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RENAL INADEQUACY, IN THE DIAGNOSIS AND PROGNOSIS OF DISEASES OF THE KIDNEY.

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I. Albumen.

Many of us can remember when the discovery and announcement of albumen in the urine were looked upon almost like a sentence of death, to be executed at an unknown but not very distant date, or, at any rate, as showing a condition of the system at which almost any medical accident might happen to the patient without further warning.

Albuminuria has held a place in medical nomenclature almost equivalent to Bright's disease until quite recently. Pathological views were not altogether at variance with these clinical ones. Bright's disease took the place of the older heart disease among the ready opinions of the coroner and policeman, and a kidney which was above reproach was among the curiosities of the post-mortem room. It was discovered however, that, whatever else albuminuria might mean, it did not point decisively and exclusively to well-marked renal lesions, but was found in many other diseases which need not be mentioned in detail, but which can largely be included in the two groups of febrile and asystolic. A step beyond this was the finding of albumen in the urine of persons in apparently good health, a part of whom, at least, continued to be so for months or years.

This is the present status, which offers several questions for examination, and this can best be made without preserving an exact historical or chronological order.

Is albumen to be found in the urine of persons in really good health? The most extensive, and among the most recent, researches bearing on this question are those of De la Celle de Chateaubourg, supplemented by the observations, some of them considerably older, of Capitan, Kleugden, Clarke, Leube, Fürbringer, Grainger Stewart, Van Noorden, and Munn; besides a considerable number of smaller groups or isolated instances, which have often the added value of having been made upon the person of the author, and carefully followed out, by Marcacci, Edlefsen, Ultzmann, Simmons, and others. According to De la Celle, albumen is to be found at times in the urine of seventy-six to one hundred per cent. of healthy persons, both young adults and children. Capitan found in soldiers forty-five and in children eighty-nine per cent.; Kleugden forty-three and a half per cent. among supposably healthy attendants in an insane asylum; and Grainger Stewart gives a general average of thirty-one per cent., which, however, covers a range of from nearly eleven per cent. among civilians to sixty-five and a half among workhouse inmates aged in the neighborhood of sixty.

The discrepancies shown by the accompanying table (Table I.) are very great, too great, in fact, to be accounted for by ordinary errors of observation or by any assumption of real differences in the classes of persons coming under the notice of the various observers; in fact, soldiers, students, and children in institutions furnish the bulk of the statistics. The discrepancies do not entirely disappear by any process of comparison of the method employed, because such a comparison cannot be accurately made for the different reagents. The figures cannot be quantitatively compared when very small amounts of albumen are in question, and even with the same method quantitative estimates of traces are only approximative at the best. The discrepancies are, however, greatly diminished by such a comparison, especially as applied to the labors of the two modern French observers who used the extremely sensitive reagent of Tanret, or the potassio-mercuric iodide, on a layer of which the urine is floated and an estimate made by the density of the cloud. Taking the figures of De la Celle, and separating the cases in which he found, by estimate, from twelve to twenty-five centigrammes to the litre, the percentage falls from seventy-seven to eighteen, from seventy-nine to twenty, from one hundred to thirty-two, and so on, as will be seen by the table. If we notice only albu-

men in the form of a flocculent precipitate, we find it in his tables only four times among one hundred and eleven soldiers who are stated to have given one hundred cases, or ninety per cent. of albuminurics.

Other groups may be examined in the same way, and it is obvious that great allowance is to be made, not for errors in observation, but for the varying criteria by which the presence of albumen is affirmed or denied, whatever be the reaction employed. Some observers distinctly state that doubtful cases are not included. It will be noticed that in the set of cases which give the highest percentages of albuminurics the maximum, if we set aside the quite small number in which flocculent albumen by heat was found, is very small—*i. e.*, from one-eightieth to one-fortieth of one per cent.; while there is a tendency to draw the line between physiological—or at least harmless—and pathological albuminuria, if such a line be possible, at a considerably higher point than this, namely, at one-tenth of one per cent.

To the delicate test (Tanret) by which the most striking results were obtained, it has been formally objected that not only does it give reactions with peptone and alkaloids, errors which may be avoided by a little further testing, but also that when the quantities are small albumen is not to be distinguished from mucin. Roberts believes a frequent source of error with the more delicate tests to be mucin.

The following conclusions may be drawn:

That the presence of albumen in minute traces, or something which gives a similar reaction with the most delicate reagents, is much more common than its absence.

That an amount of albumen detectable by heat and nitric acid may be found in a much smaller proportion of cases taken at random. This proportion varies according to the shade of opalescence which the individual observer considers conclusive, and may be approximately stated as from ten to twenty per cent. of persons examined, rising above it in certain classes to be afterward specified.

The percentage of cases of presumably healthy persons in whose urine boiling gives a flocculent precipitate is much smaller still.

As a corollary to these conclusions it may be asserted that for clinical and practical purposes Tanret's test is worse than useless. There is no reason for taking great pains to discover a sign which to the physician can have *no* significance, and to the patient, if he becomes aware of it, probably a very erroneous one, and is likely

to be the cause of groundless fears. It is chiefly in France that it has been widely used. Jaccoud says that "It is since this has become common that albumen has been so commonly found in the urine of healthy individuals."

The second question is not so easy to answer—*i. e.*, What significance is to be attached to a quantity of albumen, not large, but more than the faintest trace, occurring in a person who has no other signs of renal disease. From what has already been said, it is obvious that the number of persons in this class cannot be stated with great accuracy, but that it is not a very small one. As to the amount of albumen on the one hand which shall be considered small, we may take the limit to which many of those who have studied the subject on themselves or others, seem inclined to adopt—*i. e.*, one-tenth of one per cent. But, on the other hand, as to what amount may be absolutely neglected we cannot speak in figures, but may take the limits of the heat and nitric acid tests carefully applied. Below this point, if other signs of renal disease are not present, the trace of albumen proves nothing, and if they are, adds little or nothing to the diagnosis.

Within this class two sub-classes may be separated off with tolerable distinctness, shading, however, as most exaggerations of subnormal processes do, into each other and into the groups which cannot fairly be included within them.

First the albuminuria connected with a slight degree of anæmia, dyspepsia, headache, general depression, and disinclination to labor, bodily or mental, occurring in adolescents and often known as the albuminuria of adolescents.

Not much weight is to be attached to the remark that this is more common in the male sex, for the reason that the examinations have been made much more largely in boy's schools; in fact, the same remark may be made in regard to the statistics of other groups, soldiers, older students, and young physicians. These cases seem to have been recognized as a distinct class with well-marked symptoms for a number of years. They are certainly not to be looked upon as presenting examples of physiological albuminuria, and were, in fact, for a time thought to show a tendency to weakness of the kidneys, and to be especially liable in the future to develop a true nephritis. This suspicion has not been justified in general, but in a few cases, in which

the albumen was associated with casts, such a development has taken place. Ralfe says that, although some of these cases have a florid complexion, the degree of anæmia is sufficient to be determined by the hemacytometer. The prognosis is no more unfavorable than would be indicated by the other symptoms. The relation of albuminuria in these cases to a future nephritis is not unlike what that of a slight cough in the same patients would be in regard to a future tuberculosis; it would induce a search for other symptoms and call for attention to the general health.

The second class includes the cases of "intermittent" or "cyclic" albuminuria. In these the urine presents certain tolerably constant peculiarities beyond that of containing albumen; it is usually scanty, high colored, with a large amount of urea, and very frequently a deposit of uric acid, or oxalate of lime, the latter being the more frequent. In these cases, which are very likely to be discovered by accident, and of which naturally a large number have been found among young physicians, who have made a careful study of them, the morning urine is usually free from albumen, which appears and reaches its maximum in the forenoon, decreasing during the latter part of the day, with not infrequently a secondary rise in the evening. Exercise has a very decided effect in increasing the quantity, cold bathing perhaps even more, and digestion comparatively little or sometimes none. A few cases have, however, been noticed in which the albuminuria seemed to be determined by indigestion. The character of the food has usually but little influence. This class differs from the preceding in the absence or slightness of the accompanying general symptoms. The patients are apparently, in a large number of cases, in perfect health, though in others there may be a little general depression. The pulse is likely to be of low tension. Some cases of this kind have been followed for years without the occurrence of any symptoms leading to a suspicion of progressive renal disease. In many the albumen has disappeared without special treatment and without the change being assignable to any particular cause.

After subtracting these two classes and making some allowance for accidental cases in which there has been, perhaps, a temporary disturbance of the circulation, unusual liberties in diet, or even a slight nephritis, without alarming symptoms, which is without doubt possible, and where casts may be overlooked, we have still a number of cases

by no means insignificant, in which albumen is continuously present in the urine of persons of various ages, but beyond that of adolescence or early youth. Is this to be disregarded as of no importance, or is it to be looked upon as the early stage of nephritis? It is possible that in some of these a more minute examination, such as is by no means easy on a large scale, would bring to light casts, and settle the question of some renal disturbance, the question then becoming —What is the prognosis in slight cases of chronic nephritis?

Taking these cases, however, as they stand, and following them out carefully, as was done by Munn, we should be justified in regarding them with grave suspicion. Some of them seem to be instances of a real nephritis, running a very chronic course, and presenting at the time of their first examination no constitutional symptoms. Munn found in a considerable number of cases, in which at first only albumen was noted, that casts were subsequently present. Four of sixty-nine had died within three years, and in the majority a general deterioration of appearance was noticed.

It may further be suggested that among them there were many overweights, a class peculiarly liable to nephritis, and also that middle-aged business men, such as are the majority of those presenting themselves for life insurance, form a class especially liable to *interstitial* nephritis, a form attended with the least marked symptoms for a long time, perhaps for years.

It has undoubtedly been noticed that no allusion has been made in this paper to the *kind* of albumen found in the urine. This is not because it is a matter of indifference, but because the investigations heretofore made upon this point have been only upon a few isolated cases and are, hence, not applicable in the criticism of the statistics under consideration.

Two well-marked varieties of albumen, at least, can be distinguished, serum albumen or seralbumen, and globulin, metalbumen, or Bence Jones albumen. Beside these, hemialbumose or albumen half changed to peptone, and peptone itself are found. Mucin, although not belonging to this group, may be a source of error when very small quantities are under consideration. Any minute discussion of the chemistry of even this small group would carry us too far for our time, and at present only into the region of hypothesis; but it is by no means improbable that further experiments on the diffusibility of albumen, and

on the points of coagulability by heat, will disclose even a larger number of varieties which will have a physiological and clinical significance.

At present it appears from a small number of examinations that, when albumen in small amount is disclosed by the ordinary tests, it consists largely or even wholly of globulin, and that this has a less grave significance than serum albumen. This kind is to be detected separately from the other, by a saturated solution of sulphate of magnesia, added to the neutral urine, and the formation of a precipitate on standing. After this is filtered off the filtrate may be examined again for serum albumen.

We cannot take leave of this branch of the subject without reference to the highly important views of Semmola, according to whom albuminuria is not the early symptom, but the cause of nephritis, and finds its origin not in the anatomical changes in the kidney, but in an alteration of the serum of the blood, which alteration is in its turn the consequence of deficient action of the skin. The altered serum is, like a foreign body, eliminated through the kidneys, and on its way sets up a gradual degeneration of the renal structure. The nature of the alteration is shown by a greater diffusibility of the serum, and can only be demonstrated by physical experiments, and, as Semmola himself repeatedly points out, not by any well-marked chemical reaction.

The dyscrasic theory of Bright's disease is by no means a new one. It was held by Bright himself, and, indeed, something like it before him by Blackall. It is certainly not in disagreement with many clinical facts, but in the form advocated by Semmola it is difficult to harmonize with some of the facts we have just been considering. In the absence of clear chemical data, it is almost impossible to follow up the statements of Semmola carefully in a clinical way, but it may be remarked that his assertion that a continued subcutaneous injection of egg albumen produces renal changes obvious to the microscope, has been denied by subsequent observers. If albumen, passing for a considerable time through the kidneys, causes nephritis, the cases of innocent albuminuria, intermittent, cyclic, accidental, the albuminuria of adolescence, ought not to exist, but would inevitably lead to well-marked Bright's disease, and the question we have been discussing would never have arisen. This difficulty may be met by the state-

ment that only the altered albumen (heteralbumen) is to be looked upon as an irritating agent, and that which passes in these accidental cases, and also that accompanying renal congestion, are not of this kind, but more normal and less toxic. Such a statement is, from the reasons above given, not easy to refute absolutely; but it is, on the other hand, no more easy to prove. If nothing is the matter either with the albumen or with the kidneys in these cases, why does it keep coming through?

It seems probable that the form of albumen, so far as we can now distinguish the forms, or, to speak more correctly, so far as they are usually distinguished clinically, which has the worst prognostic significance, is that which most nearly resembles that of the blood serum. Stokvis considers pathological albumen to be serum albumen chemically. That it differs in its diffusibility is the theory of Semmola, which has not as yet the support of other experiments than his own, which are difficult to repeat in the absence of precise details of their performance.

Egg albumen has not been shown to have any special connection with the albumen of Bright's, and was arbitrarily chosen by Semmola as a representative of a foreign albumen. Whether it passes into the urine or not, as asserted by Stokvis and denied by Van Noorden, it cannot be considered to represent fairly the process taking place, according to Semmola, in the development of Bright's disease. Stokvis found that albuminous urine from a case of Bright's, injected subcutaneously into a healthy dog, produced no albuminuria, and when injected into the blood did so in only one out of several instances. This experiment is certainly more to the point as to the discharge of heteralbumen than Semmola's own, in which egg albumen was used. Hayem (*Bull. et Mém. de la Soc. Méd. des Hôp. de Paris*, March 21, 1888), though finding that egg albumen injected directly into the blood may be excreted by the kidneys, does not think that this is a fair representation of a physiological process, but that the secondary albuminuria is a result of changes produced in the blood of the recipient animal. Ascitic (albuminous) fluid could be introduced into the peritoneum of a dog in large quantity without causing albuminuria with any constancy, and when it did occur it was slight and transitory. His last experiment was more decisive than anything so far published as regards the correctness of Semmola's claims. He transfused from

a dog which had parenchymatous nephritis, as diagnosticated before, and verified after, death, a considerable quantity of blood into a healthy dog previously bled. This experiment was repeated twice with the same result, that the recipient dog had a little fever, which is usual after any transfusion, but on neither occasion albuminuria, and recovered completely.

II. Casts.

The significance of urinary casts or cylinders is a question upon which there is perhaps less necessary obscurity than in regard to albumen, but, on the other hand, less statistical information as to their presence in a state approaching health. Easy of recognition when seen, and presenting fewer doubtful appearances, the question can never arise, with a reasonable amount of experience, as to whether they have been seen or not; but as the search for them may be laborious, and the most laborious when least successful, the approximation of an unsuccessful search to a negative result depends upon the patience of the observer, and can seldom be an exact coincidence.

I can add only a few short rules to those ordinarily laid down.

Give the specimen time enough to settle, but not enough to decompose.

If a flocculent cloud appear in the middle of the liquid, look in this for casts as well as in the sediment properly speaking.

Do not use too high a power in searching for them. Find them with a low power, and examine them afterward with a high one, if necessary.

Casts are easier to class and to identify than different forms of albumen. We have first the exudative, divided into mucous, hyaline, and waxy; and the cellular, comprising pus, blood, epithelial, and degenerated epithelial. The appearance of very transparent casts, sometimes branching, irregular in diameter, and with a longitudinal striation, there is no reason to suppose has any significance, certainly no more than that of their chemical complement mucin, although it is highly probable that they are formed in the urinary tubes. These occasionally at one end appear somewhat firmer and rounded, resembling a hyaline cast, to which they seem to form a sort of transition. I have

not, however, seen that their unfavorable meaning is at all increased thereby.

I presume there can be little doubt in the mind of any one that epithelial casts indicate some form and degree of renal lesion. Normal renal epithelium is not thrown off in quantity to be recognizable, and still less in the form of casts. The significance of their appearance in regard to the diagnosis of different forms of renal disease is quite well understood. As the degeneration of the epithelium in the casts is more advanced—that is, as they become granular or fatty, so, it may fairly be inferred, is that of the kidney tubes from which they arise, except that during recovery from acute nephritis a slight degree of degeneration may affect the cells which are thrown off, while those that replace them are normal.

There is probably no form of cast more thoroughly unfavorable in its significance than the long, large, straight casts, highly granular and fatty, so as to be almost black by transmitted light, and with a very low power, or even to the naked eye, looking like fine white threads. These appear to be made up of degenerated cells welded into a more or less homogeneous mass, and are probably moulded in the straight tubes, although the material may have come from higher up. Smaller casts, coarsely granular, or with very distinct fat granules, can come from the remoter portions of the tubules, but an inspection of sections of pathological kidneys which contain casts in the cortical portion makes it seem highly probable that the most thorough degeneration may take place in the secreting tubes without the products getting into the urine in the form of casts, except as these are afterward formed by their being moulded together or enclosed in a mass of the exudation thrown out in the lower tube, and which, without the detritus floated down, would become a fibrinous or waxy cast. Some of the casts formed in the secreting tubes are undoubtedly never dislodged as such.

Returning to the exudative casts, that known as the waxy, or sometimes the amyloid (although the name is badly chosen, as tending to imply a relationship, which does not exist, with the amyloid kidney), indicates a high degree of usually chronic degeneration. I have never known but one instance of apparent recovery in which these casts were present. It was that of a young woman who entered the Boston City Hospital with "inflammation of the bowels after childbirth," and had, in addition, a copious greenish expectoration with râles, general ana-

sarca, headache, and scanty, smoky urine, with albumen and large casts, among which were many waxy. She was discharged apparently well, although still with some albumen, and much fewer casts. She was seen in the street some time afterward, apparently well, but further search has only resulted in my finding that she has not since died in Boston.

With the elimination of these forms, and the admission, which I presume few would hesitate to make, that a considerable number of casts of any kind means a distinct and more or less extensive renal lesion, the seriousness of which can be estimated by their number only in connection with other symptoms, we find ourselves in the presence of a problem not unlike that presented by a light or moderate albuminuria of the apparently healthy. Many authors speak as if the two conditions were nearly commensurate, but I believe them to be so in neither direction; that we very frequently meet with one without the other. If both mucin and mucous casts were left out of the comparison, I suspect the association would appear still less close. It is possible that a few casts may accompany a very slight amount of albumen, and, perhaps, have no more meaning than this; but it will be noticed in looking over the tables (especially Table II.) of cases of albuminuria not accompanying renal disease, that the reports of "no casts" are most frequent, and that when a statement of their presence is made it is usually in connection with the classes which border most nearly on the pathological limit.

Where hundreds of persons have been examined, the statement of "no casts" is to be received with a certain amount of allowance, but in a great many of the cases given in the second table there were small groups of persons under observation at a time, and frequently under circumstances to excite anxiety, or much scientific interest, so that we may be morally certain that many and careful microscopic examinations were made, and the statements may be accepted as being as nearly conclusive as negative ones can be.

This negative statement is made in regard to a great many of the cases of cyclic albuminuria. Where, however, the urine is distinctly irritative, *i. e.*, concentrated, and containing oxalate of lime, the presence of a few hyaline casts can hardly add to the importance of the presence of albumen. It is interesting to note that in oxalic acid poisoning (among others) albumen and casts were found in the urine by

Mürset (*Arch. f. exp. Path. und Pharm.*, xix. p. 335), and by Robert and Küssner (*Virchow's Archiv*, lxxviii.), and by von Fränkel (*Zeitschrift für klin. Med.*, 1881, Bd. 2), quoted by Mürset. In the albuminuria of adolescence, which is certainly not a physiological condition, hyaline casts have been not infrequently noted.

In old age, it is well known that the kidneys undergo a certain amount of atrophy, especially near the surface; but so long as it does not progress so rapidly that they are unable to carry off all the results of a metamorphosis, which is also, and perhaps as rapidly, decreasing, there is no reason why symptoms of any kind should arise on the part of these organs. The arterial and cardiac changes which are usually going on at the same time, are quite as likely to come into the foreground, and, perhaps, put an end to life, while the kidneys, although slowly atrophying, are still able to do all the duty likely to be required of them. Thus it comes, and very properly, that in the presence of other important symptoms referable to other organs, slight amounts of albumen and casts may be disregarded, and it is an error in diagnosis to attribute to latent Bright's disease, even when it may be actually present, everything which may happen to the patient under these circumstances.

Taking albumen and casts together, we may at first separate all the conditions of local irritation, congestion, and senile atrophy, which have before been spoken of, and in which small amounts of albumen and casts may be found. In these, neither diagnosis nor prognosis is specially affected by the combination of these two signs more than by one of them alone. If the amounts become larger, the symptoms are correspondingly important. In cases, however, in which these symptoms are the leading ones, and which cannot be brought under any of the classes already discussed, even a few casts in addition to albumen should be looked upon with suspicion, and as making the prognosis more serious. A considerable number would make renal disease highly probable, or at any rate probable enough to be taken into consideration in the treatment, and many, especially if carrying with them epithelial elements, make a diagnosis of Bright's disease almost certain.

When we have casts of epithelium, more or less degenerated, or the large homogeneous and waxy ones, we have got beyond the point at which there is room for discussion as to the presence of renal disease

of an advanced kind. Its form and acuteness are to be determined partly by the urine alone, and partly by the other symptoms which are not likely by this time to be absent.

What the nature of the lesion may be when it is clear that one exists, but when it is evident, from the length of time that the urinary signs have been present without other symptoms having arisen, that it is not a rapidly progressing one, can in many cases only be surmised.

An inflammation limited to a part of one kidney, is not a purely gratuitous assumption. The evidence of this is occasionally plain at the post-mortem. Even in the well-marked contracting kidney, the interstitial inflammation is present in patches. A small area of inflammation might for a long time furnish pathological products without extending enough to produce further symptoms.

Old renal disease may either recover or leave behind a condition which does not grow either better or worse. I have had under occasional observation a patient whose urine twenty years ago, after puerperal convulsions, contained albumen and casts. She has had one and, I think, two children since without convulsions, but the morbid elements have been found from time to time ever since. The patient was, a few months ago, when I saw her, quite as healthy looking as most women of her age, and had no definite symptoms to complain of.

An attack of scarlatina so slight as hardly to be diagnosticable otherwise, may leave behind, for some time after the patient is apparently well and after albumen has disappeared, a few casts.

The atrophy of old age has already been spoken of.

The difficulties of diagnosis may be considerably increased by the presence of other symptoms, and the resemblance between a case presenting the signs under consideration, with, for instance, severe headache, and a case of genuine Bright's is very close. No general rule can be laid down. A diagnosis depends upon the study of the individual case, and it may require the lapse of time to make it sure.

III. Renal Inadequacy.

The phrase renal inadequacy, used upon our programme, may be made to bear several shades of meaning, one of which, attached to it especially by one whom we hoped would be our guest, I shall for a moment omit from consideration and, for the earlier purposes of this

discussion, shall consider only a supposed inability of the kidney, arising from incipient organic disease, to perform its function of excreting water, urea, or the total solids. I must make this limitation, because the data, which are none too abundant as regards even these substances, are very deficient for any other of the constituents.

What is to be learned from the diminution of any of these constituents that is of value in the diagnosis or prognosis of renal disease? It is, of course, acknowledged, and it is unnecessary to dwell further upon this fact, that an extreme oliguria or anuria is a symptom calling for an immediate investigation, probably, but not necessarily, connected with renal disease, and which may carry with it an extremely serious prognosis. A continued diminution of all the constituents may have less weight in the same direction, but its existence is not to be assumed on the basis of a single hasty examination.

A point of much greater interest, as being less well determined, is whether we can diagnosticate the early stage of chronic nephritis by a moderate diminution in the amount of any of the urinary constituents. The quantity of water is well known to be subject to such individual differences and such fluctuations under various influences that no slight and temporary changes can prove anything, and when the urine in any form of nephritis is permanently diminished to a point decidedly below the physiological limit the diagnosis is usually to be made on other grounds than the quantity of the urine or of any of its constituents alone. Such a condition is likely to occur long after the diagnosis has been clearly made out, but a knowledge of it may be of service in anticipating the onset of other symptoms.

There is, however, a statement made which I believe to be misleading, if not baseless. Polyuria is now a well-recognized symptom of many lesions of the genito-urinary tract, and, barring certain nervous conditions which may produce it by changes in the blood-pressure, and surgical lesions, which act either in a similar way or by the direct effect of back pressure on the secreting structure, and not infrequently lead to a form of nephritis, it is strongly significant of chronic interstitial nephritis. It is one of the most important symptoms, should always lead to further investigation, and the reality of its presence should always be determined by measurement.

This urine is of low specific gravity, and is often said to be deficient in urea. This statement may mean that the percentage is below the

average, which, of course, may be understood of itself, and has no value whatever for diagnosis, so far as single specimens go, or it may mean that the total daily amount of urea is below a certain quantity fixed upon as a standard. The latter ought to be the invariable meaning, but it is not so, and unfortunately it is impossible to tell, in a great many analyses, which of these is intended by the chemist. When, however, the statement is made in this correct sense, it is not to be accepted without reserve until we know what is to be the standard.

The statement of many text-books is that from thirty to forty grammes is a normal, daily excretion of urea for a healthy man on an ordinary diet. This, however, is subject to many corrections, of which the most important (in health) is food. Some French writers assign a lower figure, and intimate that there may be differences of race or habits between the Germans and English on the one hand, and the French on the other. It is much more probably a difference in habits of diet than of race, for there are series of French observations (Roux, *Archives de Physiologie*, vol. vi. p. 593) in which the daily urea is never below 30 for days together, and not infrequently rises above 40.

Without attempting to gather a large number of determinations for the purpose of establishing an average, I have found enough in books upon which I can easily put my hand, to show that a much smaller figure than this is not below the physiological limit: Lehmann (*Physiological Chemistry*), vegetable diet, 22.5; non-nitrogenous, 15.4.[1] Eustratiades (quoted by Rabuteau), averages of successive weeks, 22, 20, 24; under coffee, 19, 17. Rabuteau (*Elements de Therapeutique*, p. 96), 20, 22, 18, 19. Böcker (quoted by Marvaud, *Aliments d'épargne*), 22.27; under coffee, 12.58. Mason (*Boston Med. and Surg. Journal*, 1882, vol. cvii. p. 222), 20, 22.44. Brouardel (*Arch. de Phys.*, vol. viii. p. 388), 18 to 20, or 22. Debove and Flamant (*Gaz. Heb. de Paris*, June 18, 1886) give two tables of the excretion of urea, the first of a patient weighing 58 or 59 kilos, who had a daily quantity of urine varying from 440 to 1240 per diem, with urea from 13.38 to 24.42, and total solids from 24.64 to 39.6. With the second, weighing about 40 kilos, the quantity was from 510 to 1010, and the urea from 13 to 22.58, and total solids from 31.62 to 53.76.

In *The American Journal of the Medical Sciences* for Oct. 1867, Noyes presents several elaborate and interesting tables concerning

[1] These and the subsequent figures refer to grammes in twenty-four hours.

the elimination of urinary constituents by four persons, two males and two females, whom he apparently considered to be in health, or, at any rate, fair subjects for a physiological determination. That he was right in the latter opinion is evident from the fact that none of the numerous figures was sufficiently different from the others to be thrown out, but there are some points about one of them which will make it especially interesting for our purpose. The averages for successive weeks for these four persons were: mixed diet, 15.56 grammes; animal diet, 41.98; vegetable diet, 10.55; exercise (not excessive), 10.32. On two other weeks Noyes determined on himself averages of 15.55 without, and 16.80 with coffee. A seventh week to determine the influence of sleep gave 6.50 for the night, and 8.61 for the day, a total of 15.17. Total solids, corresponding to these weeks, calculated from the specific gravity, are, omitting fractions, 43, 64, 37, 29, 40, 41, 47. It is universally stated that a low diet may reduce these figures much further, so that we may find a patient excreting less than ten grammes of urea per day, without special reference to the condition of the kidney.

It is well known since the recent advances in abdominal surgery that the secreting substance of the kidney may be reduced at least one-half without prejudice to the elimination, and it is, therefore, to be expected that chronic nephritis should have advanced to a considerable degree of atrophy before it begins to make itself manifest by diminution in the secretion. So far as water is concerned, we know that the destruction may be extreme, while the kidneys are still carrying on a discharge of two or threefold the normal amount. For the solid elements it is probable that the capacity may not go quite so far, but the following figures will show that long after nephritis can be clearly diagnosticated the discharge of urea and of total solids may be well above the physiological minimum; indeed, in some cases they may run side by side with the corresponding figures for healthy persons on the same diet. The physiological variations in the urea discharge would indicate very plainly the probability of this. Organs which can, on occasion, double their capacity of discharge as do the kidneys on a full meat diet (take, for instance, cases of diabetes as well as Noyes's figures just given) without harm, certainly ought to be able to lose a considerable percentage of secreting surface before they

become unable to take care of the much smaller but still normal quantity which is formed on a much less nitrogenous diet.

The cases given here are, of course, selected. It is not meant that under all circumstances, in nephritis, the kidneys carry off all the solids formed, but that they can continue to do so long after a diagnosis is possible on other grounds, unless in certain cases in which a nephritis makes considerable advances without the detection of albumen or casts or any other decisive symptoms. Such cases are talked about and are conceivable, but are much more likely to be the results of examinations not having been made than of their having given negative results.

Fleischer (*Deutsches Archiv für klin. Med.*, xxix., 1881) reports the following cases:

A woman, aged thirty-five years, with abundant urine containing albumen and casts and having slight œdema, headache, vertigo, and pain in the back and limbs, had the urine carefully examined daily with comparison with a healthy person on the same diet (Control-person). The urine was always more abundant, although that of the Control-person was quite copious, while for twenty-one days the urea discharged was 32.38 as against 32.33 of the healthy person. The respective quantities of phosphoric acid were 1.64 and 2.51 per cent.

A woman, aged twenty-one years, with a diagnosis both before and after death, of extreme granular atrophy of the kidneys, had for two days 26.2 and 25.2 per cent. of urea, which was less than that of the Control-person but not below the physiological limit. Then there was a period of diminished excretion corresponding to an uræmic attack and, subsequently, on three successive days, it amounted to 43.1, 40.8, 29.7 per diem. This was about three weeks before death, and shows that a very badly damaged kidney can, for a time at least, get rid of a superfluity of urea, and also that in the production of uræmic attacks by retention of the products of secretion something more than the structure of the kidney must have been at fault. The phosphates went through a similar fluctuation.

Another "Schrumpfniere," without a Control-person, passed 30.07 per cent. of urea for seven days. Another, an average of 24.7 per diem.

In another case which seems peculiarly fitted to show the value of different means of diagnosis at an early stage, a man of thirty-one who had albumen and casts but no hypertrophied heart, gave an average for seven days of 40.9 per diem. After a year there was still albumen and his aspect was less blooming, but no symptoms of hypertrophy of the left ventricle could be made out.

A weakly child, eight years old, with great œdema and ascites, the urine containing much albumen, casts, and fatty epithelium, whose post-mortem

diagnosis four months later included pleurisy, peritonitis, fatty and amyloid degeneration of various organs, as well as of the kidneys, passed a daily average of 8.88 per diem of urea against 9.91 per diem of the Control-person.

In these as well as in other cases examined by Fleischer, the diminution of uric acid and phosphoric acid was more constant than that of the urea or the chlorides.

In the interesting tables by Noyes, already cited, the second of the four persons under observation, aged fifty-eight years, constantly passed a urine of low specific gravity and in quantity considerably larger than that of the other persons upon the same diet, being most of the time near or above 2000 c. c. His total daily urea did not fall below that of the others, nor did the proportion per kilo of body-weight constantly do so, and when the amount of meat was much increased, his excretion of urea increased as much as that of the others and became as much above the physiological average as (with the others) it had been below on a vegetable diet.

No examination of the urine for albumen and casts is noted in any of these cases, but so constant an increase of quantity and diminution of specific gravity in a person not stated to have any peculiarity in the matter of beverages, would certainly, at present, be considered of itself alone, very strong presumptive evidence of interstitial nephritis, and when it is learned that this person had hemiplegia two months afterward, it seems highly probable that the author was making some observations of a very valuable kind without realizing that they were pathological. At that time polyuria was not so well recognized a symptom as it is now.

Oppenheim (*Inaug. Thesis*, Bonn, 1881) in a case of acute nephritis found the urea constantly increased—twenty-nine to forty-eight grammes.

In a case of my own, a man of thirty-five, who had been known to have interstitial nephritis for at least two years, I have found this summer, calculating that the two specimens he has each time sent me were fair representatives of the day and night respectively, and that the larger portion is passed during the day, in June, 25.7 per diem of urea and 43 per diem of total solids (the solids by calculation from the specific gravity); in July, 34.4 of urea and 54 of solids; and in August 30 of urea and 53 of solids. As the urine continues to be in about the same quantity I presume that these figures

represent nearly an average of what has been passed for some months. Some days after a hemiplegic attack, the 24 hours urea was 22.5.

We may add to these cases some others in which the urea was not determined but in which the total solids may be calculated from the quantity and the specific gravity.

Phillips's (*Lancet*, Dec. 12, 1885) patient, æt. sixty-seven years, cirrhotic kidneys, 67 grammes solids.

Charpentier's (*Thèse de Paris*, 1880) patient, æt. forty-seven years, headache, hypertrophy of heart, tuberculosis, diagnosis of interstitial nephritis. Total daily solids, 69.

Female, æt. fifty-five years, arterial nephritis. Solids 48.

Female, æt. fifty-five years, interstitial nephritis without albumen. Solids 28.

A male, æt. fifty years, with lead poisoning, emaciated, anæmic, with osteitis of ribs and beginning pulmonary tuberculosis. There was a diagnosis of some renal lesion, the urine was in quantity 2500 and of specific gravity 1.010, which gives the solids as 57 grammes.

In a thoroughly typical case of my own there were found at various times, the last not long before death, 87, 77, 51, 18, 100 of solids.

These cases are certainly enough to show that the excretion of urea and of the total urinary solids does not necessarily fall below that of a person in health on a diet of moderate nitrogenous richness. These, however, are all cases readily diagnosticated, and some of them of long standing and far advanced, so that it may safely be concluded that in cases which are less so, in which the diagnosis is still doubtful, the determination of urea is still less likely to give us assistance.

A suggestion, offered by some of Fleischer's cases, is worth following out: whether some of the other constituents, like uric acid, the phosphates, or sulphates, would give more valuable results. I have made no special examination in this direction, but certainly a deposit of uric acid in urine of low specific gravity is no unusual condition in Bright's disease.

This argument might be much strengthened, if it needed it, by reference to other conditions in which urea is found diminished. In disease of the liver it may fall below the normal, and in some acute affections of this organ it is said to have been absent. In these latter, however, it is highly probable that the kidneys also were profoundly, though rapidly, affected, as in phosphorus poisoning.

Impaired nutrition in general, with anæmia in its various forms, is

the most frequent cause of diminished urea. It is not passed, simply because it is not made, and its deficiency in a given case, in the absence of other symptoms which may fix the diagnosis more exactly, justifies us only in supposing that it is due to some one of many diseases in which nitrogenous metamorphosis is interfered with, of which Bright's disease is only one. In a large proportion of cases a considerable diminution of urea is more significant of disorder of appetite, digestion, and tissue metabolism, than of any failure of the kidneys. There may come a time, and, as we occasionally see, it may come unheralded, when a new set of symptoms indicate that even a small amount of urinary solids can no longer be taken care of by the atrophied, or degenerated, or paralyzed kidneys.

The term renal inadequacy has been recently employed in a somewhat special sense, not exactly corresponding to that in which I have been considering it, by a gentleman who was expected to give us his views in his own words. Sir Andrew Clarke says: "By renal inadequacy I mean that state of the kidney in which it is unable, without material diminution of quantity, to produce a urine containing the average amount of solids, and of a specific gravity greater than 1.014." The urine is described as pale, almost invariably free from albumen, and depositing no casts. The (conjectural) state of the kidneys is one of slight withering and induration. The physiognomy is like that of pernicious anæmia, on the one hand, and, on the other, like that of chronic Bright's, and yet seems distinct from both.

What interpretation are we to put upon this description? If there really are withering and induration of the kidneys, what can they be due to but interstitial nephritis? The account of some of the symptoms would not be inconsistent with the hypothesis of a slowly advancing cirrhotic kidney. We know that this progress may take place without albuminuria for a time, and it is said for a long time; but too much has been made of some exceptional cases. If one were to lay great stress on these exceptions, and view them in the light of the discoveries of the general distribution of albuminuria detailed in the earlier part of this paper, he might be led to the conclusion that but few people fail to present the symptoms of Bright's disease except those who really have it.

With a not inconsiderable experience with chronic nephritis in various forms, I must say that I have not met with many, and I should not be much afraid to say any, cases in which albumen and casts

could never be found, and although a few such cases are detailed as exceptionally interesting, they are not at all common even in literature.

I think it has been very clearly shown that the kidneys are able to carry off the full amount of solids formed long after more than slight shrivelling and induration have taken place; so that if we admit this to be a special form of disease, and if there is any special obstacle to the passage of the urinary solids, it must be of a functional, and not of an organic character, the existence of which is a pure hypothesis, so far as any chronic condition is concerned; or else the lesion is one already advanced, and one which has been making its progress with very few symptoms.

Another very strong point against the assumption that a diminished discharge of the urinary solids in such cases means any inability of the kidney, either functional or organic, is, that it is specially stated that if the supplies of food and wine are cut down, the amount of urea increases. This is easily to be accounted for if we suppose the diminished urea to be due to a form of dyspepsia, or, in other words, if a large amount of food passes off by the intestines without ever being received into the blood, where it can further undergo the metamorphosis into urea. A proper regulation under these circumstances would, undoubtedly, lead to improved nutrition and increased secretion. The specification of wine is somewhat significant in this point of view, since alcohol furnishes but little to the solids of the urine, but may have a very decided effect in impairing the digestion, and is well known, when taken in considerable quantities, to reduce the amount of urea with a possible, but not proportionate, increase of uric acid.

If the kidneys are already inadequate to carry off a small amount of urea, how can a change of diet in the direction of restriction increase it? If more nitrogenous material gets into the blood because the digestion is improved, as has just been supposed, and the kidneys are already inadequate to carry off the smaller amount of urea the only result can be an accumulation and not increased discharge. If, however, the previous digestion has been complete it is difficult to see how a smaller amount of excrementitious solids in the blood can make the amount which passes off any greater. If the kidneys *are* carrying off all they are capable of, then neither increasing nor diminishing the urea of the blood can make them do more. If they *are not* carrying off all they can, then a diminished amount proves no inadequacy on their part to their task, and the deficiency is to be sought in the limited formation.

Table I—Albuminuria among Persons supposedly Healthy.

Author.	Reference.	Class of cases.	Number examined.	Albumen found	Per cent.	Albumen in larger amounts, or by ordinary tests	12–25 c.gr. per litre.	Less than 12, trace.	Remarks
Clarke,	Brit. Med. Journ., Aug. 16, 1887,	Persons expecting examination,	20	3	15	...	...	...	
Leube,	Virchow's Arch., vol. 72,	Healthy soldiers,	119	19	16	Not more than 0 1 per cent.	...	...	After exercise. Before exercise, morning urine 4 per cent. albuminous. Cylinders and blood corpuscles not found.
Fürbringer,	Ztschr. für klin. Med , 1879-80,	Children,	61	7	11.5				
Munn,	Medical Investigations in Life Insurance.	Applicants for life insurance,	630	59	10.6	...	...	...	Tested by boiling.
Kleugden,	Arch. für Psych., 1880-81,	Attendants in asylum,	32	14	43.5	8	...	6	
Grainger Stewart,	Brit. Med. Journ., June 11, 1877,	Soldiers,	205	...	37.6				
" "	" " " " "	Civilians,	74	...	10.8				
" "	" " " " "	Children,	40	...	17.5				
" "	" " " " "	Workhouse inmates aged about 60,	40	...	67.5				
Van Noorden,	Deutsch. Arch. klin Med.,1885-86,	Soldiers,	53	...	8–10.5	...	...	...	Mucous threads.
Capitan,	Inaug. Thèse, Paris, 1883,	Soldiers,	98	44	45				
"	" " " "	Children,	97	86	89				
De la Celle,	" " " "	Infantry,	120	92	77	...	22	...	
" "	" " " "	Cuirassiers exercising,	88	70	79.5	1	17	...	
" "	" " " "	Soldiers returning from review,	111	100	90	4	...	...	
" "	" " " "	Cuirassiers just vaccinated,	31	31	100	...	10	...	De la Celle In 701 persons in health, 17 give more than 30 cgr. per litre; 152, 12 to 25 cgr. per litre.
" "	" " " "	Students,	50	46	92	...	29	...	
" "	" " " "	Children, 6 to 15,	61	49	80	...	9	...	
" "	" " " "	Children, 6 to 15,	81	62	76.5	...	5	...	
" "	" " " "	Infantry (cold bath)	53	53	100	10	17	...	
" "	" " " "	Soldiers after food,	94	74	79	...	9	...	
Leroux,	Revue de Méd., Paris, 1883,	Children,	330	19	5				
Roberts,	Urinary and Renal Diseases,	Candidates for life insurance,	31	29	...	0	...	...	No albumen by nitric acid or heat. Acid brine (11), picric acid (14), tungstate (28), mercuric iodide (29). Author suspects mucin.

Note.—The writer hoped to be able to include the extensive statistics of Dr. Shepherd, of Hartford, but they are not yet published

TABLE II.—ALBUMINURIA OF ADOLESCENTS, CYCLIC AND ACCIDENTAL ALBUMINURIA.

Author.	Reference.	Class of cases.	Number examined.	Casts found.	Remarks.
Moxon,	Guy's Hospital Reports, xxiii.	Young man,	...	Very few,	Albumen of adolescence; later renal calculus.
Dukes,	Brit. Med. Journ., Nov. 12, 1881,	Young men,	...	.....	Some transient; some recover after years, large proportion first [stage Bright's disease.
Johnson,	Brit. Med. Journ., Dec. 6, 1873,	Young men,	...	None,	After bathing.
Vogel,	Virchow's Handbuch, vi.	.....	...	None,	Cases observed by the year. No symptoms. May be slight organic changes.
Pavy,	Lancet, Oct. 17, 1885,	Men mostly young,	...	None,	Cyclic and intermittent. Oxalate of lime. No bad health.
Pavy,	Brit. Med. Journ., i. 271, 1876,	Weston (the pedestrian),	...	Abundance, hyaline and granul.	During walk. In 1888 in active business.
Ultzmann,	Wiener med. Presse, Jan. 23, 1870,	Physicians,	8	None,	Urine clear, dark, acid, 1025 to 1035; nothing else abnormal.
Edlefsen,	Mitth. Ver. Schl. Holst. Aertz, 1866 to 1881,	.....	3	Not mentioned; a few times.	Albumen after exertion. Supposes no renal disease (excludes doubtful opalescence).
Fürbringer,	Zeitschr. klin. Med., 1879–80	Officers, young physc'ns, blooming young people,	...	Small cylinders,	Officers after exertion, urine scanty, saturated, containing uric acid gravel.
Marcacci,	L'Imparziale, May 12, 1878,	Young physician (self),	...	None,	Albumen absent from night urine; present in day; increased by exercise [by rest.
Rooke,	Brit. Med. Journ., Oct. 19, 1878,	Young woman, 14 to 16,	...	.....	Intermittent; none in morning; always at night; disappeared
Kinnicutt,	Arch. of Med., 1882,	Young persons,	...	None,	Transient; some associated with high specific gravity; uric acid, oxalate of lime; arterial tension low.
Simmons,	Sacramento Med. Journ., April, 1887,	Young physician,	...	None,	Cyclic; none in early morning; concentrated, four years' standing; now absent; oxalate of lime; uric acid.
Canfield,	Phila. Med. News, 1887	Man, aged 32,	...	None,	Cyclic; none in early morning; maximum at 8 A. M., and in evening; well.
Klemperer,	Deutsch. Arch. f. klin. Med., xii. (as quoted by Canfield),	Student,	...	.....	Cyclic; maxima very nearly as above. [also.
Stokes,	Lancet, March 10, 1888,	.....	...	None,	Four years; lithiasis from beer: when lithiasis abates albumen
Stokes,	Lancet, March 10, 1888,	Athlete,	...	.....	Albumen twenty years; now prostatic and cystic trouble.
Ralfe,	Lancet, ii., 1886,	Man,	...	None,	Albumen six years; urine pale, abundant, density high, much pigment
Fergusson,	Brit. Med. Journ., ii., 1878,	Youth of 17,	...	Not mentioned,	Albumen five years; puffiness of eyelids.
Rendall,	Thèse de Paris, 1883,	.....	...	Very rarely,	Albuminuria from digestion (hematogenous).
Engel,	N. Y. Med. Rec., Oct. 1882,	Several young men,	...	None in those in which mention'd	Occasional albuminuria after unusually heavy meal.
Engel,	N. Y. Med. Rec., Oct. 1882,	Two young men,	...	Present,	Later symptoms of renal disease more marked.
Merklen,	Med. Press and Circular, p. 7, 1885.	Young man, 16 (symptoms acute),	...	None,	Rather weakly; albumen from noon to midnight; more in night.
Fischl,	Deutsch. Arch. klin. Med., xxix. 217,	Patients mostly with gastric or hepatic colic, jaundice,	10	None,	Albumen temporary.
Fischl,	Deutsch. Arch. klin. Med., xxix. 217,	Metrorrhagia, collapse,	4	Few,	Albumen temporary.
Bull,	Nordiskt Archiv,	Physician, aged 27,	...	.....	Continued at least two years.
Kinnier,	N. Y. Med. Record, June 19, 1886,	Young men,	3	None,	Albumen during middle of day.
Coupland,	Lancet, July 10, 1886,	Girl of 16,	...	None,	No albumen in morning; later, irregularly present; no crystals of uric acid or oxalate.

Table III.—Albuminuria among the Sick.

Author.	Reference.	Class of cases.	Number examine	Albumen found.	Per cent.
Saundby,	Brit. Med. Journ., May 10, 1879,	Out-patients,	145	105	...
Stewart,	Brit. Med. Journ., Oct. 15, 1887,	Private patients,	150	36	...
Stewart,	" " " "	Indoor infirmary,	150	74	...
Stewart,	" " " "	Outdoor infirmary,	100	19	..
Stewart,	" " " "	Sick children,	50	7	...
Stewart,	" " " "	Fever hospital,	50	33	...
Stewart,	" " " "	Maternity,	25	18	...
Kleugden,	Arch. f Psych., 1880-81,	Male epileptics,	33	13	...
Kleugden,	" " "	Insane,	60	11	...
Capitan,	Inaug. Thèse,	Various diseases, mostly acute,	?	Large number	...
Van Noorden,	Deutsch. Arch. f. klin. Med.	Surgical and ophthalmic cases,	112	...	31.3

Table IV.—Opinions.

Gull,	Guy's Hospital Reports, xxiii. (Reported by Moxon)	Albuminuria as common as spermatorrhœa.
Johnson,	Brit. Med. Journ., Dec. 13, 1879.	Latent albuminuria means serious trouble.
Teissier,	Lyon Méd., 1887.	Subjects of cyclic albuminuria; probably all destined to become gouty.
De Haviland Hall,	Lancet, Feb. 18, 1888.	Albuminurics should not be assured.
Pye-Smith,	Guy's Hospital Reports, vol xix.	No person who has albuminous urine (by usual tests) can be considered eligible for life insurance.