The Classification of Nephritis

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Classifications of the so-called hematogenous inflammations of the kidney, commonly grouped as Bright's disease, have been made from five standpoints: 1. Etiological; 2, pathogenetic or histogenetic; 3, functional or physiological; 4, clinical (according to the symptom complex); 5, descriptive (a) according to the topography or (b) according to the predominating anatomical changes.

Attempts at correlation of several of these principles have also been made, particularly the clinical and anatomical and the etiological and pathogenetic classifications have been closely identified. But the difficulties and complications which are associated with these imperfect combinations have recently led to a desire for simple and uniform methods of classification.

An effort will be made in the following lines to present a critical review of these classifications, the evidence which has been advanced in their support and to draw attention to some erroneous anatomical and histological conceptions which have acquired importance in the discussion of renal diseases. Finally, I propose to discuss just how far a classification of these kidney lesions seems practically possible.

I.

I. THE ETIOLOGICAL CLASSIFICATION

The etiological classification of nephritis has not enjoyed much confidence and support on the part of the pathologists. It has never been adopted by the best known works on pathology or medicine. In 1905, however, F. Müller,[1] in his admirable review of Bright's disease before the German Pathological Society, revived interest it. Müller proposed substitution of an etiological classification for the present anatomical one for the reason that anatomical lesions are not within the possibility of actual observation by the physician. The etiological classification, however, may be based almost directly on the experience and observation at the bedside, and appears therefore better adapted for the needs of the clinician.

* From the Russell Sage Institute of Pathology, New York.
* Submitted for publication April 4, 1913.

1. Müller, Fr.: Morbus Brightii. Verhandl. d. deutsch, path. Gesellsch., 1905, ix, 64.

But Müller was conscious of the difficulty of this undertaking, for he added guardedly that such a classification could plainly be of use only, if the different intoxications and infections always produced characteristic changes in the kidney. In outlining this classification, Müller stated that it was based to a great extent on personal observations, and he was conscious that the chronic types of nephritis could not, on account of their complexity, be included in this scheme.

As was natural, therefore, Müller's recommendations were received with much reserve by both pathologists and clinicians. Indeed, collective experience points to the untenability of this principle, even for the so-called acute inflammations of the kidney.

It is true that in cholera and mercuric bichlorid poisoning the kidney changes are regarded by some as absolutely characteristic; but even if this should be true (and it has not been established beyond all doubt), these are the only two for which such a claim may reasonably be made. We know that the majority of all infections and intoxications does not show specific characteristics.

In a previous communication[2] I enumerated several years ago those infections, which, in my experience, may lead to anatomically similar lesions; these are the general and local streptococcus diseases: angina pharyngis, tonsillitis, otitis media and others; further, recent syphilis; the exanthemata and, contrary to general belief, pneumonia. Quite recently, Fahr[3] stimulated by Müller's remarks, after a more detailed investigation, arrived at very similar conclusions. It is interesting that he, as well as Kretzschmar,[4] apparently ignorant of my statements, also report the frequent occurrence of severe nephritis in pneumonia. Indeed, the high frequency observed by Kretzschmar has been doubted by others. But this difference of opinion may be explained by the fact that one and the same infectious disease, particularly if epidemic in its appearance, may at different times produce very variable results. In the New York epidemic of pneumonia, which occurred about five years ago with a high death rate, the disease manifested throughout a general septic character. It was associated with purulent pericarditis in an extraordinary degree (almost the rule at autopsy), and generally complicated by severe nephritis. In sporadic cases these are observed much more infrequently. The difference of opinion regarding the character of nephritis in pneumonia is undoubtedly due to the variety of lesions the disease produces under different conditions. Aschoff states that the pneumococcus causes

2. Oertel, H.: The Anatomic Histological Processes of Bright's Disease. Saunders Co., Phila. and London, 1910, p. 67.

3. Fahr: Können wir die Nierenkrankheiten nach aetiologischen Gesichtspunkten eintheilen. Virchow's Arch. f. path. Anat., 1912, ccx, No. 2 (Literature).

4. Kretzschmar: Cited by Fahr, Note 3.

a tubular nephritis. Müller also states that the epithelium only is involved and the glomeruli left free, while others report with equal positiveness the occurrence of interstitial and even hemorrhagic nephritis. I have been able to observe, by fortune of a large pneumonia material, the possibility of all these lesions. This example illustrates in regard to the pneumococcus and the kidney what has been known in regard to other organisms and organs, namely, that different etiological factors may produce anatomically similar lesions, but that the same etiological factor causes at different times very different lesions.

These experiences fully agree with the well-known observations of Asch[5] and others, that the structural and consequently functional changes in the kidney during an infection vary with the presence and location of bacteria and soluble or non-soluble toxins, which in one case may produce necrosis of the epithelium, in another exudation or interstitial leukocytic infiltration, or finally, a hyaline and amyloid degeneration of the vessel walls. To these must be added further the virulence of bacterial strains, the reactive ability and peculiarity of the individual and the mechanical conditions imposed by the structural arrangement of the kidney, which are very apt to influence the distribution of bacteria and toxins.

Finally, we must consider the importance of mixed infections. It is hardly necessary to discuss this well-known point in this connection. Everyone is acquainted with the influence which mixed infections exert on the manifestations of even etiologically well established diseases.

The true pathogenetic significance of the tubercle bacillus is as much under discussion in regard to the kidney as elsewhere. Senator held that the nephritis in tuberculosis was a chronic parenchymatous nephritis. Fr. Müller finds it sufficiently characteristic to separate it from other forms, and treats it as specific nephritis, while recently Fischer and Fahr[3] doubt entirely the existence of a tuberculous nephritis without mixed infection. Even if this latter view is deemed too radical it remains certain that in at least many instances it is impossible to separate the effects of the tubercle bacillus from those of the almost always accompanying streptococcus infection. Thus it would appear that the etiological classification is open to objection, even in diseases whose etiology has been established. Wherever the etiological classification has succeeded in entirely displacing anatomical conceptions it has led to much confusion. As example, our ideas of what is meant by diphtheritic or tuberculous inflammations are extremely indefinite, and really more confused than formerly, when simple descriptive terms were in more general

5. Asch: Ueber den Einfluss der bakteriallen Stoffwechselprodukte auf die Niere. Strassburg, 1904. L. Beust.

use. Etiological terms are insufficient unless qualified by others;[6] clearly then, the etiology alone can in no instance serve as a basis for classification.

II. THE PATHOGENETIC AND HISTOGENETIC CLASSIFICATION

The question whether inflammations of the kidney may be classified according to their genesis is both old and new. Two subdivisions of this question arise: first, is it possible to determine with sufficient accuracy the genesis of every nephritis, and secondly, does an established nephritis retain the features of its development sufficiently to give it a distinct anatomical and functional character. This last point is of great consequence to the physician, because he deals almost always with established inflammations. For instance, one would be justified to speak of parenchymatous nephritis if a nephritis which commenced with involvement of the parenchyma would retain the parenchymatous alterations to the exclusion or at least indisputable subordination of all other accompanying processes.

Virchow,[7] as is well known, combined a definite pathogenetic meaning with his ideas of parenchymatous nephritis. A parenchymatous inflammation represented to him a degenerative nutritive disturbance of cells excited by an excess of nutrient material. In his opinion, this controlled the whole inflammatory process; parenchymatous degeneration was the expression of inflammation. Virchow, therefore, had a perfect right to speak of parenchymatous inflammation, because he believed that the origin and course of the disease rested solely in the parenchymatous changes. On the other hand, his contemporary opponents in this matter championed, much like the older pathologists (Vogel's definition: inflammation = capillary hyperemia + hydrops fibrinosus), the interstitial vascular genesis and character of the inflammatory process. But they, like Traube for instance, employed their idea of inflammation in a manner similar to Virchow. For, while Traube differentiated between a circumcapsular and intertubular nephritis, he neglected and even denied any parenchymatous involvement. As early as 1860, Traube[8] declared with considerable pride that he had been the first to deny the existence of parenchymatous nephritis. In other words, the adherents of the genetic classification were divided, one might say, from the very start, and it may be added, from their standpoints justly so, because their ideas of the fundamental character of inflammation differed. These

6. See my discussion on cynanche contagiosa in the New York City Hospital Medical and Surgical Report I, 1909, p. 213 and ff.

7. Virchow: Ueber parenchymatöse Entzündung. Virchow's Arch. f. path. Anat., 1852, iv, 261.

8. Traube: Ueber den Zusammerhang von Herz und Nierenkrankheiten, etc., in Gesammelte Beiträge, ii, 970.

differences have become only more accentuated since. Indeed, Virchow was consequent enough and never regarded any interstitial process in nephritis as an inflammatory phenomenon, but as a process of repair. It will, therefore, be seen that the ideas of Aschoff in this regard are very similar to what Virchow held in 1852.

These views have never been reconciled by later investigators, although many attempts have been made from Rosenstein's[9] time to the present. Both ideas, Virchow's and Traube's, contained much truth, but not all the truth, and, as is not infrequent under such conditions, both were accepted and continued on authority of tradition unfortunately as *types* of inflammation instead of *evidences* of the inflammatory process. Thus originated and continued the contrast of parenchymatous and interstitial inflammations. Indeed, the most recent ideas of inflammation are as diametrically opposed as they ever were; while some still continue to speak of parenchymatous inflammation, although in a somewhat different sense from Virchow's, others have adopted a teleological conception; they regard, again, much like the older writers, only the reactive exudative changes as inflammatory and exclude all degenerative and proliferative changes entirely. This is opposed by a third group of pathologists, who hold that only the combination of, and intimate correlation of alterative, exudative and proliferative changes constitute inflammation. This group eliminates the conception of parenchymatous inflammation entirely and separates all nutritive and alterative changes from the inflammatory conception unless combined with exudative and proliferative changes. A last group of pathologists regards the inflammatory conception in a still broader and less restricted sense, purely objectively as the sum total of genetically closely related and allied processes which are the results of certain irritants and which present passive and reactive features in varying combinations. This is not the place to enter into the details or the merits of these opinions. They are mentioned here to demonstrate that not only in regard to the genesis of nephritis, but to the very nature of inflammation there exist wide differences of opinion which defeat any attempt at a genetic classification. On one point, however, pathologists agree to-day—that any established nephritis (possibly with the exception of the so-called interstitial nephritis) is a diffuse affection of all kidney structures, but in an uneven degree. Thus whatever views were held of the genesis of nephritis, the terms parenchymatous and interstitial acquired gradually a purely descriptive or topographical significance. This is best illustrated by Orth's[10] position. He states:

> . . . I hold it justifiable to speak of various forms of kidney inflammation, because the different constituents of the kidney are concerned in a most unequal

9. Rosenstein: Die Pathologie und Therapie der Nierenkrankheiten. 1863 and 1894.

10. Orth: Lehrbuch der speciellen pathologischen Anatomie. 1893, ii, 47.

manner. Following, therefore, the principle *"a potiori fit denominatio,"* I go so far as to acknowledge a parenchymatous, interstitial and glomerulonephritis. But it must be remembered that no sharp line of demarcation between them is possible, and that their combinations are frequent findings.

Fr. Müller, finally, makes the remarkable but true statement, that these terms are used at present not so much to designate an anatomical condition, but rather a clinical picture.

This confusion of uncertain teleological conceptions, anatomical terms and clinical pictures, has necessarily led to hopeless disagreement, and Heubner declares that the majority of cases of chronic nephritis in practice do not fit in the ordinary scheme and are atypical.

It has already been mentioned that Müller endeavored to introduce the etiological principle with the purpose of preventing further confusion, which is very apt to continue by the use of old or altered terms. But it has been seen that this latter offers no more hope for a useful classification than does the genetic one.

III. THE FUNCTIONAL OR PHYSIOLOGICAL AND CLINICAL CLASSIFICATIONS AND THE RELATION OF ANATOMICAL TO FUNCTIONAL CHANGES

Functional and clinical classifications of nephritis are strictly speaking not identical, although we shall consider them together for convenience sake. The functional takes into account only the altered kidney actions, while the clinical bases its views on the symptom complex; that is the sum total of all functional disturbances in the whole body which accompany or are resultants of the kidney disease.

It would appear from the start that both these methods of classification are beset with difficulties by reason of our limited knowledge of the normal kidney function and the even greater complexity and uncertainty of pathological functions and relations. Furthermore, the variability and lack of constancy on the part of the clinical symptoms would be an additional handicap to a clinical classification.

Nevertheless, both have acquired considerable importance lately, and an effort has been made to establish a functional differentiation of kidney disease. It must therefore be considered in some detail. In this connection we must first touch on certain erroneous conceptions which have resulted from a rather indiscriminate use of anatomical terms. It has become the custom to speak of vascular and tubular nephritis very much as formerly of parenchymatous and interestitial, in a contrasting sense, and to draw a sharp distinction between glomerulo and tubular nephritis. The most elaborate and ingenious distinction between the two forms the basis of Schlayer's views and those of his co-workers. Now it cannot be sufficiently emphasized that every nephritis, be it the product of poisons, or toxins, or whatever else, involves, if one considers time

and topographical action of irritants, all structures of the kidney. It is correct, however, that these structures are affected in an unequal quantitative and qualitative manner.[11]

In corrosive sublimate poisoning, for instance, the parenchyma cells suffer very severely and conspicuously from the beginning, but there exists also capillary hyperemia and edema. They are followed rapidly by cellular exudation and proliferation. Now it is held by some that these changes are primarily not inflammatory, but purely degenerative, and that this kidney lesion is a nephrosis and later an inflammatory nephrosis. In order to make this plausible it becomes necessary to disregard the capillary hyperemia in the beginning entirely and to look on the initial edema as non-inflammatory, but of a peculiar specific type. (Heineke and Marchand.[12]) Does this explanation not seem forced? Do we not come nearer an understanding of the actual occurrence if we regard each of these evidences as an integral part of a unit, namely, what is generally spoken of as inflammatory process? We may, if we please, treat the components of this process separately for the sake of study, but is it a gain to regard them as entities? They do not present themselves as independent processes, but occur in definite genetic progression and relation. Modifications in their appearance are due to time and topographical conditions rather than to deep-seated changes in character. It is, therefore, a mistake to assume that in what is described as glomerulo or tubular nephritis, or in a nephrosis only parts of the kidney suffer and others may escape. Nor can it be claimed that it adds to clearness to know that a patient suffers primarily from a pure nephrosis and shortly afterwards from an inflammatory nephrosis.[13]

But it may further be urged that there exist many kidney injuries due to toxins, etc., in which one of the important parts of the kidney — vascular or tubular—is relatively uninvolved. That is true, but it would be another error to conclude that relatively slight morphological changes are equal to negligible functional disturbances or that apparently well-defined morphological alterations are always equal to great functional disturbances. Pearce, who of the experimentalists is perhaps the most careful one not to lose touch with the morphological side of the question, showed with Eisenbrey[14] that nephrotoxic and hemolytic immune sera cause changes, which, by physiological methods, present no evidences of vascular injury, but which are anatomically characterized by exudative

11. A fuller discussion of this much disputed question may be found in my monograph: The Anatomic Histological Processes of Bright's Disease. Saunders Co., 1910, pp. 45 to 47 and pp. 63 to 67.

12. Heineke: Die Veränderungen der menschlichen Nieren nach Sublimatvergiftung. Ziegler's Beitr., xlv, 193; Marchand's remarks, *ibidem*, p. 241.

13. The definition of "nephrosis" is necessarily as uncertain as that of "nephritis," for the views on the nature of the latter determine those of the former.

14. Pearce and Eisenbrey: Jour. Exper. Med., 1911, xiv, p. 306.

glomerular lesions of moderate severity. Vascular, they say, must, therefore, be used in the broadest sense, and that lesions of the membrane controlling the passage of fluid may occur without alteration of the power of the vessel to contract and dilate. They differentiate three groups of functional and anatomical changes: 1. In which little or no anatomical evidence of vascular injury is found, but in which physiological methods show profound vascular changes (arsenic). 2. In which anatomical evidence of vascular (exudative) injury is prominent, but in which physiological tests are negative (hemolytic serum). 3. In which both are prominent (diphtheritic toxin).

These experimental investigations agree with similar clinical and anatomical evidences in human nephritis and demonstrate that the *quality* of morphological changes is of great importance in the relation of anatomical to functional changes. Aschoff has laid much emphasis on this point as we shall see later. It has been a general practice to employ solely a not too exact quantitative measure in the determination of structural changes and certainly an insufficient amount of attention has been devoted to their qualitative character. It may be argued that after a structure has been destroyed, it matters little how it happened. But in the first place important functional changes appear during early and slight changes in a structure, and secondly, destruction is very uneven, very rarely leading to complete annihilation of all cells composing a part. Qualitative structural alterations enter, therefore, into the functional changes throughout an observation.

A last important point, and one to which again an insufficient amount of attention has been paid in the experimental investigations of the kidneys, is the compensatory action of one part for another. We are well acquainted with it in the nervous system, we know a little of it in other organs like the hemapoietic and lymphatic systems and the liver, but in the kidney we are further from understanding it, although observations indicate that it exists in this as in other organs.

These general difficulties of a functional classification are further complicated in particular by the different results and views on the toxic effects of poisons.

The importance of this phase of the subject and the general interest and enthusiasm which has been aroused in it after the brilliant observations of Schlayer, Takayasu, Hedinger and Volhard, demand a somewhat detailed review of their work.

Schlayer and his co-workers[15] base their ideas on a strict division of vascular and parenchymatous injury as revealed by the excretion of

15. Schlayer and Hedinger: Experimentelle Studien über toxische Nephritis. Deutsche. Arch. f. klin. Med., 1907, i, 90; Schlayer: Untersuchungen über die Funktion kranker menschlicher Nieren. Kongress für innere Medizin, 27 Kongress, 1910, p. 744; Hedinger: Experimentelle Studien über die Wirkungsweise von Nieren und Herzmitteln auf Kranke Nieren. Ibid, p. 735.

water, sodium chlorid, potassium iodid and milk-sugar. Their experimental investigations have lately been supplemented by observation on human renal disease. Schlayer's experimental work showed that when the tubular cells were destroyed the excretion of NaCl and KI was correspondingly interfered with, while vascular injury led to interference with the excretion of milk-sugar. Urine concentration or water excretion may be influenced in two ways: By tubular injury, which diminishes the amount of solids; or by a hypersensitiveness of the blood-vessels, which increases water secretion: tubular or vascular hyposthenuria.

Sodium chlorid is not eliminated in the tubular nephritis, hence the urine concentration is low; on the other hand, sodium chlorid is fully eliminated in the vascular type; therefore concentration is constant and high, for the blood-vessels are hypersensitive.

In human oliguria the milk-sugar excretion is slow, while that of NaCl and KI is normal; it is, therefore, vascular in character. He considers polyuria due to sensitiveness of the blood-vessels. In scarlet fever nephritis the water is increased on account of vascular irritation, while the milk-sugar excretion is decreased; in other words, the vascular activity of the kidney has become disassociated.

The same underlying conditions are found in contracted kidney. It resembles, functionally, the acute vascular nephritis in a disassociation of its vascular activity, i. e., the injury to the blood-vessels manifests itself by an increase of water elimination and diminution of milk-sugar excretion. While, however, the acute nephritis shows both a diffuse anatomical and functional involvement of blood-vessels, the early stages of contracted kidney present, according to Schlayer, a diffuse functional injury when the anatomical picture still reveals only patchy disease. These observations and ingenious deductions are very interesting, but it may be justly doubted whether such findings, even if substantiated by further observations, furnish a sufficient basis for classification and warrant utter neglect of anatomical evidence. In the first place important generalizations are drawn from the excretion of a few relatively simple substances under certain artificial and pathological conditions. We must confess, however, that very much is still uncertain of the fundamental laws which govern excretion particularly of more complex compounds. We are quite ignorant of the factors, direct or indirect, which may enter into the rapidity and manner of elimination of one or the other substance. It is only necessary to recall here the contradictory results of experimenters regarding the excretion of water and salt in the study of the normal functions of glomeruli and tubules, and the possibilities of compensatory action. We find further a certain variance in these experimental results with the direct anatomical evidence, and herein rests a possibility of error. The anatomical evidence points strongly to the fact that a strict distinction between vascular and tubular

nephritis does not exist, and that the experimental results may be explained by different reasoning. In disease the conditions may be even more complicated. Erich Meyer's[16] observations have led him to similar conclusions. Aschoff[17] and Suzuki's[18] recent experiments have demonstrated with clearness that the effects of poisons on parenchyma cells show important qualitative differences; some, like uranium and mercuric bichlorid, produce necrosis associated at times with a hyaline dropsical degeneration; others, as in the case of cantharidin, with swelling and vacuolization. More particularly in regard to cantharidin, Aschoff found contrary to the generally accepted view tubular lesions and uninvolvement of glomeruli. Aschoff, therefore, concludes that the poisons employed by Schlayer and Hedinger show individual differences and complexity in their topographical action, that cantharidin belongs histologically with greater right to the so-called tubular nephritis and that a division of poisons into vascular and tubular varieties does not seem justifiable. He states: All poisons act primarily on the parenchyma, that is, the different parts of the convoluted tubules; the resulting functional changes are the results partly of the topographical variations in the action of a poison and partly the effects of the poison on blood-pressure. Aschoff's results fully corroborate then the view previously expressed,[19] and emphasizes the necessity of a revision of prevalent ideas regarding the specific actions of poisons. There are other important points in this connection which Aschoff and Suzuki have attacked, notably the significance of vital staining and an attempt to analyze further the structural and functional differences in the tubules. So much remains to be done in this regard that we are far from the possibility of a functional classification of kidney diseases. These considerations do not detract in the least from the value of the experimental observations recorded. They remain important contributions to the secretion of the kidney under abnormal conditions. But one should hesitate, at least at present, to accept these results as a sufficient basis for a classification of kidney inflammations.

But we are even more at a loss in an attempt at clinical classification, which introduces additional difficulties. These have been fully discussed by Fr. Müller, so that it is unnecessary to enter into them again. He pointed out the uncertainty of what is meant by acute and chronic lesions, parenchymatous and interstitial, and the difficulty of the corre-

16. Meyer Erich: Discussion of Schlayer's paper. Kongress für innere Medizin, 27 Kongress, 1910.

17. Aschoff: Zur Morphologie der Nierensekretion unter physiologischen und pathologischen Bedingungen. Vorhandl. d. deutsche. path. Gesellsch., 1912, xvi.

18. Suzuki: Zur Morphologie der Nierensekretion unter normalen und pathologischen Bedingungen. Jena, 1912.

19. See my monograph on Bright's disease, p. 66 B.

lation of the clinical picture and the anatomical lesion. He recommended abolishing the uncertain anatomical nomenclature, and to employ at the bedside only descriptive clinical terms, for instance, instead chronic parenchymatous nephritis, chronic hydropic or anhydropic kidney disease. In view of what has been presented above, Müller's desire to discard old outgrown terms and to substitute a very general directly controllable descriptive terminology is praiseworthy. However, it cannot be regarded satisfactory to employ a purely clinical terminology which at the best is only a repetition of symptoms and gives no idea of the picture of the disease processes underlying them.

Indeed, the desire to correlate clinical symptoms with anatomical pictures is so strong and necessary for the scientific physician that constantly and justly such attempts are being made. The greatest difficulties are encountered, of course, in connection with prolonged kidney diseases, above all the contracted kidney. This finds its reason not only in the complexity of the disease, but in the ever-changing views of pathologists about the origin and nature of that affection. It is, therefore, worth while to present the question of contracted kidney in some detail, as it affords an excellent illustration of the difficulties of an exact classification. The latest most generally accepted views on the pathogenesis and histogenesis of contracted kidney are those of Jores and Prym.

Jores'[20] ideas are to some extent a revival of those of Gull and Sutton, namely, that one type of contracted kidney is arteriosclerotic and not inflammatory. Before Jores, Senator and Ziegler had recognized the direct relationship of arterial changes to contracted kidney and had described a type as arteriosclerotic interstitial nephritis and arteriosclerotic atrophy of the kidney. Jores makes the following subdivisions:

1. The red granular kidney with uniform fine granulations and of brownish-red color, characterized histologically by interstitial growth with atrophic tubules, which show a more or less regular arrangement. Diseased parts interchange with preserved or even hypertrophied parenchyma. Parenchymatous changes are quite inconspicuous or absent, but arteriosclerosis (?) of the small kidney arteries is very marked.

2. The secondary contracted kidney, pale or yellowish pale, characterized histologically by an irregular arrangement of atrophied parts. The still preserved glomeruli present the picture of glomerulo-nephritis. The parenchymatous degeneration is always more or less accentuated, but arteriosclerosis of the smaller arteries is very limited or absent. In this form exists little or no heart hypertrophy; it is marked in Form 1.

20. Jores: Ueber Arteriosklerose der Kleinen Organarterien und ihre Beziehung zur Nephritis. Virchows Arch. f. path. anat. Vol. clxxviii; Ueber die Beziehungen der Schrumpfniere zur Herzhypertrophie. Deutsche. Archiv. f. Klin. Med., 94.

As a result of his largely clinical observations, Volhard[21] has added a third and combined form consisting of 1 plus a nephritis. In Form 1 he found no functional disturbance; in Form 2 a prolongation of water excretion with no power of concentration, and in 3 the same deficiency plus heart hypertrophy. A fourth type of contracted kidney was occasionally met by him without any rise in blood-pressure and functionally related to the secondary contracted kidney (very rare).

Jores' observations have been supplemented by those of Fahr,[22] Gaskell,[23] and lately by an interesting study of Herxheimer,[24] which agrees in the main points with what I have had occasion to observe in this matter. He found even in the early stages of this disease never an entirely healthy parenchyma, although the vascular changes were much more prominent than those in the parenchyma. Nevertheless, I am of the opinion that these parenchymatous changes must be regarded as of some importance in relation to the character of the disease. They are present at a time when nutritive interference by vascular obstruction is out of question and must therefore be attributed to other irritating influences. The characteristic change in the small vessels should not be confounded with the ordinary arteriosclerotic elastic hyperplasia of larger vessels. It consists of a hyaline swelling of the intima associated with the appearance of fatty substances.

According to Herxheimer, it affects frequently the vasa vasorum of larger arteries, but also the vasa afferentia and loops of the glomeruli; he did not observe this in genuine nephritis. Contrary to the findings of Jores, Herxheimer missed this change in other organs with the exception of the spleen. But the latter is of no significance on account of the frequent occurrence of similar vascular changes under all sorts of conditions. Herxheimer regards the vessel lesions as part of general arteriosclerosis, and believes that toxic agents injure the small kidney vessels, thus leading to hypertonia and contracted kidney. He leaves the genesis of the lesion uncertain; it may be due to a direct poisonous action or possibly an indirect result of alterations in kidney tissue or due to nephrotoxins.

Attention has been drawn to similar vascular changes in other organs; for instance, in the capillaries of the islands of Langerhans in the pancreas. It is considered not unlikely that they form a basis for the development of disease in various organs.

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21. Volhard: Ueber die funktionelle Unterscheidung der Schrumpfniere. Kongress für innere Medizin 27. Kongress, 1910, p. 735.

22. Fahr: Ueber chronische Nephritis und ihre Beziehung zur Arteriosklerose. Virchows Arch. f. path. Anat., Vol. 195; Zur pathologisch anatomischen Unterscheidung der Schrumpfniere, etc. Frankfurter Ztschr. f. Path., ix.

23. Gaskell: On the Changes in Glomeruli and Arteries in Inflammatory and Arteriosclerotic Kidneys. Jour. Path. and Bacteriol., 1911, xii, 287.

24. Herxheimer: Verhandl. d. deutsche. path. Gesellsch., 1912, p. 211.

Now, while many modern pathologists are inclined to separate the red granular or so-called primary contracted kidney entirely from the groups of nephritis, it may in my opinion still be questioned whether we are fully justified in doing so, or whether the older standpoint, which included it among the interstitial or productive group of nephritis, has not considerable justification. Mention has already been made of the existence of parenchymatous changes, which, although quantitatively slight, show an injury beyond the vascular districts at a time when they cannot be explained by simple quantitative interference with the nutrition of these parts as a result of the vascular involvement. Furthermore, even with due consideration to the different structure in large and small vessel, the different nature of these vascular changes from arteriosclerotic or atherosclerotic lesions and its uncertain relation to the other arteriosclerotic processes, which Herxheimer himself emphasizes, rather point to a direct toxic effect.

Finally, the early focal accumulation of cells in the immediate neighborhood of injured parts closely resembling certain inflammatory reactions, the subsequent irregular formation of granulation tissue and growth of connective tissue, raise the possibility of more diffuse and specific sclerogenic irritating influences.

Conditions in the kidney may in this regard perhaps be compared to certain affections in the liver, notably the cirrhoses and subacute liver atrophies. Curiously enough, Jores himself has drawn attention to this in connection with a case of subacute liver atrophy presented to the German Pathological Society. Jores[25] says:

"If one goes so far as to regard the destruction of liver tissue as the only essential process and the connective tissue growth only dependent upon this loss, observations which I have made in connection with the case under discussion speak decidedly against such an assumption. For it is noteworthy that in this case of marked destruction of liver parenchyma with a duration of three months, no connective tissue proliferation of consequence has occurred. It demonstrates that besides the loss of parenchyma an additional factor enters into the pathogenesis of liver cirrhosis; this causes the chronic proliferating inflammation, or, as S. v. Heukelom expressed it, an equally effective degenerative and sclerogenic injury of cells." At the same time Albrecht[26] declared that "if one compared these observations (Jores case) with those of Paltauf, who had seen early connective tissue growth in the liver of phosphorus poisoning, one must arrive at the conclusion that in the first instance existed a toxic action on the liver cells alone, while in the second an irritative action on the connective tissue is added. One must question therefore decidedly whether the connective tissue formation in cirrhosis is only the expression of simple scar formation."

It appears that the conditions in contracted kidney are very similar, and indeed, as shown above, interstitial cell foci and thickening occur before loss of parenchyma would call for cicatrization.

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25. Jores: Zur Kenntniss der subakuten Leberatrophie. Verhandl. d. deutsche. path. Gesellsch., 1907, xi, 320.

26. Albrecht: In the discussion of Jores article. See note 25.

My experience is that the vascular changes do not even generally assume marked dimensions without simultaneous extension of cellular foci and connective tissue thickening, which seems to indicate that all of these changes are correlated rather than dependent. (Compare the two excellent illustrations accompanying Herxheimer's article in the *Verhandlungen der Deutschen Pathologischen Gesellschaft*, 1912, especially Figure 2.)

It must also be remembered that even extensive arteriosclerosis of small vessels in other organs does not appear to lead to the quantitative and qualitative changes which are characteristic of this form of contracted kidney.

These considerations make it probable that the processes leading to the primary or red contracted kidney are evidences of irritative influences within the kidney, of which the vascular changes only form an early and conspicuous feature.

It is somewhat doubtful whether the three cases which Gaskell reports as representatives of early and more advanced vascular contracted kidney really belong to this category or not, more properly to the arteriosclerotic kidney as recognized by Senator, Ziegler and others. In Case 34 a specific (syphilitic?) etiology may have been involved. It concerned a young man of 34 years, who died with the diagnosis of dementia praecox (?). On autopsy were found focal brain softening due to extensive and pronounced arterial changes (syphilitic?), extending from the basal arteries throughout the brain. History and other clinical data were unsatisfactory; there were no records of blood-pressure or other diagnostic measures. Moderate heart hypertrophy was present. The kidney appeared macroscopically and microscopically normal, except for thickening and fatty changes of arteries and occasional hyaline glomerules. Parenchyma and interstitial tissue were quite uninvolved. The other two cases are even more doubtful in this respect. Case 38 appears typical of the infarcted kidney of arteriosclerosis (Ziegler), and, furthermore, was complicated by a left-sided hydronephrosis and atrophy due to stone. In Case 39 the kidney is described only as decreased in size and the cortex as diminished; no microscopic examination is given.

Frey has also been unable to uphold entirely Volhard's and Jores' contentions, and Krehl[27] is very sceptical in this regard.

Volhard believes that Jores' secondary contracted kidney (macroscopically yellowish, pale, microscopically with accentuated parenchymatous degeneration and typical inflammatory glomeruli, without, or at least with very limited, arteriosclerosis and no heart hypertrophy) occurs even more frequently than the combined form. (Type 3.) Frey, how-

27. Krehl: See discussion of Schlayer's and Volhard's papers. Kongress für innere Medizin., 27. Kongress, 1910.

ever, has not one case in his series of observations which conforms with all the requirements for Type 2 of Jores. In one case existed a blood-pressure of 195; autopsy showed a kidney macroscopically corresponding to this form, and there was little arteriosclerosis, but, contrary to Jores, marked hypertrophy of the heart. Even Roth,[28] who investigated the relationship of arteriosclerosis to contracted kidney in Jores' laboratory, speaks of contracted kidney without arteriosclerosis as an exception, and of the six cases which he reports, three showed some vascular changes. My records agree with Frey's[29] conclusions in so far as occurrence of diseased renal vessels[30] and heart hypertrophy in contracted kidney are concerned. I must believe that both are the rule and that their absence is irregular and dependent on certain other influences: nutrition, atrophy of muscle, edema, rapidity with which the disease leads to fatal issue, etc. There also seems to be no question that the degree of kidney contraction stands in no direct relation to the degree of heart hypertrophy.

Frey[29] is able to recognize a type of arteriosclerotic kidney already acknowledged by Romberg. This form is characterized clinically by stasis. It was formerly regarded as nephritis and is probably identical with what Bollinger and his school described erroneously as *Stauungs-chrumpfniere*. A previous communication[31] has discussed that feature of the question fully.

In Frey's opinion the old secondary contracted kidney and Jores' Form 2 are practically identical.

According to these modified views, he differentiates between:

1. Vascular contracted kidney (Nephropathia chronica degenerativa sive circulatoria of Aschoff), (a) of larger type (Ziegler's arteriosclerotic kidney); (b) of smaller kidney vessels (may include the red granular type of Jores, and the old primary interstitial nephritis of Senator. It is in my opinion doubtful whether this really corresponds to the primary contracted kidney or interstitial nephritis, both of which are more correctly grouped, as explained above, under the productive nephritis).

28. Roth: Ueber Schrumpfniere ohne Arteriosklerose. Virchows Arch. f. path. Anat., clxxx.

29. Frey: Zur Pathologie der chronischen Nephritiden. Deutsche. Archiv. f. klin. Med., 1912, cvi.

30. It is questionable whether some of these vascular changes in contracted kidney are not the result of the local inflammatory conditions. A periarteritis may involve the adventitia and perivascular infiltration may combine with fibroblastic proliferation and lead to thickening of the adventitia. This lesion may even extend toward the lumen of the vessel, thereby adding an endarteritis obliterans. A direct toxic action on the intima, particularly in the smaller vessels, appears also very possible. The arterial changes in nephritis need reinvestigation. It appears that some of them do not belong to what is generally grouped as arteriosclerosis.

31. Oertel: The Cyanotic Induration of the Kidney. Jour. Med. Research. Boston, June, 1912, xxvi, No. 2.

2. Parenchymatous contracted kidney (Nephropathia chronica inflammatory of Aschoff) including the old secondary contracted kidney and Jores' Form 2.

3. The combined form of Volhard: nephritis plus arteriosclerosis.

According to Frey, these types differ correspondingly clinically thus:

Form 1, with high blood-pressure and urine stasis (the exact type, a or b, cannot be diagnosticated).

Form 2, with dilute urine, inability of the kidney to concentrate, no heart hypertrophy or high blood-pressure.

Form 3, like 2 but plus high blood-pressure and heart hypertrophy.

There are, of course, exceptions; the vascular type may show no urine changes, provided the heart action is good; specific gravity and power of concentration may then be normal. Again, the parenchymatous forms do not necessarily show typical functional disturbances.

Volhard's views may be summarized in this regard thus:

Form 1, normal concentration and water excretion, normal excretion of NaCl and nitrogen.

Form 2, hyposthenuria, compensated by polyuria (see Schlayer's explanation above) as long as there exists relative sufficiency of the kidney.

Form 3, combination form, probably dependent on a predisposition of Form 1 to acquire nephritis. In Volhard's opinion, it is the old genuine contracted kidney, and has a tendency to uremia.

Anatomical as well as clinical subdivisions of contracted kidney are, therefore, still much under discussion, and their character uncertain, particularly whether the old primary or genuinely contracted kidney is only arteriosclerotic in character, or whether it represents, as I am inclined to think, an inflammatory lesion with characteristic involvement of small vessels, or whether, finally, a combination of arteriosclerotic changes superseded by nephritis as Volhard believes.

In view of the complexity of the matter and the number of divergent and constantly changing views about the nature of these processes does it appear possible to arrive at any classification at all?

Indeed Krehl's remarks at the Congress for Internal Medicine in Wiesbaden in 1910 were very sceptical.

I shall endeavor in the second part of this paper to show just how far a classification appears possible.

II.

CLASSIFICATION

It must be emphasized that all classifications in medicine as well as in other branches of science carry with necessity the weakness inherent to the greater or lesser artificiality of all scientific definitions. Theseus, we are told, erected on the Isthmus of Corinth a column bearing on one

side the inscription, "Here is the Peloponnesus and not Attica," and on the other, "Here is Attica and not the Peloponnesus." But no scientific investigator could safely imitate this mythic hero, for the complexity and variability of all natural phenomena make similar strict divisions based on individual observations and ideas easily vulnerable and perishable. The scientific investigator must remain conscious of the fact that his classifications are working tools for the study of phenomena, which in reality lack isolation, but are actual only in their genetic relation and interdependence with others. Processes defy strict classification; only the fossillized remnant may be embalmed and laid at rest in a final system.

A classification, therefore, in order to be applicable to processes of life, may only cover general characteristics. It must confine itself to the substance, the nucleus of the matter, for as soon as it extends to the side lines it merges imperceptibly with others which confuse and defeat the very purpose for which it was designed.

Thus an exact classification which, not unlike that of an *actio finium regundorum* in Roman law, attempts to draw sharp boundary lines between it and its neighbors, attempts a separation, which in reality does not exist, and which in practice leads to serious disadvantage and away from truth.

Mention should perhaps here be made of a psychological complication in attempts at classification. They naturally reflect the view-point of the observer. Whatever appears most readily in the classifier's field of vision, or that which he is in the habit of thinking in, is to him the most important principle. It colors his whole scheme. It is difficult, for instance, for a morphologist to think in other than visual conceptions; his ideas represent definitely related morphological processes; one trained only in physiological methods of research needs much less a dominant morphological substratum for a satisfactory conception.

Now if one studies carefully the complicated situation which has been outlined above, one must, I believe, come to the conclusion that it is unsafe, at least at present, to leave entirely the ground of objective morphological experience. For etiological, histogenetic, functional and clinical facts at our disposal are, in the first place insufficient; in the second place too variable to serve as basis for a classification of nephritis. It appears equally mistaken, however, to introduce subjective views regarding the character of anatomical processes, or to separate more or less arbitrarily certain parts which experience has shown in close union with others. Nothing, it appears, is gained by such procedure; it is a source of confusion, leads to academic discussions and does not aid in the understanding of the nature of a disease at all. Marchand properly questions what would be gained by speaking of an inflammatory neph-

rosis, instead of an inflammation or of a degenerative or parenchymatous nephrosis? Shortly before his death, Senator expressed to me similar views. Indeed, such individual opinions and ideas regarding the nature of pathological processes change so frequently and there exist so many at one time that one can find, for instance, in a modern text-book of pathology, written by leading pathologists, three different ideas and descriptions of the inflammatory process. And that particular book is for students and practitioners.

Observation shows that "inflammation" is composed of a number of processes, which, on account of their close genetic relation and interdependence and more or less definite course, may be conveniently regarded as a unit. In other words, it is the sum total of processes which appear as the result of certain irritations. But if we go beyond this and assume on the basis of theoretical considerations which can be neither entirely proved nor disproved, that the nature of inflammation is only degenerative, or that it is only reactive for purposes of defense, and that the term inflammation should be restricted to one or the other of these features, then we introduce arbitrary lines of demarkation based on personal opinions and build on these unstable systems. This situation is not improved by the fact that another difficulty arises immediately in determining what is to be included under the passive and what under the reactive phenomena. Some, for instance, regard parenchymatous degeneration as a passive process; others as an active response to an inflammatory stimulus.

Thus the present discussions about the nature of inflammation resemble somewhat the discussions of the old psychologists about the nature of the soul. They gave first a metaphysical definition of the soul, then arranged facts according to it. A greater uniformity of views and a more satisfactory classification in psychology were only reached after psychic phenomena were no more regarded as isolated units or transcendental forces, and after it was appreciated that "soul" is a convenient term for the sum total of our inner experience. Medicine in general still suffers more than other sciences from an effort at medieval definitions. These, however, are for reasons previously given, impossible.

I attempted, therefore, several years ago[32] to rehabilitate a purely descriptive anatomical classification which has the advantage of compatability with the needs of the clinician and pathologist. It assumes that nephritis designates a unit from beginning to end, and therefore includes all processes which may enter into or may directly modify the expressions of this inflammatory process. It touches in no way on the disputable pathogenesis or the varying topographical involvement, both of which go beyond the possibility of a general classification. It indicates only the predominating pathological feature or features.

32. Oertel: Bright's Disease, pp. 22-26, 214-215.

The idea of a descriptive anatomical principle for classification is not new. It was successfully, if only partly, followed by Cohnheim, Orth and others and in this country by Delafield. They used the terms degenerative, exudative, productive or proliferative as useful qualifying adjectives. But following Müller's suggestions and efforts to eliminate antiquated and misleading terms entirely, I propose to go further and make it the underlying foundation for the entire system of classification of the inflammations of the kidney.

Such a classification may be held to be too broad, and therefore insufficient, but it may be properly questioned for reasons previously discussed, whether a scientific classification may offer more than an expression of fundamental or general characteristics.

We obtain thus a classification by groups rather than by individual diseases, and it is my belief that with growing knowledge and necessarily growing differences of opinion in regard to the exact place of diseases, classification by groups will become the best means to serve the more general needs of the physician without interfering with the necessary freedom of thought and opinion of the scientific investigator.

We may, accordingly, draw the following sketches:

1. The group of *simple nephritis,* in which occurs cloudy swelling and parenchymatous degeneration, inflammatory edema and serous exudate, associated at times by desquamation and inflammatory proliferation of parenchyma cells. Restitution to integrity.

2. The group of *degenerative and exudative nephritis,* destructive in character; represented by marked and extensive degeneration and necrosis of parenchyma cells, cellular exudate, occasionally, with hemorrhages into glomeruli, periglomerular and intertubular tissue and into tubules. Proliferation of parenchyma cells in glomeruli and tubules, abundant cast formation. The predominating feature may exist either on the degenerative or exudative side.

3. The group of *degenerative and productive nephritis,* destructive and constructive in character; with prominent degenerative, largely fatty changes, much slighter and frequently more localized exudative processes, proliferation of parenchyma cells with the formation of epithelial giant cells, cast formation, appearance of leukocytoid and fibroblastic cells, loss and collapse of glomeruli and tubules, gradual formation of mature fibrous tissue overgrowing wasted and wasting parts, first patchy, then more diffuse. Occasional hemorrhages. Thickening of renal arteries, occasional formation of infarcts.

4. The group of *productive nephritis,* associated with a marked reconstruction of kidney cells and architecture.

a. Diffuse: With less violent but general degeneration and loss of parenchyma and glomeruli by inflammatory obliteration. Marked

regeneration of flat and syncytial-like tubular epithelium with marked distortion of the tubules, and associated abundant irregular overgrowth of connective tissue. Arteriosclerosis of kidney arteries usually prominent; infarct formation occasional (includes in general the old secondary contracted kidney and Jores Form 2, Frey's Form 2, Volhard's Form 2 and probably cases of Form 3. Nephropathia chronica inflammatoria of Aschoff).

b. Focal and patchy: Characterized early by a hyaline swelling and fatty degeneration of intima and endothelial cells of the small renal vessels and capillaries, associated with cellular interstitial and periglomerular cell foci and focal parenchymatous degeneration. All of these acquire gradually more momentum, but the involvement of the small vessels remains most conspicuous. It leads to obliteration of their lumen, thereby adding quantitative to the qualitative disturbance. Thus results collapse of affected parts, the extent of which necessarily varies, so that at times the superficial appearance of the kidney may be only very finely granular. The extent of new connective tissue formation is also correspondingly irregular, usually most pronounced around Bowman's capsule. The tubules are relatively well preserved until late in the disease, and epithelial desquamation is insignificant. The disease is usually accompanied by arteriosclerosis of the kidney arteries. (Includes in general, Jores' Type 1, Frey's Type 1, Subdivision b, and Volhard's Type 1, and possibly cases of Type 3. Nephropathia chronica degenerative sive circulatoria of Aschoff. The old genuine contracted red kidney or primary interstitial nephritis.)

The difference between a and b lies in the fact that in a, a relatively strong or declinningly strong irritative influence has affected the kidney very diffusely, perhaps as the result of a previous severe degenerative and exudative nephritis; in b, a much less severe but persistent irritant, which is never sufficiently strong to produce severe diffuse degeneration and exudation, gradually involves the kidney in disease. It naturally affects the walls of the smaller blood-vessels and the glomeruli prominently first, on account of their exposure by virtue of anatomical structure to irritants and blood-pressure. By almost simultaneous extension of its irritating influence it attacks patches of parenchyma and the neighboring periglomerular parts which respond by focal cell accumulation. Their appearance is then manifest, as we have seen, before any quantitative interference by vascular obliteration is possible. In all forms of contracted kidney heart hypertrophy is the rule.

Finally, one may group as independent non-inflammatory affections the senile atrophy and the true arteriosclerotic atrophy of the Ziegler type. The latter is plainly characterized by patchy loss of substance due to elastic thickening and gradual obliteration of arteries alone. It does

not show an atrophy of glomeruli or tubules due to other reasons; scar formation remains, therefore, quite limited and follows strictly in the path of the lost substance.

In a previous communication,[33] it has been shown that a cyanotic induration, *Stauungschrumpfniere,* does not exist, and that cases thus described are either of Groups b, productive nephritis, or of the arterio-sclerotic non-inflammatory atrophy of the kidney associated with stasis.

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33. Oertel: The Cyanotic Induration of the Kidney. Jour. Med. Research, Boston, 1912, xxv, No. 2.