THE PLACENTAL TRANSMISSION OF CREATININE AND CREATINE.

BY ANDREW HUNTER AND WALTER R. CAMPBELL.

(From the Department of Pathological Chemistry, University of Toronto.)

(Received for publication, February 8, 1918.)

Some time ago, in a preliminary communication dealing with various aspects of the distribution of creatinine and creatine in blood, we reported that the concentration of each of these substances was nearly the same, at parturition, in the placental as in the maternal plasma, and we concluded that there takes place between the mother and the fetus a ready interchange of both. If we have hesitated hitherto to publish any fuller account of these observations, it is chiefly because of the necessity under which we found ourselves of first testing rather thoroughly the validity of the analytical methods used. In the meantime our results have been confirmed by the independent observations of Plass.


The work upon the placental transmission of creatinine and creatine, of which this communication contained of course no more than an abstract, constituted in our original intention one part only of an extended program, then already under way, for the study of placental interchange in general. Until we first made it public, we were not aware that an investigation of similar scope had been for some time in progress in another laboratory, and that results concerning the placental transmission of total non-protein nitrogen and urea had already been reported by Slemons and Morriss. When these circumstances were brought to our notice we felt bound to restrict ourselves, in the further prosecution of our plan, to the cases of creatinine and creatine, to which Slemons and his coworkers had not yet turned their attention. We are indebted to Dr. Slemons for the ready courtesy with which he left free to us this corner of the field in which he was engaged. It may be remarked here that such unpublished data as we had collected upon other constituents of the blood are in complete harmony with the reported conclusions of the Yale laboratory.

Creatinine and Creatine

For this reason we have deemed it unnecessary, since completing our critical study of the methods, to supplement our original data by more than a few additional determinations. The point of view from which we approached the subject has been briefly indicated in previous communications.\textsuperscript{1,5} It is identical, moreover, with that taken, in reference to the general problem of placental exchange, by Plass and by Slemons and Morriss.\textsuperscript{6} As these authors have discussed it with sufficient fullness and with ample reference to the earlier literature, any further elaboration of it here would be superfluous. The main object of the present paper is simply to record in detail the analytical results we have collected, and to consider, in the light of our lately formed estimate of their reliability, how far they justify our original conclusion.

\textit{Subjects and Methods.}

The cases selected were full term deliveries,\textsuperscript{7} complicated in two instances only (Nos. 16 and 18) by the application of forceps. The only abnormality noted in the course of pregnancy was a mild albuminuria in Case 8. In three cases (Nos. 9, 10, and 18) labor was assisted by the administration of pituitrin. In all, light chloroform-ether anesthesia was induced at the close of the second stage. As soon as the umbilical cord was cut, a sample of blood was taken from the free outflow of its placental end, and as nearly as possible at the same time a specimen was secured from the arm vein of the mother. Coagulation was prevented in each case by the addition of about one-fiftieth volume of 20 per cent potassium oxalate. Upon each sample, as secured, we determined the creatinine and creatine of whole blood and plasma, as well as, with the object of calculating the corpuscular concentration of these substances, the relative plasma volume. The details of technique adopted were those described in a former

\textsuperscript{6} Hunter and Campbell, \textit{J. Biol. Chem.}, 1918, xxxiii, 169.
\textsuperscript{7} All were inmates of the obstetrical wards of the Toronto General Hospital. For permission to utilize them in this study we are indebted to Doctors' B. P. Watson and K. C. McIlwraith, whose courtesy we wish to acknowledge.
A. Hunter and W. R. Campbell

paper. Except in Cases 1 and 4 the blood was laked before the addition of picric acid.

Results.
The results are recorded in the accompanying table. This does not reproduce any selected group, but includes every analysis made in this particular series. The order of arrangement

<table>
<thead>
<tr>
<th>No.</th>
<th>Subject</th>
<th>Age</th>
<th>Para.</th>
<th>Duration of labor</th>
<th>Creatinine per 100 cc.</th>
<th>Creatine (as creatinine) per 100 cc.</th>
<th>Relative plasma volume</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>M</td>
<td>F</td>
<td>M</td>
</tr>
<tr>
<td>1 S. G.</td>
<td>37</td>
<td>XIV</td>
<td>7</td>
<td>1</td>
<td>1.11</td>
<td>1.50</td>
<td>0.74</td>
</tr>
<tr>
<td>2 A. D.</td>
<td>23</td>
<td>III</td>
<td>2</td>
<td>1</td>
<td>1.11</td>
<td>1.40</td>
<td>0.75</td>
</tr>
<tr>
<td>3 P. A.</td>
<td>23</td>
<td>II</td>
<td>21</td>
<td>1</td>
<td>2.83</td>
<td>3.40</td>
<td>0.82</td>
</tr>
<tr>
<td>4 C. S.</td>
<td>30</td>
<td>II</td>
<td>8</td>
<td>14</td>
<td>1.41</td>
<td>1.90</td>
<td>0.87</td>
</tr>
<tr>
<td>5 F. G.</td>
<td>23</td>
<td>I</td>
<td>19</td>
<td>21</td>
<td>2.33</td>
<td>3.50</td>
<td>0.89</td>
</tr>
<tr>
<td>6 I. M.</td>
<td>21</td>
<td>I</td>
<td>9</td>
<td>29</td>
<td>2.12</td>
<td>3.02</td>
<td>0.92</td>
</tr>
<tr>
<td>7 A. S.</td>
<td>26</td>
<td>IV</td>
<td>13</td>
<td>1</td>
<td>1.83</td>
<td>3.09</td>
<td>0.92</td>
</tr>
<tr>
<td>8 M. B.</td>
<td>25</td>
<td>III</td>
<td>38</td>
<td>1</td>
<td>2.12</td>
<td>2.00</td>
<td>0.97</td>
</tr>
<tr>
<td>9 E. H.</td>
<td>29</td>
<td>II</td>
<td>9</td>
<td>2</td>
<td>2.33</td>
<td>3.81</td>
<td>1.00</td>
</tr>
<tr>
<td>10 A. C.</td>
<td>25</td>
<td>I</td>
<td>51</td>
<td>18</td>
<td>1.93</td>
<td>1.01</td>
<td>0.62</td>
</tr>
<tr>
<td>11 M. O.</td>
<td>28</td>
<td>I</td>
<td>13</td>
<td>1</td>
<td>2.53</td>
<td>3.01</td>
<td>1.02</td>
</tr>
<tr>
<td>12 N. P.</td>
<td>17</td>
<td>I</td>
<td>7</td>
<td>1</td>
<td>2.42</td>
<td>2.31</td>
<td>1.16</td>
</tr>
<tr>
<td>13 V. S.</td>
<td>18</td>
<td>I</td>
<td>22</td>
<td>1</td>
<td>4.02</td>
<td>2.41</td>
<td>2.26</td>
</tr>
<tr>
<td>14 E. A.</td>
<td>22</td>
<td>I</td>
<td>11</td>
<td>22</td>
<td>2.22</td>
<td>2.71</td>
<td>3.37</td>
</tr>
<tr>
<td>15 E. T.</td>
<td>19</td>
<td>I</td>
<td>23</td>
<td>1</td>
<td>3.23</td>
<td>5.15</td>
<td>0.51</td>
</tr>
<tr>
<td>16 M. F.</td>
<td>21</td>
<td>I</td>
<td>23</td>
<td>11</td>
<td>3.12</td>
<td>2.91</td>
<td>1.59</td>
</tr>
<tr>
<td>17 M. M.</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>2.53</td>
<td>3.01</td>
<td>1.77</td>
<td>1.71</td>
</tr>
<tr>
<td>18 B. II</td>
<td>20</td>
<td>I</td>
<td>37</td>
<td>21</td>
<td>—</td>
<td>2.20</td>
<td>1.35</td>
</tr>
</tbody>
</table>

Average.......... 2.32 | 7.11.16 | 1.21 | 6.9 | 8.5 | 2.09 | 2.14 | 62 | 53

\* M = Maternal. \( \dagger \)F = Fetal.

They are taken, for the most part, from a thesis submitted by Walter R. Campbell, in partial fulfillment of the requirements for the degree of M.D., University of Toronto, 1917.
within the table is determined by the plasma creatinine of the maternal blood. The corrections introduced in the averages are made on the basis of considerations developed in earlier communications.

DISCUSSION.

Placental Transmission of Creatinine.

For reasons that are obvious, and upon which others as well as ourselves have already sufficiently insisted, it is the plasma concentrations alone which have a direct bearing upon the problem of placental exchange. It is therefore fortunate that, although with whole blood the colorimetric method of creatinine determination is subject to a considerable and variable error, one may accept as substantially correct the results of its application to plasma. A study of such results, as they are recorded in the ninth and tenth columns of the table, reveals a general correspondence between the concentration of creatinine in the maternal and that in the fetal plasma. This correspondence is just as close at the upper end of the range illustrated as at the lower. In five instances out of the total eighteen it amounts to absolute or practical identity. In twelve the difference existing, if not negligible, is relatively unimportant. One case only (No. 10) exhibits a really conspicuous divergence. The averages for the series fall closely together, and but for the inclusion of the aberrant, and not impossibly erroneous, values of Case 10, they would have been closer still. There can be little doubt, therefore, that the structures which separate the fetal and maternal plasmas are freely permeable to creatinine, and that the passage of that substance from one circulation to the other is regulated by the ordinary laws of diffusion. Our earlier report is fully substantiated in this respect.

Whether our figures will bear any closer analysis may well be

10 It was a very prolonged dry labor during which pituitrin was administered. The possibility is suggested that these conditions led to some obstruction of the fetal circulation, and consequent accumulation of creatinine in the fetal blood; but it is equally likely that we are dealing with an accidental error of analysis. The amount of material unfortunately was too small to permit a duplicate determination.
doubted. We are tempted, nevertheless, to remark upon the fact that whereas there are only four cases (Nos. 4, 12, 15, and 18) in which the maternal concentration is distinctly higher than the fetal, there are as many as nine in which the reverse is the case. This may be no more than an accident, and yet it is conceivably of real significance. Creatinine is an excretory product of which the final disposition, even for the fetal moiety, is escape through the maternal kidney. While therefore any sudden accumulation within the maternal organism might temporarily favor its transference from mother to fetus, the main current of its diffusion must set in the opposite direction. It would therefore be not at all surprising if there existed, as seems at least to be indicated in our data, a preponderating tendency towards the establishment of a concentration gradient falling from fetus to mother. We hesitate to appeal, in further support of this conception, to the slight excess in favor of the fetal plasma which is presented in our averages; for that depends mainly, as we have stated, upon the doubtful result of Case 10. We may, however, point out that a reversal of the theoretically normal gradient does really appear to be associated as a rule with an unusual accumulation in the mother; for of the four cases which exemplify that condition one only has a maternal creatinine lower than 1.16, and 1.16, according to data already published, is at the upper limit of normality for the closing weeks of pregnancy. \[11\]

**Creatinine of Maternal and Fetal Whole Blood.**

It has been made probable\[5,9\] that the true creatinine content of whole blood is practically the same as that of its plasma. What has been said in the preceding paragraphs of the latter is therefore applicable at once to the former, and it is hardly necessary to make separate reference to the figures for whole blood yielded by direct analysis. To the extent to which these differ from the figures for plasma they are, we believe, in error. It may be

\[11\] Some evidence that these relations are not merely the result of chance is afforded by a scrutiny of the results of Plass.\[3\] Among the fourteen results for plasma creatinine which he reports (Tables III and IV) there are five which show a slight excess (of 0.05 or more) on the fetal side, as against three exhibiting the reverse condition; and in each of the latter the maternal creatinine is greater than 1.2.
remarked that, if this is granted, the results as found (columns seven and eight) not only give additional force to our suspicion that the error is especially conspicuous in the blood of pregnant women but suggest that in fetal blood, perhaps because of its high content of corpuscles, it is even more so. Many of the observed results for whole blood would, taken by themselves, indicate an accumulation of creatinine, which the corresponding result for plasma shows to be wholly imaginary. Due caution therefore is to be exercised in interpreting the data of whole blood creatinine determinations in pregnant women or new-born infants.

**Influence of Parturition upon the Creatinine Concentration of the Blood.**

During pregnancy the concentration of creatinine in the maternal plasma (or blood) does not normally exceed 1.2 mg. per 100 cc. This limit, it may now be noticed, is passed in one-third of all determinations made at the end of the second stage of labor. The maximum here attained (2.2 mg.) is practically double that of the antepartum period; and whereas the average of ten results secured during pregnancy was only 0.92, that of the present series is 1.15. The six cases (Nos. 13 to 18) responsible for these differences were, as much as the others, clinically normal individuals. The high concentration of creatinine which they showed appears therefore to have been a physiological phenomenon. Its acceptance as such would imply that a temporary accumulation of creatinine in the blood is a normal, if perhaps not invariable, consequence of the act of parturition. Of course, before such a conclusion could be taken as safely established, it would be necessary to show, by repeated determinations upon individuals, that the creatinine concentration during labor is actually higher than that of the periods immediately before and after. Systematic observations capable of affording such a demonstration have not yet been undertaken, but the few pertinent data in our possession do indicate precisely the effect postulated. In Cases 9, 13, and 15 the creatinine of the plasma was determined not only at parturition but also on the 9th to 11th day of the puerperium. In each instance its concentration was found to have fallen; for the first from 1.00 to 0.87, for the second from 1.26 to 0.70, and
A. Hunter and W. R. Campbell

for the third from 1.51 to 0.91. The observation on Case 9 suggests that even those figures of the table which fall within the normal range may represent a rise above the subject's ordinary level.

The extent of the rise in individual cases does not, as far as our limited data enable us to judge, in any way depend upon the age of the subject, the duration and character of the anesthesia, or the length of the labor. The only variable with which it appears to possess some regularity of relation is the number of previous confinements. Those cases which showed an unusual concentration of creatinine were all (with the possible exception of Case 17) in their first labor. Not only so, but among all the subjects examined there are only two primiparas out of ten (possibly eleven) who show less than 1.0 mg. per 100 cc., while of the seven multiparas not one has more. The cases are too few in number to support a generalization upon the point; but their tabulation may be admitted at least to suggest that the influence of labor upon the blood creatinine is greatest among primiparas.

The increased concentration at parturition, which our data suggest as normal for creatinine, is apparently not shared by many of the other non-protein nitrogenous constituents of the blood; for Slemons and Morriss have shown that the total non-protein nitrogen and specifically the urea remain within normal limits, while Morse observed no change during labor in the concentration of the amino-acids. Uric acid, on the other hand, presents striking analogies of behavior with creatinine. For, although Slemons and Bogert found its concentration in the majority of uncomplicated cases normal, they demonstrated in several instances a definite increase consequent upon labor, and observed the occasional occurrence in primiparas, although not in multiparas, of values abnormally high. It is of interest that the blood sugar also, according to Morriss, although normal during pregnancy and the puerperium, rises at parturition just as we believe the creatinine to do. Three then of the blood constituents show, either regularly or occasionally, an increase of concentration

Creatinine and Creatine during labor. It is perhaps worthy of note, that each of these three is believed to be connected, in one way or another, with muscular work. Morriss, accordingly, attributes the behavior of blood sugar during labor directly to the voluntary efforts of the mother during the second stage; and Slemons and Bogert incline to bring the concentration of uric acid also into relation with the duration and severity of the labor. Between this factor and the creatinine content of the blood we have been unable in our short series of cases to discover any apparent connection. If it exists, it has been obscured by other intercurrent effects. In the case therefore of creatinine the immediate cause of an increased concentration at parturition must remain a matter of speculation.

*Placental Transmission of Creatine.*

The unmodified Folin method for creatine, whether applied to whole blood or to plasma, is affected, as we have found, by a large and, for the single determination, incalculable error. This may render doubtful the significance of data for creatine in individual cases, but does not seriously affect the value, as a basis for comparison, of the averages for a reasonably large series like the present.

The plasma averages, which alone are of immediate significance for our central problem, are in mother and fetus almost identical. Between individual results, whether these lie above or below the general average, there is noticeable a correspondence, which is often nearly, or even quite, as exact; while of a really conspicuous lack of agreement there are not more than one or two instances. As regards the creatine of plasma, therefore, our original report, confirmed as it has been by the observations of Plass, requires no modification. We infer accordingly that the placental transmission of creatine, like that of creatinine, is a process of simple diffusion through structures equally permeable in either direction. It may be noted as not inconsistent with this view that, as far as there appears to exist any tendency at all to the establishment of a systematic difference of concentration, it operates again, as with creatinine, in favor of a slightly higher level in the fetal plasma.
The conclusion reached is independent of the absolute accuracy of the creatine figures, the argument assuming only that, as is probable, the average error in maternal and fetal plasma is the same. The extent of that error we have estimated as such that the true average for plasma is roughly one-fourth of the average found. The averages of the present series, corrected accordingly, become 0.52 and 0.54. If these values are added to those for creatinine, we find that the "total" creatinine of our cases averaged 1.67 for the mother, and 1.75 for the child. It must be rather more than a coincidence that Plass, utilizing an improved method of analysis, found the average "total" creatinine of twelve specimens of maternal and fetal plasma to be respectively 1.70 and 1.73. As the preformed creatinine of these particular specimens was not determined, we are left in ignorance of their content of actual creatine; but for an earlier series of nine cases Plass has given figures indicating an average creatine of 0.76 for maternal and 0.86 for fetal plasma. These are estimates which are probably at least a little too high, and which in any case are but slightly in excess of our own. Considering that the latter can be offered as approximations only, their substantial agreement with the independent observations quoted is extremely gratifying.

We have shown elsewhere that the (corrected) plasma creatine of normal individuals with creatine-free urine does not exceed, on the average, 0.41 mg. per 100 cc. Average values higher than that are yielded only by groups of individuals excreting creatine. The value 0.52, found for the mothers of the present series, is practically identical with that yielded by the twenty cases of creatinuria which we previously encountered among forty-six healthy subjects. We made no actual determinations of urinary creatine in the cases now reported, but, in view of the

15 They were reached by the use of the original method of Folin. The experience of Wilson and Plass with this method as applied to the determination of creatine in plasma has been less unfavorable than our own; for they found it to yield results not very much higher than those of their improved procedure.

16 Actually it may, as Wilson and Plass maintain, be a zero quantity; we are dealing here with approximations only.
regular occurrence of creatinuria during pregnancy, it may be assumed to have been present in practically every one. The results upon parturient women, none of which were utilized in our previous paper, may therefore be taken as additional evidence for the tentative views therein expressed upon the relation of creatinuria to the concentration of creatine in the plasma.

Creatine of Whole Blood and of Corpuscles in Mother and Fetus.

The whole blood results for creatine, individually considered, are very irregular, but permit this generalization at least, that in a decided majority of instances the fetal blood contains a higher concentration of creatine than the maternal. There are a few cases of approximate equality, but only one (No. 5) where the fetal concentration is unequivocally the lower. The impression thus created takes definite form, with something at least of quantitative meaning, in the corrected averages. According to these the maternal blood at parturition, with 3.45 mg. per 100 cc., shows practically the same concentration of creatine as that of a group of pregnant women, recently reported to contain 3.50 mg. The blood of the fetus contains distinctly (about 23 per cent) more, reaching an average (4.25) higher than we have encountered in any other group of bloods. Since the plasma concentrations are practically identical, this might at first be supposed to indicate that the fetal corpuscles possess a greater accumulation of creatine than the maternal. This is not really the case. If from the average data for relative plasma volume, whole blood creatine and creatine of plasma, one calculates the creatine content of the corpuscles, it is found to be 8.2 mg. per 100 cc. for the mother, and 8.4 for the fetus. Apparently then the superior richness in creatine of the fetal blood is due entirely to the relative polycythemia which it almost invariably presents; and the approximate equality of fetal and maternal concentrations, already established for the plasma, is seen to extend also to the corpuscles.

The corpuscular creatine of various groups of normal men and

18 The corrected average for whole blood is reached by halving the average found.
A. Hunter and W. R. Campbell

non-pregnant women we have estimated at from 6.1 to 7.0 mg. per 100 cc. The value now reached for parturient women is decidedly higher, and approximates rather that (9.1) found from 1 to 19 days antepartum in a smaller group of pregnant women. Our results suggest therefore that in the later stages of pregnancy there takes place a special accumulation of creatine in the red blood corpuscles. In this respect, as in so many others, they are in harmony with those of Plass. The harmony extends even to certain quantitative details. We have calculated that in the ten cases reported by Plass the average “total” creatinine content of the corpuscles is 10.83 and 10.49 for mother and fetus respectively; the corresponding figures in our own cases (putting the true corpuscular as equal to the observed plasma creatinine) are 9.35 and 9.61. The differences are comparatively trivial, and the two estimates may be regarded as mutually confirmatory.

SUMMARY.

The concentrations of creatinine and creatine in the maternal plasma differ little, if at all, from those of the same substances in the fetal. In either case the average concentrations in these respective situations become, in a sufficiently large series, practically identical. If there is any perceptible tendency to a systematic difference, it is in the direction of a slightly higher concentration in the fetus. It is probable, therefore, that the placental transmission of creatinine and creatine is a simple process of diffusion.

Parturition is accompanied normally, although perhaps not invariably, by a temporary rise in blood creatinine. This effect appears to be illustrated most strikingly among primiparas.

The creatine content of the plasma at parturition corresponds with that found normally in association with creatinuria.

The concentration of creatine in the whole blood is generally greater in the fetus than in the mother; but the concentration in the corpuscles, as in the plasma, is practically the same in both.

The concentration of creatine in the corpuscles of parturient women is greater than in those of non-pregnant women or of men. It would appear that pregnancy is accompanied by a special accumulation of creatine in the corpuscles.
THE PLACENTAL TRANSMISSION OF CREATININE AND CREATINE
Andrew Hunter and Walter R. Campbell


Access the most updated version of this article at http://www.jbc.org/content/34/1/5.citation

Alerts:
- When this article is cited
- When a correction for this article is posted

Click here to choose from all of JBC's e-mail alerts

This article cites 0 references, 0 of which can be accessed free at http://www.jbc.org/content/34/1/5.citation.full.html#ref-list-1