THE DETERMINATION OF SUGAR IN BLOOD AND IN NORMAL URINE.

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In a recent paper, S. R. Benedict describes a colorimetric copper method for the determination of the blood sugar which is based upon the idea that his well known copper citrate reagent should prove as superior for quantitative work on blood as it has been for qualitative tests on urine. This expectation seems to have been fulfilled to a certain extent, for by a series of parallel blood sugar determinations he shows that the new method does give materially lower values than are obtained by the method of Folin and Wu.

Benedict seems to believe that the only essential feature of his qualitative sugar reagent is the fact that its alkali is a carbonate instead of a hydroxide. This concept I think is not quite correct. When Benedict, in 1908, described his citrate reagent the most important new feature was the use of citrate instead of a tartrate, and the purpose, as stated by Benedict, was to obtain a more stable reagent than had been obtained by the use of Rochelle salt. Increased stability was, however, not the only result, or indeed the most important result achieved by substituting citrate for tartrate. The citrate exerts a powerful depressive action on the oxidative properties of dissolved copper compounds and it is because of this inhibiting effect that the original citrate reagent proved so suitable as a qualitative reagent for sugar in urine. The inhibiting effect of the citrate includes the reaction with reducing sugars, and it is because of this factor that citrate reagents are qualitatively less sensitive and quantitatively give much less cuprous oxide from a given amount of sugar (0.2 to 0.4 mg.)

than do corresponding reagents prepared by the help of tartrates. The antireducing effect of citrates is most conveniently demonstrated by introducing one or two drops of a 20 per cent sodium citrate solution to a Folin-Wu sugar tube and comparing the color obtained from the standard glucose solution in this tube with that obtained without any added citrate—by the Folin-Wu method.

The explanation given above as to the characteristic behavior of alkaline copper citrate solutions toward reducing substances, including glucose, does not agree very well with the theoretical interpretations and arguments which Benedict has advanced in support of his new method, yet neither does it necessarily, or materially, affect the validity of his main working hypothesis, namely, that the process which gives the lowest sugar values with diluted normal urine should yield the most nearly correct values when applied to blood filtrates. My own explanation on the other hand suggests that there should be other and more flexible methods for meeting the requirements of this ingenious hypothesis than through the general antireducing action of the citrates.

The first obvious inquiry in this particular problem was naturally to determine the extent to which it is permissible to reduce the alkalinity of a given copper solution. I have done this with the Folin-Wu reagent and I have thus found that sodium carbonate alone is altogether too strong an alkali with such active copper solutions as are obtained with the help of tartrates. By reducing the alkalinity almost down to the reaction of sodium bicarbonate one still gets just as much cuprous oxide from 0.2 to 0.4 mg. of glucose as with the original Folin-Wu reagent, and when such a weakly alkaline reagent is applied directly to diluted normal human urine, the reduction obtained is very much smaller than that obtained with the original reagent.

The reagent finally adopted is made as follows:

*New Alkaline Copper Tartrate Solution.*—Dissolve 12 gm. of Merck's sodium tartrate (or 15 gm. of Rochelle salt) together with 7 gm. of anhydrous sodium carbonate and 20 gm. of sodium bicarbonate in 600 to 700 cc. of distilled water. Transfer this solution to a volumetric liter flask and to it add 5 gm. of copper sulfate previously dissolved in about 200 cc. of water. Dilute to volume and mix.

In the preparation of this reagent all the carbon dioxide which is
generated when the copper sulfate is added should be retained in the solution by combining with a part of the surplus carbonate. In practice it may therefore be desirable, though scarcely necessary, to insert a stopper in the volumetric flask and shake for a few moments, immediately after the addition of the copper sulfate solution.

When the "sugar" of normal human urine is determined directly on the diluted urines by means of this copper solution and by Benedict's solution, no uniform proportionality is obtained. With some urines Benedict's reagent will give a little less sugar and with others it will give more. This is, of course, what might be expected from such widely different reagents when applied to such complex and varying reducing mixtures as human urines—which may contain no glucose at all. In order not to make such comparisons unduly favorable to the new copper reagent described above the urines should be first rendered just alkaline to phenolphthalein; though the difference in result is insignificant provided that the urines have not been preserved by means of preservatives which are acid in reaction.

Before applying the new copper reagent to actual blood sugar determinations it seemed best also to try to improve the molybdate solution which is used for the development of the blue color by means of which one measures the amount of cuprous oxide obtained in the reduction. That molybdate solution was developed specifically for use in connection with the copper tartrate reagent of Folin and Wu and it is, therefore, not surprising that Benedict found it unsuitable for use in connection with his copper reagent. In resorting to the use of the uric acid reagent for the development of the blue color I think that Benedict has not found a reagent that is particularly suitable. The uric acid reagent will give more color, to be sure, with a given quantity of cuprous copper than does the special phosphate molybdate reagent of Folin and Wu, but the uric acid reagents give almost no color with cuprous copper in mixtures sufficiently acid in reaction to dissolve promptly cuprous oxide. Benedict's reagent, for example, gives extremely little color if added directly to a freshly prepared, dilute, solution of cuprous chloride. The residual acidity obtained when 2 cc. of the uric acid reagent are added to 2 cc. of his copper reagent is so low that the mixture will develop a blue color with uric acid. Also,
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and for the same reason, the blank, that is to say, the blue color obtained on merely mixing equal volumes of the two reagents is much greater than the corresponding blank in the Folin-Wu method. The most serious consequence of the low degree of acidity obtaining in the sugar tubes is, however, the fact that the cuprous oxide sediment dissolves only very slowly. Benedict has evidently intended to provide for this flaw in his method by inserting a waiting period of 10 minutes between the addition of the uric acid reagent to the cooled contents in the sugar tube and the dilution with water. It is quite possible that this provision is adequate for most cases, but those who use the process should know that they need to be alert to see whether the cuprous oxide actually has dissolved. If the cuprous oxide is abundant and for one reason or another has settled more completely than usual, all the cuprous oxide may not dissolve even in an hour. That this is so can easily be demonstrated by heating 0.4 mg. of glucose for 20 minutes before cooling and then adding the uric acid reagent. I tried this experiment in order to see whether the yield of cuprous oxide could be increased, but was unable to determine the point, because of the insolubility of the cuprous oxide. (In order to see the undissolved cuprous oxide within the dark blue solution, close inspection against a black background is necessary.)

I had two objects in mind in trying to improve upon the phosphate-molybdate reagent of Folin and Wu. First, to try to secure a deeper color from a given amount of cuprous oxide and, second, to increase the acidity so that it could be used with almost any alkaline copper reagent. Both of these objects have been attained, though only at the expense of considerable effort. The new molybdate solution also gives more dependable proportionality between different amounts of cuprous oxide. When the standard is set at 20 mm., readings of the unknown between 10 mm. and 40 mm. are perfectly dependable.

New Acid Molybdate Reagent for the Estimation of Cuprous Copper.—The sodium molybdate at present obtainable is not very pure. It contains some insoluble material which it is best, though not strictly necessary, to remove by filtration. In addition, the molybdate contains some reducing impurity which gradually imparts a blue color to the finished reagent unless it is destroyed.
Otto Folin

by oxidation (with bromine). If the reagent is wanted for immediate use or for a short time, 3 or 4 days, one can ignore these impurities, and then the preparation of the reagent takes only a few minutes. For such purposes the preparation is made as follows:

Dissolve 40 gm. of sodium molybdate, Na₂MoO₄·2H₂O, in 100 cc. of distilled water, in a 500 cc. beaker. To this somewhat turbid solution add, with stirring, 55 cc. of 85 per cent phosphoric acid, 40 cc. of 25 per cent sulfuric acid, and 20 cc. of 99 per cent acetic acid—in the order given. (The sulfuric acid is obtained by adding one volume of concentrated acid to three volumes of water and cooling.) The resulting mixture is at once ready for use.

For the preparation of larger quantities of the reagent for permanent use, the process is as follows:

Dissolve 150 gm. of sodium molybdate, Na₂MoO₄·2H₂O, in 300 cc. of distilled water. Filter through a 15 cm. quantitative filter paper into a flask (capacity 1 liter) and wash with 75 cc. of water. To the sodium molybdate solution in the flask add several drops (0.1 to 0.2 cc.) of bromine and shake for a few minutes till the bromine has dissolved. Let stand for an hour to complete the oxidations produced by the hypobromite. Then add, with shaking, 225 cc. of 85 per cent phosphoric acid. The surplus bromine is set free and imparts a yellow color to the solution. After all the phosphoric acid has been added, add also 150 cc. of cooled 25 per cent sulfuric acid (one volume of concentrated sulfuric acid added to three volumes of water). Remove the surplus bromine by means of a moderately rapid air current. The aeration will take about half an hour. Finally, add 75 cc. of 99 per cent acetic acid, mix, and dilute to a volume of 1 liter.

If it is inconvenient to remove the bromine immediately after the addition of the sulfuric acid, let the mixture stand, covered with a beaker, till the following day. Such extra standing with bromine is just as good. The reducing impurities can in fact be destroyed just as well by adding the bromine to the acidified solutions, but 3 to 4 days standing is then required to complete the process, and it is for this reason that the hypobromite oxidation was tried. This molybdate solution is used exactly as the molybdate solution of Folin and Wu; but when used with Benedict's copper citrate
reagent it is necessary to use 4 cc. instead of 2 cc. The solution is practically colorless, and will remain so if kept free from organic impurities.

Critical readers will be apt to wonder whether there is any good reason for using both sulfuric acid and acetic acid as well as an abundance of phosphoric acid in the preparation of this molybdate reagent. To this I can only say that the given combination of acids represents the outcome of a large number of experiments and as the preparation is easy and the reagent good, I have not considered it worth while to try to secure further simplification. I suspect that the active compound in this reagent is a phosphomolybdic acid not yet isolated or described.

In taking up the application of the new solutions for quantitative sugar determinations the reader is reminded that in the new copper reagent we are dealing with a far more delicately adjusted solution than any heretofore used for such purposes. The acidity of the sugar solution or blood filtrate whose sugar content is to be determined is, therefore, a matter of importance. A small surplus alkalinity makes no appreciable difference, because it is taken care of by the bicarbonate; but, as a general rule, it may be stated that the solution should be nearly neutral.

The blood filtrates obtained according to the protein precipitation process of Folin and Wu are nearly neutral when the reagents used are properly adjusted. 10 cc. of a blood filtrate on titration with tenth normal alkali and phenolphthalein give an end-point with about 0.2 cc., indicating an acidity of only about 0.05 normal. As there is no guarantee that all are getting such practically neutral blood filtrates it seems best to require that the blood filtrate be neutralized before it is used for the sugar determination. This is most conveniently done as follows:

Transfer 2 cc. of blood filtrate to a test-tube; add one drop of phenolphthalein solution and count the number of drops of tenth normal alkali required to give the pink end-point. Then simply add the same number of drops of alkali to the sugar tube before introducing the blood filtrates. As the blood filtrates in any one laboratory and with any one set of precipitating reagents will run very uniform, the addition of the alkali to the sugar tube need not always be preceded by the actual preliminary titration. If
the conditions are right there is in fact no need for any neutraliza-
tion. These precautions are mentioned because it is to be feared
that some are still using more or less acid tungstates for the precipi-
tation of the blood proteins. Blood filtrates obtained from blood
which has been preserved with sodium fluoride are also apt to be
strongly acid, evidently because of the presence of acid impurities
in this salt.

Standard Glucose Solution.—The concentrated glucose solution
containing 10 mg. of glucose per cc. is made up, as before, with nearly
saturated benzoic acid solution as the solvent and preservative.
But in making up the dilute solutions, containing 0.1 and 0.2 mg.
per cc., it is not permissible to dilute 1 and 2 cc. of the strong sugar
solution with benzoic acid solution, because to do so would be to
introduce an unnecessary complication because of the resulting
acidity. For use with the new method the dilution is made with
water and a few drops of formalin or toluene are added as an ad-
ditional preservative.

The sugar determination on the Folin-Wu blood filtrates are
made as follows:

Transfer 2 cc. of standard sugar solution to one of two Folin-Wu
sugar tubes and transfer 2 cc. of the nearly neutral or neutralized
blood filtrate to another similar tube. Add 2 cc. of the new copper
solution to each and heat in a boiling water bath for 10 minutes.
Cool in a beaker of water for 1 minute or as much longer as may
be convenient. Then add 2 cc. of the new special acid molybdate
reagent to each test-tube. The cuprous oxide in the tubes dis-
solves practically instantly and as soon as the visible evolution of
CO₂ has nearly ceased (about 1 minute), dilute to the 25 cc. mark,
mix, and make the color comparison.

It will be noted that in the directions given above, the special
blood sugar tube of Folin and Wu is still recommended. In his
latest paper Benedict affirms that the blood sugar tube of Folin
and Wu can be replaced by an ordinary open test-tube by simply
replacing most of the air in the tube with an inert gas or vapor
(benzene) and keeping the mouth of the test-tube closed with a
cotton plug. I was rather surprised over this conclusion of
Benedict's for I had tried many such devices in the research which
led to the Folin-Wu tube. I now believe that Benedict's conclu-
sion is based on compensating experimental errors. These errors in
brief are due to the use of his uric acid reagent for the development
of the blue color. The facts seem to be that in the constricted
sugar tube the uric acid reagent dissolves the cuprous oxide more
slowly than in open test-tubes, so slowly in fact that much of the
uric acid reagent is decomposed and made useless before all the
cuprous oxide has dissolved. The loss of color thus sustained
counterbalances the loss of cuprous oxide by reoxidation in the
open tubes. By using the new molybdate reagent described in
this paper (4 cc.) together with Benedict’s process I find that the
substitute arrangement suggested by Benedict does not appreci-
ably prevent the reoxidation of cuprous oxide.

It was only after the preparation of the two reagents described
above had been worked out that I began to check up the analytical
findings reported in Benedict’s paper. When I did begin to make
blood sugar determinations I did so with the three different copper
solutions; that is to say with the new copper solution, with the

| Table I. | Mg. Glucose per 100 Cc. of Blood. |
|------------------|------------------|------------------|------------------|------------------|
| Benedict | 80 | 100 | 98 | 123 | 137 |
| Folin-Wu | 84 | 103 | 108 | 119 | 140 |

solution of Folin and Wu, and with Benedict’s. The new acid
molybdate solution was used only with the first two copper solu-
tions, for even when 4 cc. are taken it is not entirely satisfactory
with Benedict’s copper reagent, because of its huge citrate
contents.

In the course of these parallel determinations it was found that
Benedict’s method did not at all give the low values reported by
Benedict; on the contrary, it would give the same and in some
cases even higher blood sugar values than those obtained by the
copper reagent of Folin and Wu. The last five sugar determina-
tions which were made on blood taken from normal persons
(students) gave the figures in Table I.

The citrate-sulfite solution employed in these determinations
was about 2 months old. Benedict states that his copper reagent
keeps for a year, but this statement obviously cannot be entirely
correct. The sulfite in the reagent must necessarily be subject to
spontaneous oxidation to sulfate. The most practical way of
demonstrating the deterioration of the reagent is to prepare a
duplicate reagent without any added sulfite and then compare
these reagents from time to time by the amount of cuprous oxide
which they yield with the standard sugar solution.

Benedict incorporated 0.1 per cent sodium bisulfite in his copper
reagent in order to increase the yield of cuprous oxide and it
certainly does in a large measure make up for the loss produced by
the use of citrates. In the course of my efforts to discover why
Benedict's method in my hands did not yield less blood sugar than
the Folin-Wu copper reagent, it occurred to me that the disappear-
ance of the sulfite from my 2 months old citrate reagent might
have something to do with it. I therefore prepared two new cop-
per citrate reagents, one of which did not contain any added

| TABLE II. |
| Mg. Sugar per 100 Cc. of Blood. |
| Benedict 1 | 174 | 151 | 116 | 218 | 230 | 292 |
| " 2 | 131 | 121 | 89 | 180 | 184 | 242 |
| Difference | 43 | 30 | 27 | 38 | 46 | 50 |

| TABLE III. |
| Mg. Glucose per 100 Cc. of Blood. |
| Folin-Wu | 152 | 320 | 296 | 516 | 333 |
| Benedict | 120 | 277 | 246 | 448 | 304 |
| Difference | 32 | 43 | 50 | 68 | 29 |

sulfite. A series of blood sugar determinations was then made
according to Benedict's directions by means of these two copper
solutions. The figures in Table II were obtained.

It will be seen that the first row of figures obtained by the citrate
reagent to which no bisulfite had been added is much higher than
those obtained with the freshly prepared regular Benedict reagent.
It should also be pointed out that these blood filtrates represent
diabetics with high blood sugar. From figures given in Benedict's
paper one finds that he also obtained relatively just about as
large differences in blood sugar content by his method and the
Folin-Wu method in diabetic bloods with high glucose content
as was found in the blood from persons who did not carry a high
blood sugar.

His figures are given in Table III.
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The blood sugar values obtained by means of Benedict's copper solution only a few days old are the same or a little higher than those obtained with the new copper tartrate solution (see Table IV).

From Benedict's figures (Table III) one must reach the somewhat astonishing conclusion that the non-glucose products in blood capable of reducing alkaline copper solutions are much more abundant in bloods with abnormally high sugar levels than in bloods of normal persons. If such a conclusion should turn out to be correct, then it obviously becomes important to determine the non-glucose reduction as well as the glucose content of blood, particularly diabetic blood. And no one sugar method can meet the requirements of this new situation.

The figures given in Table V will serve to indicate the different sugar values obtained by the new and the Folin-Wu copper reagents in blood filtrates whose sugar levels are within the normal limits.

In Table VI are given the corresponding blood sugar figures obtained from diabetic bloods by means of the two copper reagents. All of these blood filtrates were obtained from Dr. Joslin's diabetic clinic at the Deaconess' Hospital. No attempt was made to correlate the findings with the insulin or dietetic treatment which the patients were receiving. From the figures given in Table VI it is clear that all diabetic bloods do not behave in exactly the same way. In most cases the sugar values obtained by the two copper reagents are rather farther apart than in the case of bloods from non-diabetic persons; but this is not invariably so, and at the present time it is not possible to go beyond the bare statement that all diabetic bloods do not behave alike.

In the determination of sugar in normal urine according to the method of Folin and Berglund\(^3\) one obtains strikingly different results on substituting the new copper reagent for the old one. Many of the reducing carbohydrate materials found in normal human urines have comparatively little effect on the new copper reagent and one obtains correspondingly less "sugar" in such urines. These findings are in harmony with the idea expressed by

\(^3\) Folin, O., and Berglund, H., *J. Biol. Chem.*, 1922, li, 209.
TABLE IV.
Mg. Sugar per 100 Cc. of Blood.

<table>
<thead>
<tr>
<th>Benedict</th>
<th>262</th>
<th>200</th>
<th>118</th>
<th>87</th>
<th>100</th>
<th>124</th>
</tr>
</thead>
<tbody>
<tr>
<td>Folin</td>
<td>266</td>
<td>190</td>
<td>116</td>
<td>82</td>
<td>91</td>
<td>109</td>
</tr>
<tr>
<td>Difference</td>
<td>4</td>
<td>10</td>
<td>2</td>
<td>5</td>
<td>9</td>
<td>15</td>
</tr>
</tbody>
</table>

TABLE V.
Mg. Sugar per 100 Cc. of Normal Human Blood.

<table>
<thead>
<tr>
<th>Folin-Wu.</th>
<th>130</th>
<th>111</th>
<th>110</th>
<th>118</th>
<th>94</th>
<th>84</th>
</tr>
</thead>
<tbody>
<tr>
<td>Folin</td>
<td>127</td>
<td>99</td>
<td>96</td>
<td>101</td>
<td>80</td>
<td>70</td>
</tr>
<tr>
<td>Difference</td>
<td>3</td>
<td>12</td>
<td>14</td>
<td>17</td>
<td>14</td>
<td>14</td>
</tr>
</tbody>
</table>

TABLE VI.
Blood Sugar in Mg. per 100 Cc. of Blood.

| Folin-Wu. | 103 | 108 | 119 | 109 | 286 | 121 | 212 | 240 | 236 | 172 | 180 | 352 | 232 | 250 | 220 | 236 | 140 | 144 | 220 | 230 | 272 | 228 | 286 | 300 | 364 | 312 |
|-----------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Folin     | 77  | 87  | 89  | 84  | 266 | 116 | 190 | 210 | 198 | 160 | 180 | 352 | 212 | 224 | 195 | 216 | 131 | 127 | 204 | 248 | 218 | 272 | 260 | 352 | 280 |
| Difference | 26  | 21  | 30  | 25  | 20  | 5   | 22  | 30  | 38  | 22  | 0   | 0   | 20  | 26  | 25  | 20  | 9   | 17  | 26  | 24  | 10  | 14  | 40  | 12  | 32  |
Sugar in Blood and Urine

Folin and Berglund that normal human urine contains extremely little, if any, glucose.

At my request, O. Watkins, at the Huntington Hospital, made a series of sugar determinations on urines by means of the two copper reagents. The urines were first treated with Lloyd's alkaloidal reagent as in the Folin-Berglund method. The heating period adopted was 8 minutes with the copper reagent of Folin and Wu, and 10 minutes with the copper reagent described in this paper.

The "sugar" was also determined directly on the same urines by Benedict's method and by the new method.

The results obtained are shown in Table VII. The Benedict copper citrate solution used by Watkins was also unfortunately several weeks old and may have lost most of its sulfite.

**DISCUSSION.**

It must be obvious to all that the work described in this paper was produced in response to Benedict's stimulating paper on the

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**TABLE VII.**

*Mg. of Glucose per 100 Ce. of Urine.*

<table>
<thead>
<tr>
<th>On the Lloyd filtrate.</th>
<th>On diluted urine.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Folin-Berglund.</strong></td>
<td><strong>Folin.</strong></td>
</tr>
<tr>
<td>84</td>
<td>59</td>
</tr>
<tr>
<td>315</td>
<td>155</td>
</tr>
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<td>209</td>
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<td>72</td>
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<td>9</td>
<td>Trace.</td>
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<td>15</td>
<td>10</td>
</tr>
<tr>
<td>74</td>
<td>56</td>
</tr>
</tbody>
</table>
same subject. While I have found that Benedict's concrete new
technique is open to serious criticism, the fact remains that he has experimentally demonstrated by that method that the Folin-Wu sugar values are too high—if by blood sugar is meant blood glucose. My own work has in the main confirmed his analytical findings and has also in the main verified the correctness of his working theory that the sugar method which gives the lowest sugar values when applied to urine, if it is at the same time dependable for glucose, will give blood sugar values which correspond most nearly to the glucose content of blood.

Without wishing to detract in the slightest degree from the important service which Benedict has rendered in thus giving a fruitful new turn to blood sugar investigations, I permit myself to quote a passage from my Harvey Lecture of 1919-20 on the same subject:

"In this connection I would call attention to the highly peculiar fact that bloods from nephritics having very high urea retention give by our original method, as by all other sugar methods, abnormally high values for the blood sugar. There does not seem to be any tangible reason why such bloods should contain any more sugar than does the blood of normal individuals. There is room for the suspicion that in such bloods other materials than sugar play an important part, that similar products in smaller amounts are present in all blood, that all sugar values are high and that the lowest sugar values obtained must still be regarded as maximum values."

To this passage something can perhaps be added now:

While a part of the high sugar values obtained in nephritic blood may be represented by reducing products which are not sugar or sugar derivatives, it is not only possible, but highly probable that a very large fraction of these unknown reducing materials is of exactly the same sort as the non-glucose carbohydrate materials which occur in normal urines. These more or less foreign and unusable sugars and sugar derivatives which are eliminated by normal kidneys would naturally accumulate in the blood when the kidneys fail to work. Further, there is no reason to assume that normal kidneys excrete these foreign carbohydrate derivatives except in response to a floating supply of these products in the blood. Nor can one definitely deny that the blood sugar may contain some maltose.

These conclusions are, of course, only another aspect or applica-
tion of Benedict's thesis that reducing substances encountered in
the urine must also be present in the blood. This thesis does not
imply that the various reducing substances sustain the same
quantitative ratio to one another in the blood as in the urine.
Creatinine, for example, so abundant in urine, occurs only in
negligible quantities in the blood. Every one has probably
recognized the theoretical validity of this thesis, but it remained
for Benedict to show that it is experimentally demonstrable.

The abnormally high non-glucose reducing materials in diabetic
blood would seem to require a different explanation. The non-
glucose reducing products in such bloods may in part represent
some form of intermediary carbohydrate metabolism. At all
events they would seem to merit further investigation.
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