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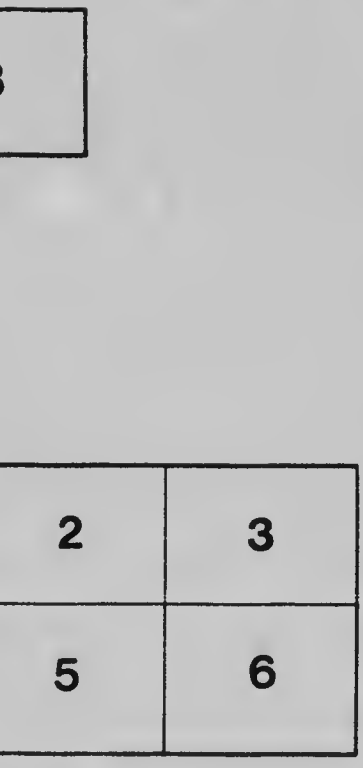

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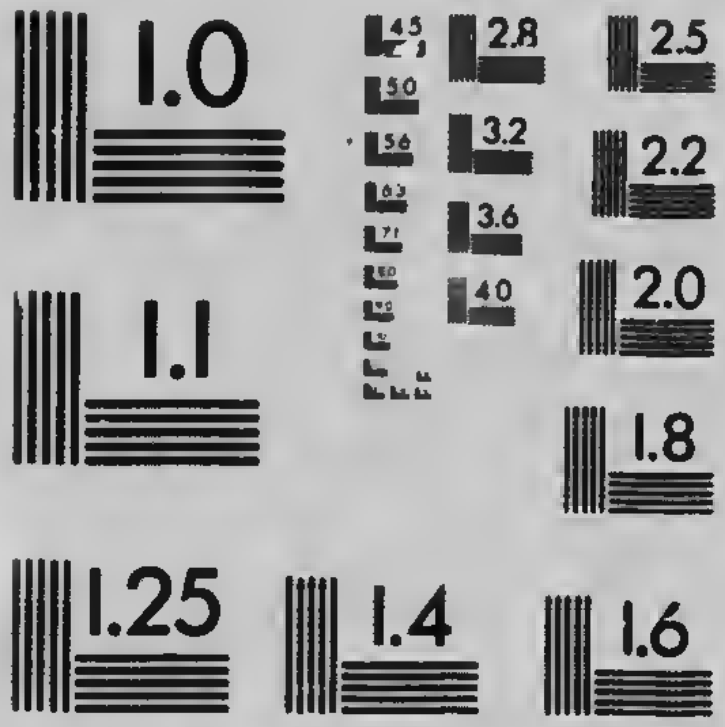

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Chronic Interstitial Nephritis and Arteriosclerosis

BY

OSKAR KLOTZ, M.D., C.M.

PITTSBURGH, PA.

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CHRONIC INTERSTITIAL NEPHRITIS AND ARTERIOSCLEROSIS.

By Oskar Klotz, M.D., C.M.,
PITTSBURGH, PA.

(From the Pathological Laboratories, University of Pittsburgh.)

No agreement has as yet been reached as to the nature of and the progressive changes leading up to the granular kidney. Almost all the factors having to do with the carrying out of the normal kidney function, as well as the known factors giving rise to processes of fibrosis in other organs, have been mentioned as the inciting cause of renal sclerosis. Particular weight has been placed upon certain of these factors, because of their presence during one stage of the disease; but the opportunity of weighing their importance as an active cause for the contracted kidney has not been sufficiently good to direct a knowing finger at them. No one has yet been able to describe in a single instance the sequence of events from the beginning to the fully developed chronic interstitial nephritis. Thus, opportunity has remained open for wide speculation on the interpretation of the pathological processes involved.

Some attempt has been made to link up the clinical and urinary findings with the successive changes that are taking place in the tissues of the kidney. These, however, have added little to our understanding of the process. True it is, that with the fully developed disease, certain manifestations make their appearance, and we believe that some light has been thrown upon the correlation of the urinary character with the altered functional capacity due to renal sclerosis. But as for saying that the clinical manifestations bear any relation to the structural change of the kidney prior to the stage of granular contraction or, better, that we can forecast the outcome or even suggest the past processes in the kidney by clinical analyses we have no definite evidence.

Thus the problem has been left in the realms of conjecture and in the absence of incontestable proof by experiment, our knowledge concerning the development of the granular kidney has not materially advanced since the days of Gull and Sutton. In the face of

this we do not wish to minimize the value of the many observations which have given us a clearer understanding of some of the finer reactions in the kidney substance; but it would appear that the minutiæ of some of these observations have led us astray from the broad aspects of the problem. That Jores should find a splitting of the internal elastic lamina of the renal arterioles, and from this finding discuss the importance of those still indefinite factors inducing arteriosclerosis as of prime importance for kidney disease, is, it seems to me, quite aside from the main issue.

For the main part, as was brought before the Association of American Physicians last year, studies upon the pathological nature of chronic interstitial nephritis have been made upon the advanced form of the disease. The criterion for the recognition of the important type of the disease is still based upon the description of the kidney as given by Richard Bright. If we adhere closely to these described characters, we will find there is a general similarity in grouping them into one class. Gradually, however, our attention has been drawn to the fact that there are other forms of renal sclerosis, differing to a greater or less degree from the type here under discussion and readily recognized by careful observation and supplemented by the microscope. Thus we have kidney fibroses associated with hydronephrosis, ascending infection of ureter and bladder, hematogenous infection (pyogenic), infarcts, thromboses, amyloid disease, syphilis and other infective granulomata, and arteriosclerosis. But when we are speaking of the small, contracted or granular kidney we have in mind a diseased condition of the kidney which is different from each of these. It is different not only in the structural changes induced, but it is different also in its progress and in the distant systemic responses. The small, granular kidney is recognized by its small size, the thickening of its capsule with adherence to the underlying cortex. The kidney substance when stripped of its capsule is distinctly granular, each granule being surrounded by a depression from which fibrous tissue radiates parallel with the ascending vessels. The kidney substance may appear red, but, on the other hand, may be quite pale with not a few of its granules as yellow as the adrenal cortex. The cortex is most markedly altered, and is commonly only half the thickness of the normal structure. Within it are found many fine wedge-like sclerotic areas which occupy the positions between the granules observed on the surface. Alternating with these areas of fibrosis a fairly normal kidney tissue is observed. Along the patch of these radiating fibroses the tubules and Malpighian corpuscles become involved. The medulla is less altered, although a hyaline fibrosis not infrequently surrounds the excretory tubules. As in other regions subject to progressive fibrosis a considerable adipose tissue develops in the surrounding structures, particularly about the pelvis.

At the present time, opinion as to the development of this form

of the interstitial nephritis has been divided mainly between two schools: the one considers it the outcome of a low grade but progressive inflammation, while the other believes it the result of a primary circulatory disturbance with a secondary atrophy and replacement fibrosis. Unfortunately the issue has been somewhat confused by the further introduction of the terms primary and secondary interstitial nephritis. Each group claims that their explanation is adequate for the so-called genuine contracted kidney. We would do well to drop such irrelevant terms and leave the application of a new nomenclature to him who clearly indicates the pathological sequence of events concerned in chronic interstitial nephritis.

Gull and Sutton considered the relationship of the arteries to the diseases of the kidneys as a peculiarly intimate one in which the arterial processes preceded and determined the interstitial nephritis. No agreement was reached by subsequent workers of the actual nature of the arterial disease, some viewing it as an endarteritis (Thoma), others as an hypertrophy (Johnson, Ewald, Friedmann), while the subsequent work by Prym and Jores drew attention to the arterial lesion as a true arteriosclerosis. Jores, furthermore, contended that the associated arterial changes in other organs, as was described by many, was also an arteriosclerotic process. The differentiation of this process rested upon the finding of deep arterial degenerations associated with a splitting of the internal elastic layer. As Jores, however, observed, arteriosclerosis may occur in the arteries of other organs in the absence of sclerosis of the renal vessels.

While the above authors were contending the dependence of chronic nephritis upon disease of the bloodvessels, Ziegler maintained the differentiation of types of chronic nephritis into groups associated or unassociated with arteriosclerosis. Those kidney lesions resulting from arteriosclerosis he believed to be individual and of a purely degenerative character, and designated them the arteriosclerotic kidney.

Both Jores and his pupils repeatedly remarked that chronic interstitial nephritis is a disease most frequently encountered in advanced life, a period when arteriosclerosis is also most prevalent. Nevertheless, they remark upon the finding of occasional cases in which they have been able to demonstrate advanced renal sclerosis unaccompanied by arteriosclerosis within the kidney. This agrees with the finding of Orth, who believes that in chronic interstitial nephritis the vascular changes are not essential because their variety does not correspond with the extent of the lesions. Roth described a number of cases in which renal sclerosis was advanced, but in which the arteries did not show the type of sclerosis defined by Jores as arteriosclerosis. He did, however, find that the arteries were affected by a connective-tissue thickening of the intima with

splitting of the elastic lamina. As, however, processes of degeneration were wanting, he refused to call it arteriosclerosis. He suggests that these vessels might subsequently show arteriosclerotic change. From his observations we can only conclude that the kidney lesions have advanced with greater rapidity than those in the intima of the renal vessels, and his cases illustrate the point we wish to make that the narrowly defined form of arteriosclerosis as given Jores is not an essential factor in bringing out subsequent interstitial nephritis.

Roth described 3 cases of chronic interstitial nephritis without arteriosclerosis. In the kidneys, however, endarteritis was present in the small arteries. The cases were of relatively young individuals, and all of them had definite chronic or recurrent heart and arterial diseases. Yet with it all neither Jores nor his pupil sees any direct relationship insofar as a common causative factor is concerned in the simultaneous and progressive lesions in these three organs. These authors lay much stress on the finding of a single sclerosed arteriole or the mildest beginning of intimal degeneration as indicative of the influence of arteriosclerosis upon the kidney. No recognition is given to the fact expressed in their own cases that the fibrosis of the kidney was markedly advanced, and in the late stages of contraction, while the arteriosclerosis was only beginning. We can in no way follow the conclusion of this author as illustrated by his own cases that the chronic interstitial nephritis was the result of the early endarteritis demonstrated.

In the admirable work of Councilman (1897) the part played by the inflammatory process in bringing about the interstitial lesions of the cortex of the kidney was well demonstrated. In part, the cases studied included some of scarlet fever, diphtheria, pneumonia, and other infections, and the lesions described were of the nature of diffuse non-suppurative interstitial nephritis or types of glomerulonephritis. Of the latter, two forms were distinguished: a non-suppurative exudative form and a proliferative type. No clear distinction can be made between the etiological factors present in these two types, and it would seem that both may arise from the same causative factor. At the time of carrying out his work, bacteriological methods were not available to make a distinction between the various forms of streptococci, and we find the author speaking of the organisms isolated from cases of heart disease as pneumococci. I believe we will be correct in interpreting these results as indicating the presence of the Streptococcus viridans group. These organisms were found in cases of glomerulonephritis in large percentage, but the author's descriptions of the lesions indicate a transition between the glomerulonephritis and the diffuse, interstitial type. The work of Wagner bears out these findings, particularly in indicating the importance of the inflammatory process of scarlet fever and other infections in bringing about permanent interstitial change.

The work of Councilman is among the few in which a study of the progressive lesions of the kidney was accompanied by bacteriological examination. Of this he says: "Various forms of disease of other organs, particularly of the heart, are often associated with them, and bacteriological investigation has frequently shown in many cases the presence of certain organisms in the kidneys. In most cases the bacteria are found in some other lesion and in the blood, and their presence in the kidneys is but a part of a general septicemia. Moreover, the same conditions in the kidneys may be found associated with various organisms, and the same organisms may be associated with widely different anatomical lesions." A very fertile field awaits the routine study of the bacteriology of the kidneys in conjunction with the histological examination of all types of infection. The work which has been performed up to the present time is very suggestive of indicating the actual presence of bacteria rather than their [illegible]ns in the interstitial response of the kidney.

Undoubtedly what appears as complete disagreement in the personal observations on chronic nephritis lies mainly in the methods and material studied. Although the anatomical classification of kidney disease has not found favor with either the clinician or the pathologist, yet in the absence of a better substitute we all revert to this method. Müller attempted an etiological classification which as yet is hardly practical, and Herrick, while finding the old anatomical grouping unsatisfactory, offers nothing to replace it.

The types of nephritis which today attract our attention as the forerunners of the contracted kidney are the acute glomerulonephritis and the acute non-suppurative interstitial nephritis. Without desiring to describe the various types of glomerulonephritis, as well as the variety of interesting lesions that may be observed in the Malpighian body and Bowman's capsule, there is ample evidence that, in the human, these glomerulonephritides are infective lesions (Councilman, Gaskell, Baehr). The important feature lies in the fact that the glomeruli become the centres of inflammatory response in which a non-suppurative exudate and endothelial proliferation of the capillaries and a proliferative response of the inner lining of the capsule is commonly observed. The occlusion of the capillaries of the glomerulus by cellular proliferation or by thrombosis is only an added complication, and the subsequent degeneration that occurs in the tubules of the kidney is also to be viewed as a secondary disturbance depending upon vascular change rather than an injury produced by the primary factor.

A study of these cases of glomerulonephritis soon convinces one of the varying picture, even during the acute stage. In some thromboses of the glomeruli are common, in others rare, or the lymphocytic infiltration of the glomerulus is great and confined to this structure; others again, show the inflammatory reaction diffuse,

surrounding Bowman's capsule, infiltrating the stroma between the tubules and following the course of the interlobular arteries and vessels of the intermediate zone. Many such cases have been described, by Councilman, Ziegler, and others. In fact, the picture presented by those kidneys in which the inflammation is more diffuse simulates more closely the type of acute interstitial non-suppurative nephritis. This latter type, which was originally discussed as a disease of the kidneys found after scarlet fever, measles, and sometimes smallpox, is now being incorporated with the glomerulonephritis, mainly because a certain amount of glomerular disturbance is always present. Fahr finds the streptococcus and pneumococcus most frequently associated with acute interstitial nephritis, and finds also that the same organisms are the chief cause of glomerulonephritis.

In short, although there are variations of glomerular lesions, and we encounter forms of inflammation of the kidney stroma, there does not appear to be any difference in the causative agent, most frequently the Streptococcus viridans. We must, however, point out that the bacterial infection reaches the kidney under different circumstances, and in a somewhat different form, in the various systemic diseases in which it is met. It is the bacterial clusters or small infective thrombotic masses which are liberated in heart disease that give rise to a type of glomerular infarction. In this way particular structures in the kidney are more intensely involved than others. So, too, in cases of bacteriemia, by organisms of low virulence, the kidney, as well as other organs, becomes a local focus of infection and this is particularly true in the bacteriemia of acute rheumatic fever in which the heart and bloodvessels are also affected. In these infections the heart may be involved in a variety of ways, and when the endocarditis becomes well-marked the kidney may be subject to embolic processes in its glomeruli, so that both the acute interstitial and the glomerulonephritis are simultaneously prominent. Hence it is obvious that to state that a definite type of kidney lesion is constantly to be found as a disease associated with infection of other organs is only voicing a rule with prominent exceptions.

The frequency with which acute interstitial and glomerulonephritis are present with infective heart disease is known to all who have observed these cases at autopsy and studied the tissues. It is, furthermore, easy to demonstrate the fate of the early inflammatory process. Fibroses of the glomeruli, of Bowman's capsules, and of the intertubular stroma may be demonstrated in all stages of formation, and recurrent attacks of these infective processes give rise to combinations of inflammatory responses in the kidney tissues. The question immediately arises whether the localization of these inflammatory processes gives us definite types whereby their future scars may be recognized. In answer to this the best reference

is made to a few experimental results. In these it has been shown that inflammatory reactions in the kidney due to bacterial agents are prone to follow and surround the course of the bloodvessels particularly the interlobular vessels, and the ascending cortical branches as well as the afferent arteries of the glomeruli. Associated with these inflammatory responses there are not infrequently glomerular reactions, infiltrative, proliferative, or thrombotic. The progress of these lesions is similar to that in the human kidney and the end-result is a process of fibrosis radiating in its character with shrinking and granulation of the cortex and contraction of the entire kidney. Such lesions were reproduced in animals by the use of organisms (various members of the Streptococcus viridans group) isolated from infective heart disease, and the responses in the kidney were found to be accompanied by a myocarditis, at times an endocarditis, and in a few cases pericarditis. In only a few instances were systemic intimal arterial lesions obtained, although the perivascular response was always noted. Here, then, we have evidence of the development of the various stages of the contracted kidney in the presence of chronic infection and in the absence of primary arterial lesions.

These findings are in accord with the observations on human material and explain the occurrence of the contracted kidney in the first half of life as well as its greater frequency in the later years. Like all chronic diseases, the frequency of chronic interstitial nephritis is greatest in the late decades, and it is also a rather depressing outlook when we find that the incidence of these chronic diseases shall increase with the saving of more lives in childhood from death from scarlet fever, acute rheumatic fever, chorea, and other Streptococcus viridans infection. We must also equally appreciate that the heart and arteries suffer, sometimes much, at other times less, by invasion of these bacteria. In the arteries an endarteritis, a mesarteritis, and a periarteritis have all been repeatedly demonstrated in these infections during the early years of life. Of the heart lesions, we need make no other comment than reference to Aschoff's studies upon focal myocarditis, and of the frequent presence of endocarditis in the human and in experimental infections.

What, then, is the relation of renal arteriosclerosis to chronic interstitial nephritis? Before one can answer this we must have a clear understanding of the nature and genesis of arteriosclerosis. It is not enough to boldly speak of general arteriosclerosis as of common type and constant origin. Nor is this true within the kidney itself. There are arterial lesions within the kidney whose origin is widely different and which vary in their character.

Ziegler has long ago demonstrated the peculiar renal fibrosis resulting from peripheral arteriosclerosis. In old age, where it is not uncommon to have various arterial tracts severely involved in

sclerosis and in which the lumina of the vessels are distinctly impeded, atrophic changes result in the area supplied. It is obvious that the amount of sclerosis varies greatly and is bound to pick out limited areas. The kidney tissues which suffer from the circulatory disturbances undergo atrophy, and even complete loss, without, however, necessarily showing evidence of intracellular degeneration (fat), as is otherwise so commonly encountered. The kidney shows areas of sharp depressions scattered irregularly over its surface so that its structure and shape are distorted. The individual depressions simulate those of infarct, but microscopically may at times be distinguished from these in that the involved areas contain some of the parenchymatous structures not completely destroyed. Furthermore, the kidney capsule is rarely adherent and the cortical surface between the areas of depression is relatively smooth.

Such depressions are the result of the obliteration of fairly large vessels within the kidney. At times, it may be, smaller vessels involving more restricted portions of the kidney are affected. This, then, leads to a local fibrosis of the glomeruli supplied by this circulation. Under these conditions the process, both in the glomeruli and tubules, is one of slow and progressive degeneration, with a secondary replacement fibrosis. It is unusual to observe under these conditions any evidence of an inflammatory reaction.

Compared with the granular contracted kidney, these changes in the arteriosclerotic kidney are quite different. It is inconceivable that a process of arteriosclerosis could so uniformly affect so many arterioles of a constant caliber to give the character found in the uniformly granular kidney. A comparable picture is to be observed in no part of the body, and we are well aware how uncertain is the distribution of arteriosclerosis. As the fibrosis following upon processes of degeneration in the atrophies of vascular scleroses is without inflammatory response, one misses entirely the presence of a granulation tissue and subsequent adhesions. The absence of these is noted in the freedom of the kidney capsule and in the lack of synechiæ about the glomerulus. Frequently, too, Bowman's capsule shows no thickening. Ziegler truly calls this the senile kidney.

It is, however, not common to meet with a clear-cut and uncomplicated case. The vascular scleroses of the kidney are most commonly the result of the same influence which has produced a primary inflammatory lesion in the kidney stroma. Hence, the development of scar tissue in the renal structures goes hand in hand with renal arteriosclerosis. Here, however, in the early stage, as well as during the years of progressive involvement, the kidney tissue and arteries show the presence of inflammation. These inflammatory deposits are easily recognized, and obviously vary in amount at the different stages. Jores has seen them in his inter-

stitial nephritis, but has taken the view that no relation between the arterial disease and the inflammation can be determined. Like the results of the Streptococcus viridans infection upon the heart, giving rise to inflammatory processes differently disposed, so, too, this same infection, which is so frequently at the bottom of the fibrosis of the contracted kidney, brings about inflammatory reactions of varying intensity in different portions of its structure. The arteries appear to form the centre of distribution for these reactions, and much of the response is spent in the tissue surrounding the small vessels coursing through the cortex. To a certain extent, however, intimal reactions are also found. The latter, however, arise somewhat later in the course of the kidney disease, so that examples are not difficult to demonstrate in which intimal sclerosis is wanting while a non-suppurative inflammation is active about the vessel. Later, however, the picture is reversed and the intimal sclerosis attracts our eye. This is now the stage when appearances suggest that a close relation of cause and effect exists between the intimal arteriosclerosis and the renal fibrosis.

The intimal disease of the arteries most commonly met with in the late stages of chronic interstitial nephritis consists of a chronic endarteritis with deep, fatty change. The presence of a true hyperplasia of the musculo-elastic layer with secondary degeneration of the inner muscle bundle has never been met with by us, nor have its advocates ever clearly demonstrated its presence. The finding of splitting of the internal elastic lamina is now found to have no specific bearing on the problem of arteriosclerosis. McMeans (of our laboratory) has shown that such splitting is the common occurrence during inflammatory reactions of the intima.

Granted, therefore, that the early reactions which lead to the granular contracted kidney, simultaneously involve portions of the kidney parenchyma and its arteries, it is often extremely difficult to distinguish in the late stages of the disease exactly how much of the scar tissue has resulted through inflammation or as replacement fibrosis following arteriosclerotic atrophy. We should, however, continue to distinguish clearly the arteriosclerotic kidney of Ziegler from the granular interstitial nephritis, the former giving rise to true atrophic processes in the parenchyma with replacement fibrosis, the latter having an inflammatory basis for the development of connective tissue variously distributed about the important structures of the organ.