THE EFFECT OF THE ADMINISTRATION OF COD LIVER OIL UPON THYROPARATHYROIDECTOMIZED DOGS.

By JAMES H. JONES.

(From the Department of Physiological Chemistry, School of Medicine, University of Pennsylvania, Philadelphia.)

(Received for publication, August 30, 1926.)

Tetany, which is caused by or associated with defective calcium metabolism, very often accompanies rickets, a disease also characterized by faulty calcium and phosphorus utilization. Within the past few years numerous attempts have been made to cure infantile tetany by the use of methods known to have a beneficial action in the prevention and cure of rickets. Shortly after Huldschinsky (1) reported that ultra-violet radiations cured rickets, Sachs (2) claimed that the symptoms of latent tetany could be alleviated by artificial sunlight. This claim was soon supported by Huldschinsky (3) who reported that he had been able to cure manifest tetany in several infants by irradiating them with ultra-violet light. Following these investigations, Casparis and Kramer (4), Hoag (5), Lestocquoy (6), and Block and Faber (7) also showed that ultra-violet light has a therapeutic action in the treatment of tetany. Hoag (5) and Liu (8) reported the same for cod liver oil although the former obtained more marked effects with ultra-violet radiations.

While our knowledge concerning the effect of antirachitic agents upon infantile tetany has thus been increased, little is known of their influence upon experimental tetany produced by the removal of the parathyroid glands from dogs. It was for the purpose of studying this subject that the experiments described here were planned. However, while the work was in progress a paper appeared by Swingle and Reinhold (9) in which they gave the results of the treatment of ten parathyroidectomized dogs with ultra-violet light. They exposed their animals for varying lengths of time both before and after the removal of the glands. They were
**TABLE I.**

*Effect of Administration of Cod Liver Oil upon Prevention of Tetany, Duration of Life, and Concentration of Serum Calcium.*

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before operation.</td>
<td>After operation.</td>
<td>Before tetany.</td>
<td>Before death.</td>
</tr>
<tr>
<td>16</td>
<td>Basal ration for 14 days.</td>
<td>None.</td>
<td>No tetany observed.</td>
<td>3+</td>
</tr>
<tr>
<td>17</td>
<td>Basal ration for 14 days.</td>
<td>“ ”</td>
<td>2</td>
<td>4+</td>
</tr>
<tr>
<td>6</td>
<td>None.</td>
<td>20 cc. cod liver oil daily.†</td>
<td>2</td>
<td>2+</td>
</tr>
<tr>
<td>7</td>
<td>“ ”</td>
<td>“ ” †</td>
<td>No tetany observed.</td>
<td>2+</td>
</tr>
<tr>
<td>21</td>
<td>Basal ration for 15 days.</td>
<td>“ ”</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>9</td>
<td>Basal ration + 10 cc. cod liver oil daily for 13 days.</td>
<td>10 cc. cod liver oil daily.†</td>
<td>No tetany.</td>
<td>Discontinued.</td>
</tr>
<tr>
<td>15</td>
<td>Basal ration + 20 cc. cod liver oil daily for 13 days.</td>
<td>20 cc. cod liver oil daily</td>
<td>“ “</td>
<td>21</td>
</tr>
<tr>
<td>----</td>
<td>--------------------------------------------------</td>
<td>---------------------------</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>20</th>
<th>Basal ration + 20 cc. cod liver oil daily for 14 days.</th>
<th>None.</th>
<th>“ “</th>
<th>54</th>
<th>(3 days.)</th>
<th>(13 days.)</th>
<th>(21 days.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8.62</td>
<td>6.22</td>
<td>5.20</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>24</th>
<th>Basal ration + 20 cc. cod liver oil daily for 13 days.</th>
<th>“ “</th>
<th>“ “</th>
<th>49</th>
<th>(2 days.)</th>
<th>(14 days.)</th>
<th>(29 days.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7.94</td>
<td>6.58</td>
<td>4.85</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>25</th>
<th>Basal ration + 20 cc. cod liver oil daily for 7 days.</th>
<th>“ “</th>
<th>4</th>
<th>21</th>
<th>(2 days.)</th>
<th>(14 days.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7.94</td>
<td>5.04</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>26</th>
<th>Basal ration + 20 cc. cod liver oil daily for 7 days.</th>
<th>“ “</th>
<th>6</th>
<th>17</th>
<th>(2 days.)</th>
<th>(6 days.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6.78</td>
<td>4.84</td>
</tr>
</tbody>
</table>

Fed meat on 2 successive days. No tetany.

Exercised on 29th day. No tetany. Died during night.

Died during night. Slight tetany observed only once.

Tetany observed only once while blood sample was being taken. Died during night.

* Number of days after operation when blood sample was taken.
† Irradiated 20 minutes daily.
able to increase considerably the length of time that their animals lived after the operation. The average for their ten dogs was about 11 days instead of the usual 2 to 5 days. They found that although the animals' lives were lengthened the concentration of calcium in the blood fell, within 2 or 3 days, from 10 or 11 mg. per 100 cc. of serum to 6 or 7 mg. with the simultaneous onset of tetany. They concluded that the increased length of life of their animals was due to the treatment after the glands had been removed.

The following report deals with the results of feeding cod liver oil although the effect of ultra-violet irradiation was studied at the same time. A few animals were given both treatments and are included in this series of experiments.

**EXPERIMENTAL.**

Dogs were used as experimental animals. They were fed a basal ration of equal parts of autoclaved rolled oats and corn-meal supplemented with 5 gm. of casein and 2 gm. of sodium chloride daily. The rolled oats and corn-meal mixture was fed in such quantities that the animals could eat of it ad libitum. The cod liver oil was fed directly into the mouth of the animals from a graduated cylinder. To minimize the possibility of incomplete removal of the parathyroid glands the thyroids were extirpated with the parathyroids. Even under these conditions a certain number of animals fail to show symptoms due, presumably, to the presence of accessory parathyroid tissue.

Blood samples were taken by heart puncture at the time of operation and at varying intervals thereafter until the experiment was discontinued. The sera were analyzed for calcium. Most of the determinations were done by the method of deWaard (10). A few were done by Clark and Collip's (11) modification of Tisdall's method which apparently gives slightly lower and more consistent results.

After the removal of the glands the dogs were watched very closely for signs of tetany. In every case the dogs were continued on the basal ration although with a few exceptions they ate very little after the 2nd or 3rd day following the operation. A study was made of the effect of administering the cod liver oil before, as well as after, the removal of the glands. The influence of cod liver
oil upon the prevention of tetany, the duration of life, and the
concentration of serum calcium is summarized in Table I, and
greater details are given in the protocols appearing at the end of
the paper.

From the data it is evident that cod liver oil is without apparent
effect if administered only after the removal of the glands. On
the other hand if the oil is given before and after the operation,
or only before, it exerts a definite influence in prolonging life and
preventing tetany. After the removal of the glands the average
length of life of the untreated animals and of those which received
the treatment only after the operation was about 3 days; whereas
the average for the animals which were treated before operation
(including Dog 15) was 32 days.

The control animals, and those which received treatment only
after the operation, developed tetany within about 2 days. Dogs
7 and 16 were not observed in active tetany, but it will be noted,
however, that both these animals died during the night. As death
frequently follows within a short time after the first outward
signs of tetany, these animals probably experienced such a condi-
tion before death. Of the animals which received treatment
only before the removal of the glands, three were never seen to
show the least signs of tetany although they were observed very
closely throughout the entire experiments which lasted on an
average of 41 days. Each of the two animals which received the cod
liver oil for only 7 days before operation showed slight signs of
tetany on one occasion only.

Although the animals which received treatment before operation
had little or no tetany, all but Dog 20 showed very definite and
quite similar signs of failure. For a few days following the opera-
tion they appeared perfectly normal. However, it was not long
before they began to eat less and finally stopped eating entirely.
The loss of appetite was accompanied by loss of weight and a
greatly decreased activity on the part of the animals. Finally the
dogs became very much emaciated. This condition was soon
followed by coma and death. These symptoms are very similar
to those observed by Thompson and Leighton (12) when they
ligated the parathyroid glands in dogs. They summarize their
results as follows:

"After ligation of all parathyroid tissue the dog passes the time limits of
tetanic death that occurs after excision of the glandules, practically with-
out symptoms. Gradually, however, chronic symptoms, trophic in nature, arise. These consist in gradual but progressive loss of weight and strength, greatly diminished resistance to infection, and a final stuporous condition ending in death without tetany."

The decrease in activity of the animals usually accompanied the loss of appetite. However, Dog 24 remained active for a number of days after it had stopped eating. Dog 20 showed none of these symptoms although the concentration of calcium fell as low as 5.20 mg. per 100 cc. of serum. This animal died very suddenly on the 54th day after operation when a sample of blood was being taken from the heart.

The fact that these animals showed little or no tetany is still more remarkable when the concentration of calcium in the blood is taken into consideration. It will be observed from the accompanying table that the cod liver oil was not efficacious in maintaining normal calcium levels. Not only did the concentration in the serum of the animals receiving treatment before operation fall as rapidly as that of the controls (and animals treated only after the removal of the glands) but it fell to even lower levels before the dogs died.

Some investigators believe that tetany is associated with excessive protein metabolism. Berkeley and Beebe (13), Marine (14), Paton and Findlay (15), and Sinelnikoff (16) all report that the symptoms of tetany are aggravated by the feeding of flesh. The latter worker was able to bring on attacks of active tetany in parathyroidectomized dogs by feeding from 400 to 800 gm. of raw meat. In view of these experiments Dog 20 was fed 1 pound of raw lean beef on the 28th day following the removal of the glands. A similar amount was given again on the following day. The dog ate the meat ravenously, but no signs of tetany developed.

It has often been observed that tetany may be made manifest by disturbing the animal. Consequently on the 29th day following the operation Dog 24 was taken from the cage, and in addition to the disturbance of taking a sample of blood, it was caused to run about the room. Although analyses on that day showed the concentration of calcium to be 4.85 mg. per 100 cc. of serum no tetany developed.

The cause of tetany has been the subject of much discussion but none of the various theories advanced has been universally ac-
cepted. Since MacCallum and Voegtlin (17) first showed that the concentration of calcium in the blood is greatly reduced during tetany, many have believed tetany to be due to the low calcium concentration per se. One of the most recent advocates of this theory is Collip (18) who has demonstrated that it is not only possible to maintain a normal calcium level and prevent tetany in parathyroidectomized dogs by the injection of the active principle of the parathyroid glands, but if the extract which he prepared is injected into a normal dog the calcium concentration is raised considerably above the ordinary level.

The low calcium theory, however, is not adhered to by all investigators. Paton and Findlay (19) were able to produce a condition of hyperirritability in cats, rats, and rabbits associated with convulsions very similar to parathyroid tetany by the injection of guanidine and methyl guanidine. Burns and Sharpe (20) also reported an increased excretion of guanidine and methyl guanidine in the urine of dogs following the removal of the parathyroid glands. However, the uncertainty concerning the accuracy of the quantitative method used makes the observations of doubtful value.

Tetany has also been observed under various conditions when the calcium was either normal or slightly reduced. Graham (21) states that he has observed cases of infantile tetany in which the calcium of the blood was normal. Steenbock, Jones, and Hart (22) noted tetany in dogs with rickets. In regard to the relation of the concentration of calcium to tetany they make the following remarks.

"It is difficult to say what significance is to be attached to the lowered Ca values. Both of the animals were observed at intervals in severe tetanic convulsions, but we have also observed this in dogs afflicted with rickets which had a normal calcium content of the blood. Apparently, a decreased calcium content cannot per se be the cause of the convulsions in these animals.'"

While these cases to which reference has just been made show that it is possible to have tetany with a normal concentration of calcium in the serum the data reported in the present paper show that it is also possible to have a greatly lowered concentration of calcium in the blood and still not have tetany. These experiments add to the data already accumulated which strongly suggest
that factors other than the low concentration of serum calcium may influence the onset of parathyroid tetany.

Although no beneficial results were obtained if the oil were administered only after the removal of the parathyroid glands, these experiments do not prove that the presence of the glands is necessary for cod liver oil to exert its influence effectively. It appears that the feeding of 20 cc. of oil for 7 days is on the borderline of prevention and non-prevention of tetany. As none of the dogs which received the treatment only after the operation lived more than 3 days there is the possibility that the animals died before the oil could become effective. However, Block and Faber (7) believe that ultra-violet light acts in preventing tetany by stimulating the parathyroid glands to greater activity, which also may be true of cod liver oil.

SUMMARY.

The daily administration of 20 cc. of cod liver oil for 2 weeks before operation, prevented tetany and greatly increased the length of life of thyroparathyroidectomized dogs. However, 20 cc. per day of the oil, if given only after the removal of the glands, had no effect in preventing tetany or in prolonging the life of the animals.

The concentration of calcium in the blood of the treated animals fell as rapidly as that of the untreated animals, and, in fact, the lowest levels attained were in the blood of the treated dogs which lived the longest. These data indicate that some factor in addition to the low concentration of serum calcium plays a part in the production of the tetany which usually follows, within 2 or 3 days, the removal of the parathyroid glands.

Similar results, but not as striking, were obtained by irradiating the dogs with ultra-violet light before the removal of the glands.

The author wishes to extend his thanks to Dr. J. E. Sweet and associates of the Department of Research Surgery who performed the operations necessary for these investigations.
J. H. Jones

BIBLIOGRAPHY.

10. deWaard, D. J., Biochem. Z., 1919, xviii, 186.

PROTOCOLS.

Series I. Controls.

Dog 10, female; weight 12.2 kilos. No treatment.
Nov. 20, 1925. Began feeding basal ration.
Dec. 4. Thyroparathyroidectomy performed.
Dec. 7. Dog quieter.
Dec. 8. Animal found dead in the morning.

Dog 17, male; weight 11.0 kilos. No treatment.
Nov. 20, 1925. Began feeding basal ration.
Dec. 4. Thyroparathyroidectomy performed.
Dec. 5. Dog normal.
Dec. 9. Animal found dead in the morning.
Case Series II. Treatment Only after Removal of Glands.

Dog 6, male; not weighed. Cod liver oil and irradiation.
Feb. 5, 1925. Thyroparathyroidectomy performed at 5:30 p.m.
Feb. 7. A.m., slight trembling of facial muscles; p.m., dog in severe tetany.
Feb. 8. Animal found dead in the morning.

Dog 7, female; not weighed. Cod liver oil and irradiation.
Feb. 12, 1925. Thyroid and parathyroid glands removed. Began giving 20 cc. of cod liver oil and 20 minutes of ultra-violet light treatment daily.
Feb. 15. Animal found dead in the morning.

Dog 21, female; weight 11.6 kilos. Cod liver oil.
Dec. 31, 1925. Began feeding basal ration.
Jan. 15, 1926. Thyroparathyroidectomy performed. Began giving 20 cc. of cod liver oil.

Case Series III. Treatment before and after Removal of Glands.

Dog 9, male; weight 13 kilos. Cod liver oil and irradiation.
May 1, 1925. Began feeding basal ration. Also began treatment of 20 minutes irradiation and 10 cc. of cod liver oil daily.
May 12. Thyroparathyroidectomy performed.
May 15-26. Dog active and eating very well. Experiment discontinued as blood calcium is still high, indicating that parathyroid tissue was not completely removed.
Dog 10, male; weight 13.2 kilos. Cod liver oil.
Nov. 20, 1925. Began feeding basal ration and 20 cc. of cod liver oil daily.
Dec. 4. Thyroid and parathyroid glands removed.
Dec. 8. Dog somewhat quieter and appetite slightly reduced.
Dec. 25. Dog dead. No change from above. At no time has dog shown tetany.

Case Series IV. Treatment Only before Removal of Glands.

Dog 20, male; weight 11.8 kilos. Cod liver oil.
Jan. 1, 1926. Began feeding basal ration and 20 cc. of cod liver oil.
Jan. 15. Thyroid and parathyroid glands extirpated. Discontinued cod liver oil feeding.
Jan. 16-Feb. 11. Dog very active, eating well. Appears perfectly normal.
Mar. 10. Died very suddenly while taking a sample of blood. At no time did it show any abnormal signs.

Dog 24, male; weight 12.8 kilos. Cod liver oil.
Feb. 20, 1926. Began feeding basal ration and 20 cc. of cod liver oil daily.
Mar. 5. Thyroparathyroidectomy performed. Discontinued giving cod liver oil.
Mar. 8. Right eye sore.
Mar. 9. No change.
Mar. 11-Apr. 2. Dog active but not eating.
Apr. 3. Dog taken out of cage and caused to run about room. No sign of tetany.
Apr. 4-22. Dog gradually becoming very thin and weak.
Apr. 23. Dog cannot stand.
Apr. 24. Dog found dead in the morning.
Dog 25, male; weight 13.6 kilos.
Feb. 26, 1926. Began feeding basal ration and 20 cc. of cod liver oil daily.
Mar. 2. Thyroids and parathyroids removed. Discontinued giving cod liver oil.
Mar. 15. Dog becoming less active. Not eating.

Dog 26, female; weight 14.5 kilos. Cod liver oil.
Mar. 27, 1926. Began feeding basal ration and 20 cc. of cod liver oil daily.
Apr. 3. Thyroids and parathyroids extirpated.
Apr. 4-5. Animal normal.
Apr. 6-8. Not eating.
Apr. 9. Slight tetany while blood sample was being taken.
Apr. 20. Animal died during night.
THE EFFECT OF THE ADMINISTRATION OF COD LIVER OIL UPON THYROPARATHYROIDECTOMIZED DOGS
James H. Jones


Access the most updated version of this article at http://www.jbc.org/content/70/3/647.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/70/3/647.citation.full.html#ref-list-1