THE DETERMINATION OF URIC ACID IN THE BLOOD.

By STANLEY R. BENEDICT.

(From the Department of Chemistry, Cornell University Medical College, New York City.)

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In a recent number of this Journal, Bulmer, Eagles, and Hunter¹ have published a study of the direct determination of uric acid in the blood as proposed by the present writer,² in which the conclusion is reached that figures obtained by the direct method are "unreliable."

We feel that a few words of comment upon that paper may be of service in connection with the still unsettled question of the determination of uric acid in the blood.

The larger proportion of the experimental work recorded by Bulmer, Eagles, and Hunter is concerned with analyses of animal blood of various species (rabbit, cat, dog, guinea pig, and ox). The investigators feel that, if the method cannot be applied to animal bloods and yield correct results, this constitutes presumptive evidence against its use in human blood. Such a conclusion hardly seems warranted. The present writer was fully aware that the direct method could not be applied to animal bloods, and so stated at the time the method was described. If methods were to be rejected because of what might be present in blood or urine, it is doubtful whether any of our present analytical methods for these fluids would survive. Fortunately the position taken by Bulmer, Eagles, and Hunter is not generally accepted, as is evidenced by the continued use of Folin's standard method for creatinine determination in urine in spite of the fact that urine of diabetics frequently contains enough acetone and diacetic acid to render the method inapplicable. Indeed, Bulmer, Eagles, and


215
Hunter would, according to their line of reasoning, have to abandon uric acid determination altogether, for as these writers seem to recognize, the figures they report by the precipitation method for animal bloods are so high as to have really little relationship to the true uric acid content of these bloods, with the exception of ox blood. It is regrettable that such highly inaccurate figures should get into the literature under any guise. It would have seemed preferable to state merely that the direct method yields results which are wholly inaccurate for animal bloods—a fact which the present writer would certainly not question. The argument is hardly strengthened by showing that the authors were unable to determine uric acid in animal bloods with reasonable accuracy by any method.

In connection with their analyses of human bloods Bulmer, Eagles, and Hunter have clearly established the interesting fact that in one condition, viz., nickel rash, which may be perhaps classed as at least moderately rare, the direct method for uric acid in blood may give figures definitely too high. This fact seems to us to represent the only argument adduced against the direct method which should have the slightest weight. The evidence here would have been more clear-cut had the writers checked their indirect results by the alkaline silver magnesia precipitation—a procedure more specific for uric acid than any other available. Even accepting that in nickel rash the direct method yields results too high, it would still seem a question in the present writer's mind as to whether such a finding should offset the fact that in hundreds of routine analyses by the direct method only a few scattered cases occur where there is a significant difference by the two methods. Indeed, Table V of Bulmer, Eagles, and Hunter would perhaps raise the question in the minds of many readers as to whether these writers did not go too far in the sweeping conclusion which they reached. In the study reported in Table V, Bulmer, Eagles, and Hunter especially wished to include cases showing wide divergence by the two methods, yet in spite of the fact that these investigators apparently had access to “nickel rash” cases and apparently did their best to find divergent bloods from any source, only two out of fourteen bloods analyzed by the two methods show a difference as great as 1 mg. of uric acid per 100 cc. of blood. Indeed the extensive row
of almost perfect duplicates offered in that table seems rather impressive and in favor of the direct method.

It is therefore at least still an open question as to whether the direct method for uric acid should be abandoned. Against this method we find the fact that nickel rash cases apparently yield high results. There is the further fact that of the usual run of human bloods a certain small proportion—perhaps 5 to 10 per cent—will show figures appreciably higher by the direct method. In favor of the use of the method we have its greater simplicity and therefore in the hands of most analysts, its greater safety as a routine procedure.

The opinion of the present writer is as follows: All analytical methods have some limitations and should be used with due regard to these limitations. The direct method for uric acid should, we believe, be first choice at present as a routine procedure in the analysis of human bloods. When special cases or groups of cases are being studied frequent checking by the precipitation method should be employed, and if a divergence is found the precipitation method should be adopted for such bloods. Any unusual or peculiar condition (nickel rash, for instance) or any case showing high uric acid where there is no other determinable retention or kidney involvement would at once call for use of a precipitation method. Where such simple rules are kept in mind the use of the direct method is wholly justifiable and will save a great amount of time as well as expense for silver, and avoid errors due to incorrect technique. The writer clearly recognized these facts and proposed two precipitation methods for use as checks, the more convenient one of which was adopted throughout their work by Bulmer, Eagles, and Hunter.

We propose now to discuss a few points raised by Bulmer, Eagles, and Hunter in connection with the substance responsible for interference in the direct method. We shall also attempt to correct certain errors which are creeping into the literature of uric acid determination, and which find a place in the discussion of Bulmer, Eagles, and Hunter.

In their paper, Bulmer, Eagles, and Hunter state concerning the probable interfering substance: "(Substance X) . . . . it is not precipitated by silver lactate." The incorrectness of this
statement is clearly shown in our paper on direct determination of uric acid in blood. We discussed this point in detail and introduced a special table which showed that the interfering substance is precipitated by silver lactate and that the fact that it does not appear in the final uric acid fraction in the Folin-Wu method is because the silver compound is not appreciably decomposed by the acid sodium chloride mixture employed. The idea repeatedly championed by Bulmer, Eagles, and Hunter that silver lactate is a highly specific reagent for the precipitation of uric acid is without the slightest foundation in fact. Acid silver lactate is not to be classed in any way with ammoniacal silver magnesia mixture as a specific precipitant for uric acid. Folin and Wu adopted silver lactate as a uric acid precipitant not because it was more specific than the ammoniacal solution, but because it would precipitate uric acid from the highly dilute blood filtrates which they wished to use. That Folin and Wu clearly recognized the lessened specificity of the acid silver lactate is shown by their introducing the extra step of decomposing the precipitate with acid sodium chloride solution, whereas accurate results could be obtained with the silver magnesia mixture when the entire precipitate is dissolved in cyanide. It should be clearly carried in mind that when dealing with any unknown mixtures, especially fluids from lower animal forms, or bacteria, etc., the test for the qualitative or quantitative presence of uric acid should involve preliminary precipitation with ammoniacal silver magnesia reagent. As the final criterion of the accuracy of a uric acid method preliminary precipitate with ammoniacal silver magnesia mixture stands first, providing a high enough concentration of uric acid (0.2 mg. of uric acid in not over 5 cc.) is used. Such statements as the following by Bulmer, Eagles, and Hunter—"We thus suspect that at least some of substance X is precipitated by the old alkaline uric acid precipitant"—are wholly misleading and are without the slightest experimental justification from any angle. Silver in weak acid solution has hundreds or thousands of known insoluble compounds. In the presence of an excess of ammonia on the contrary, iodide and the purines are practically the only known commonly occurring compounds which form insoluble derivatives with silver. In their paper Bulmer, Eagles, and Hunter state that "The contents

4 Bulmer, Eagles, and Hunter, 1 pp. 31–32.
of Table V . . . . provide indications of the presence of
a hitherto unrecognized substance in human blood. This sub-
stance is characterised by the facts that: (a) it is not precipitated
along with uric acid from protein-free blood filtrates by silver
lactate, (b) it is for the most part found in the corpuscles of human
blood, and (c) it practically disappears on standing. It is, further,
not 'combined uric acid.'” Had these writers read our discussion
of the direct determination of uric acid in blood and considered
the findings presented in Table II of that paper,5 we feel that they
could hardly have made such a reference to an “unsuspected”
substance. We clearly showed that human blood contains one
or more substances other than uric acid which give the uric acid
reaction by the carbonate-phosphotungstic acid method, and
which are precipitated by silver lactate. We further showed
that the silver compound is not decomposed by acid sodium chlor-ide solution, but that if the silver precipitate is dissolved directly
in cyanide, results are very much too high by the old process.
We had also found, though we did not specifically so state, that
precipitation with silver and dissolving in cyanide did not alter
the results by the direct method from those obtained when this
method is applied directly to the blood filtrate. It is obvious
that had such results been lower we could not have advocated
the use of the new method directly on the blood filtrate.

So impressed were we with the presence of the uric acid-reacting
compound precipitated by the silver lactate that nearly 2 years
ago a research was initiated upon the isolation of the compound in
question. The work was difficult and progress slow. Nevertheless,
within the last few months we have isolated over a gm. of the
compound in pure crystalline form from the blood of one species,
and have proved the presence of the substance (in surprisingly
large quantity) in the blood of every species (including human) so
far examined.

We are now engaged in a study of the composition and proper-
ties of the new compound, and will report concerning it as
promptly as possible. A simple quantitative method for its
determination in blood, tissues, and urine has been devised and
we are by this means studying its distribution and variation in
health and disease.

5 Benedict,2 pp. 200-203.
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