lesions were common and occurred in greater frequency and intensity than in the heart. They were associated

with the vascular system of the organ. The larger vessels were the least involved, but the interlobular vessels and the afferrent vessels of the glomeruli showed an inflammatory attack of a considerable degree. The nature of distribution of these vessels led to a radiating character of the inflammatory process, extending from the intermediate zone to the capsule. The picture was identical with that described in the spontaneous lesions in man. Moreover, all gradations from the acute process to the chronic fibrosis could be followed. A mild grade of granular kidney was produced. In three instances in which the disease had lasted over four months there appeared slight hypertrophy of the heart.

For the present I need not go into the further details of these experiments, save to indicate that the lesions produced experimentally closely resembled those which we meet with clinically. The important finding of the correlation of the heart and kidney in the inflammatory reactions, is worthy of comment to indicate how a general bacterial process may underly a pathological condition arising in each, and before either of these organs has an affect upon the other through its functional incapacity. The cardiac degeneration occurs during the early and acute stages of the disease. The repair with its accompanying fibrosis is prone to have hypertrophy develop with it. So too, the kidney lesion is individual, developing from a bacterial irritant inducing fibrosis about its blood vessels. A vicious circle may, no doubt, develop in the course of the disease which may react on other vital organs. The peculiarity of the infection in being distributed by the small arterioles and having its main action upon the tissue in the vicinity of these, is worthy of our notice. This finding is but a substantiation of the observations of Gull and Sutton. It appears, therefore, that the heart and kidneys bear to each other a relation during this infection only in proportion to the nature and distribution of the inflammation about their vascular system.

I would not have you believe that the arterial affection as an arteriosclerosis is the predominant one, but the organic changes are dependent upon the distribution and the extent of the perivascular inflammatory attack. Moreover, I further wish to indicate that the interdependence of the lesions of the heart and kidneys is through their circulatory system, but not because of an arteriosclerosis as we ordinarily understand it.

Thus our "triple alliance" is complete. Each of the three organs has its individual duty to perform, which has an important bearing upon the health of the other. Common enemies (bacteria)

attack them simultaneously, leaving one, or another, or all, badly abused. Repair of the injuries results in fibrosis which may manifest itself in the "senile syndrome."

The hypertrophy of the heart has its beginning in a process of repair of the heart muscle damaged by bacterial invasion. Subsequent factors, such as increase of the blood pressure and the effect of retained excretory products, probably assist in increasing the cardiac hypertrophy in the later stages of the disease.

The typical arterial lesions under discussion are not what is ordinarily classified as an arteriosclerosis, but consist mainly in a periarterial reaction. Just what relation there may be between the periarterial inflammation of this type and nodular intimal arteriosclerosis, we are at present unable to say. However, this is evident from our observations, that the periarterial inflammation following the vasa vasorum precedes the reaction in the intima. The late manifestations of the arterial involvement are observed in a perivascular fibrosis.

The kidney lesions are of the nature of a true non-suppurative interstitial inflammation which begins in the perivascular tissues. The inflammatory reaction follows the distribution of the arterial supply, involving also the glomeruli to a greater or less degree. The chronic stage follows with repair by fibrous tissue, and subsequent contraction of the organ leads to the small granular kidney. Tubular changes are not great and are secondary.