THE EQUILIBRIUM BETWEEN CEREBROSPINAL FLUID AND BLOOD PLASMA

IV. THE CALCIUM CONTENT OF SERUM, CEREBROSPINAL FLUID, AND AQUEOUS HUMOR AT DIFFERENT LEVELS OF PARATHYROID ACTIVITY

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The administration of an active parathyroid extract causes the serum phosphorus to fall and the serum calcium to rise (1-4). Although the effect of parathyroid injections on the serum calcium and serum phosphorus is very marked, the serum proteins remain unchanged (3); with normal parathyroid activity the serum calcium varies directly with the serum protein (5, 6). Merritt and Bauer (7) have observed a similar relationship between the calcium of the cerebrospinal fluid and the serum protein. The variations of the serum calcium at different levels of parathyroid activity have been thoroughly studied but very little is known concerning the calcium content of other body fluids in these various states. It is our purpose to report the relation of the serum calcium to cerebrospinal fluid and aqueous humor calcium at varying levels of parathyroid activity. The methods used have been previously described (7).

I. Hyperfunction of Parathyroid Glands

A. In Man—Hyperfunction of the parathyroid glands results in a rise in the serum calcium content, but there is very little information as to whether this increase is mainly or wholly in the diffusible or the non-diffusible fraction of the serum calcium. Moritz (8) working with rabbits found an increase in both frac-
tions in six animals when parathyroid extract was administered. In three instances he observed a relatively greater increase in the diffusible fraction. Stewart and Percival (9) claim that the calcium mobilized by the parathyroid glands is largely diffusible calcium. They stated that 58 to 80 per cent of the serum calcium is normally diffusible. With the administration of a parathyroid extract this increases to 80 or 90 per cent. Liu (10) found a

relatively greater rise in the diffusible fraction in two patients with parathyroid tetany when they were given parathyroid extract.

On the other hand Snell (11) reported that 45 to 60 per cent of the serum calcium is diffusible and that there is very little, if any, change in this ratio with dysfunction of the parathyroid glands.

For reasons previously stated (7) we have considered the cerebrospinal fluid calcium content to be a more accurate physiological representation of the diffusible calcium of the serum than the values obtained by the various filtration methods used to deter-
mine diffusible serum calcium. Cantarow (12), also working on this hypothesis, found in man that the cerebrospinal fluid calcium rose 3 to 4 hours after the giving of 40 units of parathyroid extract, although the serum calcium content had remained unchanged. At the end of 12 hours, however, the cerebrospinal fluid calcium had in most instances returned to or fallen below its original level whereas the serum calcium content was then at its height. Berencsy (13) reported a rise in the cerebrospinal fluid calcium content

![Chart II](http://www.ncbi.nlm.nih.gov/)

**Chart II.** The calcium content of the serum and cerebrospinal fluid of a 15 year old male with epilepsy, before and after parathormone injections. The solid line represents the serum calcium, the broken line the cerebrospinal fluid calcium.

on giving 1 unit of parathormone per kilo per day for 2 days, but his values for normal cerebrospinal fluid calcium varied from 6.10 to 8.41 mg. per 100 cc., which are outside of the range commonly accepted as normal. Therefore his results are difficult to interpret.

The results of the subcutaneous administration of parathormone (Lilly) to seven patients are shown in Charts I to VII. It will be noted that in five of the seven cases a substantial rise in the serum calcium content was obtained. In two cases, Charts VI and VII,
CHART III. The calcium content of the serum and cerebrospinal fluid of a 26 year old male with epilepsy, before and after parathormone injections. The solid line represents the serum calcium, the broken line the cerebrospinal fluid calcium.

CHART IV. The calcium content of the serum and cerebrospinal fluid of a 16 year old female convalescing from meningococcus meningitis, before and after parathormone injections. The solid line represents the serum calcium, the broken line the cerebrospinal fluid calcium.
no significant elevation in the serum calcium content was observed although larger doses of the same parathyroid extract which had been effective in the other five cases were used. In these two cases a slight fall in the cerebrospinal fluid calcium occurred. In none of the seven patients was any elevation of the cerebrospinal fluid calcium noted. In each instance the ratio of the cerebro-

![Diagram](http://www.jbc.org/)

**Chart V.** The calcium content of the serum and cerebrospinal fluid of a 56 year old male with idiopathic parathyroid tetany, before and after the daily administration of 100 units of parathormone. The solid line represents the serum calcium, the broken line the cerebrospinal fluid calcium.

spinal fluid calcium content to the serum calcium content was reduced.

In Case 2 (Chart II) the serum calcium content was maintained above normal for 6 days but no change in the cerebrospinal fluid calcium content was noted at the end of this period.

**B. In Animals**—Charts VIII and IX show the results obtained in two cats. The serum and cerebrospinal fluid calcium content was determined and then the animals were given 100 units of
CHART VI. The calcium content of the serum and cerebrospinal fluid of a 56 year old male with syphilis of the central nervous system, before and after parathormone injections. The solid line represents the serum calcium, the broken line the cerebrospinal fluid calcium.

CHART VII. The calcium content of the serum and cerebrospinal fluid of a 43 year old male with epilepsy, before and after parathormone injections. The solid line represents the serum calcium, the broken line the cerebrospinal fluid calcium.
parathormone. In these animals the serum and cerebrospinal fluid were withdrawn 3 hours and 24 hours following the injection of the parathormone. It will be noted that there was no rise in the serum calcium content 3 hours after the injection but there was a definite elevation in the cerebrospinal fluid calcium content. At the end of 24 hours the serum calcium had risen about 2 mg. and the cerebrospinal fluid calcium had returned to the preinjec-

![Graph](http://www.jbc.org/)  

**Chart VIII.** The calcium content of the serum and cerebrospinal fluid of Cat 3, before, 3 hours after, and 24 hours after the injection of 100 units of parathormone. The solid line represents the serum calcium, the broken line the cerebrospinal fluid calcium.

tion level. These results are in accord with the findings of Cantarow (12).

In an endeavor to determine the effect of parathormone administration on the bone trabeculae, daily injections were given to a litter of rabbits for a period of 91 days. The extract was given in increasing dosages until each animal was receiving 8 units per day. This dose they received for 56 to 74 days of the period. At the end of this period (24 hours after the last injection) the animals were killed by etherization. The results of the experi-
CHART IX. The calcium content of the serum and cerebrospinal fluid of Cat 4, before, 3 hours after, and 24 hours after the injection of 100 units of parathormone. The solid line represents the serum calcium, the broken line the cerebrospinal fluid calcium.

TABLE I

Effect of Prolonged Parathormone Injections (91 days) on the Serum and Aqueous Humor Calcium Content in Rabbits

<table>
<thead>
<tr>
<th>Animal No.</th>
<th>Serum (mg. per 100 cc.)</th>
<th>Aqueous humor (mg. per 100 cc.)</th>
<th>Animal No.</th>
<th>Serum (mg. per 100 cc.)</th>
<th>Aqueous humor (mg. per 100 cc.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td></td>
<td></td>
<td>Injected animals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>351</td>
<td>9.56</td>
<td>6.51</td>
<td>301</td>
<td>15.5</td>
<td>7.70</td>
</tr>
<tr>
<td>297</td>
<td>10.31</td>
<td>6.49</td>
<td>298</td>
<td>14.2</td>
<td>6.17</td>
</tr>
<tr>
<td>353</td>
<td>10.02</td>
<td>6.90</td>
<td>349</td>
<td>14.6</td>
<td>8.44</td>
</tr>
<tr>
<td>314</td>
<td>11.63</td>
<td>7.00</td>
<td>350</td>
<td>15.75</td>
<td>7.33</td>
</tr>
<tr>
<td>352</td>
<td></td>
<td></td>
<td>352</td>
<td>13.2</td>
<td>6.96</td>
</tr>
<tr>
<td>Average...</td>
<td>10.38</td>
<td>6.72</td>
<td></td>
<td>14.65</td>
<td>7.82</td>
</tr>
</tbody>
</table>
ments have been previously reported by one of us (W. B. (14)).
The serum and the aqueous humor were withdrawn just before
the animals were killed, and the results of the calcium determina-
tions on these fluids are reported herewith. Table I shows that
the serum calcium content for four normal control rabbits aver-
aged 10.38 mg. per 100 cc. and the aqueous humor calcium content
averaged 6.72 mg. per 100 cc. The average values for the five
injected animals were 14.65 mg. of calcium per 100 cc. for the
serum and 7.32 mg. per 100 cc. for the aqueous humor. This
gives an average increase of 4.27 mg. for the serum and only 0.6
mg. increase for the aqueous humor. From these results it would
appear that the injection of parathyroid extract causes only a
slight increase in the calcium content of the aqueous humor. The
relatively high calcium content of the aqueous humor of the rabbit
as compared to that of the cerebrospinal fluid of man or cat is
possibly explained by the fact that when aqueous humor is re-
moved the last portion of the sample usually contains a large
excess of protein and therefore approaches the serum in
composition.

II. Hypofunction of Parathyroid Glands

It has been consistently observed that with hypofunction of the
parathyroid glands there is a decrease in the serum calcium
content, but there has been some disagreement as to what portion
of the serum calcium is most affected. Salvesen and Linder (15)
removed the parathyroid glands from two dogs and obtained a
fall in the serum calcium content without any change in the serum
proteins, so they concluded that the calcium loss must be from
the non-protein bound, or diffusible portion. Moritz (8) working
with parathyroidectomized rabbits found by diffusion experiments
that the decrease of the calcium content was in both portions, but
in six of his seven animals the decrease was relatively greater in
the diffusible portion. Von Meysenbug and McCann (16)
observed in two cases of human rickets and four cases of parathy-
roid tetany in dogs that the total calcium content of the serum
was much reduced, but the portion of the calcium diffusible
through a collodion membrane was 60 to 70 per cent of the total
amount, which was the percentage that they had obtained for
normal dog and human sera. Cruickshank (17) reported that 60
to 70 per cent of the serum calcium would normally diffuse through a collodion membrane, but in severe parathyroid tetany the percentage of diffusible calcium increased to as much as 94 per cent of the total. He postulated that in parathyroid tetany there was a rapid breakdown of the protein-bound calcium in order to supply the tissue demands for calcium. Cameron and Moorhouse (18), considering the cerebrospinal fluid calcium as representing the diffusible calcium, found in normal dogs that the cerebrospinal fluid calcium equalled 53 per cent of the serum calcium; whereas in the parathyroidectomized animals the cerebrospinal fluid calcium, while decreased in absolute amount, equalled 70 to 100 per cent of the serum calcium.

Table II shows the results of our determinations of the serum and cerebrospinal fluid calcium contents in three cases of human parathyroid tetany. In these cases there was a marked reduction of the serum calcium content with only a very slight or no decrease of the cerebrospinal fluid calcium content, and the ratio of cerebrospinal fluid to serum calcium was markedly increased reaching 100 per cent in one instance.

Table III shows the values for the serum and cerebrospinal fluid calcium contents in all of the parathormone experiments, before and after the injections. Before the injections the ratio of cerebrospinal fluid calcium to serum calcium varied from 49 to 53 per

### Table II

<table>
<thead>
<tr>
<th>Case</th>
<th>Ca content</th>
<th>P content</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Serum</td>
<td>Cerebrospinal fluid</td>
</tr>
<tr>
<td></td>
<td>mg. per 100 cc.</td>
<td>mg. per 100 cc.</td>
</tr>
<tr>
<td>K. L.</td>
<td>8.20</td>
<td>4.42</td>
</tr>
<tr>
<td>B. W.</td>
<td>4.50</td>
<td>4.55</td>
</tr>
<tr>
<td>B. W.*</td>
<td>6.70</td>
<td>4.40</td>
</tr>
<tr>
<td>H. T.</td>
<td>5.93</td>
<td>5.18</td>
</tr>
</tbody>
</table>

* After receiving 100 units of parathormone each day for 3 days.
cent with an average of 51 per cent. After the injections the ratio varied from 37 to 49 per cent with an average of 42 per cent. If the cerebrospinal fluid calcium is considered as the diffusible calcium it would seem that parathormone affects only the non-diffusible portion. Table III also shows the values for the phosphorus content of the serum and the cerebrospinal fluid. Although there were individual variations there tended to be a decrease in both the serum and cerebrospinal fluid phosphorus content with a rise in the calcium content. This occurred also in one of the cases of parathyroid tetany when given parathormone (B. W. in Table II).

Chart X shows the serum and cerebrospinal fluid calcium content in the cases of parathyroid tetany and in the cases with high serum calcium resulting from parathormone injections as compared with forty-nine normal cases. This chart shows that the parathyroid hormone has only a slight influence on the cerebrospinal fluid calcium content. The serum calcium content ranged from 4.5 mg.
to 14.1 mg. per 100 cc. while the cerebrospinal fluid calcium content was within the normal range of 4.5 to 5.5 mg. per 100 cc.

CHART X. Graphic presentation of data contained in Table I of the preceding paper and Tables II and III of this paper. Each point on the graph represents the simultaneous determination of calcium both in serum and in cerebrospinal fluid. In these experiments, although the serum calcium varied from 4.5 mg. per 100 cc. to 13.9 mg. per 100 cc., the cerebrospinal fluid calcium remained within the range of 4.45 mg. per 100 cc. to 5.6 mg. per 100 cc.

SUMMARY

The constancy of the serum calcium level needs no comment. The constancy of the cerebrospinal fluid calcium level is more remarkable. The serum calcium varies with serum proteins, low serum proteins being regularly associated with low serum calcium. The variations in serum calcium which accompany changes in parathyroid activity are, however, independent of the serum protein level (3). It is interesting therefore to compare the effect upon the cerebrospinal fluid calcium level of these two apparently different types of variation in the serum calcium. The outstanding result in both cases is that the cerebrospinal fluid
calcium remains remarkably constant in spite of well marked changes in the serum calcium level. The striking lowering of the serum calcium occurring in parathyroid tetany and the sustained elevation of the serum calcium following parathormone administration were without appreciable effect upon the cerebrospinal fluid calcium level. Variations in serum calcium associated with different levels of serum protein were reflected to a slight degree in the cerebrospinal fluid. Our data (7), however, were not sufficient to bring out this relationship clearly. We observed the greatest variation in the cerebrospinal fluid calcium in patients who took water by mouth during the antidiuretic action of vasopressin (7). In these cases we noted a dilution of both the blood serum and the cerebrospinal fluid (19).

If we accept the cerebrospinal fluid as a dialysate in osmotic and hydrostatic equilibrium with the blood plasma, our data would indicate that variations in serum calcium occurring during parathyroid tetany or following the administration of parathyroid gland extract are chiefly and perhaps wholly limited to the non-diffusible calcium. Our data would also suggest that those variations in serum calcium which are associated with different levels of serum protein involve both the diffusible and the non-diffusible calcium.1

1 Since this was written an important paper has appeared (Morgulis, S., and Perley, A. M., J. Biol. Chem., 88, 169 (1930)). In dogs the marked increase in serum calcium, produced by feeding calcium in conjunction with injections of parathyroid extract, or by prolonged intravenous injections of calcium salts, was associated with but minor increases in the cerebrospinal fluid calcium. Similarly the marked fall in serum calcium following parathyroidectomy was associated with but minor decreases in the cerebrospinal fluid calcium. In one instance, however, a serum calcium of 4.0 mg. per 100 cc. was accompanied by a cerebrospinal fluid calcium of 3.7 mg. per 100 cc. With the exception of this case the lowest cerebrospinal fluid calcium after parathyroidectomy was 4.6 mg. per 100 cc., while the highest cerebrospinal fluid calcium after parathyroid extract injection was 6.5 mg. per 100 cc. These figures are only slightly outside their range for normal dogs—5.2 to 5.9 mg. per 100 cc. It is interesting that the greatest rise in cerebrospinal fluid calcium was obtained after intravenous injection of calcium salts—5.6 to 8.3 mg. per 100 cc. Our greatest fall in cerebrospinal fluid calcium occurred after water drinking during the antidiuretic action of posterior lobe pituitary extract—4.9 to 4.1 mg. per 100 cc. (7). Their results as well as ours emphasize the remarkable constancy of the cerebrospinal fluid calcium level.
BIBLIOGRAPHY

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