UREA RETENTION

A SIMPLE METHOD FOR ITS ESTIMATION BY THE MERCURY COMBINING POWER OF BLOOD

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Simple clinical methods that furnish accurate data are desirable in the study of renal function, particularly for the physician to whom the complicated methods of analyzing the blood are not available. The method reported in this article is of interest as an accurate index to the urea of the blood. The standard determination of blood urea by the urease method is an admirable test but requires very careful technic, certain laboratory facilities and is somewhat time consuming. The method herein reported requires only elementary laboratory knowledge and very simple equipment; only about fifteen minutes are required, and it gives adequate clinical results. It is the estimation of the mercury combining power of deproteinized blood.

NOTES ON THE LITERATURE

Liebig ¹ in 1853 made use of the ability of mercury to combine with nitrogenous products in a method for the determination of urea in urine. In 1921 Friedländer ² reported a titrametric method with mercuric chloride for the determination of urea in urine. In 1922 we ³ demonstrated the quantitative relationship between the urea in saliva and in blood, a finding since corroborated by Schmitz,⁴ Stitt,⁵ Landsberg ⁶ and Viotti.⁷ In 1923 we ⁸ developed a mercury titration method.

¹ From the Division of Medicine, Mayo Clinic.
⁷ Viotti, G.: Sulla possibilità di stabilire la concentrazione in urea del sangue colla misura della concentrazione in urea della saliva, Pathologica ¹⁶: 47-50, 1924.
method for the determination of urea in saliva. We found that mercury combined with other nitrogenous constituents of saliva besides urea, but that because of the preponderant influence of the urea of the saliva on its mercury combining power this could be used as an index to the salivary urea and therefore to the blood urea. We advocated the use of the mercury combining power of saliva, the “salivary urea index,” as an index to urea retention in the body in cases in which blood was not readily available.

The principle, clinical application and accuracy of the salivary urea index as an index to urea retention have been confirmed by several investigators. Calvin and Isaacs\(^9\) reported about 200 determinations on children at the Michael Reese Dispensary, Chicago. Corkill,\(^10\) Fairley\(^11\) and Meyers\(^12\) of Australia and Rockwood and Rockwood,\(^13\) individually report satisfactory results, while Pacetto\(^14\) of the University of Pavia in Italy and Simmel and Künscher\(^15\) of the Medical Polyclinic at Jena also report corroborating results, with certain slight variations in their interpretation of the formula for the salivary urea index. Graham and MacCarty\(^16\) of the University of Alabama confirmed its use with saliva and applied the method successfully to spinal fluid.

There are conditions such as coma or states of dehydration in which blood can be more readily obtained than saliva. Furthermore, the blood presents a more stable medium physiologically, and is less subject to contamination than saliva, so that determinations on blood give more direct evidence of urea retention in the body.

**METHOD FOR DETERMINING THE MERCURY COMBINING POWER**

The method is based on the principle that mercury combines with such products as urea, creatinine and uric acid, when a solution of a mercuric salt is added to a solution containing these nitrogenous products.


\(^10\) Corkill, A. B.: The Estimation of the Salivary Urea as an Index to Renal Prognosis, M. J. Australia 1:236-238 (March 7) 1925.


\(^12\) Meyers, E. S.: Personal communication to the author.

\(^13\) Rockwood, E. W., and Rockwood, P. R.: Laboratory Manual of Physiological Chemistry, ed. 5, Philadelphia, F. A. Davis Company, 1924, pp. 131-132; also personal communication to the authors.


As mercury is added combination continues until the mercury combining power of the solution is satisfied, after which excess mercury appears in the solution. The excess mercury is readily detected by adding a drop of the solution to be tested to a drop of saturated sodium carbonate on a white spot-plate. A dark reddish brown precipitate indicates the presence of excess mercury. The method is here applied to the protein free blood filtrate obtained by the use of trichloracetic acid. The mercury combining power of this filtrate will vary with changes in the concentration of blood urea.

**TECHNIC 17**

The mercury combining power of the blood is determined essentially as in saliva except that the protein in the blood is first precipitated with trichloracetic acid. The precipitation of the protein by the use of acetic acid and heat, or by the tungstic acid method of Folin and Wu, was not satisfactory.

Our method is as follows: 5 cc. of oxalated blood is added drop by drop to 5 cc. of 10 per cent trichloracetic acid in a centrifuge tube. The contents of the tube are thoroughly mixed and centrifugalized for about five minutes. If a centrifuge is not available the mixture may be filtered, although this is less rapid and convenient, and may necessitate the use of more than 5 cc. of blood to obtain 5 cc. of filtrate. Five cubic centimeters of the clear protein free filtrate is then titrated with 5 per cent solution of mercuric chloride. The mercury solution is added from a buret until a test drop of the mixture when added to a drop of saturated sodium carbonate on a porcelain spot-plate gives a reddish brown precipitate which appears within three seconds. It is important to mix the mercuric chloride and filtrate very thoroughly before the test drop is removed. A yellow precipitate may occur before the reddish brown, but the titration must be continued until the precipitate becomes reddish brown promptly within three seconds. A minimum of 1.5 cc. of mercury solution can be added before test drops are removed. As few test drops as possible should be removed.

The mercury combining power of blood is defined as the number of cubic centimeters of 5 per cent solution of mercuric chloride that will combine with 100 cc. of deproteinized blood. If a buret is used, the number of cubic centimeters of 5 per cent solution of mercuric chloride used for the 5 cc. of blood filtrate is multiplied by 20 to obtain the mercury combining power of 100 cc. of blood filtrate. The mercury combining power of 100 cc. of filtrate is then multiplied by 2 to estimate the mercury combining power of 100 cc. of blood, since the blood was diluted by an equal volume of trichloracetic acid to obtain the filtrate.

Therefore, the mercury combining power of 100 cc. of blood equals 40 times the mercury combining power of 5 cc. of blood filtrate.

The titration of the filtrate may be made from a buret or more conveniently in the index tube of the apparatus described for the determination of the salivary index (fig. 1). If the salivary index apparatus is used, the technic is identical to that used for saliva. With the black tipped dropper, one drop of saturated sodium carbonate is placed in each depression of the porcelain plate. The supernatant blood filtrate is poured from the centrifuge tube into the calibrated index tube up to the line marked “5 cc.” Then with the red tipped dropper the 5 per cent solution of mercuric chloride is added until the mark “30” in the index tube is reached. With the cork inserted the tube is inverted about three or four times for thorough mixing. With the small pipet one drop is added to a drop of saturated sodium carbonate on the porcelain plate. The remainder of the contents of the pipet is returned to the index tube. If a brownish red precipitate promptly appears on the porcelain plate, the end point has been reached; but if no color or a canary yellow appears, the titration must be carried further. In this case from 3 to 6 drops of mercuric chloride solution should be added, the solution mixed and tested again with sodium carbonate; one thus adds mercuric chloride into the index tube until the test drop first shows a definite brownish precipitate, developing promptly within three seconds. The amount of fluid used for the test drops removed should be replaced as accurately as possible by water or mercury solution as convenient.

Fig. 1.—Apparatus used to determine the salivary urea index.

19. The precipitate remaining in the centrifuge tube is very adherent but the tubes are readily cleaned by boiling from five to ten minutes.
Fig. 2.—Parallel rise and fall of the urea, nonprotein nitrogen and mercury combining power of the blood in a dog after uremia was induced by feeding urea. Solid dot solid line, blood urea milligrams for each 100 cc. of blood; open dot broken line, mercury combining power—cubic centimeters of mercuric chloride for each 100 cc. of blood; open dot solid line, nonprotein nitrogen milligrams for each 100 cc. of blood.

Fig. 3.—Increase in the mercury combining power, urea, creatinine, and non-protein nitrogen of the blood of a dog after bilateral ureteral ligation. Solid dot solid line, mercury combining power of blood; solid dot broken line, blood urea; open dot solid line, nonprotein nitrogen of blood, and solid dot broken line, blood creatinine.
and when this replacement is made the number of cubic centimeters of mercury solution used for 100 cc. of filtrate may be read directly from the index tube. To estimate the mercury combining power of blood this figure must be multiplied by 2, as the mercury combining power of blood equals twice the mercury combining power of filtrate because of the previously mentioned dilution of blood by trichloracetic acid.

THE CLINICAL SIGNIFICANCE OF THE MERCURY COMBINING POWER OF BLOOD

The mercury combining power of the blood is an accurate index of the retention of nitrogen and especially of urea in the blood. This is illustrated experimentally by the changes observed when chemical uremia is induced in a dog by giving 15 Gm. of urea through a stomach tube (fig. 2). There was a parallel rise and fall of the values of the blood urea determined by the urease method, the mercury combining power of the blood and the total nonprotein nitrogen. It will also be noted that in spite of the rapid fluctuations in these values, an almost constant difference of 60 points between the values for the blood urea in terms of milligrams for each 100 cc. and the values for the mercury combining power of blood was maintained throughout.

Estimations of the blood urea by means of the urease method, the total nonprotein nitrogen and the creatinine, and the mercury combining power of the blood were made in a dog after bilateral ureteral ligation (fig. 3). A resultant rise in all values occurred. Again will be noted (except for the last very high value) the almost constant difference between the mercury combining power of the blood and the value for the blood urea, the former being 60 points higher.

In normal persons and patients with retention of urea a proportional correlation between the mercury combining power of the blood filtrate and the blood urea (by the urease method) likewise was found over a large range of blood urea values from 10 to 560 mg. for each 100 cc. of blood (fig. 4).

It will be seen that the mercury combining power of the filtrate rises in direct agreement with the rise of the blood urea with but slight occasional deviation. It will also be seen that as the blood urea theoretically reaches zero, the blood filtrate will theoretically still take up 30 cc. of 5 per cent solution of mercuric chloride. Since the mercury combining power of blood equals twice the mercury combining power of filtrate, the mercury combining power of blood without any urea in it would be 60 cc., the constant difference noted in the preceding figures. In patients with nephritis and retention of nitrogen, urea is the chief retained product. Other substances that combine with mercury, such
as amino-acids, uric acid and creatinine, either are not increased in nephritis or the increase is relatively unimportant from the standpoint of the mercury combining power. The linear proportionality between the blood urea and the mercury combining power of blood filtrate demonstrated on the charts is striking. Apparently the amount of mercury combined with substances other than urea is a constant (60 cc.) and further variations depend almost entirely on the urea content of the blood. It is obvious, therefore, that the mercury combining power of deproteinized blood can be used in such cases as a rapid clinical method for the estimation of the blood urea. The latter may be calculated by means of the formula: probable blood urea (in milligrams for each

\[
\text{probable blood urea} \left(\text{in milligrams for each 100 cc.}\right) = 2 \times \text{mercury combining power of filtrate} - 60.
\]

Since the mercury combining power of blood equals twice the mercury combining power of filtrate, probable blood urea (in milligrams for each 100 cc.) equals twice the mercury combining power of filtrate minus 60.

Example.—If 5 cc. of blood filtrate requires 4 cc. of 5 per cent solution of mercuric chloride to titrate to the end point, the mercury combining power of 100 cc. of filtrate would therefore be 20 times 4, or 80. The mercury combining power of 100 cc. of blood would be 2 times 80, or 160, and the probable blood urea would be 160 minus 60, or 100 mg. for each 100 cc.

Figure 5 shows in a different way the extent of variation between the actual blood urea determined by the urease method and the blood urea calculated from the mercury combining power by the formula. The estimations made on patients with leukemia or polycythemia are omitted from figures 4 and 5 and will be discussed separately.

![Graph showing comparison of blood urea determined by urease method and calculated from mercury combining power.](https://jamanetwork.com/)

Fig. 5.—Comparison of values for the blood urea calculated from the mercury combining power with those actually determined by the urease method. If exact proportionality existed the dots would all be on the line. Values for urea by the urease method are plotted on the abscissa, those calculated from the mercury combining power on the ordinate.

Variations.—It will be noted that over the wide range of values determined there are a few variations from theoretical values. The number and degree of these deviations are within the limits of acceptable
clinical and laboratory methods. These variations must occur because, while urea is the substance chiefly responsible for the variations in the mercury combining power of the blood above the constant of 60 cc., it is not the only substance that combines with mercury. Variations in the others may slightly affect the value of the constant 60 and therefore the calculation of the blood urea. However, for all practical purposes such variations in the constant may be ignored and the foregoing formula considered correct. This is shown by a comparison of 250 estimations of the calculated urea with the urea values directly determined by the urease method.

In 76 per cent the calculated value was equal to or within 5 mg. of the urea determined by the urease method. In 20 per cent the difference was from 6 to 10 mg.; and in 4 per cent the difference was more than 10 mg. The 4 per cent may be considered an inaccuracy of the method, but in no instance did it lead to a clinical error. That is, in no instance were the differences sufficient to give an erroneous clinical impression.

The mercury combining power may also be used as a guide to changes in the total nonprotein nitrogen but, in general, we have found a much closer relation between the urea and the mercury combining power of blood than between the total nonprotein nitrogen and the mercury combining power of blood.

THE MERCURY COMBINING POWER OF PLASMA AND SERUM

The urea content of whole blood, plasma and serum is generally considered to be substantially identical, especially in normal persons.\textsuperscript{21} Plass \textsuperscript{22} and Madsen \textsuperscript{23} have recently pointed out that this constancy of distribution of urea is not maintained in certain pathologic states, particularly when there are rapid fluctuations in the nitrogen content of the blood. We have occasionally observed a discrepancy between the urea of whole blood and that of plasma or serum not only in abnormal but normal states (table 1).

The mercury combining powers of serum and plasma are about the same, though lower than the mercury combining power of whole blood. In normal persons the mercury combining power of plasma or serum is apparently between 60 and 90 as compared to the mercury combining power of whole blood, which is normally between 70 and 100. In case of nitrogen retention the mercury combining power of plasma and


\textsuperscript{22} Plass, E. D.: Variations in the Distribution of the Nonprotein Nitrogenous Constituents of Whole Blood and Plasma During Acute Retention and Elimination, J. Biol. Chem. \textbf{56}:17-29 (May) 1923.

\textsuperscript{23} Madsen, St. Tschudi: Researches on the Distribution of RN (Nonprotein Nitrogen) and Urea in the Body, Acta med. Scandinav. \textbf{6-7}:318-326, 1923-1924.
serum is increased proportionately to the urea content, and the urea content may be approximated from the mercury combining power by the subtraction of a constant 50 instead of the figure 60 given in the formula for the estimation of the blood urea from the mercury combining power of whole blood; for example, probable plasma (or serum) urea (in milligrams for each 100 cc.) equals mercury combining power of plasma (or serum) minus 50.24

The constant may perhaps be used as an index to the amount of the substances present in the trichloracetic acid filtrate which combine with mercuric chloride but which do not change appreciably in any condition.

The table below shows the mercury combining power of whole blood, plasma, serum, and corpuscles in normal and nephritic states.

<table>
<thead>
<tr>
<th>Whole Blood</th>
<th>Plasma</th>
<th>Serum</th>
<th>Corpuscles</th>
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</thead>
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<tr>
<td>Urea</td>
<td>from Combining Power</td>
<td>Urea</td>
<td>Actual</td>
</tr>
<tr>
<td>92</td>
<td>32</td>
<td>33</td>
<td>41.6</td>
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<tr>
<td>104</td>
<td>106</td>
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<td>26</td>
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<td>104</td>
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<tr>
<td>144</td>
<td>88</td>
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<tr>
<td>344</td>
<td>284</td>
<td>273</td>
<td>360</td>
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</table>

Observed (except those to be noted further on). The lower constant observed in the estimation of plasma (or serum) urea from the mercury combining power of the plasma (or serum) likewise suggests that these unknown substances occur in greater quantity in the corpuscles. Changes in the unknown substances are apparently of minor importance, except those to be noted presently, and for routine clinical use we have found the analysis of whole blood more convenient than that of plasma or serum.

24. The formula was based on sixty-seven cases; a few illustrative comparisons are given.
THE MERCURY COMBINING POWER IN LEUKEMIA AND POLYCYTHEMIA

The urea nitrogen of the blood is normally about 50 per cent of the total nonprotein nitrogen, although this ratio may vary considerably. In certain states, leukemia, polycythemia and acute yellow atrophy of the liver, and certain types of the eclampsia of pregnancy, it has been observed that there may be a profound alteration of this ratio, and the blood urea nitrogen may fall to much smaller proportions than 50 per cent of the total nonprotein nitrogen. In four cases of lymphatic and two cases of myelogenous leukemia and in five cases of polycythemia which we have studied, a normal or slightly increased concentration of urea was often encountered in the presence of a distinctly increased total nonprotein nitrogen. This increase of the total nonprotein nitrogen may be explained in part on the basis of an increase in amino-acids which we know are increased in leukemia and polycythemia, but this increase does not serve to account for the total increase in the rest nitrogen. Analyses of the whole blood, serum, plasma and corpuscles were made in the cases of leukemia and polycythemia (table 2). It was noted that the formula for the estimation of the blood urea from the mercury combining power of the blood could not be correctly used (columns 6 and 7, table 2). When the urea was calculated (column 6, table 2) from the mercury combining power of blood in these cases, it gave much higher values than when it was determined by the urease method (column 7, table 2). Calculations of the probable plasma or serum urea from the mercury combining power of plasma or serum gave values comparable to those actually determined. In two cases the estimation of the blood urea from the salivary index gave figures comparable to those found in the actual determination of blood urea.


## Table 2.—Analysis of Blood and Saliva in Leukemia and Polycythemia

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Leukocytes</th>
<th>Erythrocytes</th>
<th>Hemoglobin, per Cent</th>
<th>Mercury Combining Power</th>
<th>Urea</th>
<th>Calculation from Combination Power</th>
<th>Actual Determination</th>
<th>Nonprotein Nitrogen</th>
<th>Amino-Acids</th>
<th>Mercury Combining Power</th>
<th>Urea</th>
<th>Calculation from Combination Power</th>
<th>Actual Determination</th>
<th>Nonprotein Nitrogen</th>
<th>Urea</th>
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<th>Urea</th>
<th>Calculation from Combination Power</th>
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<th>Nonprotein Nitrogen</th>
<th>Urea</th>
<th>Amino-Acids</th>
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<td>110</td>
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<td>1.0</td>
<td>1.0</td>
<td>0.7</td>
<td>3.0</td>
<td>2.0</td>
<td>7.1</td>
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<td>1.0</td>
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* By the Hayden scale.

† Diagnosis made on clinical syndrome.
It is therefore apparent that, in the presence of abnormal numbers of corpuscles, either red or white, as in polycythemia and leukemia, the trichloracetic acid filtrate contains substances that combine with larger amounts of mercury than normal. When these disturbing elements are eliminated by using plasma, serum or saliva, the mercury combining power may be used to estimate the urea. Analysis of the cells themselves suggests that the mercury combining power of leukocytes is greater than that of erythrocytes. The total nonprotein nitrogen is also higher than the blood urea values would lead one to expect. This is due partly to an increase in amino-acids, but this increase alone is not sufficient explanation.

Many nitrogenous substances in the blood (amino-acids, polypeptides, proteoses, thiasine,\textsuperscript{29} creatine, and so forth) normally occur wholly or in greatest concentration within the cells and are recognized as responsible for the increased rest-nitrogen of the cells compared to that of the plasma. The increase in the mercury combining power of the blood in leukemia and polycythemia is apparently due to the larger proportion of cells, white or red, in such blood. Tables 1 and 2 show that in polycythemia there was but little difference between the mercury combining power of the erythrocytes and that of normal erythrocytes.

**THE MERCURY COMBINING POWER OF STANDARD SOLUTIONS OF NORMAL NITROGENOUS CONSTITUENTS OF BLOOD**

Determinations of the mercury combining power of some standard solutions of the known constituents of the blood show that these substances combine in very different proportions with mercury. Urea, creatinine, ammonium salts and the amino-acid, glycine, were tested. This method of approach, however, cannot be used to determine what elements actually make up the total nonprotein nitrogen of the blood, because of the impossibility of synthesizing so complex a mixture as blood and testing the mercury combining power of the different elements composing it.

**THE USE OF THE METHOD: INTERPRETATION AND COMMENT**

Determination of the clinical significance of albuminuria is one of the commonest problems of the practitioner. Five per cent of apparently healthy persons and more than 50 per cent of Mayo Clinic patients have albuminuria. However, in less than half of these cases is the albuminuria of consequence. The presence or absence of renal lesions can be

\textsuperscript{29} It is of interest to note here that a new sulphur containing compound, thiasine, recently isolated from the blood and contained wholly in corpuscles, is isolated partly by its ability to combine with mercuric chloride. Benedict, S. R.; Newton, Eleanor B., and Behre, Jeanette A.: A New Sulphur Containing Compound (Thiasine) in the Blood, J. Biol. Chem. \textbf{67}:267-277 (Jan.) 1926.
accurately determined only by the use of tests of renal function. Disregarding classifications, one of two phenomena is present in nephritis, first, the retention of products of protein metabolism with consequent increase in the nonprotein nitrogen (urea, and so forth) in the blood and, second, the retention of salts and water; in diffuse renal lesions both phenomena may be observed.

The routine management of patients with nephritis by means of a milk diet of from 2 to 4 quarts daily is not scientific treatment. If urea retention is present, such a diet includes too much protein; if edema is present it contains too much fluid. Water retention speedily manifests itself by edema. A marked degree of nitrogen retention, however, may occur without producing clinical symptoms of uremia. The determination of the presence or absence of retention is the sine qua non of rational treatment.

The determination of the blood urea by the urease method is not used extensively in small hospitals or by physicians in general practice because the technic seems complicated and time consuming. When the relatively inaccurate determination of the hemoglobin in the blood by the blotting paper method is compared with the more accurate chemical methods, Cabot’s defense is recalled: that the blotting paper method is the most inaccurate but, withal, the most useful. Thus it is that simple laboratory methods alone become popular and widely used. They are desirable so long as the necessary accuracy is not sacrificed to convenience. The simple method presented for determining urea retention by means of the mercury combining power of blood is accurate. In the hands of the inexperienced worker, it is more accurate than the blood urea method because it offers less chances of error in technic. The speed and simplicity of the method especially recommend it for clinical use. It should therefore be of particular value to the general practitioner in routine work, to the small hospital, and for use as a rapid method in emergencies by the consultant in the large hospital. It is not meant to replace urea determinations when these may be readily done, although it is felt to be equally accurate for practical purposes. It is comparable in practicability to the universally used phenolsulphonphthalein test of Rowntree and Geraghty, and the water test and concentration test of Volhard and Fahr. By means of these four tests,30 which may be readily carried out by any practitioner with a minimum of laboratory equipment and training, all essential information regarding renal function can be obtained.

CONCLUSIONS

1. The presence or absence of urea retention in body fluids can be determined by the estimation of the mercury combining power.

2. The mercury combining power of blood is defined as the number of cubic centimeters of 5 per cent solution of mercuric chloride capable of combining with 100 cc. of deproteinized blood. The normal values vary between 70 and 100.

3. The blood urea can generally be estimated from the mercury combining power by use of a simple formula.

4. The mercury combining power of serum and plasma are approximately equal, though lower than the mercury combining power of whole blood. The urea of serum and plasma can also be approximated by formula.

5. The mercury combining power of the blood in polycythemia and leukemia varies with the total nonprotein nitrogen rather than with the blood urea, on account of the abnormal composition of the blood in such cases. The mercury combining power of the serum or plasma or of the saliva (the salivary urea index) is not so affected, and may be used for the estimation of the urea.

6. The deviations of the method are within the limits of acceptable clinical and laboratory procedures and the speed and simplicity of the test recommend the estimation of the mercury combining power of blood for general use.