HEREDITARY ACHONDROPLASIA IN THE RABBIT

III. GENETIC ASPECTS; GENERAL CONSIDERATIONS

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(Received for publication, May 25, 1945)

The hereditary nature of achondroplastic dwarfism (chondrodystrophia foetalis) in the rabbit was pointed out in the first paper of this series in which the physical appearance of the animals was described (1). The second paper was devoted to the pathologic features of the condition (2). In the present report, the results of genetic studies are described, the circumstances of the original cases are considered with particular reference to certain disease complexes carried in their parental lines which might have a bearing on the abnormality and, finally, the condition is briefly discussed in relation to achondroplasia in other animal species.

Materials and Methods

Since achondroplasia in the rabbit is invariably lethal, the animals either being born dead or dying within a few hours of birth, and since transmitters of the condition have so far been identified only by breeding tests, genetic studies were necessarily carried out with such animals. Identified transmitters were mated with unrelated animals, including examples of pure breeds, to form an F₁ generation, and these animals in turn were tested for transmission of the condition. Those found to be transmitters were then interbred to form an F₂ generation.

The proportion of achondroplastic and normal animals in the progeny derived from these various breeding experiments has been determined. A selected number of transmitters, both male and female, have been compared from the standpoint of the character of their progeny. Special attention has also been paid to the occurrence of negative litters obtained from transmitting parents, that is, litters in which the expected achondroplastic dwarfs were not observed.

Results of Genetic Studies

The number of achondroplastic dwarfs so far observed is 228; they occurred among 788 total births contained in 132 litters. The incidence of the condition is 28.93 per cent. On the basis of a simple recessive unit factor, one-fourth, or 197 animals, would be expected to show the condition. There is no significant deviation between the observed distribution of achondroplastic dwarfs and normal litter mates and the expected distribution on the basis of genetic principles as shown by the χ² test of homogeneity ($N = 1, P = 0.05+)$.

Of the total number of the progeny, 227 animals contained in 43 litters were derived from F₁ matings, their F₁ parents being outcrossed hybrids and of this number, 59, or 25.99 per cent, were achondroplastic dwarfs. There
were 25 litters which were the progeny of mother-son or father-daughter matings. Of the 132 young, 33, or 25.0 per cent, were achondroplastic individuals.

The frequency distribution of the 228 achondroplastic dwarfs with reference to litter size is shown in Table I and Chart 1. The 132 litters contained from 1 to 11 animals. It will be noted that the curve in Chart 1 representing the proportionate number of achondroplastic dwarfs (percentage of total number of dwarfs) in each litter class closely parallels the curve representing the proportionate number of animals (percentage of total births) in each litter class. The relative position of the curves indicates, however, that a slightly higher percentage of the total number of dwarfs occurred in the smaller litters of from 1 to 5 than in the larger litters of from 6 to 11 individuals. For comparison, a curve has been included which represents the frequency distribution of 778 young according to litter size of 132 negative litters. These animals were the progeny of test matings made for the identification of transmitters. It will be noted that all three curves approach a normal frequency curve but those representing litters which contained achondroplastic animals are more irregular, particularly in the central portions corresponding to litters of 5 to 8 young.

The fourth curve in Chart 1 represents the frequency distribution according to litter size of the percentage ratio of achondroplastic dwarfs to the total number of animals in each litter class. In the smaller litters of from 1 to 4

### Table I

<table>
<thead>
<tr>
<th>No. per litter</th>
<th>No. of litters</th>
<th>Total births</th>
<th>Achondroplastic dwarfs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Per cent of total births</td>
<td>No.</td>
</tr>
<tr>
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<td>1</td>
<td>0.13</td>
<td>1</td>
</tr>
<tr>
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<tr>
<td>3</td>
<td>11</td>
<td>4.19</td>
<td>14</td>
</tr>
<tr>
<td>4</td>
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<td>19</td>
</tr>
<tr>
<td>5</td>
<td>28</td>
<td>17.77</td>
<td>42</td>
</tr>
<tr>
<td>6</td>
<td>47</td>
<td>12.94</td>
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</tr>
<tr>
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<td>1.40</td>
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<tr>
<td></td>
<td>132</td>
<td>788</td>
<td>228</td>
</tr>
</tbody>
</table>
animals, the proportion of dwarfs was high, ranging from 100.0 to 42.42 per cent, and in a single litter of 11 young it was only 9.09 per cent. The majority of litters, however, comprised 5 to 9 animals and the proportion of achondroplastic dwarfs ranged from 20.0 to 30.0 per cent.

In addition to litters containing achondroplastic animals, there were 36 litters numbering 139 young in which no achondroplastic dwarfs were observed although both parents were known transmitters. That the classification of such litters as negative may in reality be erroneous is not unlikely. Some does are prone to destroy weak or dead young and cases of partly eaten achondroplastic individuals have been seen. Furthermore, uterine resorption of dead fetuses is not an infrequent occurrence. The difference in litter size of positive and negative litters bears on these points. The average size of the 132 positive litters was 5.97 young and of the 36 negative litters, 3.86 young. If it be assumed that each negative litter once contained an additional achondroplastic animal, the total progeny of known transmitting parents would than number 963, of which 264, or 27.41 per cent, were achondroplastic dwarfs.

It would appear from the analysis of these observations that the variation of lethal achondroplastic dwarfism in the rabbit is inherited through the operation of a single recessive unit factor. Animals showing the condition are homozygous for the factor and do not survive, while heterozygous animals

![Chart 1. Frequency distribution of achondroplastic dwarfs in relation to the number of animals in each litter. Three curves are drawn from the data in Table I which are based upon 132 litters containing 788 total births including 228 achondroplastic dwarfs. A fourth curve represents the frequency distribution of 778 normal young contained in 132 negative litters of the same stock.](chart1.png)
exhibit none of the stigmata of the disease and live. Up to the present time, all non-achondroplastic progeny of transmitting parents at birth or in later life, and whether they be transmitters or not, have shown no unusual or distinctive features, and their physical appearance is that of normal animals.

### TABLE II

**Breeding Records of 25 Male and 30 Female Transmitters. The Other Parent of Each Litter Was Also a Transmitter**

<table>
<thead>
<tr>
<th>No. of males</th>
<th>Litters No. per parent</th>
<th>Total No.</th>
<th>Total births</th>
<th>No. of normals</th>
<th>No. of achondroplastic dwarfs</th>
<th>No. of males</th>
<th>Total No. of litters</th>
<th>Total births</th>
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<td>5</td>
<td>2</td>
<td>10</td>
<td>67</td>
<td>52</td>
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<td>22.39</td>
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<td>12</td>
<td>85</td>
<td>64</td>
<td>21</td>
<td>24.71</td>
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<td>19</td>
<td>33.93</td>
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<td>6</td>
<td>18</td>
<td>102</td>
<td>70</td>
<td>32</td>
<td>31.37</td>
<td>2</td>
<td>3</td>
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<tr>
<td>5*</td>
<td>8</td>
<td>39</td>
<td>209</td>
<td>140</td>
<td>69</td>
<td>33.01</td>
<td>3</td>
<td>3</td>
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<tr>
<td>1</td>
<td>10</td>
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<td>52</td>
<td>39</td>
<td>13</td>
<td>25.00</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

| Total No.   | 117                    | 675       | 475          | 200            | 29.49                       | 18           | 32                  | 122         |

<table>
<thead>
<tr>
<th>No. of females</th>
<th>Litters No. per parent</th>
<th>Total No.</th>
<th>Total births</th>
<th>No. of normals</th>
<th>Achondroplastic dwarfs</th>
<th>No. of females</th>
</tr>
</thead>
<tbody>
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<td>17</td>
<td>2</td>
<td>34</td>
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<td>129</td>
<td>64</td>
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<td>5</td>
<td>5</td>
<td>24</td>
<td>17</td>
<td>7</td>
<td>29.17</td>
</tr>
</tbody>
</table>

| Total No.     | 79                     | 470       | 338          | 132            | 28.08                    | 12           | 17                  | 66          |

Estimated totals for males: 829, 597, 232, 27.99
Estimated totals for females: 553, 404, 149, 26.94

*Four males each had 8 and one male had 7 positive litters.

From a comparison of the breeding records of 25 males and 30 females, there appears to be no sex difference as far as transmission of the condition is concerned (Table II).

These particular animals were selected on the basis that each was the parent of at least two positive litters, that is, litters containing achondroplastic dwarfs. The other parent of all the litters was likewise a transmitter. In addition to the positive litters in the progeny of these
particular parents, there were other litters in which the expected achondroplastic dwarfs were not observed. The data of the comparison as shown in Table II are arranged according to the number of positive litters per male or female parent under consideration. Of the total number of litters tabulated, 63 positive and 16 negative litters are included in the progeny of both male and female parents listed. In the case of litters tabulated in the progeny of the male parents, 54 positive and 2 negative litters do not appear in the progeny of the female parents; in the case of litters listed as the progeny of the female parents, 16 positive and 1 negative litter are not included in the progeny of the male parents.

The progeny of the selected 25 male transmitters comprised 117 positive litters, ranging in number from 2 to 8, and in 1 case 10, per male parent (Table II). The number of litters in these several classes ranged from 10 to 39. The total births contained in them were 675, of which 200, or 29.49 per cent, were achondroplastic dwarfs. The average size of the litters was 5.77 young. A considerable proportion of these male transmitters, 18 in number, also sired one or two negative litters in which achondroplastic individuals were expected since the maternal parent was also a transmitter. There were 32 negative litters containing a total of 122 young, or an average of 3.81 young to a litter.

Similar results are seen in the data on 30 female transmitters (Table II). The number of positive litters ranged from 2 to 4 and in one instance 5, per female parent. The total number of litters was 79 and they contained 470 young, of which 132 were achondroplastic dwarfs, an incidence of 28.08 per cent. The average size of the litters was 5.95 young. Again, negative litters were seen in the progeny of 12 of the 30 females, although the paternal parent was also a transmitter. There were 17 such litters containing 66 animals, or an average of 3.88 young to a litter.

The proportion of males which had negative litters was higher than the proportion of females, 72 and 40 per cent respectively. The difference is probably artificial and due to the much greater extent to which male rabbits may be tested. The total number of litters sired by the 25 males was 149 as compared with the total of 96 litters born of the 30 does. The smaller opportunities for testing females is also shown by the fact that the majority of them had 2 and 3 positive litters each while the great majority of the males sired 4 or more positive litters.

On the grounds that the negative litters in these 2 selected groups might have contained an achondroplastic dwarf as was suggested in describing the results for the entire group of animals, the probable incidence of the condition is 27.99 per cent for the progeny of the 25 males and 26.94 per cent for the progeny of the 30 females (Table II).

In concluding these remarks on the genetic aspects of lethal achondroplastic dwarfism in the rabbit, it should be repeated for the sake of completeness that the condition is not sex-linked (1). Females are somewhat more frequently affected than males, the proportions in the series being 54.5 and 45.5 per cent respectively, but the difference between observed and expected values is not statistically significant. Similar reference (1) should also be made to the
occurrence of a cleft palate in 25 per cent of the achondroplastic dwarfs. This
abnormality was equally distributed between male and female animals.

The Original Cases and Their Ancestry

The first instance of achondroplastic dwarfism in the colony occurred in
June, 1939.

A litter of 5 young containing 2 typical examples of the condition and 3 living normal ani-
mals was the offspring of a brother-sister mating (Chart 2, I). In this colony, weaned young
are kept in large cages for about 2 months before being separated. In the present instance, 2
brothers and 3 sisters belonging to a pure bred Havana litter were caged together. The mother
of the achondroplastic litter could be identified and the father was thought almost certainly
to be one of her two brothers. Members of more than one litter are frequently kept in the
same nursery cage and animals may be shifted from one cage to another, but in this case, it
was not known that any male except the 2 brothers was ever caged with their 3 sisters.

At this time, the Havana stock had been under observation 10 years and
among its numerous progeny, some of which was derived from close inbreeding,
small or diminutive but normally proportioned forms were not infrequently
seen but abnormally proportioned individuals had not hitherto been observed.
There had been, however, a comparatively recent introduction of other Havana
blood, designated as the “new Havana stock” and represented in the present
case by a great grandsire. Although no abnormalities of the achondroplastic
type had been seen in this stock during the 2 1/2 years it had been in the colony,
the available information concerning it was much less extensive than was that
of the old Havana line and consequently its implication in the achondroplastic
condition seemed not unlikely.

The attempts to reproduce the abnormality during the next 2 years were
unsuccessful. The breeding experiments included the mating of the presump-
tive father with the mother of the litter and with another sister; the other
brother was mated with the third sister and with the only survivor of the
achondroplastic litter. All the progeny from these test matings were normal
as was also the case with offspring derived from animals more or less closely
related to the 5 Havana animals, including representatives of the new Havana
stock. Further tests with 4 of the 5 animals was not possible since by the end
of the year only one of the sisters survived and it was thought that with the
death of both parents the chance of a repetition of the condition was lost.
However, 2 years after the first cases were seen, another litter containing
achondroplastic dwarfs was born and the following fall there was another.
With these results at hand, breeding experiments designed to perpetuate the
condition were undertaken.

The first of these new litters, X21207, comprised 5 young, 2 of which were achondroplastic
dwarfs (Chart 2, II; reference 1, Fig. 1). The litter was the progeny of a backcross test mating
in stock of mixed but principally Belgian ancestry which carries a disease complex known in
the colony as the “downy-rusty-dwarf” or D.R.D. complex. One of its characteristic features
is a size reduction present at birth; the bodily proportions, however, are normal. The major
importance of the condition is the development of premature senescence. The father of the litter, X17736-1, was a transmitter of this condition. He was the son of a male animal with well marked D.R.D. symptoms and an unrelated normal Havana female, HA494-2. The choice of animals for the normal partners in a variety of F₁ hybrid matings including that of the D.R.D. line and of the abnormal stock next to be described in connection with the third

```
I. HA750
   HA679-3
   |   HA527
   |   HA502
   |   HA679-1 ?
   or " -2 ?
   or ?

   HA494-2
   HA152
   HA14-1
   HA10-2
```

Old Havana stock
Old Havana stock
Old Havana stock
New Havana stock

```
II. X21207
   X17736-1
   X18250
   X20111-2
   HA494-2
   X15812-1
   D.R.D. stock
   D.R.D. stock
   Old Havana stock
   Old Havana stock

   HA679-4
   HA527
   X19194-6
   X19194-2
```

New Havana stock
H.B.E. stock
H.B.E. stock

```
III. X21571
    X19194-2
    D742-1
    D338-3
    D369-1
    H.B.E. stock
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IV. X21685
    X17736-1
    HA494-2
    HA679-4
    HA527
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Chart 2. Pedigrees of the first litters containing achondroplastic dwarfs. The upper of each pair of numbers represents the female and the lower, the male parent. HA and D represent pure bred Havana and Dutch animals; X are animals of hybrid or mixed ancestry. D.R.D. and H.B.E. refer to particular disease complexes carried in the respective stocks and which are discussed in the text.

An instance of achondroplasia, was determined by the freedom of the normal stock from such conditions. Nothing resembling these particular disease complexes had been seen in the Havana stock. The mother of the achondroplastic litter, X20111-2, was not obviously a D.R.D. animal; she was, however, the daughter of one, X18250, and of the F₁ male D.R.D. transmitter, X17736-1, just described.
With the occurrence of the second example of achondroplasia, its Havana origin seemed practically certain. Reference to pedigrees I and II in Chart 2 shows that the mother of the first achondroplastic litter, HA679-3, was the daughter of HA494-2, who, in turn, figured in both parental lines of the second litter. The latter female, HA494-2, belonged to the old Havana stock and had no admixture of the new Havana blood which, as has been mentioned, had been under suspicion as the possible source of the variation. Neither of these Havana females, HA679-3 or HA494-2, was alive at the time the second achondroplastic litter was born and the mother of this litter died during the summer before the mating could be repeated. The father, X17736-1, however, was still in the colony and when work was resumed in the fall, he was bred to several closely related does. But, just before any of these litters was born, the third instance of achondroplasia occurred.

The third litter, X21571, contained 8 young of which 3 were achondroplastic individuals (Chart 2, III). The litter was the F2 progeny of a brother-sister F1 hybrid mating of a pure bred Dutch line which carries a peculiar disease complex known in the colony as the "hydrobugeye" or H.B.E. stock. At birth or shortly thereafter, hydrocephalus and prominent eyeballs are fairly frequent symptoms. In the full expression of the condition, body size is somewhat reduced but bodily proportions are normal. Other characteristic features in the nursling include marked tooth abnormalities, unusual peculiarities of the bones which, however, are not those seen in achondroplasia, and deficient growth; survival longer than 6 or 7 weeks has not been observed. It will be noted in the pedigree of this litter (Chart 2, III) that the normal partner of the F1 hybrid mating of the grandparents was HA679-4. This Havana female was a full sister of HA679-3, the mother of the first achondroplastic litter (Chart 2, I) and a half sister of the male X17736-1, the father of the second achondroplastic litter. She was one of the related females which, as has just been mentioned, had been mated with this male transmitter, prior to the birth of the third case. The offspring of this mating was a litter of 6 young of which 1 was a typical achondroplastic dwarf (Chart 2, IV).

With the birth of the third and fourth litters, and others born at this time, several transmitters of the condition were identified. Some of them, and in particular the male X17736-1 (Chart 2, II and IV), were outcrossed to unrelated normal stock to form an F1 hybrid generation, and certain of these animals in turn were found by breeding tests to be transmitters. No peculiarities of appearance or abnormalities of conformation were detected in any of the F1 animals, either at birth or in later life. In this connection, it is of interest to note that 2 litters of 6 and 2 young respectively, derived from subsequent matings of the Havana female HA679-4 (Chart 2, III and IV) and a distantly related pure bred male of the old Havana line, did not contain achondroplastic dwarfs. Several animals of these 2 litters, however, were found to be transmitters but when bred to representatives of both the old and the new Havana lines, all progeny had an entirely normal appearance. It thus seems reasonably certain that the achondroplastic variation did not arise in the so called new Havana stock and in addition, that it was carried by very few animals of the old stock.
Up to the present, no transmitters have been found other than those whose ancestry includes the female HA479-2 (Chart 2, I, II, III, and IV). From the available evidence, it is clear that this female transmitted the factor for the development of achondroplastic dwarfism but when and under what circumstances the variation itself occurred is not known. She belonged to a litter of 3 young, all of which were normal; and the litters to which her parents belonged likewise contained only normal animals, 7 in each litter. Furthermore, as has already been mentioned, the numerous Havana progeny, some of which represent close inbreeding of this female's ancestors, had been observed over a period of 10 years, without an example of achondroplasia having been seen. The condition was not observed until the birth of the offspring of a daughter and a son of this particular female.

Early in the course of these observations before the full information concerning HA494-2 and her daughter HA679-4 (Chart 2, III and IV) was available, the question arose as to whether factors carried in the "downy-rusty-dwarf" stock represented in the second achondroplastic litter (Chart 2, II), could have contributed to the abnormality. It will be remembered that the identity of the father of the first litter was not unquestionably known. The implication of the D.R.D. line was considered on the grounds of a recent variation or mutation arising in this stock and also on the basis of the modification of a condition by the presence of another through the association of the gene or genes responsible for each condition, in this case the Havana diminutive and the D.R.D. disease complex. The situation was further complicated as far as ancestry was concerned by the fact that the D.R.D. stock was mixed or mongrel in character, although the Belgian breed in which the disease complex was first seen predominated.

Later, when the third achondroplastic litter was born (Chart 2, III) the same question arose in connection with another disease complex, the "hydrobugeye" condition but with less emphasis, for by this time the probable origin of the variation had become much more certain because of the identity of the Havana grandmother and great grandmother of the third litter. The H.B.E. stock, it should be added, comprised only pure bred Dutch rabbits.

In the case of both the D.R.D. and the H.B.E. complexes, the characteristic symptoms at birth include size reduction. In addition, litter mates which do not show these symptoms at birth or during the first weeks of life but which may later develop characteristic features are frequently, although not invariably, small animals. A further point which was considered in assessing the possibilities of the situation was, as has already been mentioned, the undersized form or runt that not infrequently appears in the offspring of our pure bred Havana stocks. In the immediate ancestry of the first 3 achondroplastic litters, there were thus represented 3 diminutive or dwarf-like forms, each of which, however, had never been observed to have other than normal bodily proportions.
The birth of the fourth achondroplastic litter (Chart 2, IV) clarified the situation with respect to the elimination of a possible source of the variation in the Dutch breed. Later breeding experiments with the pure bred Havana mother of this litter, HA679-4, which have been mentioned, confirmed the elimination of the other possible source, namely, the D.R.D. mixed stock. It thus seems clear that the variation originated in the old Havana stock.

In connection with the normally proportioned diminutive forms carried in the various ancestral lines of these first achondroplastic litters, it is interesting to note that in the present extracted pure bred Havana line which carries achondroplasia, instances of viable normally proportioned dwarf-like forms or runts are still occasionally seen. The one condition has not eliminated or taken the place of the other. Animals showing definite general symptoms of the "downy-rusty-dwarf" complex but no achondroplastic stigmata (1, Fig. 5) are also seen in the progeny of the descendants of X17736-1 (Chart 2, II and III). From outward appearance alone, it would be difficult to determine whether any achondroplastic individuals in these litters were also D.R.D. animals. Certain postmortem findings, however, suggest that this combination may occur and the question is now under investigation. The same possibility obtains in the case of the "hydro-bugeye" complex carried in the Dutch line (Chart 2, III). Finally, reference should again be made to the character of some of the F₂ offspring derived from F₁ hybrid crosses of the achondroplastic transmitter X17736-1 and Polish females carrying the lethal dwarf character described by Greene (12). Since this subject has already been discussed (1), it will suffice here to say that certain very small achondroplastic individuals (1, Fig. 5) were considered to represent a combination of the 2 conditions, that is, they showed an achondroplastic modification of Polish dwarf forms.

DISCUSSION

Hereditary achondroplasia (chondrodystrophia foetalis) in the rabbit has been described for the first time in the present and the two preceding papers (1, 2). It is also the first instance of this condition in rodents to be reported. The original cases which were entirely similar to all later ones occurred in pure bred Havana stock which had been under observation for 10 years. The condition is present at birth and lethal in its effect, no case having survived more than a few hours.¹

¹ Unusually short extremities and particularly of the fore legs, were seen in another rabbit stock of the colony derived from animals brought from Peiping, China. The condition, which was not apparent during early life, became evident at 2 to 3 months of age. As a class the animals were small. The stock was lost in a pandemic of rabbit pox while preliminary studies were in progress but the information available indicated that the condition was inherited. At the time it was tentatively considered to be an achondroplasia similar to that seen in dogs. Whatever its actual nature was, however, it could not be confused with the abnormality described in these papers.
In many important respects, achondroplasia in the rabbit strikingly resembles achondroplasia in other species. The characteristically shortened extremities and large squarish head with prominent calvarium and the flat or receding face with a transverse nasal depression at once recall the appearance of the human case, of affected calves, and of creeper fowls. Achondroplasia of the dog, as pointed out by Stockard (3), comprises several apparently independent areas of involvement in different breeds, the best known of which being the shortened extremities of the basset hound, dachshund, and Pekingese breeds; the distorted skull shapes of the English bulldog, French bulldog, and Boston terrier, and the short bent "screw tail" of the English bulldog, however, are other examples.

A cleft palate was found in 25 per cent of the rabbit cases and was equally distributed between males and females. It is a frequent finding in achondroplastic calves and has been reported in human cases and occasionally in dogs. The redundancy of the skin and the conspicuous skin folds in the cervical, shoulder girdle, and pelvic areas and in the upper segments of the extremities have their counterparts in achondroplasia of other species.

Analysis of the present material shows that achondroplasia in the rabbit is inherited as a single factor recessive character. In homozygous form, the variation is lethal and produces an undersized individual with disproportionately bodily parts and other characteristic features which have been described. Heterozygous forms appear to be perfectly normal and survive.

Achondroplasia in man is currently regarded as the expression of a dominant factor (4, 5). In the "bulldog" calf, the condition is inherited as a dominant or semidominant (6) while other forms in cattle are recessive in character (7–10). In the dog (3), the condition of achondroplastic extremities is inherited as a single factor dominant character while the localized chondrodystrophic deformity of the tail of the bulldog, or "screwtail," is recessive to the normal long straight tail of the basset hound. Hereditary chondrodystrophy of the fowl is determined by a dominant factor which in homozygous form acts as a lethal (11).

The characteristic histological features of deficient and distorted endochondral cartilage and bone found in achondroplastic rabbits (2) closely resemble if they are not identical with those in achondroplasia of other species.

Histological examination of other tissues and organs reveals comparatively little of interest. Vascular dilatation and congestion and edema of various degrees and of variable distribution are frequently observed. The amount of hematopoietic tissue is decreased in bone marrow foci as would be expected but in the liver and spleen as well; the lymphoid elements of the spleen and probably also of other structures are depleted. These changes are reflected in the blood picture. The histology of the thyroid suggests a very active gland. In the pituitary, the cellular pattern appears to be normal or, in some cases, the proportion of basophiles is increased.

The character of the histological findings in both the thyroid and pituitary does not suggest a responsible or causal association but rather an effect of the general condition. In this connection, the histological observations in the
lethal hereditary form of proportionate dwarfism in Polish rabbits are of interest (12).

The rare surviving examples of the Polish form were characterized by a complete replacement of the normal histological elements of the anterior lobe of the pituitary by hypertrophic acidophiles and by atrophy of the gonads. These survivors were obtained from crosses involving a cretinoid line of rabbits and it was thought that the factor responsible for the longer survival “results in a greater activity of the acidophilic cells and thus supplies growth-stimulating substances which are absent in ordinary dwarfs.” At present, similar results have not yet been suggested from the preliminary tests of crosses between the cretinoid and achondroplastic lines.

The failure of all achondroplastic individuals to live more than a few minutes or at most a few hours, although development and survival to birth at term take place, suggests that the cause of death may be associated with the withdrawal of some substance or substances of maternal origin which are essential to life. One naturally thinks of hormonal substances but so far no convincing evidence bearing on this point has developed. A product or process of metabolism must also be considered and in this connection, one striking characteristic of achondroplastic animals, namely the absence of rigor mortis to develop, may have a bearing. No unusual histological features in the muscles, including those of the diaphragm, were found. Is it possible that some phase of carbohydrate metabolism necessary for survival is lacking or is abnormal in these animals? Up to the present, there has been little opportunity for investigating this question. It would be desirable and probably essential to work with material obtained immediately after death and so far comparatively few achondroplastic dwarfs have been found alive. Appropriately stained sections of the liver show a glycogen content which is possibly smaller than is usually found in new-born young and a fat content which is somewhat greater. Sections of the pancreas reveal nothing abnormal and determinations of blood sugar made on the few available specimens of heart's blood showed amounts that were within normal limits.

The absence of milk in the stomach of the great majority of achondroplastic dwarfs has been noted and the failure to nurse was ascribed to the weakness of the sucking muscles. Although rabbits customarily nurse soon after birth, it is not rare to see new-born young which have not been fed but which survive for many hours. With achondroplastic dwarfs, on the other hand, in which a generally low level of vigor is conceivable, it is possible that the lack of an immediate food supply is sufficient to tip the scales toward an early fatal issue.

These speculations may be concluded by referring to still another possibility suggested by certain characteristic features of the disease which are invariably found; namely, an extremely large protuberant abdomen with thin relaxed walls and large abdominal viscera. The abrupt change from an immobile fetal existence to a mobile state after birth must be associated with compara-
tively rapid adjustments of a mechanical or positional nature involving hepatic and other abdominal vascular connections as well as other structures. The support or pressure exerted by a firm abdominal wall would undoubtedly aid in such adjustments while the flaccid wall of achondroplastic animals would have quite the opposite effect, the consequences of which might well contribute to a fatal outcome.

The question of the condition of the mother during pregnancy and in particular the adequacy of her diet, has been considered with respect to the pathogenesis of the chondrodystrophic abnormality and the cause of death of affected individuals. From the evidence furnished by the population of the colony as a whole and by pregnant does in particular, the dietary requirements appear to have been fully met. The health of pregnant animals is generally excellent as judged by eating habits, body weight determinations, and the continuance of pregnancies to term. The breeding records of female achondroplastic transmitters show no deviation from this general rule. These observations and the fact that the abnormality is confined to a particular stock in the colony, appear to exclude a dietary insufficiency as its primary cause.

In this connection, Warkany and Nelson's experiments on congenital malformations in the rat produced by maternal dietary deficiencies are of special interest. The condition could be prevented by the addition of liver (13, 14) or of riboflavin (15) to the deficient diets. Abnormalities were also produced in the offspring of female rats fed a rachitogenic diet (16). The malformations are largely skeletal, certain bones such as the tibia, mandible, and ribs being frequently affected while others, such as the femur, being only rarely involved. The vertebral column is not grossly affected. Shortening, or even absence, of the bones is found. Histologically, the abnormal structures show a delay in ossification with a disturbance of the orderly relationship between the calcifying cartilage and the osseous parts of the bone. Persistence of cartilage is found in areas where ossification should have taken place and the cartilage itself shows signs of abnormal development (17).

As far as individual bone lesions are concerned, certain gross and microscopic findings recall those of achondroplasia of the rabbit. In the latter condition, however, the manifestations are not locally distributed but involve the entire skeleton and in a remarkably uniform and symmetrical manner. Of particular importance in the present connection, moreover, is the demonstration in Warkany's experiments of the effect of the reversal of diets, that is, female rats which had had an abnormal litter while on an insufficient diet will regularly have only normal offspring if the diet has been changed to a sufficient one.

As far as hereditary achondroplasia of the rabbit is concerned, it seems certain that the primary cause responsible for its development is the genetic constitution of the animal. A comparison with the congenital malformations reported by Warkany suggests that the two conditions may be another instance of the resemblance in certain effects produced, although in different species, by genetic causes in the one case and environmental modifications in the other. This is not to say, however, that a vitamin imbalance of the pregnant doe as a contributing factor in the pathogenesis of achondroplasia can be arbitrarily
excluded or, more likely, that it should not be considered in connection with the cause of death of achondroplastic animals. In view of the profound effect of the maternal diet on the developmental processes of the offspring, these questions cannot at present be categorically answered in the negative.

Before concluding these remarks, one further point should be referred to. The relative frequency of prenatal losses in many animal species now appears to be generally accepted and for the rabbit, figures of 18 to 33 per cent of the embryos have been reported (18). It will be recalled that the incidence of achondroplasia in relation to litter size was highest in small litters (Table I, Chart 1). It is not known, of course, whether there were any prenatal losses in these litters but on the basis of the mode of inheritance of the condition as a single factor recessive character, such presumptive forms should have been normal. If this was actually the case, the survival of markedly abnormal achondroplastic forms rather than normal ones, is curious and unexpected. On the other hand, if the prenatal deaths included many achondroplastic forms, the incidence of the condition might be significantly higher than the one-fourth ratio of a recessive factor. The question is now being investigated by direct examination of the uterine contents at various stages of pregnancy. This material is also expected to furnish information on the period of development in which the chondrodystrophic abnormality is determined.

SUMMARY

Hereditary achondroplasia (chondrodystrophia foetalis) in the rabbit has been described in the present and preceding papers (1, 2). It is the first instance of this abnormality in rodents to be reported. The variation arose in pure bred Havana stock.

The abnormality is determined by the expression of a simple recessive unit factor, affected individuals being homozygous for the factor. Females are somewhat more frequently affected than males, but the character is not sex-linked. Rabbits heterozygous for the factor as determined by appropriate breeding tests have a perfectly normal appearance at birth and in later life.

The condition appears to be determined solely by the genetic constitution of the animal. Attention was drawn to the fact that although the development of the achondroplastic form proceeds to birth at term, death regularly occurs at the time of or very shortly after parturition. This feature of the condition is briefly discussed.

BIBLIOGRAPHY