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DEFICIENCIES IN OUR METHODS FOR THE TREATMENT OF CHRONIC NEPHRITIS

NEED FOR INVESTIGATION *

HENRY A. CHRISTIAN, M.D.
BOSTON

In considering the best methods for the treatment of chronic nephritis (Bright's disease) we labor under the disadvantage of dealing with a disease regarding which there are many gaps in our knowledge. Of its etiology we know surprisingly little in any exact sense, though the view is receiving increasing support that many of the cases have their primal cause in an infection of bacterial nature, most frequently of the streptococcus group. Even granted, however, that organisms of the streptococcus group originate the renal disturbance, we are not helped much in the matter of treatment, because, in case of the known nonrenal streptococcus lesions, we are able to treat only by elimination or drainage of a focus of infection, and can do little, if anything, toward counteracting the toxic substances that are produced and distributed to the body organs. If actually resulting from an infection, the chronic renal lesion presents itself months or years afterward, too late to be helped much by removal of the focus of infection even if still present. In other words, in the earlier, easily treated stages of the infection, the infection may pass unrecognized; or, what happens more frequently, there is nothing to indicate the beginning of a lesion in the kidney which slowly and gradually will develop into a recognizable nephritis. In the later stages when the renal lesion is easily recognized, the focus is no longer existent, or if present, its removal can change but little the renal damage already done. I have been very much struck, in my own experience, with the relatively few cases of chronic nephritis that seem to have been a direct sequence to a demonstrated infection or infectious disease; most of these have belonged to a rather distinctive group of cases, progressing rapidly to a fatal issue and perhaps better thought of as subacute than chronic nephritis. In these none of the methods of treatment seem to have had the slightest effect on the course of the disease; that is to say, knowledge of a close association with an infection, so far, in this group, has not shown the way to a successful treatment.

As to the actual type of lesion developing in the kidney, we know very little while the disease is progressing. Clinical classification cannot be accurately

correlated with structural classification, and there are so many gaps in our knowledge of the pathologic lesion in the kidney, particularly in regard to its histogenesis and its effect on function, that a structural consideration of renal lesions helps but little in treatment. During life, anatomic diagnosis in any narrow sense is almost impossible and even when successfully made helps but little in treatment.

In many of the patients with chronic nephritis there are coincident vascular lesions, in the main of degenerative nature; but of these we know as little as of the renal disturbances, so that their presence merely handicaps us all the more in applying a rational treatment.

In recent years, much attention has been given to the study of renal function in nephritis, and we have learned many facts in regard to it. The question naturally arises: How much has this newer knowledge of renal function aided us toward a more satisfactory method of treating these patients?

Except for the removal of recognized foci of infection and as prompt and efficient treatment as is possible of all acute infections, we at present can do practically nothing for the prevention of nephritis. Preventive treatment in a practical sense is almost nil for chronic nephritis, and will remain so until we learn more of the etiology and particularly of the factors that influence the progressive development of renal lesions.

THE AIMS IN THE TREATMENT OF CHRONIC NEPHRITIS

As we treat the chronic nephritic today, we aim (1) to stay the progress of the lesion; (2) to remove edema if present to an annoying degree, and (3) to prevent the formation and combat the effects of toxic substances, the result of the presence of the renal lesion. Let us briefly take stock of these methods and the knowledge on which they are founded.

1. *To Stay the Progress of the Lesion.*—With this in view we make two points of attack: (a) We remove foci of infection and guard against repetition of infections, and (b) we attempt to give the renal tissue as much of a chance as possible for recuperation by reducing its work, largely by limitations of diet.

(a) As already intimated, frequently we discover no focus of infection; and when we find one its removal usually accomplishes little, for the damage to the kidney has been done and we do not know how to increase renal repair. Yet it remains rational to seek for and remove, so far as is possible, foci of infection when found; we must not, however, promise the patient any striking result from such treatment, though occasionally great improvement may result. To guard against repetitions of infection, we urge the avoidance of exposure to contagious diseases and the reduction of contacts with infection. For a better

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resistance we urge the best possible hygiene, but these are all very general directions in very general terms; they are easy to state in a general way but difficult to carry out.

(b) To decrease renal work we limit diet. The kidney is an excretory organ concerned in the elimination from the body of water, salts, and nitrogenous and other substances; some well understood, others, such as various toxic substances believed to be eliminated by the kidneys, little understood. We assume that by limiting the intake of food and fluid we decrease the work of the kidney and give the kidney physiologic rest and so opportunity for repair. The tendency today is to decrease fluid intake, especially water. What is the basis for this? We have evidence that water excretion causes renal work, and to an injured kidney an increased fluid intake can lead to a decreased output of urine. When edema is present, we can see it increase as fluid intake increases. We also know that there is a limit to the reduction of water intake below which it is injurious to go because of the concentration of other substances to be excreted which is incident to great water restriction. Very likely, too, a much decreased fluid intake will cause injury to renal cells. Consequently, it seems reasonable to assume that there is an optimum mean of water intake. Do we really know this mean? I think not, except in the sense of the effect of fluid limitations over rather short periods; and even here, knowledge is imperfect. There has been surprisingly little critical study of the effects of different water intakes, especially over long periods of time. What we need to know is the comparative effect of a water intake at a level of 1,000, 1,500, 2,000, 2,500, etc., c.c. for weeks and months in comparable cases. Until these observations have been made, much of the value of a prescribed water intake in influencing the course of nephritis must remain guesswork. Again, we are by no means sure that increased water intake is harmful in all types of nephritis. Just what has been said of water applies to food constituents. Salt intake, protein intake, the problem of an adequate diet in the newer sense, all need to be studied over prolonged periods. If we find that nitrogen elimination is decreased and there is nitrogen increase in the blood in the form of urea, uric acid, etc., we decrease protein intake, often with prompt improvement; but this condition of evident disturbance in nitrogen metabolism really comes late in nephritis. We need to know the optimum protein intake for the early stages, if we are to help matters. War conditions have shown that prolonged reduction of protein intake with a probable imbalance in amino-acid constituents is harmful. Excessive protein intake in the later stages is often observed to be harmful. Between these two extremes there are great gaps in our knowledge at present, and what the optimum intake over a long period of time should be with a mildly damaged kidney, we need to know.

So for salts, of which sodium chlorid almost alone has been studied and that only over relatively short periods of time. I want to impress on you that as to water, salt and protein intake, which we reduce with the idea of affording the kidney rest, and this seems to be sound in principle, we lack the knowledge as to what amount of each in combination is best for the developing nephritis in the sense of reducing renal work without causing other damage, and so affording a physiologic rest that will give the kidney the best opportunity to repair its damage. This information

apparently can be obtained by a thorough, careful study of a large group of patients, followed over a period of not less than five years, to whom we apply a considerable number of the methods of studying renal function at present available; and this surely should be done to give us a better basis for the dieting of patients with nephritis.

Apart from the various constituents of food, should the calory value of the intake in the nephritic be reduced to a level that will cause a loss of body weight, or should body weight remain in equilibrium? In diabetes, evidence seems to favor a lowered level of body weight. In the latter stages of both diabetes and nephritis there is a marked loss in body weight which cannot be made up by an increased calory intake. As to whether a lower level of body weight in the earlier stages of nephritis would be beneficial, we do not know. Careful observation here is almost lacking.

Muscle exertion increases substances to be eliminated by the kidney. Excessive muscular effort appears to lead to renal irritation. Too little exercise lowers the general efficiency of the body. We need to advise our patients with early nephritis in regard to exercise, yet we have few data on which to base our advice. Still, data would be obtainable if an adequate investigation of the effects of varying sorts and degrees of exercise repeated daily for a period of time should be undertaken.

2. *To Remove Edema.*—For this purpose we restrict salt and fluid intake and increase elimination. If we are to deal satisfactorily with edema we should know why the edema is produced. In some patients, apparently few in number, sodium chlorid retention in the body seems to be a very important causative factor in the edema. If salt retention is due to defective renal elimination, in such cases restriction in the salt intake frequently leads to disappearance of the edema. Whether or not this occurs seems to depend on whether, with a lowered intake, there is some excess excretion representing sodium chlorid taken from body stores. In ratio to this excess excretion, accumulated water leaves the body and edema decreases. With the reduction in salt intake, fluid intake too should be reduced to facilitate loss of fluid from the body. To reduce fluid and salt intake is evidently a rational procedure for patients with edema when we have evidence of faulty elimination of one or both. Unfortunately, however, in some cases water and salt excretion by the kidney is at such a low level that we are unable so to reduce intake as to bring about an elimination in excess of intake, and therefore our restrictive measures are ineffective. Fixation of salt and water by body tissues may play a part in causing edema. In many patients with edema we find a very poor salt elimination, and usually a decrease in fluid elimination. So far as can be detected, there is no considerable increase in salt and water in the vascular area as determined by analysis of the blood. In some of these patients a large part of the ingested salt, not excreted by the kidney, is found in such accumulations of fluid as ascites. We know that protoplasm contains both salt and water. Are these amounts, under certain conditions, increased in some way, more of these substances being incorporated or fixed in body cells? This is a phase of the subject, a biophysical one, about which we have little knowledge at present. There is much evidence that edema is by no means a simple question of salt and water retention

by reason of fault in the kidney. Certain edemas in which there is no evidence of renal lesion are proof of this. Anyhow, in actual practice, salt reduction and fluid restriction often fail to decrease the edema of chronic nephritis.

Another view has been expressed that in the edematous nephritic, blood proteins, mainly albumin, are decreased, and this decreases osmotic pressure to be exerted on the filtration membrane of the glomerulus and so increases water retention. To correct this, protein-rich feeding with high carbohydrate intake is advised. In my own trials such treatment has been ineffectual, and several observers fail to find evidence of decreased blood proteins. It would seem for both reasons that this is a factor in the edema in few cases. Usually protein-low feeding is advised on the basis of the principle of securing physiologic rest already referred to.

Another view of the causation of edema attributes it to swelling of colloids on account of increased acidity and variations in salt content. Alkalis are given on this basis; in my hands this treatment has been ineffectual and seems to be harmful.

Other theories as to the causation of edema do not lend themselves to therapeutic application. The entire question of the causation of edema needs thorough study; little is really known about it.

Failing to influence the edema by means planned to change conditions leading to its formation, we are forced to rely on increasing fluid elimination while restricting fluid intake. Naturally, the attempt is made to increase renal elimination by prodding the kidney to do more work; that is, diuretics are used. In edema of nephritis they are almost invariably ineffectual, and often are harmful. In circulatory edema they strikingly increase the excretion of urine, and in mixed circulatory and renal edema they may help. In my own experience I have never seen effective diuresis from a diuretic when the basis of the edema was a renal lesion. They may be tried cautiously, because one cannot be sure of the absence in a given case of a circulatory element in the edema responsive to diuretics, and perhaps there are cases with renal edema which may respond to a diuretic.

Fluid elimination can be brought about through skin and intestine, and sweating and catharsis will increase elimination of water. Unfortunately, they are processes that cannot be repeated very frequently (more than daily); they are debilitating at best, and progress by means of them is rather slow, even when it is obtained.

Mechanical removal of fluid can be carried out, and it always gives temporary relief; rarely is it of permanent help.

3. *To Prevent the Formation of Toxic Products and to Combat Their Effects.*—What causes uremia we do not know. It is a purely hypothetical toxic substance whose formation we seek to prevent or whose elimination we try to bring about. High protein feeding directly or indirectly frequently seems to precipitate toxic manifestations. Conversely low protein feeding should retard or prevent the formation of these toxic substances. We have evidence that it so works; therefore this type of nephritic (usually the nonedematous type), with reason, has a restricted protein diet prescribed. If these toxic substances are formed, we know of no way of neutralizing them; we can only seek to eliminate them. This we attempt by diuresis if possible, by catharsis and by diaphoresis; the last

two are the most effective means. With these we combine an increased fluid intake. Mechanical removal by bleeding is the promptest and most effectual means at hand. With bleeding, transfusion of normal blood is indicated in the anemic or when repeated bleeding is required.

In this review of the treatment of nephritis I have stressed the gaps in our knowledge with the idea of emphasizing the importance of further investigation of the problem of nephritis. Methods of treatment that we use are largely empiric; to recognize this fact is more conducive to investigation than if we assumed that treatment was on a rational basis. Notwithstanding the many deficiencies in our knowledge, we are able to do much to improve the condition of the nephritic, and probably we can retard the progress of the lesion which we cannot cure.

SUMMARY

Deficiencies in knowledge as to the etiology and pathology of chronic nephritis and associated vascular lesions handicap our treatment. Treatment is largely symptomatic and based on such knowledge as we possess of renal function. Preventive treatment is very unsatisfactory. In treating chronic nephritis we aim: (1) to stay the progress of the lesion; (2) to remove edema, and (3) to prevent the formation and combat the effects of toxic substances. To stay the progress, we seek to prevent infections, and by dietary restrictions to decrease renal work and so afford physiologic rest and opportunity for repair. The latter seems a rational procedure, but we need much knowledge for a basis of determining the optimum for a prolonged intake of water, salt and protein. To remove edema, we restrict salt and fluid intake and increase elimination; but we know very little as to the cause of edema, and hence are handicapped in treatment. Increased elimination by diuretics rarely succeeds when a renal lesion causes edema. Elimination by sweating and catharsis is slow, but may succeed. Mechanical removal is effectual, but temporary. To prevent toxic manifestations, we reduce protein intake; to combat them, we increase elimination by diuresis, diaphoresis, catharsis and bleeding. Bleeding is the promptest and most effectual method of elimination of toxic substances.

Peter Bent Brigham Hospital.

ABSTRACT OF DISCUSSION

DR. LEWELLYS F. BARKER, Baltimore: Dr. Christian distinguishes three main types: acute nephritis, the less acute or subchronic form with edema, and the chronic forms that go on for a long time without edema, though they sometimes develop a terminal edema from circulatory lesions. These groups correspond closely to the three generally described as acute diffuse nephritis, subacute or subchronic glomerular renal disease, and hypertension renal disease without edema, known as interstitial nephritis and as the arteriosclerotic kidney. I do not use the term interstitial nephritis unless confronted with an inflammatory condition. Ordinarily, I prefer the term nephropathy. The etiology of these diseases is not clear. Acute nephritis and acute inflammations are doubtless often toxic in origin and very often streptococci are responsible, especially for the subacute or subchronic glomerular tubular forms with dropsy and with edema. The cause of most chronic forms without edema is hypertension. We know less about these forms as far as etiology is concerned. Probably when we know the etiology of hypertension and of arteriosclerosis, we will be more familiar with the etiology of the chronic types. Obesity, hyperthyroidism and slight

infections occurring over and over again may be responsible. As to therapy: In focal diseases without any loss of renal tension, the therapy is simple, but in diffuse lesions with disturbance of the water output, with changes in or near the cardia, disturbance of the nitrogen output and the toxemia that seems to be associated with nitrogen retention, therapy is not so simple. Once nephritis in chronic form has occurred it is impossible to remove it. In the acute forms complete recovery sometimes occurs. Chronic renal disease with hypertension may go on for ten or twenty years and death finally occurs from uremia or myocardial insufficiency. As to the methods of protecting the kidney: The two principles followed are protection of the kidney and support of the heart and circulation. Protection of the kidney is most important in the first two groups and support of the heart is most important in the third group. The three dietetic regimens used are, first, water and milk, or a milk regimen; second, the chlorid-free regimen, and third, the nitrogen-free regimen. In any case of renal deficiency often only water, a wine-glassful every hour, will do good. The patient will suffer no harm by going without food for a few days. Often uremia and marked Cheyne-Stokes breathing will disappear under water regimen. Then give equal parts of water and milk, and finally, milk, but warning against a long continuance of such a regimen. To keep patients on nothing but milk for months is a mistake, since milk alone cannot support the patient properly. There is not enough iron in milk, and it is well to give iron in some form, such as Basham's mixture.

The indication for the chlorin-poor method is water retention with dropsy. In some cases this diet does get rid of the edema, but do not give a chlorin-free diet for too long a period. Give a chlorin-poor rather than a chlorin-free diet. Milk is not chlorin-free, but a pure vegetable diet is more nearly so. Chlorin-poor diet is so unpalatable that patients use pepper and mustard to flavor it. These substances are sometimes irritating to the kidney, and following large intakes of mustard many patients have developed gastric ulcer and hematemesis. The reduction of nitrogenous substances produces good results in the early stages but cannot be continued too long. It is important to keep the intestinal tract freely open by salines and to keep the skin moist. At the same time, avoid prolonged catharsis. Venesection is the quickest way of relieving uremia; often the withdrawal of from 300 to 600 c.c. of blood without any other measures will prove of value.

Some diuretics, such as theobromin sodium salicylate and theocin, may injure the kidney cells. I never give theobromin sodium salicylate for more than three days at a time or theocin for more than two days. The effects of these drugs are much more marked in the edemas due to myocardial insufficiency than to renal insufficiency. Squill also has some effect, but aside from theobromin sodium salicylate and theocin, diuretics do very little good. Support of the heart is important in the subacute cases with edema. Rest in bed with digitalis or strophanthus, reduction of the fluid intake to 500 c.c., five small meals, and laxatives, are the things that restore the heart muscle and circulation through the kidney. Prophylaxis is what we should preach. If we keep every patient with an acute tonsillitis in bed until the throat is well, if we take care of every acute infection by rest in bed, if we get rid of abscessed teeth and other focal infections before damage is done, if we keep patients from being 40 or 50 pounds overweight, if patients will have their family doctor examine them while they are well rather than wait until they are ill, we will accomplish more of what we desire.

DR. GEORGE DOCK, St. Louis: I do not think any advance has been made in our knowledge of kidney disease by trying to substitute the term nephropathy for nephritis. Some of the most typical cases of acute kidney disease are degenerative rather than inflammatory, hence the suffix "itis" cannot be limited to inflammatory processes. Nephritis can be translated "kidney trouble" rather than kidney inflammation. But kidney trouble is the same as nephropathy or nephrosis, and so nephritis is as accurate as any other term so far proposed. At the time the early classifications of kidney disease were

made, function was practically unknown. We have learned much about kidney function, but we have not translated kidney function into pathologic anatomy. There is much to learn. Dr. W. H. Olmsted has been working on a novel method, and with promising results. It consists, briefly, in letting the patient starve over night, examining the urine in concentrated form for the most important chemical constituents, then letting the patient drink large quantities of water (several liters), and then making a new series of chemical tests. I agree with Dr. Barker as to the preventive treatment of chronic nephritis. Osler called attention to the advantage of finding a small amount of albumin in the urine because the patient can be told that he has nephritis and his life be regulated so as not to be cut as short by the disease as it would be if he had no treatment. Often patients are given a bad prognosis because they have chronic Bright's disease and they live accordingly. Important points in practice are: Put the patient on a low calory diet early. A milk diet is fairly safe. Eggs are also good food in nephritic cases. Calcium, iron, bread and vegetables should be included in the diet. I prefer a salt free diet, because so many people do better with little salt. Some patients do better with red meat; some do better without meat, especially chronic cases of low grade without serious cardiac degeneration. I agree entirely with what has been said about diuretics. Exercise is important for these patients but it must be exercise suited to their condition. Chronic nephritis patients must be taught how to live.

DR. NELSON W. JANNEY, Santa Barbara, Calif.: There is still an overgreat tendency to overemphasize protein restriction in nephritics. One reason for this is the many laboratory investigations dealing with proteins, protein production, blood urea, etc., which has emphasized, perhaps too greatly, this phase of treatment. I have become accustomed to see nephritics in not a particularly favorable condition so far as the dietetic side of the treatment is concerned because of the low protein intake for a long period. Those patients are frequently rather weak and obese because the average man will make up promptly in fats and carbohydrates for what he is prevented from taking in the way of protein food. Obesity must be avoided in nephritis. The obese nephritic is usually weak and neurasthenic. Some of these patients are taking as low as 30 or 40 gm. of protein over long periods and really suffering protein starvation. Cutting down the fats and increasing the proteins help considerably. As regards the minimum protein requirement, Sherman allows 0.737 kg. of body weight. Many of these patients are given one fourth of that amount over long periods. When our knowledge of thyroid function increases, many patients with latent nephritis will be cured by treating the hypothyroidism. As in the treatment of diabetes we need a standardized dietary chart to record all data as to tests, etc. The correlation of treatment and the time period could then be worked out, in a much more satisfactory condition.

DR. EUGENE S. KILGORE, San Francisco: So long as we remain ignorant of the etiology of chronic nephritis it will be necessary to keep under suspicion a number of chemical substances used as medicines and food preservatives. Experience in investigating the effects on the kidneys of certain food preservatives has convinced me that such investigations as were possible heretofore are not decisive even if they fail to show kidney damage. It is possible that such substances may be injurious only when they have been administered over a very long time or only when in conjunction with an infectious or other agent. Still more suspicion must be attached to substances known to produce definite signs of kidney irritation. I refer particularly to the salicylates, which Hanzlik and his associates have shown to be followed quite regularly by the appearance of blood in the urine whenever the drug is given in full therapeutic doses. According to present evidence, salicylates seem to be more likely to injure the kidneys than to effect a cure. They are necessary for the relief of certain kinds of pain, but they should be used much less frequently than at present. For any other purpose than the relief of symptoms the legitimacy of their use is highly questionable.

DR. HENRY A. CHRISTIAN, Boston: I am heartily in accord with everything that has been said. I am a skeptic but not a pessimist. I have my doubts but I am not without hope. I expect to see great advances in this field. What we really need is not so many studies over a short period of time of such chronic conditions as nephritis, but studies over a long period of time. We cannot find out much about a disease that probably takes from five to twenty-five years from its inception to its end by studying it for a few days or a few weeks. We cannot find out very much about the methods of treatment unless we observe carefully the effect of remedial agents over a long period of time. What we need is combined study, because no one clinic is physically able to carry out such studies. An effort is being made through the National Research Council to carry out such a plan. That means finding the money because we have plenty of good people to carry out the work and to conduct such combined investigation over, let us say, a minimum period of five years. In regard to classification: study of a condition should be followed by simplicity rather than complexity. I sometimes take more liberties with classification than others, probably because I was trained as a pathologist who dealt with minute classifications. I think in dividing the disease clinically into acute nephritis, chronic nephritis with edema and chronic nephritis without edema, probably with the addition of a group of subacute nephritis, we have gone as far as we should in classification at present. A more satisfactory classification can come only from a more complete knowledge of nephritis clinically, etiologically and pathologically.

ARTERIAL HYPERTENSION ASSOCIATED WITH ENDOCRINE DYSCRASIA *

WILLIAM ENGELBACH, M.D.
ST. LOUIS

The purport of this paper is to offer additional evidence to the recent literature in which attempts have been made to associate a certain selected group of cases of arterial hypertension with disturbed internal secretions. In doing this the burden of proof is, first, to establish the existence of positive endocrine states in these cases; and, second, definitely to exclude the presence of a possible vasculorenal or other lesion as the cause of the arterial hypertension. With a few exceptions, the negative diagnosis of cardiovascular lesions in the cases here reported was based on the absence of present-day clinical manifestations and the course of the disease. The diagnoses of different endocrine dyscrasias were based on clinical evidence considered sufficient for the demonstration of positive endocrine disease, plus the exclusion of other possible diseases as a cause for the symptomatology. The personal observations here reported were deduced from an analysis of 500 uncomplicated endocrine diseases, in which accurate blood pressure records and other determinations worthy of report had been made. Of these 500 patients, forty-six had a systolic pressure of 160 or above. This surprisingly high number, almost 10 per cent., was considered of sufficient clinical importance to be worthy of attention, and serves as the pretext for this paper. In a considerable number of these cases, the abnormal blood pressure had been diagnosed as being due to "neurosis," or to lesions of the renal or vascular system. Contrary to the unfavorable prognosis based on renal or vascular disease, many of these patients had lived a considerable number of years, completely disregarding their high

blood pressure or other serious lesions held responsible for this sign. The treatment which had been prescribed, definitely indicated, no doubt, by the foregoing diagnosis, if in any way effective, had only served to add materially to the affliction of these patients.

In order to avoid early misconception regarding the possible relationship of endocrine states to arterial hypertension, it should be stated that there is no intention to disconnect arterial hypertension from the already well-established groups of arteriorenal lesions. The scope of this paper covers an entirely different division of cases, perhaps a small percentage of the entire number of arterial hypertensions, the clinical studies of which suggest an entirely different cause for the high blood pressure. Granted that this premise is correct, then the prognosis and treatment in these cases must, of necessity, be radically different from those that are accepted in arterial hypertension.

RELATIONSHIP OF ARTERIAL HYPOTENSION TO ENDOCRINE DISEASE

Since Addison first described epinephrin insufficiency in 1855, there has been a tendency to relate different blood pressure states to abnormal activities of the endocrine glands. The gradual decrease in blood pressure in complete insufficiency of the suprarenal glands not only attracted the attention of physiologists and clinicians (Vaquez and Aubertin,¹ Schur and Wiesel,² Ehrmann, Schlayer,³ Fränkel,⁴ Aschoff and Cohn,⁵ Oberndorfer,⁶ Stewart,⁷ Ingier and Schmorl,⁸ Janeway and Park⁹) to this relationship, but the trend of experimentation has been along the line of attempting to connect arterial diseases and those substances of the internal secretions which are known to influence markedly the unstriated muscle contractions producing constriction of these vessels. Allbutt¹⁰ has described and proved the involutionary or decreescent type of arteriosclerosis in which the arterial tension gradually decreases, adding to the clinical groups of arteriosclerosis an entirely different syndrome from that in which hypertension is associated with sclerotic changes of the vascular system.

For many years the secretion from the thyroid gland has been thought to be an antagonistic hormone to epinephrin in its effect on vasoconstriction. For instance, it is thought that thyroid secretion neutralizes the effect of epinephrin on the general muscular tonus, and particularly on the vasomotor constriction of the vascular system. Mikulicz, in his description of senility, gave, as a probable cause, the early atrophy and decreased secretion of the thyroid gland and consequent withdrawal of the vasodilator neutralizing effect of this secretion on the vascular system, allowing the epinephrin secretion to exert its pressor effect uninfluenced. Many other authorities (Weber, Lorand, Ewald, Rolleston and Williams¹¹) suggested insufficiency of the thyroid secretion as a possible cause for

* Read before the Section on Practice of Medicine at the Seventy-First Annual Session of the American Medical Association, New Orleans, April, 1920.

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