Changing Frequency of Arteriosclerosis in Mammals and Birds at the Philadelphia Zoological Garden

Review of Autopsy Records

By H. L. Ratcliffe, Sc.D., and M. T. I. Cronin, M.R.C.V.S., Ph.D.

From 1901 through 1932 arteriosclerosis was found in less than 3 per cent of autopsies on mammals and birds at the Philadelphia Zoological Garden, but thereafter its frequency has increased to about 20 per cent. This study has attempted to identify factors that may be associated with this change in frequency.

A considerable volume of clinical and experimental evidence supports the opinion that the frequency of arteriosclerosis in human populations is determined to a large degree by the level of dietary fats. However, other studies suggest instead that the development of this disease reflects the interaction of several factors some of which, at least, are not related to fat intake. The observations to be reported here support the latter view, insofar as it may apply to captive wild mammals and birds.

Material

The material used in this review was collected over a period of 40 years, January 1, 1916, to January 1, 1956. During the greater part of this period the late Herbert Fox, M.D., supervised its collection. One of us (H. L. R.) assisted Dr. Fox from August 1929 until his death early in 1942, and succeeded Dr. Fox in the direction of this work. Thus the standards of observation, collecting, and recording have been reasonably uniform throughout the period of this study.

During the initial 20 years of this period, nutritional disease was a common cause of death among the animals of this Zoo and arteriosclerosis relatively uncommon. But in 1935 the traditional and often inadequate diets then common to zoological gardens were replaced by controlled diets. Under these conditions arteriosclerosis has developed much more frequently.

The diagnosis of arteriosclerosis in these animals has been based upon macroscopic and microscopic examination of the aorta, heart, and other organs of the body cavities. Vessels of the extremities rarely have been studied. Intimal thickening, whether accompanied by signs of lipid deposits or by changes in the media, has been taken as evidence of the disease. However, this does not include examples of intimal thickening that might be interpreted as having developed in association with inflammatory lesions in or adjacent to the wall of an artery.

Our practice has been to ignore small isolated plaques of the aorta and its larger branches unless these were accompanied by vascular disease of the heart, kidney, or spleen. We have included animals in which lesions of the arteries of the heart and kidneys were not accompanied by disease of the aorta.

In routine practice tissues were embedded in paraffin and stained with hematoxylin and eosin. During the present study additional sections have been prepared from selected cases by the following methods: Gomori's reticulum stain, Verhoeff's elastic stain, and Lillie's allochrome stain.

Few of the animals in this series were born in captivity. Thus age at death rarely may be stated accurately, but must be given as the "exhibition age," i.e., the length of life in the Zoo. Inaccuracies from this source are distributed about equally to all taxonomic groups, for wild animals usually are imported as immature specimens.

Age may be expressed most conveniently in months, because a majority of deaths fall into the lower age groups, which reflects the high mortality of animals in zoos. In discussing age we shall have occasion to refer to estimates of "potential longevity." The basis for these estimates was outlined earlier, although present evidence demands some upward revision of the published values.

During the period of this review arteriosclerosis was found in mammals of 45 families and in birds of 65 families. These groups are represented in the records by 3,360 and 7,660 autopsies, with 360...
Table 1.—Diets

<table>
<thead>
<tr>
<th>Families</th>
<th>1916 to 1936</th>
<th>1936 to present</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Cervidae</td>
<td>60-70% of intake equal parts (by volume) cracked corn, crushed oats, wheat bran; balance—timothy and clover hay, about 3% fat.</td>
<td>60-70% of intake the following mixture (parts by weight)</td>
</tr>
<tr>
<td>2. Bovidae</td>
<td>60-70% of intake equal parts (by volume) cracked corn, crushed oats, wheat bran; balance—timothy and clover hay, about 3% fat.</td>
<td>Codliver oil 0.135 Ground oats 4.5</td>
</tr>
<tr>
<td>3. Macropodidae</td>
<td>40-50% of intake bread*; balance—potatoes, carrots, beets, apples, lettuce. About 2% fat.</td>
<td>Iodized salt 0.45 Ground wheat 4.5</td>
</tr>
<tr>
<td>4. Sciuridae</td>
<td>60-70% of intake bread*, corn, sunflower seed; balance—carrots, beets, etc. About 2% fat.</td>
<td>Oystershell flour 1.125 Brewers' grains 4.5</td>
</tr>
<tr>
<td>5. Capromyidae</td>
<td>40-50% of intake bread*; balance—potatoes, carrots, beets, etc. About 2% fat.</td>
<td>Brewers' yeast 2.34 Ground corn 6.75</td>
</tr>
<tr>
<td>6. Dasyproctidae</td>
<td>40-50% of intake bread*, balance—potatoes, carrots, beets, etc. About 2% fat.</td>
<td>Alfalfa leaf meal 11.7 Dry beet pulp 45.0</td>
</tr>
<tr>
<td>7. Cebidae</td>
<td>70-80% of intake bread*</td>
<td>Linseed meal 4.5 Chopped carrots 10.0</td>
</tr>
<tr>
<td>8. Cercopithecidae</td>
<td>70-80% of intake bread*; boiled rice, bananas.</td>
<td>Balance—alfalfa, timothy, and clover hay for Cervidae and Bovidae; alfalfa hay, kale, and carrots for Macropodidae. About 3% fat.</td>
</tr>
<tr>
<td>9. Pongidae</td>
<td>Potatoes; balance—apples, lettuce, onions; except Pongidae for which milk and eggs supplied about 5% of intake. About 2% fat.</td>
<td>70-75% of intake the following mixture (parts by weight)</td>
</tr>
<tr>
<td>10. Ursidae</td>
<td>40-50% of intake bread*; 20-25% meat; 20-25% suet; 2-3% fish; 3-4% carrots and apples. 15-20% fat.</td>
<td>Ground corn 10.5 Dry skim milk 7.0</td>
</tr>
<tr>
<td>11. Procyonidae</td>
<td>50-55% intake meat; 10-12% fish; 35-40% bread*; balance bananas, apples, carrots. About 8% fat.</td>
<td>Ground wheat 10.5 Oystershell flour 1.4</td>
</tr>
<tr>
<td>12. Mustelidae</td>
<td>Intake limited to unselected ground or unground cuts of horse meat, with fat estimated to range from 10 to 20% by weight.</td>
<td>Ground barley 7.0 Iodized salt 0.7</td>
</tr>
<tr>
<td>13. Viverridae</td>
<td>Unselected cuts of horse meat (10-20% fat by weight) with 2-3% mineral-vitamin mixture spread on the surface. Leopards—whole chickens (2-3 lbs.) twice weekly. 10-20% fat.</td>
<td>Ground rolled oats 7.0 Alfalfa leaf meal 3.5</td>
</tr>
<tr>
<td>14. Canidae</td>
<td>Intake limited to unselected ground or unground cuts of horse meat, with fat estimated to range from 10 to 20% by weight.</td>
<td>Peanut meal 7.0 Codliver oil 1.4</td>
</tr>
<tr>
<td>15. Felidae</td>
<td>Intake limited to unselected ground or unground cuts of horse meat, with fat estimated to range from 10 to 20% by weight.</td>
<td>Soybean meal 7.0 Ground boiled meat 10.0</td>
</tr>
</tbody>
</table>

* A Zoo formula: molasses, bran, wheat and rye flour, yeast, and lard. About 5 per cent fat.
† A product of Lederle Laboratories, Pearl River, N. Y.

and 580 examples of the disease, respectively. However, about 65 per cent of the autopsies and examples of arteriosclerosis were from 15 families of mammals and 18 families of birds, which have been exhibited in approximately equal numbers during each half of the period of this study, i.e., 20 years before and 20 years after diets were improved.

Moreover, these 33 families have been represented in the records by about equal numbers of males and females, among which the disease has been about equally frequent. Thus, this review will be limited to the records of the 33 families, and sexes will not be considered separately.

The 15 families of mammals and their diets before and after 1935 are listed in table 1.
Families 1 and 2 in table 1 are ruminants. The Cervidae are deer; the Bovidae include buffalo, goats, sheep, and antelopes. Family 3, Macropodidae, are the relatively large marsupials of Australia and adjacent islands—kangaroos, wallaroos, and wallabies—which are nonruminant herbivores.

Families 4, 5, and 6 are rodents. The Sciuridae include squirrels, prairie dogs, and woodchucks; the Capromyidae, coypus or nutria; the Dasyproctidae, agoutis and certain cavy.

Three families of primates follow. The Cebidae are New World monkeys: squirrel, cebus, spider, and wooly-monkeys. The Cercopithecidae are the Asiatic monkeys, the African monkeys, and baboons. The Pongidae are anthropoid apes, represented here by gibbons, orang-utans, and chimpanzees.

Six families of carnivores complete the list. The Ursidae are bears, the most nearly omnivorous of the carnivores. The Procyonidae include raccoons, coatis, and kinkajous; the Mustelidae, mink, skunks, otters, and badgers; the Viverridae, civets, genets, paradoxures, and binturonges; the Canidae, wolves, foxes, and coyotes; the Felidae, tigers, lions, leopards, pumas, jaguars, and smaller cats.

Controlled diets were introduced during 1935 but the change was not completed for several months. Hence January 1, 1936, is taken as the start of the present feeding system.

Inspection of the chart shows that the earlier diets for herbivorous and omnivorous animals (families 1 to 10) were largely carbohydrate. Dietary protein was low even for herbivores, and certainly inadequate for rodents and primates. Vitamin and mineral supplements were not used. These defects were corrected by the current diets, which supply about 3 per cent of fat to herbivores and about 5 per cent of fat to omnivores (rodents and primates). These levels represent moderate increases over those provided by the earlier diets but still are well within the range of "low-fat" diets. Dietary fat for the carnivores was not changed materially.

As a rule the nutritional diseases that developed under the original system of feeding represented chronic deficiencies. Thus, in respect to caloric intake the animals were not undernourished.

We have not attempted to determine whether caloric intake has been changed by the improved rations, for among captive wild animals intake may be influenced by factors that are not related to the composition of the ration. Improved nutrition has been indicated by hair and feather growth, fecundity, and growth of young. Obesity rarely has been observed.

Observations

Mammals. During the period of this study 15 families of mammals whose records have been selected for review supplied 2,499 autopsies and 299 examples of arteriosclerosis. The distribution of these autopsies and examples of arteriosclerosis, by family, is given in table 2. Each family is listed in this table in the sequence used in the chart on diets (table 1). The autopsies for each family have been separated into those negative and those positive for arteriosclerosis, with the mean and median ages for each subdivision.

The number of autopsies for families of this series ranged from 37 (Dasyproctidae) to 423 (Cercopithecidae), and the frequency of arteriosclerosis from about 5 to 30 per cent.

With one exception, the Capromyidae, the mean and median ages of positive animals considerably exceeded the mean and median ages of the negative animals. These relatively low values for the negative animals usually reflect a high death rate, especially for the period before diets were improved. Thus, these records may be taken to suggest that arteriosclerosis generally has been associated with age, and occurred chiefly in that segment of each group that adapted to captivity and survived to advanced age.

Still, the differences between mean and median ages of the negative animals of many families, as well as the differences between the means of negatives and positives, show that their range in age often overlapped. Certainly, age has been a factor in the development of the disease, especially in its extent and severity, but age alone does not account for all differences in incidence.

A comparison of the average ages attained by animals of these 15 families is hampered by wide differences in their natural life spans. We have resolved this difficulty by the arrangement that is given in table 3. Here each family is listed in the sequence used in table 2, with its frequency of arteriosclerosis per 100 deaths, the mean ages of its negatives and positives expressed as fractions of potential longevity, its potential longevity, and the range in age of positive animals. This allows the frequency of arteriosclerosis in each fami-
The frequency of arteriosclerosis in this series of mammals has ranged from 5.6 per cent in the Sciuridae to 32.4 per cent in the Dasyproctidae. The Macropodidae has had the second highest frequency, 28.0 per cent; the Capromyidae third with 22.4 per cent; followed by the Ursidae and the Viverridae with 19.8 and 17.0 per cent respectively. Frequencies for the remaining carnivores, the primates, and the ruminants have overlapped.

The ratios of mean ages of negative and positive Sciuridae to potential longevity of this family suggest that the disease actually has developed chiefly in that segment of this group that chanced to survive for a reasonable fraction of its natural life span. Moreover, the higher frequencies for the Dasyproctidae and the Viverridae have been associated with proportionately higher values for both of these ratios.

On the other hand, these ratios for the Macropodidae, the Cebidae, and the Capromyidae, show arteriosclerosis developing in younger animals. Then too, these values for the Dasyproctidae and the Viverridae are approximately equal, while their frequencies of arteriosclerosis differ about 2-fold. In fact, the differences in frequency among the 15 families rarely seem to be correlated closely with the relative ages attained. Either we have erred in our estimates of potential longevity or frequencies have been influenced by factors other than age. There is evidence to support this latter explanation.

For example, the higher frequencies of arteriosclerosis, 32 and 17 per cent, in the Dasyproctidae and the Viverridae respectively, have been associated with relative in-

<table>
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<tr>
<th>Families</th>
<th>Negatives</th>
<th>Positives</th>
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<tbody>
<tr>
<td></td>
<td>Age at death: months</td>
<td>Age at death: months</td>
</tr>
<tr>
<td></td>
<td>Number</td>
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</tr>
<tr>
<td>1. Cervidae</td>
<td>280</td>
<td>50</td>
</tr>
<tr>
<td>2. Bovidae</td>
<td>260</td>
<td>50</td>
</tr>
<tr>
<td>3. Macropodidae</td>
<td>82</td>
<td>25</td>
</tr>
<tr>
<td>4. Sciuridae</td>
<td>202</td>
<td>15</td>
</tr>
<tr>
<td>5. Capromyidae</td>
<td>37</td>
<td>40</td>
</tr>
<tr>
<td>6. Dasyproctida</td>
<td>25</td>
<td>40</td>
</tr>
<tr>
<td>7. Cebidae</td>
<td>197</td>
<td>20</td>
</tr>
<tr>
<td>8. Cercopithecida</td>
<td>380</td>
<td>35</td>
</tr>
<tr>
<td>9. Pongidae</td>
<td>41</td>
<td>40</td>
</tr>
<tr>
<td>10. Ursidae</td>
<td>53</td>
<td>95</td>
</tr>
<tr>
<td>11. Procyonidae</td>
<td>133</td>
<td>35</td>
</tr>
<tr>
<td>12. Mustelidae</td>
<td>134</td>
<td>35</td>
</tr>
<tr>
<td>13. Viverridae</td>
<td>44</td>
<td>70</td>
</tr>
<tr>
<td>14. Canidae</td>
<td>180</td>
<td>35</td>
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<td>15. Felidae</td>
<td>152</td>
<td>55</td>
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<table>
<thead>
<tr>
<th>Families</th>
<th>Negatives</th>
<th>Positives</th>
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<tr>
<td></td>
<td>Age at death: months</td>
<td>Age at death: months</td>
</tr>
<tr>
<td></td>
<td>Number</td>
<td>Mean</td>
</tr>
<tr>
<td></td>
<td>2,200</td>
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</table>

*Records for 15 families from January 1, 1916 through December 31, 1955; the number negative for arteriosclerosis for each family, with their mean and median ages in months, and the number positive with their mean and median ages also in months.
activity as well as with age. The cages for these animals are about 3 feet square and, as a rule, they have been caged separately.

Dasyproctidae are relatively large terrestrial rodents whose activity must be limited to cage floors. Moreover, these floors sometimes have induced persistent ulcers of the footpads of the animals, which further suppress activity. Seven of the 12 examples of arteriosclerosis in this family were associated with peripheral ulceration. Their ages ranged from 7 to 108 months. Other positive animals of this group survived from 96 to 193 months. Only one negative of the group, dead at 47 months, developed a focus of peripheral ulceration.

Viverridae are small nocturnal carnivores that climb easily. Thus their activity has not been limited to cage floors, for they also climb about the wire panels of the walls, which provide about 4 times the space allowed to Dasyproctidae. Moreover, their activity has not been hampered by ulcers of the feet. However, they rarely have been active animals.

Then, more than half of the examples of arteriosclerosis in the Macropodidae and Capromyidae (frequencies of 28 and 22.4 per cent) developed while these animals were exhibited, as expanding populations, in exhibition areas of constant size. Here, improved nutrition apparently has contributed to the frequency of arteriosclerosis by ensuring high-level reproductive drives in groups that lacked space for dispersion.

Thus, in the first decade of controlled feeding (1936 to 1945) 20 Macropodidae were exhibited and 5 died, 4 of which were positive for arteriosclerosis at ages ranging from 86 to 168 months (mean 130 months). None of the 9 young born during this period died of failure in lactation.

But from 1946 through 1955 purchases and births increased the number of Macropodidae on exhibition to 70 animals, with 43 deaths, approximately half caused by injury. Eighteen of the 32 positives for this family were found within this period. Their exhibition ages ranged from 1 to 198 months (mean 80 months) and only 5 of them were more than 99 months of age. Also within this period 10 nursing young (about half of all born but not included in the total for the group) died through failures in lactation.

And, in the Capromyidae, 10 of the 11 positives of this group were found within a 5-year period (1951 to 1955). They, and 11 negatives (all captive-born) died of injuries...
within this period, at an age range of 6 to 58 months.

These 21 animals were from a breeding group that had increased rapidly for about 3 years. Then, as it neared a peak of about 30 animals, reproduction ceased and fights became increasingly frequent.

At autopsy the thyroid glands and adrenal cortex of these animals were hypertrophied, and spermatogenesis and oogenesis were suppressed, changes that were most pronounced in animals that died in the latter half of the 4-year period, when arteriosclerosis was most frequent and extensive. The eleventh positive animal of this family died at 77 months. It was one of 27 that had been exhibited singly or in nonbreeding groups prior to 1950.

These observations on the Macropodidae and the Capromyidae suggest that social pressure (group relationships) may contribute more than age to the frequency of arteriosclerosis. The increasing frequency of injury as a cause of death, as numbers increased, is evidence of mounting social pressure in these groups. Failures in lactation, suppressed spermatogenesis and oogenesis, as well as hypertrophy of the adrenal cortex and thyroid glands also are recognized as effects of rapidly developing social pressure.17-20

Thus, as illustrated by the records for the Dasyproctidae and the Viverridae, the range in frequency of arteriosclerosis in the families of this series (table 3) may reflect the effects of inactivity and age. Or, as illustrated by the records for the Capromyidae and the Macropodidae, age and inactivity may be overshadowed by the number in each exhibition group and their reproductive activity.

This series of mammals, as a whole, has had a 10-fold increase in the frequency of arteriosclerosis during the 40 years of this review (actually within the last 25 years). The first increases were associated with increasing age. More recently, however, mean ages have decreased while the frequency of arteriosclerosis has risen. These changes in frequency and age are illustrated by the values given in table 4, in which records of the series have been grouped by 5-year periods, and ages have been calculated as adjusted means, the number of positives (N+), their age in months, also as adjusted means, and the frequency of arteriosclerosis per 100 deaths.

The adjusted mean ages given in table 4 were derived from actual mean ages for each family at each interval, by the following method: Mean ages of negatives (N) or of positives (N+) × 100/potential longevity = Correction Factors (CF) or (CFp), which are used in the following formula to give the adjusted means:

\[(N1 \times CF) + (N2 \times CFp) + \ldots (Nn \times CFp)/N1 + N2 + \ldots Nn,\] and similarly for the positive animals.

Two sources of error are recognized in the values thus derived: exhibition ages, which do not allow for age on arrival, and the estimates of potential longevity. Since we are uncertain that these errors are truly random, we have omitted elaborate statistical tests for possible differences.*

Table 4 shows that arteriosclerosis was found in some 3 per cent of the mammals that died during the initial 15 years of this study (1916 to 1930). The fourth 5-year period,
however, found an abrupt increase in frequency to 13 per cent. A lesser increase in the fifth 5-year period (1936 to 1940) brought the frequency to 20.5 per cent, at which level it continued through 1950, then increased to 25.5 per cent during the final 5-year period. Autopsies since 1955 indicate that this trend is continuing.

From 1916 through 1930 the Zoo maintained a relatively large number of mammals on exhibition and lost about 20 per cent of them annually. The onset of unfavorable economic conditions in 1930, followed by restricted commerce of World War II, caused a decrease in this population that continued through 1946. Subsequently, numbers have been increased, but had not returned to earlier values within the period of this study.15

The first increase in the frequency of arteriosclerosis coincided with decreases in the number on exhibition, which apparently improved the chances of survival of older animals. The increased number of positive animals and their increased mean age support this suggestion.

The introduction of controlled diets (1936 to 1940) was followed by further rises in frequency, but until the last 5-year period (1951 to 1955) these reflected the death rate rather than increased numbers of positives. The mean ages for both negative and positive animals during the fifth and sixth 5-year periods (1936 to 1945) suggest that the length of life in the Zoo was an important factor in maintaining frequency of arteriosclerosis. The new diets apparently contributed to frequency chiefly by improving the chances for survival.

Subsequently, however, the mean ages of the negative and positive animals have decreased in spite of adequate diets until, within the terminal 5-year period (1951 to 1955), these values equaled those of the 1916 to 1920 period. Meanwhile the frequency of arteriosclerosis continued at the 1936 to 1940 level for a decade, then increased to 25.5 per cent.

The last rise in frequency occurred in association with increasing numbers of animals on exhibition, and an over-all rise in injury as a cause of death.21 Thus, it seems reasonable to suggest that improved diets have led to an increased frequency of arteriosclerosis by either of 2 mechanisms: increased life spans of relatively inactive animals, or increased vigor and reproductive drives. The second seems to have been the more important during the last decade of this study, especially the terminal 5-year period.

**Birds.** The diets for birds in this Zoo prior to 1935 ranged from complex mixtures of prepared foods, grain, seed, insect larvae, and fruit, through combinations of grain and seed, to lean meat and fish. The instructions for preparing these mixtures were vague at best, and the actual composition is known to have varied with the keeper on duty and the supplies on hand. Therefore an attempt to reduce these practices to a reasonable statement of food intake would be futile.

Since 1935, diets for birds have corresponded closely to or have been identical with those for mammals (see section on Mammals). These diets will be identified when particular groups of birds are discussed.

The 18 families of birds that have been selected for this review are represented in the records by 5900 autopsies and 456 examples of arteriosclerosis, a frequency of 7.7 per cent. From 1916 to 1931 arteriosclerosis was found in less than one per cent of these birds: 20 of 3181 autopsies.

The changes in frequency and age by 5-year intervals during the period of this study are shown in table 5. The values for the adjusted mean ages given in this table were derived by treating the records for these birds by the methods described for table 4. In applying this method to the birds we have used the maximum exhibition age for each family to the closest multiple of 10, instead of potential longevity, as the factor from which adjusted mean ages might be computed. This seemed the better course, since we are uncertain that we have sufficient data for applying the Lancaster formula for potential longevity to birds.

The frequency of arteriosclerosis by 5-year
Table 5.—Arteriosclerosis in Birds at the Philadelphia Zoological Garden: Records of Eighteen Families for Forty Years, Grouped by Five-Year Periods to Show the Number Negative for the Disease (N—) and Their Adjusted Mean Age, the Number Positive (N+) and Their Adjusted Mean Age, and the Frequency of Arteriosclerosis per 100 Deaths

<table>
<thead>
<tr>
<th>Periods</th>
<th>Death rate (per cent)</th>
<th>Negatives</th>
<th>Positives</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N—)</td>
<td>Adjusted mean age (mos.)</td>
<td>(N+)</td>
</tr>
<tr>
<td>1916-20</td>
<td>23</td>
<td>1160</td>
<td>8</td>
</tr>
<tr>
<td>1921-25</td>
<td>23</td>
<td>1185</td>
<td>9</td>
</tr>
<tr>
<td>1926-30</td>
<td>21</td>
<td>811</td>
<td>14</td>
</tr>
<tr>
<td>1931-35</td>
<td>18</td>
<td>548</td>
<td>14</td>
</tr>
<tr>
<td>1936-40</td>
<td>13</td>
<td>452</td>
<td>18</td>
</tr>
<tr>
<td>1941-45</td>
<td>10</td>
<td>305</td>
<td>20</td>
</tr>
<tr>
<td>1946-50</td>
<td>15</td>
<td>576</td>
<td>11</td>
</tr>
<tr>
<td>1951-55</td>
<td>13</td>
<td>407</td>
<td>10</td>
</tr>
</tbody>
</table>

periods in this series of birds has fluctuated more than in the mammals. Still, as in the mammals (table 4), the first pronounced increase in frequency came within the fourth 5-year period (1931 to 1935), prior to the change in diets and in association with decreases in the number on exhibition and annual death rates, and increases in mean age at death for both negatives and positives.

Then, in the 5-year period immediately after the new diets were introduced the number of positives (and the frequency) dropped to about half that for the preceding 5-year period, even though mean ages of both negatives and positives were increased. Subsequently the number of positives has increased with each succeeding period while mean ages dropped until they again equalled those for 1916 to 1920.

Changes in the number of birds on exhibition in this Zoo have paralleled closely those in the mammals. The decrease ended in 1946, and within the following decade (especially since 1950) purchases and breeding have returned the number on exhibition to that of the period from 1916 through 1925.

Thus, as in the mammals, age apparently contributed to the first increases in arteriosclerosis. However, the further increase in age that came with improved nutrition seemed to reverse this trend, while the more recent rises in frequency have been accompanied by decreasing age. Autopsies since 1955 indicate that the latter trend is continuing. At the same time arteriosclerosis has come to be a relatively frequent cause of death rather than an incidental lesion.

Tables of the records for individual families of birds reveal nothing that is not already evident from tables 2 and 3 for mammals. However, the range in frequency has been greater among birds, from less than 2 to more than 30 per cent.

The groups in which less than 5 per cent have been involved are represented in this series by about 3500 autopsies. These groups include only the smaller omnivorous birds: finches, sparrows, starlings, troupials, doves, and parakeets, all of which have been exhibited in enclosures that have allowed them to maintain a high order of activity. Few of these birds have had opportunities for breeding, although seasonal nest-building activity has followed improvements in feeding.

The diets for these birds, after 1935, supply upwards of 12 per cent of fat which is at least a 2- to 4-fold increase over that supplied by earlier foods. Their relatively small increase in arteriosclerosis after 1935 may be explained, however, by increases in exhibition age.

The higher frequencies of arteriosclerosis have been found chiefly among larger birds that have little tendency to or opportunity for approximating natural activity. These groups include pheasants, ducks, geese, swans, the larger psittacine birds such as cockatoos, parrots, and macaws, and the storks, herons, hawks, and eagles, i.e., both omnivorous and carnivorous birds.

Among the cranes, storks, and herons especially, inactivity often has been augmented by chronic inflammatory lesions of the feet. However, the records do not permit an estimate of the importance of this combination of factors to the frequency of arteriosclerosis generally. The most convincing evidence provided by the birds for this asso-
Association was the death of 4 shoebill storks (Balaeniceps rex) of arteriosclerosis within 5 months after the peripheral lesions developed. Their exhibition ages ranged from 8 to 238 months.

Since 1935 the omnivorous birds have received a diet that is identical with or that corresponds closely to the current diet for primates. Hawks and eagles have been fed the ground meat ration that was designed for the Procyonidae and other carnivorous mammals, while storks and herons have received only fish or fish in combination with this meat mixture. These mixed rations for primates and carnivores allow fat intake of about 6 and 15 per cent for the omnivorous and carnivorous birds, respectively, which are estimated to be about a 2-fold increase over levels available before 1935.

Both dietary types of birds have had approximately the same changes in frequency of arteriosclerosis in association with changes in mean ages shown in table 5. Thus, apparently, diets and dietary fat have not been a factor in these changes. Moreover, the current diet for parrots, macaws, and cockatoos has reduced dietary fat from about 25 to about 6 per cent. During the period of 20 years following this change these birds had only a 2-fold increase in age while the frequency of arteriosclerosis increased about 6-fold.

As mentioned earlier, improved nutrition has increased reproductive drives. These have been much more evident among the larger types of birds than among the smaller ones. On the whole, however, successful breeding has been limited to ducks and their relatives, and to pheasants and cranes which, in spite of restricted space and increasing population, maintain a reasonable level of productivity. Young usually have been separated from adults immediately after hatching.

Still, irrespective of success in breeding or the presence of suitable mates, the reproductive drives of an adequately nourished population apparently result in pressures that increase with its density. The frequency of injury as a cause of death among these birds during the last decade of the present study is believed to reflect these increasing pressures.

**Discussion**

The material for this review represents records of routine autopsies on highly heterogeneous animals that died during a period of 40 years. Therefore inferences based upon this material must be presented cautiously.

Nevertheless, the frequency of arteriosclerosis in both mammals and birds has increased 10- to 20-fold during the period of this study. The more striking increases occurred within the last decade, 10 years after diets were improved, and in association with decreases in mean age.

This change has involved a wide variety of both mammals and birds and shows that, in the development of this disease, factors other than age or diets may have a major influence, the effects of which have not been limited to any one group of animals. Thus, a tentative identification of these factors should suggest new avenues for experimental and clinical investigation.

The records of this series through 1935 represent relatively malnourished animals among which successful breeding was rare. To a large degree therefore, they must have lacked the reproductive drives normal to the animals that have been exhibited in this Zoo since diets were improved. Thus the number of animals on exhibition before 1936 was not reflected in mounting social pressure.

But since 1936 the intensity of social pressure seems to have increased as an exponent of the increase in population. The increasing frequency of injury as a cause of death, especially in breeding groups, and the loss of young through failure in lactation support this suggestion. It also is supported by observations on the development of social pressure within freely growing experimental populations. Therefore, we suggest that social pressure has been a major factor in the recently increased frequency of arteriosclerosis in mammals and birds of the Philadelphia Zoological Garden. Inactivity is believed to
have been a second factor. This has been particularly evident in animals that were caged alone.

Hypertrophy of the zona fasciculata of the adrenal glands has been one measure of increasing social pressure in freely growing experimental populations.\textsuperscript{18-20} In the present series this change has been associated with the development of arteriosclerosis only in animals of the Capromyidae.

Other animals of this series may be regarded as having undergone partial adrenalectomy through more or less atrophy of the zonae fasciculata and reticularis of the adrenal cortex, because of reduced activity during life in the Zoo.\textsuperscript{22} In these animals the zona glomerulosa and the medulla of the adrenal glands have been found to persist intact or to undergo hypertrophy. Presumably the adrenal glands of birds undergo corresponding changes with inactivity. For the present, however, the complex cellular patterns of avian adrenal glands usually have discouraged our attempts to demonstrate such changes.

The adrenal response of the Capromyidae and of the more rapidly growing experimental populations to increasing social pressure seems to differ from that common to other animals of this series. This difference possibly reflects the rate at which the stimulus has been applied. And actually the difference may be more apparent than real, for hypertrophy of the zona fasciculata in response to rapidly increasing social pressure may change the secretory pattern of the adrenal glands.\textsuperscript{18-20} Presumably this change may contribute quite as much to an imbalance of the total output of the adrenal glands as if the zonae fasciculata and reticularis had undergone partial atrophy, while the medulla and zona glomerulosa were intact or hypertrophied.\textsuperscript{23}

These considerations lead us to suggest that the primary factors in the observed increase in the frequency of arteriosclerosis in this series of mammals and birds has been an imbalance of adrenal secretion. Imbalance may follow inactivity, when animals are caged alone, or it may result from the development of social pressure in exhibition groups. This hypothesis is offered as a tentative explanation of the increased frequency of arteriosclerosis in mammals and birds in this Zoo. Its validity must depend, of course, upon appropriate experiments.

However, a preliminary test of the effects of inactivity on growing chickens has found that arteriosclerosis of the coronary arteries may develop within 11 weeks. Control birds that were allowed about a 10-fold greater space did not develop lesions within this period. Both groups were on a "low-fat" diet.\textsuperscript{24}

Moreover, forced exercise (walking on a horizontal surface) is reported to protect chickens from the effects of feeding cholesterol in oil.\textsuperscript{25} These results are in accord with observations on the frequency of coronary disease in human males in occupations that differ widely in their demands for muscular activity.\textsuperscript{11} However, cholesterol-fed rabbits were not protected by forced exercise in a revolving drum.\textsuperscript{26} In fact, the descriptions of the adrenal glands of these rabbits suggest that this form of exercise was quite as much of an abnormal stimulus as is rapidly developing social pressure.\textsuperscript{18-20}

**Summary**

From 1916 to 1931 arteriosclerosis was found at autopsy in about 2 per cent of the mammals and birds that died in the Philadelphia Zoological Garden. But from 1931 to 1956 the frequency of this disease increased by about 10-fold in mammals and by about 20-fold in birds. This change in frequency began with decreasing populations and increasing age. It continued for a time after improved nutrition had given further increases in age. However, it has been most pronounced since 1946, when population densities were again increased, and mean ages decreased to about the levels of the 1916 to 1931 period. That is, the more recent increases in the frequency of the disease apparently have been independent of age and diets, but were associated with rises in popu-
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lation densities. These observations suggest that social pressure, through an imbalance in adrenal secretion, has become a major factor in the frequency of arteriosclerosis in these animals.

SUMMARIO IN INTERLINGUA

Inter 1916 e 1931, arteriosclerosis esseva constatate in circa 2 pro cento del necropsias de mammales e aves que habeva morite al Jardin Zoologic De Philadelphia. Sed ab 1931 usque a 1956 le frequentia del morbo se decuplava in mammales e se vintuplava in aves. Iste disveloppamento comenciava con le reduction del populazion e con le augmento del etates. Le disveloppamento continuava durante un certe periodo de tempo e post que un meliorate nutrition habeva resultate in augmentos additional del etates. Tamen, illo deveniva le plus marcate post 1946 quando le densitate del populatione reascendeva e le etates medie re-descendeva a circa le nivellos del periodo ab 1916 a 1931. Assi, le recente augmento in le frequentia del morbo esseva apparentemente independente de etate e dieta sed esseva associate con augmentos del densitate del population. Iste observationes suggere que le pression social—per imbalanza del secretion adrenal—ha devenite un factor de alte signification in determinar le frequentia de arteriosclerosis in iste animales.

REFERENCES


Medical Eponyms

By Robert W. Buck, M.D.

Moebius' Sign. The first mention of this sign was made by Moebius in a review of Pierre Marie's Contribution à l'étude et au diagnostic des formes frustes de la maladie de Basedow, Paris, 1883. The review appeared in Schmidt's Jahrbücher der Inneren und Ausländischen Gesamten Medicin 200: 100, 1883.

"Von Graefe has said that lessening or abolition of the synerge movement of the upper lids in raising and lowering the eyes is pathognostic. The reviewer has failed to find Graefe's symptom in a series of cases including some with and some without exophthalmos. He not only disbelieves in its pathognostic character, but considers it rather rare. On the other hand, the reviewer has recently observed a disturbance of convergence in two patients with Basedow's disease, both of whom had a moderate bilateral exophthalmos of equal degree. If the patient was asked to fix his vision upon the examiner's finger, both eyes looked to the right or to the left. That is, the patient fixed with one eye, and the external muscles of the other eye contracted consensually. On monocular examination, both internal recti functioned normally. In a third patient with exophthalmos, the symptom was absent. Whether the phenomenon is directly dependent upon the exophthalmus is uncertain."

The subject was again discussed, and observations in eight additional cases were reported in an article on "Convergence Insufficiency in Basedow's Disease" (Ueber Insufficienz der Convergenz bei Morbus Basedowii) which was published in the Centralblatt für Nervenheilkunde, Psychiatrie und gerichtliche Psychopathologie 9: 356-358 (June 15) 1886.
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