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Original Articles

THE PATHOLOGY OF THE KIDNEY.

SOME GENERAL CONSIDERATIONS.

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There are few organs in the body in which both structure and circulation are so complex as in the kidney. There is some variation in the size of the kidneys, depending on the life of the individual. The increased exercise of function as in potatoes is accompanied by increased size. The congenital anomalies are chiefly those of position and do not especially influence either intimate structure or function. In the congenital absence of one kidney we find in the other practically the same tissue arrangement, but the amount is doubled. In no other secreting organ do we find such differentiation of structure as that represented by the glomeruli and tubules. It is possible to think of the tubules not only as glandular secreting organs with a remarkable differentiation of epithelium in different parts, but as serving simply as the excretory ducts of the glomeruli. No other organ in the body has precisely the same character of vessels or the same circulation as the kidney. The blood supply to the organ is enormous. Landergren has estimated that in a minute's time under the action of strong diuretics the amount of blood which passes through the kidney is equal to the weight of the organ. That is, an amount from four to nineteen times as great as the average supply of the other organs. Regarding the vessels of the glomeruli as capillaries from which they differ, however, in several respects, the blood pressure within them must be high, because they spring directly from arteries of relatively large caliber. The pressure outside them is low because the space about them is protected from tissue pressure by the capsule. In the interior of the tubules there prevails normally the same low pressure, the circular wall of the epithelium preventing the action of tissue pressure. While it is true that the secretory pressure is usually low, various pathologic conditions show that the secretion can take place against greatly increased pressure. After passing through the glomerular vessels the blood again enters a series of long capillaries. How numerous these capillaries are can only be appreciated by the study of the injected kidney. From the capillaries the blood enters into numerous thin walled veins in which the pressure is low, and current slow, the pressure having been almost obliterated by the two capillary systems which intervene between the arterial pressure and the veins. The tendency of foreign cells, and, in certain cases bacteria, to accumulate within the veins is due to the slowness of the current.

There is a marked capacity for repair of injury in the kidney and but little capacity for perfect regeneration of tissue. The general law of the inverse relation

between high differentiation of structure and capacity for regeneration holds good in the kidney, as does also the law that capacity for both regeneration and repair diminishes with age. After extirpation of one kidney the remaining organ fulfills the function of both and does this by increase of tissue by growth. Epithelial cells become larger and more numerous, tubules larger and longer, and glomeruli larger, but after the completion of development there is no new formation either of tubules or glomeruli. The embryonic development of the kidney is delayed until some time after birth. The completion of development is readily recognized by the absence of embryonic glomeruli. The study of the kidneys in a large series of children who died of diphtheria showed embryonic glomeruli constantly present at two years and rarely present up to the sixth year.

The physiologic function of both kidneys is the same. The activity of secretion depends on the rapidity of blood flow through the organ, and on the activity of the renal epithelium. There seems now little doubt that there is a differentiation in the secretory function of the kidney in that the water of the urine comes chiefly through the glomeruli and the solids chiefly through the epithelium of the tubules. It is also true that certain portions of the tubules differ in function. The rapidity of blood flow through the kidney is regulated both by the general arterial pressure and by the varying degrees of dilatation of the renal arteries. Under normal conditions the kidneys discharge from the body the products of tissue waste represented chiefly by urea. They regulate also the concentration of the blood; their activity is excited by an increase in blood volume due to an increase of water. Under conditions of disease they remove from the body certain abnormal soluble substances, whether these are introduced from without or formed in the body as the result of defective metabolism or by the action of bacteria.

The kidney, like the other tissues of the body, shows various impairments of structure in old age, consisting in destruction or degeneration of the secreting structure, accompanied by increase in connective tissue. In the interpretation of these senile changes we are confronted with the usual difficulty of determining how much they are due to interference with circulation from the constantly accompanying arterial disease, and how much to the gradual wearing out of tissue. To these causes must certainly be added the accumulated effect of slight lesions with the constantly increasing inability of repair. These slight lesions, though of themselves relatively unimportant, may gradually increase the initial damage by interfering with the circulation or in other ways. Under normal conditions, aside from the imperfectly understood cases of physiologic albuminuria, no albumin appears in the urine. Its presence is usually an indication of damage to the glomerular epithelium. Although such cases are rare, it would seem possible in a purely focal inflammatory lesion of the

pyramids for an albuminous exudation to enter the tubules. How dependent the presence of albumin is on damage of the glomerular epithelium is shown in cases of the common acute non-suppurative interstitial nephritis of the infectious diseases. A high degree of this leading to marked changes in the tissue may be present without any involvement of the glomeruli and without albuminuria. The published cases of acute nephritis without albuminuria are probably of this character. The epithelial covering of the glomerulus is probably easily damaged and easily repaired.

The most easily understood lesions of the kidney are focal in character and due to the presence of bacteria in the tissue. The infection may be either hematogenous, the bacteria entering from the blood stream, or urinogenous, the bacteria entering from the urinary passages. The latter affections may be either ascending, from the bladder and ureters, or descending from a focus in the cortex. Bacteria often pass through the two capillary systems and lodge in the veins of the pyramids. This is particularly the case in hematogenous infections by the staphylococcus aureus. In this connection comes the question of the passage of bacteria through the intact epithelium. Experimentally this has not been shown to take place. It is true that in certain of the infectious diseases, notably in typhoid fever, bacteria are found in the urine, but it has not been shown in these cases that the kidneys are intact or that the bacteria come from the kidneys. That the kidneys may be injured by interference with the circulation is also evident. The pressure in the veins of the kidney is low and the exit of blood must be interfered with by obstruction in front, as in chronic passive congestion. The kidney is also damaged by obstruction of the urinary outflow. The damage here results both from the effect of the increased pressure within the tubules and on the epithelium and from the interference with the circulation produced by the increased tissue pressure within the kidney and the increased pressure in the pelvis. It is not possible to consider arterial hyperemia of the kidney as a pathologic condition. The blood supply of the kidney is regulated by the activity of the organ. That the activity may be excited and the blood supply increased by the presence of substances in the blood which are excreted by the kidney is evident, and also that such substances may damage the organ by injuring the epithelium of glomeruli and tubules and the endothelium of the blood vessels. The hemorrhages which are frequently found in connection with acute toxic hyperemia are due, not to the increased pressure, but to endothelial injury.

How the varying degree of damage to the kidney which constantly accompanies diffuse arteriosclerosis is brought about we do not know. These changes consist in degeneration and destruction of parenchyma and increase in interstitial tissue.

It is generally accepted now that the interstitial change is secondary to the damage of the parenchyma. There is no evidence in favor of a general fibrosis or independent increase of connective tissue in arteriosclerosis. There is, of course, in arteriosclerosis interference with the circulation, loss of regulatory power of arteries, increased arterial pressure, the injurious effect of substances in the blood due to deranged metabolism elsewhere, and the constantly increasing effect on the kidneys themselves, of their impaired action. It is probable that the condition in the kidneys is due to the combined effect of a great many factors rather than to any single one.

The greatest difficulty in understanding the pathology of the kidney is found in the acute, subacute and chronic diffuse lesions of the kidney not due to alterations in the flow of either blood or urine, nor to the immediate action of bacteria.

The acute interstitial non-suppurative nephritis gives the least trouble. It is found in acute infectious diseases, notably in the acute exanthemata, and consists in the presence in the blood vessels and interstitial tissue of the kidney of cells belonging to the lymphoid series which are formed in the bone marrow, spleen and lymph nodes, and which are brought to the kidneys by the blood. They accumulate in the renal veins, pass from these into the interstitial tissue and proliferate actively in both places. To what their accumulation in the renal veins is due, whether to an attraction exerted by the kidney or to the mechanical conditions of the circulation, I do not know. Unless the cell accumulation is so great as to interfere with the circulation or nutrition they need not give rise to any interference with function, though usually degenerative changes in the kidney due to the toxins of the disease accompany the interstitial changes. These cells never accumulate in the capillaries of the glomeruli, but are found to a slight extent in the capillaries of the cortex and chiefly in the veins of the pyramids.

Degeneration of the epithelium of the kidney varying in character and in degree is the most common condition found in all cases of diffuse nephritis. It is often exquisitely focal, affecting groups of tubules. It often shows a remarkable selection. Thus the degeneration which is constantly found in diabetes only affects the cells of Henle's loops. In cases of diphtheria I have found hyaline degeneration with extensive cell destruction confined to the proximal ends of the convoluted tubules. The degeneration may vary from such slight alterations of protoplasm or nucleus up to complete necrosis. The injured cells, entire or in fragments, may be desquamated and make their appearance in the urine. The degeneration may be the only change or be accompanied by extensive alterations of structure. If the degeneration does not affect the glomerular epithelium it may not be accompanied by albuminuria. Extensive degeneration may produce but little change in the microscopic appearance of the kidney.

Of the more severe lesions of the kidney due to the diffuse action of soluble substances, one group may be separated in which the lesions in the glomeruli are the most obvious condition. Severe lesions of the glomeruli do not occur alone, for they are all of such a nature as to interfere with the circulation in the glomerulus, and as the circulation of the kidney demands that the chief mass of its blood must first pass through the glomeruli, any interference here is felt in the remainder of the organ. The glomerular changes are varied. One of the most interesting is the obstruction of the vessels by peculiar hyaline thrombi, which Flexner interprets as being formed by agglutinated red blood corpuscles. This condition is rare, and I have found it most often in cases of staphylococcus septicemia, but the most marked case was in a kidney from acute plague which was sent from Manila. The most common cause of the glomerular affections I believe to be acute infections. Some organisms seem to be more inclined to give rise to them than others. They are found in the acute exanthemata, and are due, not to the specific agent of the disease, but to the organisms of the secondary infections. We have had a number of cases of glomerular nephritis, in which

the accompanying infection was acute endocarditis, due to the pneumococcus. The condition is not due to the direct action of bacteria, but to the action of toxic substances produced either by the bacteria or by the tissues. The glomerular affections may be acute, subacute or chronic. Clinically, they are usually accompanied by edema, the relation of which to the nephritis is imperfectly understood. The chronic cases lead to a small, fatty rather pale kidney with an irregular surface, to which the capsule does not cling closely.

The other form of chronic nephritis (chronic diffuse, chronic interstitial nephritis), slow in process, marked by slow destruction, affecting all parts of the kidney, but the glomeruli least and usually secondarily, with a marked increase in connective tissue, which of itself increases the damage, is most usually accompanied by arteriosclerosis.

The disease is composite; not one organ, but many are affected. The determination of the inter-relation of renal disease with defective metabolism, bacterial poisons, vascular and cardiac disturbances, dropsy and edema, lowered resistance to infections, must continue to be one of the paths along which investigation and experiment leading to exact knowledge must follow. The possibility of the production in animals of renal diseases, offering much similarity to those of man, which has been shown, is sure, by giving a field in which investigation can be more exact, to lead to advance of knowledge.

A question of great interest from both the clinical and pathologic point of view is that of the origin of tube casts. I think it is certain that these may be formed directly from the cells of the convoluted tubules by hyaline degeneration. Balls of hyaline material appear in the swollen cells, which finally break down, and the separate masses fuse together and pass into the lumen. This hyaline degeneration, though common in all pathologic conditions, is most marked in amyloid disease, and in the acute infections in which the highly refractive waxy casts are found. Casts into whose formation fibrin enters may be formed by an inflammatory exudation coming from the glomeruli or tubules. It is also possible that casts may be formed from a change in albumin during its passage through the tubules. The first two methods of formation are certain, though they will not account for the casts in all cases. The granules in the granular casts I think always come from the partial or complete disintegration of epithelium.

I present here some of the results which have come from the anatomic study of the cases of nephritis taken from the autopsies of the last ten years at the Boston City Hospital. The autopsies are carefully carried out, all organs are described and weighed and cultures made. The description embraces both the macroscopic and microscopic conditions, and the sections are preserved for future reference and control. The routine microscopic examination embraces the kidneys, liver, spleen, heart, lungs, pancreas and lymph nodes, and is extended to all pathologic conditions found outside of these organs. In going over these autopsies I have in many cases rejected the autopsy diagnosis on referring to the preserved sections, particularly in cases in which chronic interstitial nephritis was diagnosed. If the diagnosis of chronic interstitial nephritis is made in all cases which show some degree of atrophy of parenchyma and increase in interstitial tissue, few individuals over 50 escape it.

The diagnosis must be made from a consideration of the extent, the degree and the diffuseness of the lesions. I have only considered those cases as chronic interstitial nephritis, in which there was diffuse atrophy of the cortex, generally associated with decrease in weight of kidney, adhesion of capsule and irregularity of the surface. Glomeruli, as well as tubules, are affected, the main lesion being degeneration with atrophy. It is seldom that all parts of the kidney are equally affected. Enormously hypertrophied glomeruli and tubules are found along with those which have undergone atrophy, and the anatomic examination will not enable us to say to what degree this compensating hypertrophy has restored function. That it may do so seems apparent from the frequency with which the condition is not diagnosed clinically.

In the ten years there were 80 cases of chronic interstitial nephritis; 33 in females, 47 in males. Four of the cases were under 20, the youngest being a child of 2 years, in which there was a combination between acute non-suppurative interstitial and chronic interstitial nephritis, the condition following scarlet fever. The heart in this case was hypertrophied, weighing 165 grams. But little importance can be attached to the age, owing to the rarity of autopsies on children. Taken as a group, the cases show a considerable degree of heart hypertrophy. The cases are included in which the hypertrophy was accentuated by causes outside of the kidneys. In the 33 females the average weight of the heart was 412 grams. There were four marked exceptions to the hypertrophy. In one, aged 48, the kidneys with advanced interstitial atrophy weighed 165 grams, and the heart 275 grams. In one the heart weighed 200 grams, the kidneys 180 grams; in one there was typical interstitial with marked atrophy and death from uremia, the kidneys weighing 110 grams and the heart 260 grams; and in a case, aged 65, the heart weighed 260 grams, with kidneys weighing 210 grams. The males showed about the same degree of heart hypertrophy, the average weight of the heart in the 47 cases being 494 grams. Here also there were exceptions. In one case in a large individual the heart weighed 390 grams, and the kidneys, in which the lesions were of high degree, weighed 165 grams. Two of the cases of males without heart hypertrophy were senile with atrophy of all organs, and in another case the renal lesions were not of great degree. There were four hearts of over 700 grams, and in six others the weight was over 600 grams. Without exception in both males and females, the largest hearts were given by the combination between arteriosclerosis and chronic interstitial nephritis in large and well-nourished individuals. There is a close association between arterial disease and chronic interstitial nephritis. Which of the two conditions should be regarded as the primary and which the secondary, or whether they should both be regarded as parts of a whole can not be determined by anatomic investigation. It is certain, however, that the conditions can exist separately. Among the cases many can be selected which show both a high degree of arteriosclerosis involving even the renal arteries with but little change in the kidney and *vice versa*. The extreme degrees of atrophy in renal tuberculosis show no relation to arterial disease.

Closely associated with chronic interstitial nephritis are the cases of amyloid infiltration. The amyloid may be limited to the glomeruli and the different vessels or it may be more generally deposited. It may occur in

kidneys as simply superadded to chronic interstitial changes or it may be the predominant lesion. With it there is always associated degeneration of epithelium, marked by presence of fat and hyaline, and a varying degree of atrophy. In the extreme degree of amyloid infiltration characterized by a small pale kidney with irregular surface, no tissue approaching normal character may be found. The most of the glomeruli are converted into completely amyloid masses, and all the tubules belonging to them are atrophied and replaced by connective tissue. The amyloid kidney is in one way separated from chronic interstitial nephritis, and that is by the absence of heart hypertrophy. Thirty-six cases of amyloid infiltration of the kidney were found, seventeen in females and nineteen in males. The average weight of the heart in females was 269 grams and in males 320 grams. In the females there were two cases in which some degree of heart hypertrophy was found. In one case there was extensive arteriosclerosis, chronic interstitial nephritis with amyloid and in the other case arteriosclerosis with slight amyloid confined to the glomeruli. In the males there was one case of hypertrophy, the heart weighing 525 grams. In this there was arteriosclerosis with aneurism and an osteomyelitis, to which the amyloid infiltration was probably due.

There were twenty-two cases of subacute and chronic glomerulonephritis. In this form of nephritis the lesions are certainly primary in the glomeruli and consist in changes which must interfere with their function by means of the cell degeneration and the occlusion of vessels. The term chronic parenchymatous nephritis, which is that generally used to designate the condition, is less descriptive of the lesions than is the term chronic interstitial nephritis, descriptive of atrophy with increase of connective tissue. It is difficult to estimate the relation of this lesion to heart hypertrophy, owing to the frequency of the association of heart lesions which in themselves should be regarded as causes of hypertrophy. Excluding such cases, the weight of the heart in males was 433 grams, denoting a considerable degree of hypertrophy, though much less than in chronic interstitial nephritis. There is one form of glomerulonephritis to which I wish to call attention. It consists in homogeneous thickening of the walls of the vascular tufts of the glomerulus, thereby narrowing the lumen. It may affect all the vessels or occur in patches, and may lead to complete obliteration of the entire glomerulus or of single groups of vessels. The thickened walls do not give the reaction of connective tissue in staining. The thickening is not due to the presence of demonstrable fibers. There was nothing in the histories of the individuals nor in the associated lesions to throw any light on the condition.

Acute glomerular nephritis (acute parenchymatous nephritis) was found in thirty-two cases, twenty-two male and ten female. The acuteness of the process was judged by the prevailing cellular character of the lesions and the absence or slight development of connective tissue. I have elsewhere called attention to the frequent association of this lesion of the kidneys with pneumococcus infections, particularly with acute pneumococcus endocarditis. In the numerous autopsies on acute croupous pneumonia only in two cases was there the complication of acute glomerular nephritis. Why this, the most frequent form of pneumococcus infection, should so rarely be accompanied by nephritis I do not know. Next to the pneumococcus the frequent associated infection is with the streptococcus pyogenes.

Cultures of the kidneys in these cases show the presence of the infecting organisms, but they can not be regarded as directly causing the lesions. The lesions are too diffuse to be regarded as produced by direct bacterial action, and when organisms are found on microscopic examination they are not associated with the lesions. None of the cases of typhoid were complicated by nephritis. Of all of the acute infectious diseases, acute endocarditis is most frequently accompanied by this most serious form of nephritis.

One of the most interesting forms of nephritis is the acute interstitial non-suppurative form. It has nothing to do with chronic interstitial nephritis, for this has no acute form, but is the result of a slow, progressive disease. Acute glomerular nephritis passes into the subacute and chronic form, and probably mild degrees are recovered from. Acute interstitial non-suppurative nephritis consists in the accumulation in the interstitial tissue of the kidney of large cells belonging to the lymphoid series which are brought to the kidney by the blood. The cells are generally in foci situated beneath the capsule, around the glomeruli, and just above the pyramids. Only in the most extreme cases is there a diffuse infiltration of all parts of the kidney. There may be very considerable lesions without producing any easily recognized changes in the microscopic appearance of the kidneys. When the lesion is very pronounced and diffuse, the kidney is greatly enlarged, the capsule is tense, the markings are obscure, the tissue pale, succulent and resembles the section of a lymph node in lymphatic leukemia. The largest kidneys I have found were 480 grams in a child of 3 years; 300 grams in a child of 5 years, and 250 grams in a child of 4. The chief interest in the condition of the kidneys is that the cell infiltration is not secondary to injury or degeneration. It may exist with normal epithelium. The glomeruli are never affected. The large cells, prelymphocytes, are formed in the bone marrow, spleen and lymph nodes. They enter into the blood and seem to be mechanically held in the slow capillary and venous circulation. It is evident that they migrate through the wall and proliferate both within the vessels and in the interstitial tissue, as is shown by the numerous nuclear figures in these places. Polynuclear leucocytes are only found among them when there is associated necrosis. There were found twenty-eight cases with this condition. All were in cases of diphtheria or scarlet fever, with the exception of one case, that of croupous pneumonia. I have elsewhere called attention to the frequency of acute interstitial nephritis in diphtheria and smallpox and discussed the origin of the cells.

The study of the pathologic anatomy of the kidneys has thrown but little light on the essential nature of those acute and chronic diseases in which lesions of the kidneys form a part of the pathologic process. It early led to a classification of the lesions and to a nomenclature which was intended to be expressive of their nature and histogenesis, but which is not. Even the term nephritis has come to mean merely a diseased condition of the kidneys. The anatomic study has led to a better appreciation of the extraordinary complexity of chronic disease and to a recognition of the interrelations of affected organs.

There are certain conclusions forced on one by the careful routine examination of the kidneys in a large number of autopsies. Probably the most important is that the lesions of the kidneys are only part of a whole. Almost invariably there are lesions in other organs

sometimes of the same general character as the lesions in the kidney, sometimes of a different character. We can not consider kidney disease as an entity. The injuries which are produced in the kidneys are either due to agents which are formed in the body as a result of disease in other organs or they enter the body from without, affecting the kidneys secondarily. Even the simplest lesions due to the direct action of bacteria are secondary to infections elsewhere. The frequency of lesions, especially when the examination is by the microscope as well as by the naked eye, is striking. Apart from the acute degenerations of epithelium which are almost constant in the acute infectious diseases, chronic lesions of greater or less degree are common, and with increasing age increase greatly in frequency and in degree. It is probable that we rarely pass through an acute infection without some injury being produced in the kidneys. When the injury produced is of such a character that perfect repair can not take place the evidences of it will remain. Slight injuries may produce no impairment of the renal function and there may be no means of clinical recognition by the usual tests of albumin and casts. Provided the injury leads to complete destruction of glomeruli and tubules with consequent absence of function in the part affected, as in the case of an infarction, neither casts nor albumin may appear in the urine, though the remaining tissue be insufficient for the work of the organ to be accomplished. On the other hand injuries which have not led to complete destruction and where the injured tissue functions, though imperfectly, will be accompanied by the clinical evidence of albumin and casts. The presence of albumin and casts may simply mean that a part, and often a very small part, of the tissue is functioning imperfectly, though the whole amount of renal tissue and function may be ample. Anatomically it is not uncommon to find casts in a few tubules connected with foci of injury, the remainder of the tissue being perfectly normal. Comparing clinical reports of routine urine examinations with the results of routine necropsies, it often appears that too much importance may be attached to the presence of albumin and casts, though they always mean injury of the organ. Too much importance can not be attached to the results of urinary examination directed to the ascertaining of kidney sufficiency. In cases of acute interstitial nephritis of high degree with compression of tubules and destruction of epithelium, the routine clinical examination has often given only the common "slight trace of albumin" and the anatomic examination showed no casts in the tubules. In such cases it has seemed sure that the function of the kidney must have been impaired, though the clinical examination gave no evidence of it.

It is difficult to understand the association of lesions, which is shown at autopsies. Thus we know that in the great majority of cases atrophy of the kidneys will give rise to heart hypertrophy. The average weight of the heart in chronic interstitial nephritis is far above the weight of the heart at corresponding ages. But there are many exceptions even to the association between renal atrophy and heart hypertrophy. We may find a great degree of heart hypertrophy associated with slight atrophy, and a great deal of atrophy with but slight change in the heart. It is not uncommon to find in hydronephrosis or in chronic pyelonephritis or in chronic renal tuberculosis extreme renal atrophy with a heart of normal size. The absence of heart hypertrophy in renal atrophy is particularly striking in the case of

amyloid disease. Even the association of such conditions as renal atrophy and arteriosclerosis, which, in the absence of amyloid, seem sure to lead to heart hypertrophy, fail to produce this if any degree of amyloid infiltration be present. At present we are without any acceptable hypothesis in explanation of this association, and the number of hypotheses which have been advanced serve to show our ignorance. The same thing is true in regard to edema. We are accustomed to think of the association of certain forms of nephritis, particularly those involving the glomeruli, with edema, but the exceptions are almost as frequent as the rule.

It is not probable that much light will be thrown on the numerous obscure questions relating to nephritis by anatomic investigations. The work which has been done in pathologic anatomy in chronic disease is imperfect and has consisted chiefly in making artificial classifications and giving these names. The study of the histogenesis of lesions has been fruitful in enabling us to ascertain the general sequence of lesions, but has thrown little light on their causes and interrelations. At an autopsy even under the best conditions it is impossible, in the absence of definite questions, for the routine examinations in every territory to be so fully carried out that they will shed much light on the disease. The questions which are present to the pathologist and which he endeavors to answer in his work are not the same as are presented to the clinician by his study of vital phenomena, and the clinician can not take the observations of the pathologist and seek by them to answer his questions. The observations of the pathologist are directed by a different set of questions. What is needed in the study of chronic disease is not the attempted analysis of numbers of cases and dividing them into groups, but the careful placing of questions by the clinician and pathologist and the thorough study of individual cases by clinical, pathologic, chemical and anatomic methods. The questions should be divided into their simplest components, and the hypotheses derived from study should be tried by animal experiments. The acute infectious diseases seemed more obscure than did chronic diseases before their etiology was ascertained, and even with this and the possibility of simple direct animal experimentation the knowledge which has enabled us to form acceptable hypotheses in explanation of certain acute infectious diseases has come but slowly. Knowledge of chronic diseases which will enable us to form acceptable hypotheses in explanation can come in no other way.

THE RELATION OF THE KIDNEYS TO ECLAMPSIA.*

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The sources of my information for this paper are:

1. Statistics from hospitals and private sources on eclampsia and kidney conditions.
2. The literature on eclampsia and metabolism.
3. Personal observations on urica elimination in pathologic conditions of pregnancy.
4. Experiments on the muscular irritability of pregnant and non-pregnant animals.

From the 54,010 records of births in which I could get at least a few important data concerning the frequency of eclampsia in cases of nephritis, renal irritation and

*Read in the Section on Practice of Medicine of the American Medical Association, at the Fifty-sixth Annual Session, July, 1905.