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A Cyclopian Fetus Resulting from Oral Ingestion of *Veratrum californicum*

By Stanley Allen*

Teratology, that branch of embryology and pathology which deals with abnormal development and congenital malformations, is not a new science. Since the very beginning of medical science, men have described anomalies; however, in comparatively recent times efforts have been made to do more than just describe them. This paper deals with the experimental production of a cyclopian lamb fetus by the oral administration of *Veratrum californicum* and reports of two field cases of cyclopians from central Iowa, one in a pig and one in a lamb.

Kalter divides anomalies of the central nervous system into these (1) experimentally produced and these (2) spontaneous in origin. Those spontaneous in origin are usually only descriptions, their origin or cause being unknown. Experimentally produced malformations have been produced by such factors as nutrient deficiencies, hyper-vitaminoses, trypan blue, and ionizing radiation.

Experimentally produced anomalies can be divided into three groups:

1. Those of laboratory occurrence only. These have been of great help in elucidating the processes of developmental anatomy.

2. Laboratory produced malformations which are the result of man's intervention into the developmental process which has occurred first outside the laboratory, then reproduced during subsequent research investigation in the laboratory. An example of this is the drug thalidomide used first outside the laboratory where it caused malformations and subsequently investigated in the laboratory for its teratogenic effect.

3. Those which occur spontaneously in nature in circumstances where man has not intervened; and after extensive investigation, man has reproduced these natural events in controlled experimentation.

A case of the latter type was first reported by Binns and others in 1959. In this report cyclopians were described. "The anomaly is always restricted to the head and varies from a complete cyclops to a slightly deformed upper jaw." Associated with this anomaly is a condition of prolonged gestation where the lamb continues to grow in utero to excessive size and may be carried by the ewe for up to 230 days. It was later shown by experimental feeding that this malformation was produced by the ingestion of *Veratrum californicum*. Veratrum grows on moist, open meadows and

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hillsides at elevations of 5,000 to 11,000 feet. The plant reaches a height of 6 to 8 feet. It is a robust perennial of the lily family. It emerges as soon as snow melts in the spring. Leaves of Veratrum may measure 9 to 12 inches long and 3 to 6 inches broad. Cream-colored flowers grow in clusters at the top of a single, unbranched stalk in a way that resembles corn. The time of insult caused by Veratrum was narrowed down to the 14th day after conception. Keeler, by extraction of the plant and experimental trial feeding of the extracted fractions and further study of the nature of the fractions, has found that there are primarily three compounds, alkaloid in nature, which are capable of producing the cyclopian defect. They are Veratrosine, Alkaloid X, and Cyclopamine. Keeler states: “The structure of Cyclopamine and its glycocide Alkaloid X have yet to be elucidated; but on the basis of infrared data, they are apparently very similar to Jervine and Veratrovine.”

**Material and Methods**

Ten sheep of mixed origin were selected to be given oral doses of dried and ground *Veratrum californicum* roots. The sheep were divided into two groups of five each. In Group I the ram was placed in the pen with a breeding marker to mark those sheep he mounted. The sheep were then checked morning and evening and breeding dates were recorded upon the basis of the marking made by the ram. In Group II the ram was brought to the sheep each morning and notations were made of which animal he mounted. On the basis of the breeding dates obtained, the plant *Veratrum californicum*, ground and given via stomach tube, was fed in two doses on the fourteenth day. One dose was in the morning; the other in the afternoon. The doses of the plant given are noted in Table I. The ewes were then maintained on a hay and grain diet until parturition time.

**Findings**

Clinical signs of immediate toxicity were observed in those animals on the 70 and 75 gram levels. These included depression and salivation. The animals assumed a posture of attempting to vomit; head raised and neck extended. These clinical signs were investigated by Mullendyke, Buck, Keeler, and Binns. They attributed these effects to certain ester alkaloidal fractions in the plants.

In the ten ewes tested, nine became pregnant. Of these nine, two came back into heat and were bred a second time; the plant was not fed to these sheep fourteen days after their second breeding. (Table I) Van Kampen and others report that *Veratrum californicum* can cause early embryonic death. We have no evidence to indicate that this did or did not occur in these two sheep. Of the other seven ewes, six had normal lambs, four had singles, and two had twins. The other lamb was a cyclopian. (Figure 1) These re-

<table>
<thead>
<tr>
<th>Sheep Number</th>
<th>Breeding Date</th>
<th>Date Plant Fed</th>
<th>Total Dose</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Sept. 24</td>
<td>Oct. 8</td>
<td>40 grams</td>
<td>Normal Single</td>
</tr>
<tr>
<td>10</td>
<td>Sept. 28</td>
<td>Oct. 8</td>
<td>50 grams</td>
<td>Rebred Oct. 14</td>
</tr>
<tr>
<td>12</td>
<td>Sept. 28</td>
<td>Oct. 12</td>
<td>50 grams</td>
<td>Normal Twins</td>
</tr>
<tr>
<td>13</td>
<td>Oct. 1</td>
<td>Oct. 15</td>
<td>50 grams</td>
<td>Normal Single</td>
</tr>
<tr>
<td>2</td>
<td>Oct. 1</td>
<td>Oct. 15</td>
<td>50 grams</td>
<td>Cyclopian Single</td>
</tr>
<tr>
<td>Group II</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>150</td>
<td>Oct. 10</td>
<td>Oct. 24</td>
<td>70 grams</td>
<td>Normal Twins</td>
</tr>
<tr>
<td>172</td>
<td>Oct. 13</td>
<td>Oct. 27</td>
<td>70 grams</td>
<td>Normal Twins</td>
</tr>
<tr>
<td>173</td>
<td>Oct. 10</td>
<td>Oct. 24</td>
<td>70 grams</td>
<td>Normal Single</td>
</tr>
<tr>
<td>174</td>
<td>Oct. 6</td>
<td>Oct. 20</td>
<td>60 grams</td>
<td>Failed to conceive</td>
</tr>
<tr>
<td>175</td>
<td>Oct. 30</td>
<td>Nov. 12</td>
<td>75 grams</td>
<td>Rebred Nov. 17</td>
</tr>
</tbody>
</table>

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results are comparable to those of the research workers in Utah is reported by Van Kampen. (Table II) The Utah Group fed the plant at varying intervals during the first thirty days of gestation. Those animals reported here were only fed on the fourteenth day. When the Utah Group feed the plant only on the fourteenth day of gestation, they were able to produce thirteen malformed fetuses and one embryonic death in fourteen ewes.¹

**Table II**

<table>
<thead>
<tr>
<th>Number with Abnormal Heat</th>
<th>Utah Group</th>
<th>Iowa Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aborted or Had</td>
<td>Over 4 Years</td>
<td>Iowa Group</td>
</tr>
<tr>
<td>Dead Fetuses</td>
<td>60 (16.6%)</td>
<td>19 (5.3%)</td>
</tr>
<tr>
<td>Deformed Lambs</td>
<td>43 (11.9%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Normal Lambs</td>
<td>239 (66.2%)</td>
<td>6 (60%)</td>
</tr>
<tr>
<td>Total Number</td>
<td>361</td>
<td>10</td>
</tr>
</tbody>
</table>

**Discussion**

*Veratrum californicum* does produce the result as reported by Binns, Keeler, James, Van Kampen, and others. The time of this insult in development may be toward the end of the fourteenth day or beginning of the fifteenth day. In those animals where the breeding time was known exactly (by observation of the ram), the plant was administered exactly fourteen days to the hour for the first dose and fourteen days plus six hours for the second dose. There were no malformations produced in this group. In the case where a cyclopian was produced in Group I, the breeding time could only be approximated within several hours; it was from the first observation after breeding when the animal had been marked that the fourteen days was calculated. It is, therefore, possible that the time of insult is late in the fourteenth or even early in the fifteenth day. In either case the fetus is susceptible only for a short period of time.

A question which might be asked is, from what point do we start to count the fourteen day period. The Utah Group considers the last time the ram is accepted by the ewe as day “zero”.⁵ We used the first time the ewe accepted the ram as our day “zero”. This could account for our low percentage of cyclopian fetuses. The exact time of conception in relation to acceptance of the ram needs further consideration and study.

**Observation of Cyclopianism in Animals in Iowa**

In considering all of the central nervous system anomalies, cyclopianism is one of
The most frequently seen. The cause of these malformations in most cases is not known. Stockard points out, as quoted by Binns\(^5\), that a given structural abnormality may be induced in the embryo of various species by a great number of different experimental treatments. We, therefore, must assume that cyclopianism in domestic animals could be produced by several different agents. Included herein are reports of two cases of cyclopianism which have occurred in the Central Iowa area in the past year; one in a lamb and the other is a pig. The insulting agent in either case is not known.

The pig in Figure 2 was born with normal littermates in the spring of 1967 on a farm south of Ames near Ankeny. The pig was given to Dr. Gary Osweiler* as he visited the farm on an ambulatory call concerning other animals on the premises. There was no detectable abnormal circumstances associated with the gestation period of the mother of this malformed pig that could be reported by the owner.

The lamb in Figure 3 was born in February 1970 near Boone, Iowa. It was born as a twin with a normal lamb which subsequently died due to circumstances unrelated to the presence of the cyclopian fetus twin. It was reported that the ewe had been on a timber pasture along the Des Moines River during the first few days of her pregnancy. The ewe was later taken to a cultivated pasture. The exact date of this change in pastures could not be determined. The author investigated this case.

Summary

One cyclopian fetus was produced by the oral administration of dried ground root of the plant Veratrum californicum. The time of insult was on the fourteenth day of gestation or shortly thereafter. This work confirms the work of Binns, Keeler, and others concerning the presence of a cyclopian-producing agent in the plant Veratrum californicum. Two cases of cyclopianism in central Iowa were reported.

The author expresses his appreciation to Dr. Wayne Binns,\(^5\) Dr. Richard Keeler,\(^5\) and Mr. Dell Balls for providing the sheep. and again to Dr. William M. Adams for feed and space for the experiment and for his interest and assistance in this project. Dr. Adams was directly responsible for Group I and the author for Group II. Dr. Adams was investigating the effects of Dexamethzone in these animals concurrently. Publication of his findings in this experiment will be in the near future.

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