BRITISH MEDICAL JOURNAL

LONDON SATURDAY FEBRUARY 24 1962

ATHEROSCLEROSIS: A COMPARATIVE STUDY

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The diversity of opinion currently held concerning the pathogenesis of atherosclerosis suggested that a comparative study of spontaneous arterial disease would prove of value in emphasizing any factor common to this condition in animals and man, particularly as experimental methods have failed to reproduce the exact picture of human atheroma. Florey (1960) has discussed the importance of such a study, but apart from Fox (1923, 1933, 1939) and Ratcliffe and Cronin (1958) there have been few reports of the frequency of occurrence and the comparative pathology of atherosclerosis in any large mixed group of animals. This paper describes our findings from a fairly wide selection of material obtained from the London Zoological Gardens. We have attempted to correlate post-mortem findings with some aspects of dietetic and clinical history and the serum cholesterol obtained after death.

Material and Methods

The heart, attached aorta, and branch arteries were obtained *post mortem* from 816 animals (birds, mammals, and reptiles), the majority of which died in the London Zoological Gardens from natural causes from mid-1958 to mid-1961. Some of the specimens for examination had been received for necropsy from other zoos or from private collections in this country. All the material was taken from available consecutive post-mortem examinations, and, to this extent, was unselected. The heart and thoracic aorta were examined in every case, but in only about a third of the total number was the complete aorta available for study. The naked-eye appearance and distribution of any lesions in the opened heart and vessels were noted, and in order to facilitate recognition of small lipid deposits in arterial walls the gross specimens were treated with Sudan IV. Representative histological sections were prepared and examined from 348 cases, and these included all specimens with gross vascular lesions. The staining techniques used have been described in a previous report (Rigg *et al.*, 1960).

Specimens from 485 birds were examined (231 males, 164 females, 90 sex not recorded). This was a large and varied group comprising examples from 19 orders. The largest numbers were from the following orders, the figures referring to the number of specimens examined in each group: Psittaciformes (parrots, love-birds, etc.) 126; Passeriformes (finches, starlings, sun-

birds, etc.) 103; Anseriformes (geese, ducks, etc.) 63; Galliformes (turkeys, pheasants, etc.) 36; Sphenisciformes (penguins) 30; Charadriiformes (gulls, plovers, etc.) 18; Falconiformes (vultures, eagles, etc.) 17; Coraciiformes (hornbills, frogmouths, etc.) 14; Ciconiiformes (herons, etc.) 14; Gruiformes (cranes, trumpeters, etc.) 14; Piciformes (toucans, barbets, etc.) 12; and Columbiformes (pigeons, etc.) 10.

Material from 233 mammals was studied (90 males, 94 females, 49 sex not recorded). This comprised examples from 11 orders, and included specimens from 63 Primates, 61 Carnivora, 41 Rodentia, 40 Artiodactyla (goats, antelopes, etc.) and Perissodactyla (horses, etc.), and 20 Marsupialia.

In a third group there were 98 reptiles (48 males, 32 females, 18 sex not recorded), including 59 Serpentes, 21 Testudines (tortoises, etc.), and 10 Sauria (lizards, etc.).

The duration in captivity of the animals was usually known, except where the specimen had come from a source outside the Zoological Gardens. The actual age of the animal was available in only a small number of cases; this meant that no more than an approximate estimate could be made of the true age, but this was probably sufficient for our purposes of analysis as many of the new arrivals at the Zoo are immature specimens.

In 128 animals in the survey suitable samples of blood were obtained within a few hours after death for estimation of serum cholesterol. Sackett's (1925) modification of Bloor's method, which estimates total cholesterol, was used.

Anatomical Pattern of Lipid-containing Lesions

The lipid-containing vascular lesions were divisible broadly into two groups: firstly, fatty streaking only, consisting of small focal accumulations in the arterial intima and/or inner media and presenting as red streaks or patches after gross staining with Sudan IV; and, secondly, atherosclerotic lesions which were clearly elevated intimal plaques containing sudanophilic lipid.

The earliest foci of fatty streaking were usually small irregular patches at the junction of the aorta and its large branches or at the bifurcation of the brachiocephalic trunks. Longitudinal linear fatty streaking was most prominent in the lower thoracic and upper abdominal aorta. Lipid foci in the upper abdominal aorta of some avian species were frequently located in

an area slightly above the ostium of the coeliac artery. Less commonly, the first patches of lipid were seen in the ascending or arch of the aorta immediately cephalad to the aortic valve cusps or at the obliterated ductus site; in some cases there was a fine stippling or blotching of the arterial intima, unrelated to vessel ostia. Histologically, these lesions showed focal accumulations of fine droplets of sudanophilic lipid, usually isotropic and mainly extracellular, either beneath the endothelium, occasionally in small fibromuscular intimal thickenings, or parallel to the internal elastic fibres. In some specimens fat droplets appeared to be within the cytoplasm of histiocytes and possibly smooth-muscle cells. In the avian thoracic aorta and brachiocephalic arteries fatty streaks were found especially in the non-muscular laminae between the bundles of smooth-muscle fibres of the juxta-intimal media. Lipid droplets were often associated with an increase of mucopolysaccharide material, which appeared to precede the lipid accumulation in some instances.

The atherosclerotic lesions, which were associated commonly with some degree of fatty streaking, usually presented as focal raised nodules or plaques, with a circular, elongated, or irregular outline on the intimal aspect of the vessel. Sometimes the artery showed diffuse segmental thickening with a variable degree of luminal stenosis (Fig. 1). In some instances the vessel was dilated, and in one specimen, from a grey-winged trumpeter, an aortic aneurysm had formed. The colour of the plaques was usually pearly white or yellow, some-

FIG. 1.—Amazon parrot. Section of subclavian artery showing severe stenosis with numerous lipid spaces in thickened intima. (Weigert's elastic and van Gieson's stain. $\times 30$.)

times closely matching the body fat. The surface of the lesions was usually smooth, occasionally corrugated; gross ulceration and mural thrombus formation were observed in two cases only. The relatively larger plaques were seen in the thoracic aorta and brachiocephalic arteries of birds, but in many cases the lesions were more extensive though somewhat flatter in the abdominal segment of the aorta. The abdominal aorta was more severely affected in Galliformes and the thick thoracic aorta and brachiocephalic trunks in Psittaciformes. The aortic lesions appeared to be more equally distributed in Anseriformes and Falconiformes.

Microscopically the lesions resembled each other in that they were confined either to the intima or to the intima and inner media and consisted of subendothelial thickenings formed of mesenchymal elements and accumulations of lipid in variable proportions (Figs. 2, 3, and 4). Medial involvement was more pronounced in plaques from the thoracic aorta of birds, where a structural dissimilarity between normal thoracic and abdominal aorta is even more evident than in mammals. Lipid, predominantly isotropic, was present both as intracellular and extracellular sudanophilic droplets of varying size and as anisotropic crystalline material with histochemical properties of cholesterol. The connective tissue varied from loose almost myxomatous tissue rich in mucopolysaccharide to dense fibrous tissue; sometimes it had a pseudocartilaginous appearance (Fig. 4) and in rare instances it showed definite osseous metaplasia. The latter had occurred in the aorta of a slender-billed cockatoo, reputedly 106 years old, and a 14-year-old llama born in the menagerie. Elastic fibres and smooth-muscle cells were identified in several lesions, but there was very little evidence of heavy vascularization or of recent or previous haemorrhage into the plaques. The endothelium over the surface of

FIG. 2.—Horned screamer. Section of atherosclerotic aortic plaque showing abundant sudanophilic lipid in depths of lesion. Media in lower field. (Sudan IV and haematoxylin. $\times 65$.)

FIG. 3.—Horned screamer. As Fig. 2 but photographed by polarized light to show anisotropic lipid.

the lesions appeared intact unless lost from post-mortem autolysis; very rarely, a little thrombus adhered to the intimal surface and, in one case only, abundant fibrin was demonstrated in the substance of the plaques by conventional histological methods. Tiny haematoxylinophilic spherules and granules were seen frequently in the lesions; extensive calcification was uncommon. The proportions of lipid and mesenchymal elements in plaques varied considerably from specimen to specimen and in individual lesions from the same animal.

FIG. 4.—Grey parrot. Section of thoracic aorta showing cholesterol clefts and pseudocartilaginous change in a plaque involving intima and inner media. (Haematoxylin and eosin. $\times 125$.)

Incidence of Arterial Lesions

The frequency of occurrence of aortic lipid-containing lesions in 816 animals is shown in the accompanying Table. The true incidence would be somewhat higher, as the whole aorta was not always available for study. In 257 selected specimens in which the complete aorta and main branch arteries were examined, 30% showed

Incidence of Aortic Lesions in 816 Animals

	No. Examined	No. with Fatty Streaking	No. with Atherosclerosis	No. with Other Lesions
Mammals ..	233	56 (24%)	6 (3%)	42 (18%)
Birds ..	485	119 (25%)	87 (18%)	19 (4%)
Reptiles ..	98	3 (3%)	1 (1%)	7 (7%)
Total ..	816	178 (22%)	94 (12%)	68 (8%)

fatty streaking only, 18% had atherosclerosis (with or without fatty streaking), and 10% had aortic lesions other than fatty streaking or atheroma. The other aortic lesions, grouped together in the last column of the Table, included focal intimal thickening devoid of lipid, various lesions of the musculo-elastic tissue of the arterial media frequently heavily calcified, occurring commonly in marsupials (Fig. 5) and ungulates, and lesions regarded as inflammatory in origin showing evidence of an active aortitis or fibrous scarring.

Atheroma was present in 18% of all birds, and this was found particularly in the following orders (each figure refers to the percentage of animals with atheroma in each group): Falconiformes 53, Coraciiformes 36, Galliformes 30, Columbiformes 30, Ciconiiformes 29, Piciformes 25, Anseriformes 24, Psittaciformes 22, Gruiformes 21. Fatty streaking was widely distributed, affecting most groups. The incidence of atheroma was less than 10% in Passeriformes and Charadriiformes, and none of 30 Sphenisciformes showed atheroma.

Atheroma was found in only six mammals (three primates, two llamas, and a sheep). Fatty streaking was more widely distributed, occurring in 41% of primates, 24% of rodents, 21% of ungulates, and 8% of carnivores. The lion was little affected by either type of lesion; of eight specimens only one showed fatty streaking.

Of the reptiles, a tegu showed a few lipid-containing aortic nodules, and three snakes had slight fatty streaking.

FIG. 5.—Dama wallaby. Sections of aorta showing focal destruction of media with associated calcification. A, haematoxylin and eosin. B, von Kossa. ($\times 65$.)

The heart and coronary vessels were examined microscopically in 208 specimens (154 birds, 44 mammals, and 10 reptiles). Coronary atheroma was seen in 3 birds out of a group of 71 cases (68 birds and 3 mammals) with aortic atheroma; and in 2 birds a coronary artery was markedly narrowed by a sub-endothelial mass of fibro-hyaline material which may have represented old organized thrombus. Ten cases in this group showed focal fibrous intimal thickenings in the small intramural coronary arteries. Atheroma localized to the coronary tree was not observed. Fatty streaking of the coronary arteries, invariably associated with aortic fatty streaking or atheroma, was seen in a small number of mammalian and avian specimens stained grossly with Sudan IV. This gross technique was not readily applicable unless the coronary vessels were of a reasonable size, and since many of the hearts examined weighed less than 5 g. no attempt was made to determine the overall incidence of coronary fatty streaking.

Examples of heart disease included 18 cases of active pericarditis (13 birds, 4 mammals, and 1 reptile), 14 cases of parasitic or suppurative myocarditis (10 birds, 1 mammal, and 3 reptiles), and 8 cases of endocarditis and/or valvulitis (4 birds and 4 mammals). Parasitic infestation of the heart was observed in 3 out of the 10 reptilian hearts examined histologically. Subendocardial and interstitial and/or perivascular myocardial fibrosis, usually of low intensity, was seen in 20 specimens (18 birds and 2 mammals), 9 of which showed some evidence of coronary disease. The only case of myocardial infarction was represented by a microscopic focus of myocardial degeneration and necrosis associated with severe stenosis of a small coronary artery from a male Edward's pheasant, which had lived in the Zoological Gardens for 11 years. The main pulmonary arteries occasionally showed slight fatty streaking; atherosclerosis was never observed.

Relationship of Age, Sex, and Serum Cholesterol to the Lipid-containing Lesions

Unfortunately, it is impossible to estimate the life-span of the great majority of animals with any degree of accuracy, but it was known that 118 birds in this survey lived at least five years. Data were sufficient for analysis in 310 birds and 146 mammals. From

FIG. 6.—Frequency of occurrence of lesions in each age-group (duration in captivity), expressed as the proportion of total number of animals in the group. Dark hatching indicates aortic atheroma; cross-hatching indicates fatty streaking only. Figures at the top of each column are the total number of animals in each group.

Fig. 6 it may be seen that, as the estimated age of the animal increased, fatty streaking and atheroma became more common.

Lipid-containing lesions occurred with equal frequency in male and female animals.

Post-mortem serum cholesterol levels were estimated in 128 cases and the results are shown in Fig. 7. The median level was slightly higher in birds (120 mg./100 ml.) compared to mammals (105 mg./100 ml.) and

FIG. 7.—Level of serum cholesterol in birds, mammals, and reptiles, estimated from post-mortem blood. One bird with aortic fatty streaking, a scarlet ibis, had a cholesterol of 1,300 mg./100 ml., and another, a penguin with a normal aorta, 780 mg./100 ml. (For convenience these two levels are not indicated in this figure.) N=Normal aorta. FS=Aortic fatty streaking. A=Aortic atheroma.

lowest in reptiles (75 mg./100 ml.). In birds and mammals the level of the serum cholesterol did not increase in the cases with fatty streaking, and in birds the presence of atheroma did not connote a higher serum cholesterol.

Diet

All animals in the Zoological Gardens are provided with balanced diets in respect of their estimated requirements, and so far as is possible these approximate to the type of food that is taken in the wild state. It was broadly possible to classify animals into herbivores, carnivores, and omnivores, according to the diets they received in the menagerie. In the mammals, aortic lipid-containing lesions were found more commonly in herbivores (45 with fatty streaking and 4 with atheroma out of 151 specimens) as compared with 11 with fatty streaking and 2 with atheroma out of 82 carnivores and omnivores combined. Reptiles, mainly carnivorous, had very few lesions. In birds, overall, atheroma occurred with equal frequency in herbivores compared with carnivores and omnivores; but, comparing groups,

Falconiformes, which are meat-eaters, had a very high incidence of atheroma, and penguins, fish-eaters, almost no lesions. Fatty streaking was slightly less common in the herbivorous group (71 with fatty streaking and 58 with atheroma out of 322 specimens) compared with 48 with fatty streaking and 29 with atheroma in 163 carnivores and omnivores combined. It must be remembered that to a certain extent the diet provided by the authorities is "augmented" by the public, and in addition fish may be the staple food of some carnivores.

Discussion

It is evident from this survey that arterial lesions occur spontaneously in many vertebrates and that the incidence is much higher in mammals and birds than in reptiles. It is also apparent that, although fatty streaking often occurs in both mammals and birds, the larger lipid-containing plaques, which to avoid a neologism we refer to as atherosclerosis, are seen commonly only in birds. Although close comparison of these lipid-containing lesions might not be strictly a valid procedure, it is clear that there are several anatomical points of similarity. Major lesions were found, as is the case in man, principally in the large elastic arteries—for example, the brachiocephalic trunks of birds—but in no species did they form with any particular frequency in smaller muscular vessels such as the coronary arteries. Patches of fatty streaking were often found at arterial branches and bifurcations, and it is worth noting that atheromatous plaques were common in birds, in which it is known that the systemic blood-pressure is relatively very high, and distinctly rare in reptiles, which have a low blood-pressure. The main pulmonary artery, presumably a low-pressure area, was generally free from disease. Nodular lesions, observed both in the aorta and in the pulmonary trunk of several marsupials, bore no histological resemblance to the lesions of human atherosclerosis.

Our material was not well suited for microscopical study of slight aberrations in vascular histology. Immediate post-mortem fixation was rarely possible, and for this reason artifacts resulting from autolysis could not be excluded. Although there was some variation in the site of small lipid deposits in the arterial wall, the primary lesion in the relatively thick proximal aorta and brachiocephalic trunks of avian tissue appeared to occur in the intermuscular laminae of the inner media of the affected artery. Focal thickening, associated both with an increase or spreading of mucopolysaccharide material and with an accumulation of fine sudanophilic lipid droplets, encroached on the vessel lumen; additional lipid, deposited superficially, tended to build up the lesion. Elsewhere the fatty plaques were largely confined to the intima, but this difference may be an expression of the structural difference between vessels rather than of a dissimilar pathogenesis. The small lipid patches adjacent to vessel ostia were sometimes located in small fibromuscular or elastic intimal thickenings, but it is questionable if all these structures are pathological. Deposits of fibrin were not observed in association with the small lipid accumulations and were identified only very rarely in the larger plaques.

Gross ulceration of plaques did not occur and atherothrombosis was found on only one occasion, when it was associated with severe vascular disease. The paucity of thrombotic lesions was surprising and it is interesting

to speculate whether man has evolved a particularly complex system of blood coagulation unstable in the presence of severe vascular disease. In our experience, vascular thrombosis in animals is usually a sequel of local physical injury or infection, and spontaneous thrombosis, with or without associated atheroma, is a rare condition. A few cases of spontaneous atherothrombosis in animals have been recorded in the literature (Manning, 1942; Ratcliffe *et al.*, 1960; Vastesaege *et al.*, 1960), but as one investigator is unlikely to collect sufficient material it might be rewarding to refer all such cases to a central institute.

The present study does not support a primary thrombogenic concept of atheroma. Unfortunately, although points of histological similarity encourage comparison among species they do not indicate that the cause or causes of arterial disease are necessarily the same in all. The presence of focal fine droplets of fat in the inner media in some early lesions suggests a localized failure in the metabolism of the arterial wall, while the more superficial lipid deposits may well be a result of plasma insudation from the vessel lumen. Lipid deposits dominate the histological picture simply because the tissues may be incapable of removing excess lipid, and the variation of lesions among different species may be due to some animals possessing a more efficient lipid "removal" mechanism than others.

"Minor lesions in minor vessels" summarizes the extent of coronary disease in our material. Serial histological sectioning of all hearts would certainly have revealed additional information, but from the data available it would seem that severe coronary atheroma and myocardial infarction are rare. The reason for this is obscure, but it could support the view that human coronary disease is predominantly a thrombotic process and may well be a separate pathological entity from atheroma elsewhere in the body. Ratcliffe *et al.* (1960) have reported a sharp increase during the past decade in the incidence of coronary arteriosclerosis in mammals and birds at the Philadelphia Zoo, and in their material this was frequently associated with myocardial fibrosis and, to a less extent, with fatal myocardial infarction.

We have examined a number of factors—for example, age, sex, diet, stress, physical activity, and blood cholesterol levels—which may have been correlated with the occurrence of arterial lesions, but we have found that age differences were probably the only relevant factor in direct relationship to fatty streaking and atheroma. The high incidence of atheroma in birds was the obvious feature of this analysis, and this was associated with a greater proportion of lesions in older specimens. In mammals, most of which were young specimens, fatty streaking was common whereas atheroma was infrequent, again suggesting that older age was a significant factor. So far as aortic atheroma is concerned, this relationship is present in man, and previous workers have reported it in animals in their descriptions of spontaneous lesions (Wilens and Sproul, 1938; Dauber, 1944; Lindsay *et al.*, 1952; Gottlieb and Lalich, 1954). Nevertheless, the spontaneous development of atheroma in some quite young animals and its absence in several old animals—for example, Felidae—must indicate the importance of other factors. Lofland and Clarkson (1959) have reported that there is a high incidence of spontaneous aortic atherosclerosis in some breeds of pigeons and an absence of this condition in others. These differences could not be correlated with

age, sex, diet, or physical activity, and the authors suggested that atherogenesis in pigeons may be genetically determined.

Normally, animals in the London Zoo are well nourished, although terminal illness may interfere with nutrition in some respects. Broadly classifying animals as herbivores, carnivores, and omnivores, we were unable to find any firm association of arterial lesion with the type of diet. We have seen atheroma in a truly vegetarian, middle-aged orang-utan, in the carnivorous eagle, and in animals as omnivorous as man. Nevertheless, the incidence of atheroma is much higher in some species of meat-eating than in fish-eating carnivorous birds; but lesions do occur in some largely fish-eating birds, while some mammalian meat-eating carnivores are almost free from the disease. One animal in particular, a night heron, is worthy of note. This bird, a fish-eater in natural surroundings, was born in the menagerie and fed on meat and fish during the whole of its life of 12 years. It was one of the few cases with coronary atheroma and the only specimen with advanced atherothrombotic lesions in other systemic arteries. In wild life this bird would have been an active forager, but in captivity exercise was limited. This instance the difficulty experienced in assessing age, diet, and activity in relation to disease, and it would be speculative to suggest that the supplementary meat diet was thrombogenic.

Captive animals are naturally restricted in their movements, either because they are physically contained in cages or enclosures or because they are disinclined to exercise, primarily as there is no need to strive for food. Any comparison, therefore, between activity and non-activity as a factor in the production of atheroma must compare free-range with captive life, and, except on a limited scale, this would be a difficult study. Inactivity, as a result of captivity, may play some part in favouring the deposition of fatty plaques, but it is more likely that restriction of movement and protection allow certain animals to live to an old age and thus develop atheroma. It is noteworthy that mammals, which generally did not live to a great age in our series but which must have been inactive compared with those in the wild, had relatively little atherosclerosis. A detailed survey of arterial disease in truly wild animals, as distinct from wild animals in captivity, has never been made.

McGill *et al.* (1960) have reported that the majority of wild adult baboons they had examined showed some degree of aortic intimal lipid deposition, but fibrous plaques were infrequent; and Fox (1939) has recorded a few cases of arteriosclerosis in truly wild animals. We have observed atheromatous lesions in the aortae of several ducks which had lived a quasi-wild life in the London Royal Parks and in a snow goose from the Wildfowl Trust in Gloucestershire. We have also seen a case of advanced atheroma in a kite, found dead in the Welsh hills, which, so far as is known, had led a completely natural life in the wild. A difference in physical activity is only one of many differences that separate wild from captive animals, but on the scanty evidence available it would seem that inactivity is not a major factor in the genesis of atheroma.

A certain amount of stress may be produced when animals are introduced to the collection, but we have not found any acute arterial lesions as a result of this. Likewise, no arterial change was consistently present in animals that succumbed suddenly from severe infection.

However, Ratcliffe and Cronin (1958) suggested that stress factors may be important in the increase of arteriosclerosis which has occurred in the Philadelphia Zoo since 1946.

We have not investigated the relationship between atherosclerosis and hypertensive vascular disease, but it was noted that a frogmouth with almost confluent aortic atheroma showed vascular lesions in small renal vessels that were indistinguishable from those occurring in malignant hypertension in man. On the other hand, we have also seen a normotensive laboratory rabbit with severe atheroma (Stansfeld and Finlayson, 1961). Gross arterial lesions were also observed in a few birds with visceral gout, but this is not surprising in view of the known association of gout with renal and arterial disease in man.

The level of the serum or plasma cholesterol in man and experimental animals is thought to bear a direct relationship to the level of total lipid in the blood, but whether a raised blood cholesterol indicates an increased tendency to form atheroma is by no means certain. In our three main classes, birds in general had the highest serum cholesterol and most atheroma, and reptiles the lowest cholesterol level and the least atheroma. Nevertheless, within each group it was not possible to correlate a high serum cholesterol with either fatty streaking or atheroma. More detailed investigation of the lipids in the blood, taken during life, and in the arterial wall of animals is desirable, particularly in view of the report by Swell *et al.* (1960) that the proportions of arachidonic acid in the cholesterol ester fatty acids of sera are apparently high in animals resistant to atherosclerosis and low in those which are susceptible to the disease.

Conclusion

This comparative study of atheroma was made to learn something of the natural history of this condition in species other than man and to attempt to add some facet to the incomplete picture of the pathogenesis of human atheroma. It might be contended that the cause, or causes, of the arterial lesions are entirely different from those in man and only the morphology tends to have some similarities. It might also be said that we have studied experimental lesions, albeit completely uncontrolled, and not spontaneous disease. But some features are outstanding, particularly the absence of thrombotic lesions and the infrequency of severe coronary arterial disease. Increase in age appears to favour the development of atheroma; the level of blood cholesterol is probably only secondarily associated with arterial disease, but much more detailed lipid and dietetic studies in each species are required.

Summary

A study has been made of the pathology of spontaneous arterial disease in a series of 816 exotic animals (mammals, birds, and reptiles) that died in captivity from natural causes. Aortic lesions occurred frequently in both mammals and birds, but only the latter showed a fairly high incidence of atherosclerosis. Several factors of possible significance in the pathogenesis of atheroma of man were investigated; age difference was the only factor that appeared to be directly related to atheroma in animals.

Thrombotic complications and severe coronary atheroma were found rarely in animals, and the relationship between these two observations is discussed. The present investigation does not support a general

thrombogenic concept of atheroma. It is suggested that more detailed studies of the small lipid-containing arterial lesions in animals and of the comparatively rare cases of atherothrombosis might lead to a better understanding of essentially similar lesions in man.

We thank Mr. H. Corbett, Mr. J. W. Miller, and Miss G. R. Latham for skilled technical assistance; Mr. P. Crocker for the photomicrographs; and several other colleagues for their helpful advice. We are indebted to Dr. D. N. Baron and Dr. T. R. E. Pilkington for lipid studies and to Dr. J. V. Beer for material from the Wildfowl Trust. One of us (R.F.) is indebted to Eli Lilly and Company Limited for generous financial assistance.

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ATHEROSCLEROSIS OF ARTERIES OF LOWER LIMBS

BY

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This report is concerned with the clinical course of atherosclerosis obliteration of the leg arteries and compares the progress of patients treated by lumbar sympathectomy with those in whom no operation was performed. Patients treated by direct arterial surgery are not considered here and will be the subject of a separate communication.

The survey is based on a follow-up of 454 patients with atherosclerosis of the leg arteries who were treated in the Surgical Professorial Unit at St. Bartholomew's Hospital. They were observed from a minimum of three years to a maximum of 12 years. Forty-two patients could not be traced, leaving 412 on whom long-term observations were complete (Table I).

Sex and Age Distribution.—The age of onset of symptoms is shown in Fig. 1; 92% of the patients were

men. The age of onset of the occlusive process is of prognostic importance, and in our patients the incidence of amputation increased sharply in disease beginning in the later decades of life (Fig. 2).

Survival Rate.—During the period of observation 88 patients died. The overall mortality rate was 21%, with an average survival of eight years below the age of 50 and of four years above that age. Atherosclerosis is a generalized disease, and it is not surprising that coronary occlusion accounted for 40% of the deaths. The incidence of fatal cerebrovascular accidents (11%) was, however, lower than in other series.

Associated Diseases.—Hypertension (systolic B.P. over 180 mm. Hg) was present in 114 (28%) patients. It is of interest to note that the limb-amputation rate in these patients was only 5% as compared with the overall incidence of 10%. Coronary disease, as evidenced clinically by angina of effort, was present in 71 (17%) patients. This latter figure is surprisingly low, as is also the incidence of diabetics, who numbered only 18 (4.5%).

TABLE I.—Period of Observation in 454 Patients

Years of observation	3-5	5-8	8-10	10+	Not traced
No. of patients	115	117	70	110	42

FIG. 1

FIG. 2

FIG. 3

FIG. 1.—Incidence of onset of first ischaemic symptoms by decades. Black areas indicate the number of eventual amputations in each group. FIG. 2.—Incidence of amputations in groups of age of onset of symptoms by decades. FIG. 3.—Incidence of level of arterial occlusion.