Stewart (D. D.)

# A SERIOUS FALLACY ATTENDING THE EMPLOYMENT OF CERTAIN DELICATE TESTS FOR THE DETECTION OF SERUM-ALBUMIN IN THE URINE, ESPECIALLY THE TRICHLOR-ACETIC ACID TEST.

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# A SERIOUS FALLACY ATTENDING THE EMPLOYMENT OF CERTAIN DELICATE TESTS FOR THE DETECTION OF SERUM-ALBUMIN IN THE URINE, ESPECIALLY THE TRICHLOR-ACETIC ACID TEST.[1]

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THERE is no point in medicine about which there is more universal disagreement and misapprehension than that relating to the absolute and relative value of recently introduced delicate tests for albumin in the urine. Certain it is that in the hands of any save those fully conscious of the many fallacies attending the use of these tests, and with disbelief in the existence of a normal albumina minima, it is far better to depend upon the less misleading, if also less delicate, and more practical time-honored methods—those by boiling[2] and by the use of nitric acid. Although certain complications attend the use of these, they are more easily overcome and are less likely to mislead than those surrounding such

[1] Read as part of a discussion before the Society for Clinical Research, March 27, 1894.

[2] Applied to the upper stratum of clear acid urine in a test-tube, to be viewed with a light from above and a dark background for comparison with the unboiled stratum.

tests as trichloracetic acid, the reagents of Tanret, Sebelein, and Millard, glacial phosphoric and picric acids. Sources of error are so numerous with most of the latter tests that our best urinologists strongly question their practical clinical utility. Saundby, for instance, remarks[1] that "there are albuminoid bodies in the urine that have no known clinical significance, and these can only embarrass the practitioner who finds them when he is looking for a sign to which he attributes a significance based upon purely empirical foundation." Saundby discards all tests save that by boiling with a drop or two of dilute acetic acid. Many others, among whom is our own distinguished Tyson, hold very similar opinions, and view with small favor the substitution for the heat and the nitric-acid tests the more recent aspirants for favor. The many fallacies attending a reaction from these delicate tests are sufficiently dwelt upon in systematic treatises on urine-testing ; for example, the presence in the urine of albumoses, peptone, drugs previously ingested, such as an alkaloid or a coal-tar derivative, an excess of urates and the like—all may at times confuse.

One source of error but little noticed, to which I wish now to direct especial attention, is that relating to the presence in normal urine of an albuminous body or bodies allied to serum-albumin, the so-called nucleo-albumin, the precise chemic nature of which is unfortunately little understood. Much that has been written in the past regarding the

[1] Bright's Disease, p. 125. Bristol, 1889.

presence normally of traces of serum-albumin in the urine, as ascertained by the employment of most refined tests for its detection, is valueless, because of disregard of the fact of the existence of this substance in most urines in amount sufficient to respond to most of the delicate tests used for serum-albumin, and from which the reactions could not be distinguished. Such observers were either unaware of or disregarded the fact that nucleo-albumin[1] derived from the extra-renal urinary passages might readily have caused the response to the tests employed for the detection of traces of serum-albumin.[2] This substance is normally present in the urine of all in varying amount. The quantity, which is usually infinitesimal, though generally sufficient to react without concentration of urine to certain tests used for the detection of serum-albumin—notably such as the trichloracetic acid, the reagents of Tanret, and also Sebelein—may increase in conditions of irritation of the urinary passages induced by muscular exercise, or by the presence of a urine too acid and irritating (concentrated) to an amount to cause even doubt as to its differentiation by Heller's nitric-acid-contact method, a test regarded as a very certain one for the detection of serum-albumin.[3]

[1] There seems doubt whether or not urinary nucleo-albumin is a single body and identical with mucin. At all events it possesses a remarkable similarity to the nucleo-albumin of the bile, the basis of biliary mucin. Neubauer and Vogel fully discuss these points in their splendid work on the urine.

[2] Posner's researches as to a physiologic albuminuria are faulty in this particular, as are those of Capitan, Chateaubourg, and several others.

[3] Reissner, by estimation, found urinary mucin present to an amount varying from 0.05 to 0.1 per cent., and v. Noorden noted

In the thoroughly healthy, with urine normal as regards nitrogenous ingredients and free from ordinary indications of catarrhal conditions of the urinary passages, it is not unusual to obtain a trace of response from contact for from a few moments to a half-hour with a cold picric-acid solution, and I have found it common to obtain an almost instantaneous fine white ring by the other tests mentioned, the trichloracetic acid and that of Sebelein especially, but also by that of Tanret, and, less often, by that of Millard. Glacial phosphoric acid also reacts after from three to five minutes' contact. The presence of mucin in these same urines, if they be not too rich in salts,[1] may often be readily shown by the use of acetic acid as a precipitant. My own urine almost habitually responds to several of these very delicate tests, such as trichloracetic

as much as 0.6 grm. to a liter of normal urine. (See Neubauer and Vogel, Wiesbaden, 1890.) Kirk, in a most admirable paper on "Urine-testing for Mucin" (*Lancet*, April 26 and May 3, 1890), gives instructive data as to the differentiation of mucin from serum-albumin. Kirk regards urinary mucin as a substance occupying an intermediate place between other forms of mucin and albumin. The first-mentioned authorities, than which there are no more exact, do not look upon this body as true mucin, but call it nucleo-albumin, or *mucinähnliche Substanz*, as do, indeed, also Hammersten (Physiological Chemistry) and others of our best authorities.

[1] The urinary salts maintain mucin in solution. Concentrated urines, *i. e.*, those rich in salts, will not yield mucin to a small amount of acid, save by special treatment. In diluted or in dialyzed urines, or in those naturally poor in saline ingredients, the presence of mucin may be usually detected by the addition of a small amount of dilute acetic acid, and allowing to stand, care being taken not to add too much after dialysis. Some urines, from presumably normal individuals, cloud markedly almost instantly on the addition of an excess of the acid.

acid, to the reagents of Tanret and of Sebelein, and often to picric acid and to Millard's reagent, though it is absolutely normal as regards urea and freedom from casts. This response is probably due to the presence of mucin, perhaps derived from the bladder, which has a tendency toward irritability. I have often treated specimens with acetic acid after the manner detailed in the papers on "Non-albuminuric Nephritis," and have then always failed to obtain response with the treated specimen on subsequent testing with picric-acid. The test of Tanret, and the trichloracetic acid test, then, also, occasionally tried for experiment, would still not unfrequently give a response, but not to any extent the sharp reaction previously obtained.

I have in the past so repeatedly obtained a reaction to these tests in urines which I had with good reason regarded as normal that I long ago ceased to place any confidence in a positive response unless first, among other sources of error, the presence of this urinary mucin could be excluded. Unfortunately, this is impossible as regards several, and especially that of trichloracetic acid, that now most in vogue as a delicate test for albumin.[1] This acid, from its

[1] Other of the delicate tests, such as those of Tanret, Sebelein, etc., containing free acetic acid, and also a mercurial salt, or tannin, are also unreliable, from their readiness to respond to traces of mucin, not at all in the dusty contact-haze that many advocating the use of these tests teach, but often as a sharply-defined ring, the appearance of which cannot be distinguished from serum-albumin. The best of the refined tests are the plain saturated solution of picric acid and Millard's solution. Although acetic acid enters into the composition of the latter, it is partly as an acetate, the action of which, as a precipitant of mucin, is slight. Yet this solution, too, reacts with mucin, as its originator acknowledged.

possessing properties similar to acetic acid, of which it is a substitution-derivative, I have become convinced is an absolutely uncertain and even dangerous reagent in this particular, so likely is it to mislead. As is well known to those accustomed to urinary analysis, it is an impossibility to separate traces of a mucinous substance from the urine even by the use of acetic acid with prolonged contact, though the latter be added in sufficient amount to overcome the neutralizing effects of the urinary salts;[1] and even should all be precipitated by long contact, which is doubtful, if it be present in any amount, as is so common with specimens of the diurnal urine, its complete separation on the filter is impossible. Insoluble substances, such as chalk, magnesia, barium sulphate, added to assist its precipitation, will also carry down traces of serum-albumin if naturally present or artificially added. I have, however, found again and again that with urines which I was convinced contained no serum-albumin, but which responded to picric acid and more markedly to the trichloracetic-acid contact-test, sufficient mucin could be removed with acetic acid to prevent further trace of response to the former, but not to the latter.

It is for these reasons that, though I have for the past eight years employed the unacidulated picric-acid test as a routine method, first overlaying the suspected urine with it before proceeding to the application of the heat or of other tests, I have placed far more confidence in a negative than in a positive result obtained by it. A reaction not

[1] One-tenth bulk of glacial, or its proportion of 25 per cent. acid.

occurring within a few moments, the employment of other tests was, naturally, regarded as unnecessary. A slight response appearing within this time, and not attributable to the other sources of error before mentioned, I had, until recently, attributed to traces of serum-albumin, and was inclined to believe in the existence of a normal slight albuminuria. More lately, however, experiments have convinced me that this response is due to the presence in the urine of a mucinous body.

To ascertain the frequency of reaction to the more delicate tests for albumin, of urines from normal individuals, those so far as was known that were without indications of renal disease, I recently examined specimens from 105 young men, all of whom save one regarded themselves in good health at the time, and but three of whom were known to be taking drugs of any sort. It was certain that none was a gonorrheal subject. The specimens were collected for me by my friend Dr. Wolff, in the course of laboratory instruction, and in a manner that admitted of no deception being practised by the donors. The urethra was first flushed with urine which was discarded, so that mucus from this situation might be excluded.

The specimens were divided into two sets, one of 52, the other of 53. All of the 105 urines were those of the day. All save three of the first series were voided about three hours after breakfast, and as with the second series, which specimens were passed about four hours succeeding dinner, after the donors had been standing at laboratory work at least three-quarters of an hour. All of these speci-

mens, therefore, represented the diurnal urine and food urine, in which the erect posture and evidences of muscular fatigue would aggravate an albuminuria if already present, and would likewise tend to induce an increase of mucinous substance in the urine such as would be similarly present in a mixed twenty-four-hour specimen from the same individuals.[1]

In the first series (52) three of the commonly-used delicate tests were employed—saturated solution of plain picric acid, trichloracetic acid, and glacial (meta)phosphoric acid.[2] In the second series (53), trichloracetic acid was the only one of the three tests employed.

For convenience, positive or negative response to the tests employed was noted at the end of three periods, and marked as occurring within these: ten seconds (which in the application of the contact-tests by picric acid and by trichloracetic acid was practically instantaneous), one minute, and five minutes.

In the first series the trichloracetic acid used was

[1] This was not intentional. Morning specimens would have been preferred if obtainable without chance of deception. It is, however, of value, for the reasons stated.

[2] Picric acid was chosen as the test I most frequently employ; trichloracetic acid as one now coming much into vogue, and with which I had been disappointed in the past, as with Tanret's and Sebelein's reagents, from the too extreme delicacy misleading, as already stated. Millard's was not now employed, as I was satisfied from some comparative tests with it in the past that it corresponded very nearly in point of delicacy and exactness with picric acid. Tanret's solution was not used, as experiments had shown that it is a less delicate reagent for the detection of mucin or serum-albumin than trichloracetic acid. Metaphosphoric acid was used, as doubt existed as to its relative delicacy with the others employed.

a specimen of Merck's C. P.,[1] which, originally crystalline, had liquefied after nearly two years' standing on the laboratory shelf, through the slow absorption of moisture from the air, the glass stopper of the bottle not having hermetically closed the neck. No water whatever had been added. The specimen, therefore, represented a highly-concentrated solution. I had previously found that the delicacy of reaction to the acid depended very greatly upon the degree of concentration of the solution. A solution which at one time I regarded as quite saturated, to which water had been added and no heat employed to insure solution, was noticed to react with no more delicacy than did Millard's solution or metaphosphoric acid. This fact is of importance, and probably explains the variation in result obtained by different experimenters with the acid.

In the second set of examinations, a freshly-obtained specimen[2] (labelled Kahlbaum, Berlin) of the crystalline acid was used, which was first liquefied in a water-bath and fluidity maintained by the addition of a small quantity of a concentrated, but not completely saturated, solution of the acid (Merck's C. P.). There was only sufficient of the first solution remaining for one comparative test with the last. By it the latter solution was found to not quite equal the former in

[1] Given me by Dr. Leffmann. He had opened the bottle occasionally to remove a few crystals, using them and not a solution in his testing with it.

[2] From the Chemical Laboratory of the Jefferson Medical College, through Dr. Lawrence Wolff.

delicacy of response, the reaction appearing somewhat later, and being less decided.

An unacidulated, saturated solution of picric acid was used. This and the trichloracetic acid were applied by the contact-method, viewed with a dark background by a light from above. The technique in examinations of this sort is of the greatest importance. It should be stated that as a background a piece of black cloth was always used. Most of the examinations were made at night, by aid of gaslight. When by day, illumination by sunlight was, of course, avoided. Inclination of the *upper part* of the tube toward one, with proper shading often demonstrated with the trichloracetic acid, a sharp, white, undoubted, though fine ring, that otherwise would have been overlooked in the contact-time mentioned. Tubes of three-eighths-inch diameter were used in applying the trichloracetic acid, the cost of the acid not permitting too large a quantity to be employed in each test. The urine was first added to the tube, and the acid subsequently deposited at the bottom with a pipet drawn out to a very capillary extremity.

In testing with picric acid the urine was overlaid. With the metaphosphoric acid, a small, thoroughly clean and clear portion of a cylinder was dropped into the urine, and the time of development of the slightest cloud about it noted within the time-limits stated. All the specimens tested were undecomposed. A small quantity of dilute acetic acid was added to all that were not decidedly acid. Any specimens that were at all cloudy were

filtered.[1] With but three exceptions all of the 105 specimens gave an undoubted response[2] to the trichloracetic-acid solutions, prepared as indicated, in the shape of a contact-ring within the five-minute limit. This reaction varied from a very narrow, always white, ring in the least marked to one of many lines in thickness in the most decided. Fifty nine responded within ten seconds; of these, 22 reacted very markedly instantaneously;[3] 10 others by a sharp, though very thin white ring, becoming, as with nearly all, broader with longer contact. The remainder of the 59 reacted at first slightly, though undoubtedly the line became sharper with from one to five minutes' contact; 34 of the remaining responded within one minute, and of these, 13 only reacted slightly within the minute, becoming, however, except in two instances, more marked at the expiration of five minutes.

[1] Swedish filtering-paper was used. This is important, as the French gray paper contains, and will yield to the filtrate, sufficient vegetable albumin to cause response to the finer tests, as Millard pointed out.

[2] As regards comparative time of response, it is interesting that with the first series (of 52) the reaction appeared within ten seconds in 41, of which 6 were markedly serum-albuminous; while in the second set tested (53), with a different solution of trichloracetic acid, as already detailed, but 18 reacted within the ten seconds, of which 14 were also markedly albuminous. Of the first series, 2 only of the 52 failed to respond within the one-minute limit. These 2, however, reacted within the five minutes. Of course, this wide dissimilarity in time of reaction may be due to differences in the character of the urines, instead of in the degree of concentration of the two test-solutions.

[3] In 20 of these the reaction was so instantaneous and very decided as to leave no doubt as to the presence of serum-albumin in some amount, afterward confirmed by other tests.

Nine only of the 102 reacting showed no response at the end of a minute, the precipitate forming within the five minute limit.

The three that gave no response save a trace of haze within the five minutes—the only ones of the 105 that did not unquestionably react—showed a pronounced contact-cloud of from three to four lines in depth within a few seconds after placing the tubes in hot water. The influence of heat, applied in all instances and most satisfactorily by placing the tube in a vessel containing water at the boiling-point, was found without exception to render the previously-obtained reaction more decided, developing in certain of them a contact-cloud instantly, which was almost a minute in appearing in a second tube not subjected to heat. So that trichloracetic acid seems a test the delicacy of which is even intensified by the application of heat.

With picric acid, 41 of the 52 tested responded within five minutes; 16 reacted within ten seconds; 7 of these 16 responded very markedly instantly (these were all albuminous). Four others of the 16 gave a sharp, but very narrow ring. The reaction in the remainder of the 16 (5) was a mere contact-haze, which in 3 deepened into a sharply-defined, though narrow ring, within one minute, the remaining 2 within five minutes. Thirteen of the 52 that did not respond in ten seconds reacted within the minute; of which 13, 2 showed a hazy contact-ring only, not increasing at the expiration of five minutes. Six others displayed a fine, sharply defined, though not broad ring, which had considerably increased at the expiration of five minutes.

In the remainder of these the ring was better defined, though not broad. Of the 23 remaining of the 52 which gave no response at the end of one minute, 11 showed no trace of haze within five minutes, while the 12 reacted within this time. In 6 of these 12 the reaction amounted to a haze only; the remaining 6 gave a sharply-defined though narrow ring. Of the 11 giving no reaction to picric acid at the end of five minutes, all gave a precipitate, as has been stated, with trichloracetic acid—5 within one minute, 4 within five minutes, the remainder within ten seconds. In this same 11, metaphosphoric acid gave absolutely no reaction in 6; in the others, the response with the glacial acid was very slight or questionable (at five-minute contact).

With metaphosphoric acid, 10 of the 52 tested failed to show signs of cloud in five minutes, and 36 in one minute; 4 only responded at the end of a few seconds, and these were of those showing albumin by nitric acid. Twelve reacted within one minute that did not within ten seconds; of these, 7 responded very slightly and 5 markedly. Of the 5, 2 gave the $HNO_3$ contact-reaction. Ten of the 36 that failed to show a haze within one minute also gave no response within the five minutes. Of the remaining 26, 23 had reacted slightly at the end of five minutes; the other 3 had responded markedly.

The influence of heat on the reaction obtained with trichloracetic acid and with picric acid, applied in all cases after the occurrence of the response noted, showed that the precipitate was not due to urates or to a proteose or peptone. In several of

these urines, other than those responding to coarser tests, there was a decided mucous precipitate, though the urines filtered perfectly clear. The action of acetic acid was tried on only one of these—this specimen was voided about four hours after dinner by a man with whom I am thrown much in contact and whom I know to be in the best of physical condition. This urine gave a slight ten-second response to trichloracetic acid; at the end of one minute the faint, white ring had become decided. A haze was shown in ten seconds' contact with picric acid. This, at the end of a minute, had also become a sharp ring. With metaphosphoric acid the reaction was but slight at the end of five minutes. With the nitric acid contact-test, at a distance of about four lines above the meeting-line of acid and urine, there occurred a cloud three or four lines in depth, unaffected by heat.[1] At the junction of the two fluids a marked chromogen ring was so decided as to obscure any slight reaction which might then be produced by traces of albumin; 5 c.c. of 25 per cent. glacial acetic acid added to 15 c.c. of this cold urine filtered, which was perfectly free from a trace of cloud, gave after standing a few moments a very marked smoky haze, unaffected by gentle heat, indicating a decidedly mucinous condition of the urine. It was impossible to separate by repeated filtration this precipitate, so that no further tests were proceeded with.

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[1] This reaction, so often met with in both albuminous and non-albuminous urines, has been shown by Kirk to be due to mucin (*Lancet*, May 3, 1890), as was first suggested by Roberts (*Medical Chronicle*, October, 1884, p. 1.)

Though this interrogation was not undertaken for the purpose of ascertaining the frequency of occurrence of so-called "physiologic" albuminuria, it is of interest here to note that of 105 urines from adolescents and young men, all save one of whom regarded themselves as in very good health, 20 (19 per cent.) gave an undoubted serum-albumin reaction to nitric acid by the contact-method. The percentage of albumin in these urines, subsequently estimated by Esbach's method in nearly all, lay from one-fourth to one and one-fifth grams to the liter. I have carefully examined, physically,[1] all save one of the 20. No one of the 19 show evidences of renal disease. In nearly all the albuminuria is intermittent, and is probably the result of circulatory disturbances, due to the erect posture and a weak heart. In these albumin is absent from the urine on rising, but present in that after exercise during the day; and pulse-tension, ascertained by the sphygmograph as well as by the finger, is low, in several markedly so.

Excluding these cases of undoubted albuminuria, the results obtained indicate with little question either that, normally, urine contains traces of serum-albumin, or, more probably, that the response to trichloracetic acid and that occurring less frequently to picric and metaphosphoric acid was due

[1] Time has not yet permitted microscopic examination of more than two of these urines. One of these men has a weak heart; he is an overtrained athlete. A second has a mitral systolic, and a third an aortic diastolic murmur. In neither of these two, however, are there other indications of back-working apparent. Compensation seems perfect.

to the presence of a body of nucleo-albuminous (or mucinous) character of extra-renal origin. The results obtained with these 83 urines reacting to trichloracetic acid and not to the coarse tests[1] were so constant and agree so perfectly with those I had obtained in prior examinations of urine from those with presumably healthy kidneys that I have no doubt as to the validity of this inference.

To my mind these results show conclusively that as a practicable *delicate* test[2] for albumin, the much

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[1] The contact nitric-acid test, supplemented by heat, was made with all urines responding in a suspiciously decided manner to trichloracetic acid.

[2] In a note concerning the test, by Reese of Johns Hopkins Hospital (*J. H. H. Bulletin*, February, 1890), it was regarded as one worthy of extended use in clinical work, because of its utility and delicacy. It was narrated that many cases had been encountered the urine of which responded to it (used in saturated solution), and not to control-tests, such as picric acid—that frequent source of error, urinary mucin, or an extra-renal albuminous body, not being regarded in question. In a number of these cases (eleven) granular, epithelial, and hyaline casts were found in the urine, and a subsequent necropsy showed distinct changes in the kidneys. This is of especial interest to me, indicating as it does the frequency of non-albuminuric nephritis; for in this category these cases must certainly be placed. The so-general response of the urine of the healthy to this test, and often to picric acid as I have shown, indicates beyond doubt in my mind that in the cases referred to by Dr. Reese, the trichloracetic-acid reaction was but a coincidence, obtainable markedly in as many consecutive healthy subjects.

[Since writing the foregoing I have learned that trichloracetic acid has ceased to be regarded with its former favor in this hospital, especially by Prof. Kelly, for the reason stated—its impracticable delicacy. Prof. Osler has recently written me that he is "rapidly coming to the conclusion that about one-half of the chronic degenerative changes in the kidneys are unaccompanied by albumin in the urine. The word comes over so constantly from the lab-

vaunted trichloracetic acid is of little value. Responding as it does so universally, its utility is much less than that of metaphosphoric and especially that of picric acid, the last of which not only furnishes useful negative information, but also, from its less refined delicacy, positive results of value, excluding reactions to a few drugs when present in the urine,[1] a precipitate from urates, the proteoses or peptone,[2] and mucin or allied bodies, all readily differentiated, except the latter if in excess.[3]

With trichloracetic acid, unless the response be frank and outspoken—*i. e.*, unquestionable to tests less delicate but reliable, such as ebullition with the addition of a few drops of dilute acetic acid, than which there is none less likely to err; those tests, in other words, that do not so readily react to urinary mucin—the nature of the result must remain in doubt and cannot be utilized to account for the symptoms if nephritis be suspected, as it is, perhaps, more than likely not due to serum-albumin.

From the results here obtained and from those I have before published, with those of many other observers, notably Kirk, and those who preceded

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oratory '*degenerative changes in the kidneys*' in patients whose urine showed no especial alterations," Prof. Osler has begun to think that " there are no normal kidneys in hospital patients above forty years of age."]

[1] Which, if in no other way, may be obviated by the withdrawal of medicines for the time.

[2] None of which is often obtained, but all of which may be recognized by placing the tube for a short time in hot water, the heat of which will immediately greatly diminish or dissipate the response.

[3] By removal with acetic acid in the manner I shall detail in a future communication.

him on similar lines, but who, unlike him, regarded the frequency of response in the healthy to refined tests as indicative of a normal, constant albumina minima, it may be finally concluded that the recognition by such reagents as trichloracetic acid of mere traces in the urine of what the most skeptical regard as albumin, even with symptoms suggestive of renal disturbance, can have little significance, because of the very general frequency of reaction of urines of normal individuals to the same test. If this reaction be due to serum-albumin, its significance is actually *nil*, as it would follow that a normal, slight albuminuria is common. It is, however, more probably, in the vast majority of instances, due to the presence of an albuminuous body of extra-renal origin, a nucleo-albumin, or so-called mucin. In certain other cases—pathologic subjects, with symptoms indicative of a type of chronic nephritis, in which serum-albumin, as ascertained by more reliable tests, is persistently absent from the urine—it may, and probably does, also arise from the epithelium of the tubules of the kidney,[1] due to a faulty metamorphosis of the same producing a renal mucinuria.[2] Its recognition in the latter, in which, for purposes of diagnosis, its differentiation from serum-albumin would be unnecessary, if further differentiation from the common extra-renal mucinuria could be arrived at, as by obtaining urine directly from

[1] See remarks as to the presence of renal mucin in the urine in such cases, in the two papers on non-albuminuric nephritis, in the *Amer. Journ. Med. Sciences*, December, 1893, and THE MEDICAL NEWS, April 14, 1894.

[2] Associated usually with a cylindruria.

ureter or kidney, would be of the highest value. But as the latter is a clinical impossibility, we must fall back upon our only actual reliable aids in the diagnosis of such renal suspects—the microscope and the ureometer—the examination of the measured twenty-four-hour urine for urea and its sediment for casts.

I am greatly indebted to Dr. L. Wolff, and his assistants Drs. Jacob and Strecker, for the trouble taken in obtaining the series of specimens of students' urine for examination; and to Professor H. Leffmann and Dr. G. P. Thomas, for great assistance in the examinations. In all the specimens examined, save some six, all reactions that appeared were carefully noted and timed by one of the latter of these, as well as by myself.

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