EXPERIMENTAL PRODUCTION OF GIGANTISM BY
FEEDING THE ANTERIOR LOBE OF
THE HYPOPHYSIS.

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Perhaps the most reliable information as to what may be the func-
tion of the hypophysis (or any other endocrine gland) may be ex-
pected to be obtained through experiments on the extirpation and
transplantation of the gland. The majority of these experiments have
shown in a rather conclusive way, that growth and development are
inhibited in the partial (mammalian) or total (amphibian) absence
of the anterior lobe; an increase of the rate of growth ensues if anterior
lobes are grafted to the animals.1 Particularly clear are the results
obtained in amphibians. As shown by Smith2 and by Allen,3 the extir-
pation of the anterior lobe of the hypophysis results in an inhibition
of growth and metamorphosis of the operated tadpoles. Recently
Allen4 has shown that grafting the anterior lobe of adult frogs on
tadpoles causes an acceleration of growth and development in normal
larvae, and that it also restores the power of growth and develop-
ment after they had been lost through extirpation of the anterior lobe.

These experiments seem to demonstrate that the anterior lobe of
the hypophysis is the organ which makes growth possible during the
normal growth period of life. They do not afford, however, any evi-
dence as to whether the substance of the anterior lobe can cause growth
to continue beyond the period of life in which, under normal condi-
tions, the ability of growth is lost and whether in this way the anterior

1 For a more complete discussion of the literature see Uhlenhuth, E., The rôle
of the internal secretions in growth and development, in a book on Internal
lobe substance can increase the size of the individual over the normal "maximum" size of the species. It is well known that growth of every individual stops as soon as the specific size of the species is reached. Many problems pertaining to this phenomenon would appear in a new light if it were possible to cause gigantism by a particular substance.

Clinical observations point to the conclusion that at least one form of gigantism is caused by an excessive production of anterior lobe substance; nevertheless, attempts to produce experimental gigantism have so far been unsuccessful. The only way to attack this problem seems to be the feeding of the anterior lobe substance by mouth. Such experiments have been attempted in large numbers but the results have for the most part been contradictory and difficult to interpret. The majority of investigators have merely desired to determine whether or not feeding of anterior lobe modifies in a specific way the rate of growth. It will be pointed out later that the greatest care is necessary in the interpretation of results obtained from feeding experiments. From the more recent feeding experiments, and especially those performed by Hoskins and Hoskins\(^6\) and by Smith\(^6\) on tadpoles, by Robertson\(^7\) and his coworkers on white mice, and by Wulzen\(^8,9\) on chickens, most students of endocrinology have concluded that the anterior lobe substance retards growth in early periods of life, while later on it may cause an acceleration of growth. But in these experiments none of the animals fed with anterior lobe developed into giants, except in two cases in which the slightly greater size of the experimental animals may have been due to the effect of the anterior lobe substance. Robertson and Ray\(^10\) claim that they obtained unusually large mice, when the feeding of anterior lobe substance was started at an age of 4 weeks and discontinued at an age


of 12 weeks. In experiments in which the chicks were fed anterior lobe from an early stage, Wulzen succeeded in raising one anterior lobe-fed cock which weighed 1,882 gm. as against the weight of only 1,597 gm. of the control animal; no normal cock raised by Wulzen grew to the size of the hypophysis-fed bird. Wulzen, however, raised only one cock of this kind; moreover, no records are given in the paper as to the normal maximum size of that race of chickens, and, therefore, it is not certain that this cock could be actually considered a true giant.

From the experiments to be reported in this paper, it will become evident that at least in one group of cold blooded animals, namely in salamanders, feeding of anterior lobe leads to the attainment of a size considerably in excess of not only the normal “average” size, but of even the greatest known size of the two species (Ambystoma opacum and Ambystoma tigrinum) employed in these experiments.

Critical Remarks Concerning the Methods of Feeding.

It is usually stated that in order to obtain reliable results in feeding experiments of this kind, only small amounts of the glandular product should be added to an otherwise normal diet. I, however, am of the opinion that this method, although considered at present as the standard method, cannot, at least under all conditions, give conclusive results. It is possible that a gland may contain a specific growth-promoting principle and yet may not give, with the above mentioned method, positive results if the amount of the hormone fed is too small. We do not know how much of a supposedly hormonic substance is contained in a definite amount of the fresh product, nor do we know how much of it may be required to produce gigantism or accelerated growth. While most hormones act in small quantities, it would be premature to conclude that all hormones should act in small amounts. The main point in experiments of this kind is to be able to prove that the control animals are fed in such a way as to show the maximal rate of normal growth known to exist in the species experimented upon.

In my experiments the controls were fed exclusively the normal diet, while the experimental animals were fed exclusively on the anterior lobes of the hypophysis of cattle. This method is based on the
following considerations. If earthworms are a complete diet for salamanders, the worm-fed animals should grow at the maximum rate characteristic of the species, provided that the calories and vitamins are in sufficient quantity to make the maximum rate of growth at that particular temperature possible. If by chance the anterior lobe should have a higher food value than the earthworm, this could not result in a better growth as long as the food value of the earthworm suffices for the maximum normal growth. If the anterior lobe of the hypophysis contains only ordinary food substances and no specific hormone for growth, the rate of growth of the animal should not exceed the specific maximum rate.

Hence only two conditions had to be provided for. First, all animals, controls and experimental, had to be kept at the same temperature, a condition which was carefully provided for. Second, all animals were given as much food as they desired to take. This condition was approached as nearly as possible.

The worm-fed animals took the worms readily and voluntarily. The gland-fed animals, however, had to be fed by pushing the pieces of gland into their mouths; yet it was possible to adjust the quantity of food according to the appetite of the animals. They yield readily if the food is gently pressed against their jaws, and swallow the food quickly when they are hungry; while they push the food back by means of the tongue or eject it when it is forced into the mouth, if they are not hungry.

The quantity of food taken up by the controls was generally greater than the quantity of hypophysis taken by the experimental animals.

**Characteristics of Growth of Normal Salamanders.**

Two species of salamanders were employed in these experiments, *Ambystoma opacum* and *Ambystoma tigrinum*. Since little is known about the normal growth of these animals, some data pertaining to it may be recorded here.

Large numbers of *Ambystoma opacum* were reared from eggs in my laboratory and the growth of the species has been recorded over long periods. The longest record I possess is that of four animals which at present are 3 years (161 weeks) of age and were raised from eggs of
two different females. Many animals of this species were observed for a period of over 2 years and behaved essentially the same way. Fig. 1 shows the growth curves of the four 3 year old animals and illustrates the most important characteristics of the growth of that species. Although each animal, during the larval period, was treated in a different way (D₁ normal, E₃ underfed, W₈Ca₅ kept in water + a small amount of Ca lactate, W₉Na₄ kept in water + a small amount of Na lactate) all four curves are about the same. The most rapid growth takes place during the larval period (first period of growth); at the end of this period a decrease in size is noticeable which may last for several weeks and corresponds to metamorphosis. The second period of growth lasts from after metamorphosis till the first breeding season, at which the animals are about 1 year old. The beginning of the breeding season in the male may be recognized by the swelling and reddening of the cloacal region and in both males and females by the cessation of food intake. During the second period of growth the animals continue to grow at a fairly high rate; during the first as well as the following breeding seasons little growth or even a decrease in size may be noticed. The third period of growth begins after the first breeding season and lasts till the third breeding season, and is characterized by slow growth. No records are available to determine the behavior after the third breeding season, but to conclude from the normal maximum size of the species growth seems to be nearly completed at the end of the third period. The control animals of the hypophysis-fed series exhibit a similar type of growth (Fig. 2), although they were from a different season (1918). It is safe to assume that this is the type of growth characteristic for the species *Ambystoma opacum*. The most important feature of it, in connection with the following experiments, is the considerable slowing down of growth after the first breeding season.

As to the normal size of the species, the following records are available. The largest animal on record in my laboratory was 115 mm. long at an age of 79 weeks (it was one of the controls of the hypophysis-fed animals). The largest animal among fifteen specimens of from 2 to 3 years of age, still alive at present, measures 113.5 mm., the average size of these fifteen animals being 103.5 mm. (the small size of some of them may be due to the abnormal conditions under
FIG. 1. Growth of four specimens of *Ambystoma opacum* during a period of 3 years. All four animals were fed normal diet, but E₅ was underfed during the larval period and W₅ and W₆ and W₇ and W₈ were kept in water + small amounts of Ca lactate and Na lactate respectively during the larval period. The figure is drawn to a smaller scale than Figs. 2, 3, 4, and 5.
which they were kept during the larval period). Two breeding females, collected recently outdoors, measured 112 mm. and 106 mm. respectively. Cope, in his book on North American batrachians, mentions the specimen, from which he described the species, as measuring 3.8 inches (about 100 mm.). The largest animal found in the collection of the American Museum of Natural History measured 117.7 mm.; the average of the eight largest animals was 100.3 mm.

To conclude from these data the maximum size of the species is nearly 118 mm., while specimens measuring more than 115 mm. are of very rare occurrence.

I am obliged to Mr. George P. Engelhardt, of the Brooklyn Museum, for this record.


I wish to express my appreciation to Miss M. Dickerson for giving me the opportunity of examining the collection of salamanders at the American Museum of Natural History.
I have no other records concerning the growth of the species *Ambystoma tigrinum* except those afforded by the control animals of these experiments. These give information on the growth during a period of only 1½ years (84 weeks), the present age of the animals of Series A, XLVI, and LV. Apparently this species, as illustrated in Figs. 3, 4, and 5, behaves very much in the same way as the species *Ambystoma opacum*, growth being most rapid during the larval period, and continuing at a fairly high rate till about the end of the 1st year, after which it becomes rather slow.

It is not so simple to determine the maximum size of this species as in the case of *Ambystoma opacum*, since there are two races of the tiger salamander, a western and an eastern one, which are very different in respect to the type of growth. The western race seems to be naturally a giant race; this is true at least for the specimens which metamorphose from the well known neotenous larvae found in the western lakes. This condition, however, is doubtlessly caused by disturbances of the endocrine system and is rather pathological than normal. My experiments, performed with eastern animals, cannot be checked by means of these giants although they are apt to throw some light on the gigantism of the neotenous specimens and those that have metamorphosed from neotenous larvae. Cope in describing a large number of specimens of *Ambystoma tigrinum* mentions that the largest specimen among them measured 10 inches (about 244 mm.) and that De Kay described a still larger one measuring 11 inches (about 280 mm.). The largest specimen among 55 neotenous larvae which I myself collected in the vicinity of Tolland, in the Colorado Rocky Mountains, measured 257 mm., while all the metamorphosed specimens collected in the same locality were much smaller. As pointed out above, I have used in my experiments only eggs that were from females of the eastern race. Unfortunately, I have not reared enough animals of this species to form a conclusive idea as to the normal maximum size of the species. But the largest individual on record in my laboratory (one of the controls of these experiments) measures 200 mm. at an age of 84 months; it is, however, still growing, although very slowly. In the collection of the American Museum of Natural History I found the largest specimen among the nine largest animals, eastern as well as western, to measure 208.7 mm.
Fig. 3. Experiment 2 (Ambystoma tigrinum, 1919, Series XLVI). The unbroken line illustrates the growth of the controls, the dotted line that of the anterior lobe-fed animals.
Fig. 4. Experiment 3 (*Ambystoma tigrinum*, 1919, Series LV). The unbroken line represents the growth of the controls, the dotted line that of the anterior lobe-fed animals.
Fig. 5. Experiment 4 (*Ambystoma tigrinum*, 1919, Series A and XXXVII). The unbroken line represents the growth of the controls, the dotted line that of the anterior lobe-fed animals.
while the average was 200.8 mm. From these data it seems that while the largest specimen that could be found among eastern animals of this species measured 208.7 mm., pathological conditions of the endocrine system may produce giants of a maximum size of 280 mm.


Experiment 1.—Of four normal metamorphosed specimens (Series XIV) of *Ambystoma opacum* which had been reared in the laboratory from eggs of the same female (Brood 1918) two were started on a diet of anterior lobe of cattle hypophysis at an age of 60 weeks, *i.e.* at the beginning of the third period of growth; the other two animals were controls and were kept on an abundant diet of earthworms. The size of the animals at the beginning of the experiment may be seen from Table I.

<table>
<thead>
<tr>
<th>TABLE I.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypophysis-Fed Ambystoma opacum, Experiment I.</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Animal No.</th>
<th>Size of animals.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>60 weeks</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Control</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Anterior lobe-fed animals</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
</tbody>
</table>

The rate of growth of the anterior lobe-fed animals, after 2 weeks of feeding, rose over that of the controls and continued at such a height as is usually observed only in the second period of growth (Fig. 2). The two control animals, although they were fed on an abundant diet, continued to grow at a slow rate (Fig. 2) characteristic of the third period of growth (Fig. 1). In consequence of their rapid growth the anterior lobe-fed animals, 12 weeks after the beginning of the experiment, had reached a size exceeding that of the largest animals of this species on record (Table I, 72 weeks). At the end of the experiments (caused by the death of the animals) the largest anterior lobe-fed animal measured 138 mm., the smaller one 130 mm., while the controls had reached a size of only 115 and 108 mm. respectively. Unfortu-
nately both of the controls were lost before the anterior lobe-fed animals had reached such an extraordinary size, but from our experiences with many other animals as well as from the maximum size of this species it is safe to conclude that the growth of the controls in this experiment was nearly completed. On the other hand, the size of the anterior lobe-fed animals exceeded the normal maximum size of the species so much as to leave no doubt that both of them were giants. The size of the larger experimental giant exceeded the size of the largest normal animal of this species on record by 20 mm., and the size of the smaller experimental giant exceeded the largest normal animal on record by 12 mm. It is certain that both animals would have become still larger had they survived, since they were still growing before they died.

**TABLE II.**

_Hypophysis-Fed Ambystoma tigrinum, Experiment 2._

<table>
<thead>
<tr>
<th>Animal No.</th>
<th>37 weeks</th>
<th>63 weeks</th>
<th>84 weeks</th>
<th>86 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Size</td>
<td></td>
<td>Size</td>
<td></td>
</tr>
<tr>
<td></td>
<td>mm.</td>
<td>mm.</td>
<td>mg.</td>
<td>mm.</td>
</tr>
<tr>
<td>Controls</td>
<td>2</td>
<td>152.4</td>
<td>163.0</td>
<td>22,400</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>163.5</td>
<td>183.0</td>
<td>31,200</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>167.9</td>
<td>179.0</td>
<td>27,900</td>
</tr>
<tr>
<td>Anterior lobe-fed animals</td>
<td>5</td>
<td>163.5</td>
<td>233.0</td>
<td>57,200</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>142.5</td>
<td>199.0</td>
<td>50,500</td>
</tr>
</tbody>
</table>

Similar results were obtained when metamorphosed specimens of the species _Ambystoma tigrinum_ were fed on anterior lobe.

__Experiment 2.__—Five larvæ (Series XLVI) were reared from eggs of the same female and fed on earthworms. At the end of the second growth period, about 24 weeks after metamorphosis, when the animals were 37 weeks old, three of them, among them the largest one of the series, were kept on earthworms, while two, among them the smallest one, were started on an exclusive diet of anterior lobe (for initial sizes see Table II).

Although the control animals were fed on an abundant supply of earthworms, their rate of growth remained low as compared with that during the second period of growth. The animals fed on anterior
lobe, however, commenced to grow so rapidly that their rate of growth soon exceeded that which prevailed even during the earlier period of life (see Fig. 3). At an age of 63 weeks, 26 weeks after the beginning of the experiment, the smallest animal fed on anterior lobe was 20 mm. larger than the largest control animal, although at the beginning of the experiment it was 10 mm. smaller than the smallest control specimen; its weight was more than twice the weight of that of the smallest control animal. At an age of 84 weeks the largest animal of this series fed on anterior lobe measured 268 mm. as compared with 197 mm., the latter being the size of the largest control animal. Hence the size of the largest anterior lobe-fed animal exceeds at present the size of the largest normal animal, on record in the laboratory, by 68 mm. and the size of the largest specimen of the eastern race of *Ambystoma tigrinum* by 60 mm. It is 12 mm. smaller than the largest specimen of the western race on record, which, however, cannot be considered normal, as pointed out above. Both the controls and the anterior lobe-fed animals are still growing and at the present time the rate of growth of the anterior lobe-fed specimens is still higher than that of the control animals (see Fig. 3). It is possible, therefore, that in a short time, the largest anterior lobe-fed animal will exceed in size even the largest western specimen known to the writer.

**Experiment 3.**—Six larvae (Series LV), of the same brood from which the animals of Experiment 2 were taken, were raised on earthworms. At the end of the second period of growth, about 19 weeks after metamorphosis and at an age of 39 weeks, three of them (Nos. 1, 2, and 4), among them the largest one, were used as worm-fed controls; the other three animals, among them the smallest one, were kept on a pure anterior lobe diet (Table III). The largest of these latter animals died soon after commencement of the experiment.

The results were similar to those obtained in Experiment 2 and may be seen from Table III and Fig. 4. At an age of 84 weeks the larger one of the two hypophysis-fed animals measured 51 mm. more than the largest control animal, and 44 mm. more than the largest animal of the eastern race of the species known to the writer. The hypophysis-fed specimens as well as the control animals are still growing, but at present the growth of the anterior lobe-fed specimens of this series is less vigorous than that of the controls.
Experiment 4.—In this experiment (Series XXXVII and Series A) the controls were underfed and therefore cannot be used for comparison. Both the experimental as well as the control series were obtained from the eggs of the same female; but the control animals were underfed for several weeks during the larval period and the experimental animal, which was fed abundantly on anterior lobe from the beginning of its life, was kept in distilled water during the larval period, which tends to retard growth. The results are seen in Fig. 5. The anterior lobe-fed animal measured 258 mm. at an age of 84 weeks; i.e., 58 mm. more than the largest normal animal kept in the laboratory and 50 mm. more than the largest specimen of the eastern race. At present, however, it is growing very slowly and less vigorously than the animals of Series A.

### TABLE III.

*Hypophysis-Fed Ambystoma tigrinum, Experiment 3.*

<table>
<thead>
<tr>
<th>Animal No.</th>
<th>39 weeks.</th>
<th>63 weeks.</th>
<th>84 weeks.</th>
<th>86 weeks.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Size.</td>
<td>Weight.</td>
<td>Size.</td>
<td>Weight.</td>
</tr>
<tr>
<td>Controls</td>
<td>mm.</td>
<td>mm.</td>
<td>mg.</td>
<td>mm.</td>
</tr>
<tr>
<td>1</td>
<td>163.8</td>
<td>182.2</td>
<td>27,400</td>
<td>200.2</td>
</tr>
<tr>
<td>2</td>
<td>156.1</td>
<td>176.4</td>
<td>30,000</td>
<td>182.0</td>
</tr>
<tr>
<td>4</td>
<td>137.2</td>
<td>161.5</td>
<td>22,500</td>
<td>176.5</td>
</tr>
<tr>
<td>Anterior lobe-fed animals</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>136.4</td>
<td>208.5</td>
<td>54,200</td>
<td>251.6</td>
</tr>
<tr>
<td>5</td>
<td>146.7</td>
<td>204.0</td>
<td>60,000</td>
<td>221.5</td>
</tr>
<tr>
<td>6</td>
<td>156.1</td>
<td>Dead.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Since this paper went to press, Dr. Leonhard Stejneger, head curator of the United States National Museum, was kind enough to go over the entire collection of the museum and let me have the measurements of the largest specimens of the species *Ambystoma opacum* and *Ambystoma tigrinum*. Since the measurements are based on a far larger collection of material than my own data reported in the preceding pages, they are of greater importance and will be added below. They confirm the opinion expressed in this article that feeding the anterior lobes of hypophysis produces gigantism in salamanders.

### Ambystoma opacum.

<table>
<thead>
<tr>
<th>Normal.</th>
<th>Hypophysis-fed.</th>
</tr>
</thead>
<tbody>
<tr>
<td>mm.</td>
<td>mm.</td>
</tr>
<tr>
<td>119</td>
<td>138</td>
</tr>
<tr>
<td>116</td>
<td>130</td>
</tr>
</tbody>
</table>
DISCUSSION.

The feeding of anterior lobe to metamorphosed salamanders has two different effects on the growth of the animals: first, it increases the rate of growth over that of normal animals; and, second, it maintains growth after the normal "maximum" size of the species has been attained. Have we any reason to consider these effects as the result of a "specific" growth-promoting hormone?

As to the first point, we cannot be quite certain that the rate of growth of our control salamanders was the highest rate of growth which can be obtained with a normal diet. Unfortunately the data available on the growth of metamorphosed salamanders are not numerous enough to decide if earthworms form a sufficiently complete diet for the two species in question. Although it is quite certain that these animals do not require a plant diet, not enough food materials have been tested by the writer to state on which food they nat-

The two largest hypophysis-fed specimens of *Ambystoma opacum* exceed in size the largest known animal of this species by 19 and 11 mm. respectively.

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Hypophysis-fed, (Age 88 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mm.</td>
<td>mm.</td>
</tr>
<tr>
<td>235</td>
<td>223</td>
<td>273.5 (Experiment 2, No. 5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>235.5 ( &quot; 2, &quot; 6)</td>
</tr>
<tr>
<td>257.1</td>
<td></td>
<td>3, &quot; 3)</td>
</tr>
<tr>
<td>226.2</td>
<td></td>
<td>3, &quot; 5)</td>
</tr>
<tr>
<td>263.0</td>
<td></td>
<td>4, &quot; 2)</td>
</tr>
</tbody>
</table>

Among the five hypophysis-fed specimens of *Ambystoma tigrinum* three are considerably larger than the largest known specimens of the eastern race, the largest hypophysis-fed specimen exceeding in size the largest eastern specimen by 28.5 mm.

There is, as stated above, a western giant race of *Ambystoma tigrinum*. Dr. Stejneger gives 258, 265, 285, 285, and 292 mm. as measurements of the five largest specimens of this race. The largest of our hypophysis-fed animals, which has grown 5.5 mm. in the last 4 weeks and measures at the time of writing 273.5 mm., has already outgrown two of the western giants and will soon outgrow the three others if it continues to grow at the present rate.
urally grow best. Feeding of calf thymus or posterior lobe of hypophysis of cattle does not induce any growth equal to that of worm-fed animals. In the feeding of salamander larvae I have used many different substances (frog muscle, beef muscle, lymph gland, parathyroids, thymus, spleen, cheese, milk) with and without the addition of normal food; it is certain that in larvae no other diet can produce a rate of growth higher than that produced by earthworms. But, of course, the metabolic processes involved in growth may be quite different for the larvae and the metamorphosed animals.

On the other hand, if we look at the curves of the various series, it is noticeable that the curves for the worm-fed animals are very much like the normal growth curves of most other animals whose growth has been studied carefully. In particular they show the gradual flattening out of the growth curves of warm blooded animals. The curves of the anterior lobe-fed animals, especially those of *Ambystoma opacum* (Fig. 2), with their sudden rise above the flat level of the normal curve, differ from this general normal type.

Although at present we must postpone more definite conclusions, it seems at least probable that the rate of growth of the animals fed exclusively on anterior lobe is the result of a specific growth-promoting hormone contained in the anterior lobe of the hypophysis.

It is beyond doubt that the size of the hypophysis-fed animals exceeds the "maximum" size of the species. The animals fed on anterior lobe are true giants. The hormone of the anterior lobe is not only able to accelerate growth, but also—and this is of far greater importance—possesses the property of maintaining growth when the normal size of the species has been reached. The production of experimental gigantism by means of feeding anterior lobe proves that this organ contains actually a specific substance which can overcome the obstacles which are responsible for the discontinuation of growth when the normal size is reached.

These experiments do not give any clue as to whether the cells of the body are directly affected by the hormone or whether this hormone acts by the intermediation of another organ. In view of the results obtained with single cells, it is probable that the cells are not directly affected by the anterior lobe hormone. It was found by Shumway, by
Chambers, and by Nowikoff\textsuperscript{15} that the division rate of Protozoa is not increased if anterior lobe extract is added to the culture medium. The same is true for the cells of warm blooded animals. In as yet unpublished experiments Carrel found that in tissue cultures the growth of the cells of warm blooded animals cannot be accelerated if anterior lobe extract is added to the culture medium.\textsuperscript{16} Our experiments show, however, that the cells of the organism are still capable of dividing at a time at which the organism as a whole has stopped to grow. Apparently the cessation of growth of the organism as a whole is not caused by a fundamental property of the cell to become incapable of growth, after growth has been going on for some time. This corroborates the well known tissue culture experiments of Carrel which would suggest that the cell protoplasm, if kept under proper conditions, can go on dividing for indefinite periods. Since the hypophysis-fed salamanders are still growing, it is impossible, at present, to say how long the anterior lobe hormone can maintain, within the organism as a whole, a condition permitting active growth of the cell. But it is possible to say that the size of the individual is not an obstacle to the further growth of an organism. It has frequently been claimed that the size of every species is determined by the mechanics and statics of the substances constituting the body of the organism. Although these principles may be among the reasons why the organism stops growing after it has attained a definite size, they cannot be the only reason; the occurrence of giants shows that at least a considerable increase in the specific size of the species would result if the size of the organism would be determined by the mechanic and static principles alone.

As pointed out above, the evidence that anterior lobe feeding can produce gigantism in warm blooded animals is not yet sufficient. It would be of great importance if it should be demonstrated that this difference is due to the difference in the body temperature of amphibians and warm blooded animals. Lenz\textsuperscript{17} has recently called atten-

\textsuperscript{16} I am indebted to Dr. Alexis Carrel for permission to quote these, as yet unpublished, experiments, which were carried out in Dr. Carrel’s laboratory.
\textsuperscript{17} Lenz, F., \textit{Münch. Med. Woch.}, 1919, lxvi, 992.
tion to the fact that in acromegaly the tendency to abnormal growth is confined to the prominent parts of the body, in which the temperature is lower than in the main body.

SUMMARY.

1. Metamorphosed salamanders of the species *Ambystoma opacum* and *Ambystoma tigrinum* were fed on a pure diet of the anterior lobe of the hypophysis of cattle; the controls were fed on an abundant diet of earthworms.

2. The rate of growth of the animals fed on the anterior lobe of the hypophysis was greatly increased over the rate of growth of normal animals.

3. Growth of the animals fed on anterior lobe did not cease after they had reached the normal "maximum" size of the species, and experimental giants were produced.

4. The largest animal of the species *Ambystoma opacum* fed on anterior lobe of the hypophysis was 19 mm. larger than the largest normal animal of this species known to the writer; the largest animal of the species *Ambystoma tigrinum* fed on anterior lobe is at present about 28 mm. larger than the largest normal animal of the eastern race of this species known to the writer.