THE RELATION OF LESIONS OF THE ADRENAL GLAND TO CHRONIC NEPHRITIS AND TO ARTERIOSCLEROSIS; AN ANATOMICAL STUDY.[1]

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This investigation has for its object the determination, as far as may be possible by anatomical study, of the relation which exists between arteriosclerosis and changes in the adrenal gland on the one hand, and between chronic interstitial nephritis and adrenal lesions on the other.

The problem is of considerable general interest at the present moment in view of the numerous recent publications of French clinicians on this subject and has attracted my attention in connection with a recent critical study of the theory of chemical correlation as applied to the kidney.[2] It would appear natural, in view of our knowledge of the pressor effect of adrenalin and of the experimental lesions produced in the rabbit by this substance, as well as of our knowledge of the frequent association of hypertension with chronic interstitial nephritis and arteriosclerosis, to associate both the renal and arterial disturbances with some alteration of the adrenal. These suggestive facts, taken in connection with the rapidly accumulating evidence of intimate chemical correlation between widely separated organs, renders the problem an exceedingly interesting and suggestive one.

Within the past three years French investigators, led by Vaquez, have contributed a large mass of literature which indicates that localized or diffuse hyperplasia of the adrenal is commonly associated, when the disease does not run too rapid a course, with con-

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[2] Pearce, R. M., The Theory of Chemical Correlation as Applied to the Pathology of the Kidney. Annual address before the Philadelphia Pathological Society, April 23, 1908.

tracted kidney and arteriosclerosis. The hyperplasia is considered as an indication of hyperactivity of the antitoxic and angiotonic functions of the gland, what we might call perhaps hyperadrenalism.

The literature of this subject is now so voluminous that it would be unwise to review it completely, especially as the anatomical studies have been recently very completely collected and described by Rose,[3] and the somewhat scanty and not very convincing experimental studies have been similarly treated by Darré.[4] To indicate, however, the observations upon which this theory is based a portion of the earlier literature should be given briefly:

The first case described by Vaquez was one of adenoma of the cortex of the adrenal associated with a contracted kidney. Josué described three instances of diffuse arteriosclerosis with hypertrophy of the adrenal. Aubertin and Ambard studied eight cases in which there was contracted kidney and found fatty adenoma in three, diffuse hyperplasia in four and in the remaining case with a rapid clinical course a normal adrenal. Lemaire in a single instance, and Froin and Rivet in six out of seven cases of nephritis found adenomata or nodular hyperplasia; the remaining patient, in whom the rise in blood pressure was slight, had a normal adrenal. Menetrier found two adenomata in seven patients with contracted kidney. These figures indicate the frequency with which pathological changes have been described in the adrenals in association with renal and vascular lesions. There are many negative findings however and the frequency of similar lesions with diseases other than those of the kidney and the vascular system have not been sufficiently investigated. On the other hand Landau[5] who has examined the adrenals of sixteen individuals, suffering from general arteriosclerosis between the ages of forty-nine and ninety-six years found no changes which might not be ascribed to the effect on the gland of arteriosclerosis of the vessels of the adrenal itself.

In the hope of throwing more light on the subject by purely anatomical studies I have examined the autopsy records of the Bender Laboratory and have attempted to determine the relation of vascular and nephritic lesions to changes in the adrenal. Attention has been paid also to the occurrence of hyperplasia of the adrenal in association with conditions other than chronic vascular or renal disease.

[3] Rose, F., Blutdrucksteigerung, Schrumpfniere und Nebennieren, *Med. Klinik*, 1907, iii, 1405.

[4] Darré, H., De l'influence des altérations du rein sur les glandes surrénales, Paris, 1907.

[5] Landau, H., Ueber die anatomischen Veränderungen in den Nebennieren bei Arteriosklerose, *Zeitschr. f. klin. Med.*, 1907, lxiv, 227.

It has not been an easy matter in all instances, on account of the slighter variations so common in the adrenal, to establish a dividing line between a "normal picture" and the changes in the gland considered by the French writers to be characteristic of chronic interstitial nephritis. An arbitrary normal standard was finally established by comparing the descriptions of several histologists with sections of the adrenal of twelve individuals between the ages of forty and fifty-six years who had met death by violence and were free from chronic disease of any kind, and whose glands were therefore presumably normal for the ages given. The validity of the establishment of this normal picture was further strengthened by the study of glands of forty-six individuals under thirty years of age dying as the result of various acute infectious diseases. In this way the more acute degenerative changes were controlled.

On the other hand the descriptions of Aubertin and Ambard[6] and of Vaquez and Aubertin[7] have been taken as depicting accurately the changes deemed by the French writers to be characteristic of chronic interstitial nephritis with hypertension. Their histological descriptions may be summarized as follows: The earliest lesion is a "non-fatty" nodule of the glomerular zone involving to some extent the fascicular zone. This change may be found in other conditions, but is more marked in chronic interstitial nephritis. Another early appearance is a "fatty" nodule well limited and isolated in the midst of normal cells and seen especially in the fascicular zone. The latter may sometimes be very numerous and not sharply limited. The final stage is a *hyperplasia adenomatosa totale* with definite increase in the weight of the gland. A true macroscopic adenoma of the adrenal they state to be of no significance, unless associated with diffuse hyperplasia. It differs from the so-called adenoma of nephritis in that the latter is a more marked or accentuated local manifestation of a diffuse process, while the ordinary macroscopic adenoma develops in an otherwise normal gland.

[6] Aubertin, C., and Ambard, L., Lésions des capsules surrénales dans les néphrites avec hypertension, *Bull. et mem. d. l. soc. med. d. hôp. d. Paris,* 1904, xxi, 175.

[7] Vaquez and Aubertin, C., Sur l'hyperplasie surrénale des néphrites hypertensives, *ibid.,* 1905, xxii, 705.

It must be here stated that these writers have never limited these lesions to the adrenal of chronic interstitial nephritis but have said, that if individuals of very advanced age are eliminated, the lesions are found in nineteen of twenty cases of the interstitial type of nephritis and but once in twenty cases of the parenchymatous type, or in other diseases than interstitial nephritis. They do insist, however, that these lesions are always accompanied by hypertension except in those cases of chronic nephritis running a very rapid course.

The material of the present study consists of 163 adrenals which have been divided into groups according to the ages of the individual and the presence or absence of chronic renal and vascular lesions. They were selected from a group of 1,200 autopsies and include all sections of the adrenal which pass through the center of the entire gland and are well preserved and well stained. They are therefore representative of the lesions occurring in the average run of autopsy material. In no case, however, have we notes of the blood pressure during life. For this reason the study of material of this kind is not comparable, strictly speaking, to the studies of the French investigators as the latter, for the most part, used only material from individuals who during life showed definite hypertension. The purely anatomical studies here presented are, however, of value as control observations and form a basis for a detailed study, now in progress, of the adrenal from individuals exhibiting hypertension clinically.

Group I. Normal Glands.—This group includes twelve glands from individuals between forty and fifty years of age (average forty-four years) who met sudden death from some form of violence. They are taken as normal controls.

Group II. Glands from Individuals under Thirty Years of Age Dying of Infectious Diseases.—This group includes forty-seven glands of which fourteen are from infants and sixteen from children. They were taken as controls of the acute degenerative or other lesions which might be caused by infection. The diseases represented are diphtheria, typhoid fever, tuberculosis and noma, acute infections of the respiratory system, and diseases of the gastro-intestinal tract, middle ear, and uterus. In only eight ex-

amples could departures from the normal structure be found. These occurred in three glands of general tuberculosis, in two of typhoid fever, and one gland each of diphtheria, pelvic abscess and septic endometritis. All were in individuals over twenty years of age. In one gland of the tuberculosis group, a diffuse hyperplasia of the fascicular zone with the characteristic spongy appearance, and in another a very definite nodular hyperplasia of the glomerular zone occurred; in two excessive pigmentation and in all a hyperplasia of the medulla existed. In one also a slight diffuse increase of connective tissue was present and in another some round cell infiltration. In the case of acute septic endometritis a very definite hyperplasia of the medulla with round cell infiltration existed. In one gland from a case of typhoid fever were noted focal necroses with extensive leucocytic infiltration and in the other multiple nodular hyperplasia of the glomerular and fascicular zones and diffuse hyperplasia of the medulla. In the glands from cases of diphtheria and pelvic abscess nodular adenomata were also present with more or less diffuse "fatty" changes. In connection with the changes in the adrenals of tuberculous individuals here described it is noteworthy that Aubertin and Clunet[8] have described hyperplasia of the medulla in five cases of tuberculosis.

Group III. Glands from Individuals over Thirty Years of Age, Free of Chronic Vascular and Renal Disease.—This group includes nineteen glands from individuals between thirty-one and fifty-seven years of age (average forty-four years). They are to be regarded as controls for the glands derived from individuals of the arteriosclerotic period. Eight showed no adenomatous changes, while in eleven were found the changes described by Vaquez and Aubertin. The hyperplasia was nodular in eight, diffuse in three and combined in two; in three of the nodular variety the lesion was of the "fatty" type. Increase of connective tissue was found in three glands from cases of syphilis, tuberculosis and cancer, respectively, with, in the first, considerable round cell infiltration. Excessive pigmentation was present in two glands of chronic mitral endocarditis. Hyperplasia of the medulla occurred in two instances

[8] Aubertin, C., et Clunet, J., Hypertrophie cardiaque et hyperplaise médullaire des surrénales, *C. r. Soc. de Biol.*, 1907, lxiii, 595.

in association with syphilis and chronic mitral disease, an association which has also been noted by Aubertin and Clunet.

Group IV. Glands from Individuals over Thirty Years of Age, with Contracted Kidney, Arteriosclerosis and Heart Hypertrophy.—This group has been very carefully selected and comprises twenty-four glands from individuals who suffered from typical chronic nephritis of the interstitial type (contracted kidney) associated with well-marked general arteriosclerosis, involving the aorta or its larger branches, and with hypertrophy of the left ventricle (in four instances both ventricles) of the heart. That is, it represents the anatomical material corresponding to the typical clinical features of chronic vascular and renal disease with which hypertension is usually associated. The ages varied from thirty-eight to eighty-seven years (average, fifty-nine years).

Only one of these glands could be considered absolutely normal. Sixteen showed changes which must be considered as the result of the effect on the gland of the arteriosclerotic changes in its own vessels. These changes are similar to those found in the kidney, pancreas and other organs when their vessels are altered by arteriosclerosis. The vessels of the medulla and capsule show fibrous and hyaline thickening with diminution of lumen, the capsule is thickened and both cortex and medulla show various grades of connective tissue increase and round cell infiltration.

In all instances, in addition to these productive changes, certain lesions described by the French writers were present to some degree, and most frequently the diffuse hyperplasia combined with simple nodules of either the "fatty" or "non-fatty" type.

Similar hyperplastic lesions were found in the seven glands in which evident fibrous and local vascular changes were absent, though in three of them, it should be noted, round cell infiltration was a prominent condition.

In six glands of this group a definite hyperplasia of the medulla was apparent, and in two pigmentation was very marked; in almost all the glands it was greater than normal.

The relation of the adenomatous changes to the local lesions due to arteriosclerosis, in the sixteen glands first described, might be explained as compensatory to gland injury and analogous to the

"multiple nodular hyperplasia" seen in the liver in cirrhosis and in repair of acute yellow atrophy or after other destructive lesions. This explanation cannot on the other hand be applied to the simple hyperplasia observed in the seven glands without connective tissue proliferation. The hyperplasia however is no more frequent in these glands than in Groups II and III in which chronic vascular and renal lesions do not come into question.

Group V. Arteriosclerosis Associated with Chronic Nephritis of the Parenchymatous Type.—This group includes thirteen glands from individuals who showed arteriosclerosis of the same grade as the previous group, but in whom chronic parenchymatous nephritis instead of the interstitial type existed. This material was very carefully selected in order to exclude the latter and to include examples of general vascular lesions of the same degree as in the latter disease. The ages varied from thirty-eight to eighty years (average, fifty-seven years).

Of these glands two were normal, five showed vascular and connective tissue lesions of the character seen in Group IV, associated in three with hyperplasia, and six showed hyperplasia only.

The conditions therefore are not essentially different from those of the previous group and do not support the view of the greater importance of chronic interstitial nephritis as productive of hyperplasia of the adrenal.

Group VI. Arteriosclerosis without Chronic Nephritis.—This group comprises sixteen glands obtained from individuals with well-marked arteriosclerosis of the aorta and larger vessels but without chronic nephritis of any type. The fatalities include various infections and the chronic diseases common to the latter half of life. The ages vary from thirty-five to seventy-four years (average, fifty years).

Of the sixteen glands, ten showed the vascular and connective tissue changes previously described as characteristic of the arteriosclerotic gland. In all but three of these, adenomatous lesions also exist. Four exhibited hyperplasia only, and two were normal.

These observations compared with those made of Groups IV and V indicate that the constant factor in producing the hyperplasia is arteriosclerosis; and hyperplasia occurs indifferently in chronic

nephritis of the parenchymatous type, of the interstitial type, and in absence of chronic nephritis of all types.

Group VII. Chronic Nephritis without Arteriosclerosis.—This group includes twelve glands obtained from individuals without arteriosclerosis but who had definite chronic nephritis, which in ten was of the parenchymatous and in two of the interstitial type. Incidentally this group bears on the question of the frequency with which chronic interstitial nephritis occurs in the absence of arteriosclerosis. The ages ranged from twenty-three to fifty years (average, thirty-six years).

Five of the glands were normal. Two, from individuals with pneumonia and gangrene of the leg, respectively, showed diffuse hyperplasia with discrete non-fatty nodules; and four showed nodular adenomata only. The remaining gland from an individual with tertiary syphilis presented very extensive round cell infiltration of the medulla, but no hyperplasia. Extensive round cell infiltration was present also in the gland from an individual with gangrene of the leg; and slight infiltration in one of chronic mitral disease. In no instance was an increase of connective tissue present. Of the two cases of interstitial nephritis one gland showed nodular hyperplasia and the other none.

These findings are in accord with those previously presented as far as the influence of chronic nephritis of the interstitial type is concerned and indicate, as do the findings in Groups II and III, the relative frequency of hyperplasia of the adrenal in the absence of arteriosclerosis.

Group VIII. Does Hyperplasia Occur in Chronic Destructive Lesions of the Adrenal?—In another section (Group IV) the statement has been made that the adenomatous hyperplasia of the adrenal, in chronic productive lesions of the gland, might be in part a compensatory process analogous to the nodular hyperplasia occurring in the liver of cirrhosis. An attempt has been made to determine whether such a hyperplasia occurs in the persisting tissue of adrenals which are the seat of extensive chronic destructive processes. Two glands invaded by carcinoma, two with amyloid and ten with tuberculosis have been studied. In two of these, cancer and amyloid respectively, a nodular hyperplasia of the "non-fatty" type was demonstrable in the glomerular and fascicular zones, while

in four of the tuberculous organs areas were found which could be interpreted only as the result of hyperplasia. These masses do not show the normal architecture of the adrenal, but are atypical and consist of very large pale vacuolated cells usually containing considerable pigment. The masses are located, frequently, at a distance from the tuberculous lesions and encased in connective tissue. In one gland in which considerable portions of the organ remained intact a diffuse hyperplasia was present.

These findings support the theory of a compensatory nodular hyperplasia of the adrenal, and suggest a possible explanation of the relatively constant hyperplasia of the arteriosclerotic gland.

Group IX. Macroscopic Adenoma of the Adrenal and Kidney (Hypernephroma).—Although Vaquez and Aubertin state that macroscopic adenomata are of no importance in the production of hypertension or in the relation of the adrenal to chronic nephritis, I have grouped these cases in order to present the subject in complete form.

Three hypernephromata of the kidney and three adenomata of the adrenal were available for study. One of the latter was from an individual of thirty-eight years of age who was free from renal and cardio-vascular lesions. The other five were all from individuals between fifty and sixty years of age. Chronic nephritis of the parenchymatous type was present in two and of the interstitial type in two individuals; and the kidney was normal in one individual. In three of the cases a well-marked general arteriosclerosis and in two slight lesions of the aorta and coronary arteries existed. Heart hypertrophy was absent in all.

Macroscopic adrenal adenomata would therefore appear to have no definite relation to chronic interstitial nephritis; whether they bear any relation to arteriosclerosis cannot be concluded from the small number of examples in my studies.

SUMMARY.

Vaquez and Aubertin advance three theories in explanation of the adrenal hyperplasia; first, that it may not be the cause of hypertension but "an antitoxic hyperplasia" caused by the retained products of metabolism which may be responsible also for the hypertension; second, that it may be the cause of hypertension but

secondary to the renal lesion; third, that it may be the cause of hypertension but may antedate the renal lesion or be entirely independent of it. They, as well as other French writers, insist that this hyperplasia is almost constantly associated with chronic nephritis of the interstitial type and it is seldom found with the parenchymatous type of nephritis, or with other lesions.

Hyperplasia of the adrenal, as far as my material enables one to judge, does not occur during the first and second decades. In the third decade it is relatively frequent in the absence of chronic arterial and renal disease but reaches the maximum in association with such disease after the fourth decade. It is an almost constant lesion in arteriosclerosis associated with chronic interstitial nephritis and left-sided heart hypertrophy, but occurs with almost equal frequency in arteriosclerosis with chronic nephritis of the parenchymatous type. It is a relatively frequent lesion of arteriosclerosis without chronic nephritis and of the latter without arteriosclerosis also. As the result of this analysis one is led to the view that while hyperplasia of the adrenal is a very frequent concomitant of chronic renal and arterial disease it is not exclusively a feature of either type of nephritis or yet of chronic vascular disease; but it probably represents the effect of some factor operating in that period of life in which chronic renal and arterial affections are most frequent.

Worthy of special emphasis is the observation that the characteristic lesion of an adrenal, the seat of local arteriosclerosis, is of the type of the chronic productive inflammation seen in arteriosclerosis of the pancreas and kidney; that is, thickening of the vessels, increase of connective tissue and round cell infiltration. Associated with these changes is a hyperplasia which is very constant, and which may be, in part, of the nature of a compensatory hyperplasia similar to that seen in the liver of cirrhosis and acute yellow atrophy. A hyperplasia of this type, as has been shown, may occur in destructive lesions of the gland. This, however, does not explain hyperplasia in the absence of local vascular changes which fact is, possibly, as suggested by Landau, evidence, not of a correlation between kidney and adrenal, but of a vicarious hypertrophy depending upon lesions of some other organ of the body than the kidney, possibly some other ductless gland, affected by arteriosclerosis or other disease.