PULMONARY ARTERIAL DISEASE OF THE CAT

BY

JOHN MASTERSON HAMILTON

THESIS

submitted to

THE UNIVERSITY OF GLASGOW

for the degree of

DOCTOR OF VETERINARY MEDICINE

The Pathology Department,
University of Glasgow Veterinary School,
83 - 85, Bucoleuch Street,
GLASGOW.

DECEMBER 1964

C O N T E N T S

PART THREE.

FURTHER INVESTIGATION OF THE CIRCUMSTANCES SURROUNDING THE OCCURRENCE OF PULMONARY ARTERIAL DISEASE OF THE CAT.

ACKNOWLEDGEMENTS.

The author desires to record his gratitude to Professor J.W. Smalle for the facilities, generously made available, which enabled the investigations to be pursued and for advice and criticism, freely given, during the preparation of this thesis. For general advice on, and criticism of, the parasitological detail the author is indebted to Dr. Angus Dunn, Senior Lecturer in Veterinary Parasitology in this University. To Mr. W. Penny, F.I.M.L.T. and his technical staff thanks are due for the vast amount of histological preparation provided over the years. Mr. A. Finnie, with customary skill, provided the majority of the illustrations for which the author is duly grateful.

INTRODUCTION

During the course of examinations of feline tissues made for the purposes of routine diagnosis, the author noted in the lungs arterial changes that consisted of medial hypertrophy and hyperplasia with occasional intimal and endothelial alterations. Accompanying those lesions, in the majority of affected animals, there was a hypertrophy of the muscular elements of the walls of the bronchioles and of the alveolar ducts. When it was realised that the condition was fairly common and that little recorded information was available, its nature and significance were considered worthy of investigation. Accordingly, a programme of research was instituted which examined in turn the normal pulmonary vasculature of the cat, the incidence of the arterial abnormality and its association with the age and the sex of the animals and concluded with the influence of particular diseases on the aetiology of the pathological alteration. Elucidation of some of the problems concerned in the arteriopathy led to attempts to reproduce the same disease by experimental means. The thesis which follows is a record of the work completed and of the conclusions reached pertaining to the subject of pulmonary arterial disorders of the cat.

PART ONE.

THE PULMONARY ARTERIAL SYSTEM OF THE CAT.

1. NORMAL PULMONARY VASCULATURE.
2. MODES OF MEASUREMENT.
3. MATERIALS AND METHODS.
4. RESULTS.
5. DISCUSSION.

1. NORMAL PULMONARY VASCULATURE.

Any effort to assess the pathological changes encountered in an organ hangs on an understanding of the normal structural characteristics and the following statements concerning the pulmonary vasculature of the healthy cat are given for that purpose.

There are seven lobes in the normal pulmonary architecture of the cat the right lung having four (designated the apical, the cardiac, the diaphragmatic and the mediastinal) while the left lung has three (called the apical, the cardiac and the diaphragmatic) and branches of the main pulmonary arteries supply those divisions. The pulmonary trunk and the large pulmonary vessels (exceeding 150 microns in diameter) are classified as elastic arteries, the media of which consists of concentrically arranged elastic fibrils together with some smooth muscle fibres, collagen and an acid mucopolysaccharide ground-substance. There is a thick internal elastic membrane, the intima is comprised of fibrous tissue lined by endothelium and the adventitia consists of acellular fibrous tissue. In the smaller elastic arteries an external elastic lamina is also prominent.

As in the case of the systemic vasculature, the elastic arteries merge into those of a muscular type in which the comparatively thin media consists of circularly arranged muscle fibres, bounded by an internal and an external elastic

membrane, but the adventitia is small in amount. The vessels may range from 20 to 150 microns in diameter. The muscular arteries give way to the arterioles which display an endothelial lining, a single elastic lamina, little adventitia, not any muscular media and have a diameter of 20 microns, or less.

The muscular pulmonary arteries branch with the bronchial tree and lie close to the bronchi, bronchioles and alveolar ducts which they supply before they extend to the pleura. The alveolar capillaries open into the pulmonary venules which are similar in histological appearance to the arterioles already described. Venules drain into the pulmonary veins, the adventitial coat of which is moderately thick and fibrous while the media is constituted of smooth muscle intermixed with collagen and, sometimes, with elastic fibres. When the latter are present, they are of delicate structure and rather haphazardly arranged. The internal and the external elastic laminae are not closely defined and, because of the lack of secondary lobules and the absence of limiting supportive septal tissue, the veins pursue a more direct route to the hilum of the lung whereby a close relationship with the bronchial tree is not maintained. (McLaughlin et al., (1961).

The bronchial arteries follow the course of the bronchial tree, closely adhere to the bronchial walls and bifurcate with the bronchi, branching and anastomosing

repeatedly to supply the lymph-nodes, the adventitia of the larger muscular pulmonary arteries, veins, bronchi and bronchioles. They terminate in a capillary bed, common with the pulmonary artery at the level of the respiratory bronchioles, and finally drain into either the left atrium or the pulmonary veins (McLaughlin et al., 1961). The arteries are composed of an intima of endothelium, a thick internal elastic membrane, a regular media of circular smooth muscle and a thin external elastic lamina which is frequently absent. The longitudinal muscle conspicuous in the bronchial arteries of many other animal species is not a feature of the cat.

Differentiation between arteries and arterioles has been confused in the past. In human lungs, Brenner (1935) designated as elastic arteries those vessels with a diameter greater than 1000 microns, as muscular arteries those between 100 and 1000 microns in diameter and applied the term arterioles when the diameter was less than 100 microns.

Harris and Heath (1962) agreed with Brenner (1935) but Hecht et al. (1959) stated that, in the ox, vessels down to 20 microns in diameter may be muscular.

In a study of the pulmonary vessels of 14 animal species, Best and Heath (1961) remarked on the enhanced muscular content encountered in vessels of as little as 20 microns in diameter. They asserted that in the cat, muscular pulmonary arteries ranged in size from 20 to 80

microns and were from 30 to 90 microns in diameter in the case of the ox.

Alexander and Jensen (1963) considered that muscular arteries of the ox lay between 150 and 300 microns in diameter. They suggested that the discrepancy between their figures and those of Best and Heath (1961) was probably not as serious as it seemed since the transition from muscular to elastic arteries was a gradual one without any abrupt limitations. Additionally, the determination of size of vessels was greatly influenced by the age of the animal and the state of vascular contraction, both of which factors may vary within the same lung as well as among different lungs.

By the same token, it was considered that the figures given for the cat were rather low and that values between 20 and 150 microns in diameter were more appropriate for the pulmonary muscular arteries of that species.

2. MODES OF MEASUREMENT.

Some standard means of assessing and comparing differences in the size of arteries are essential and, towards that end, there are several possible methods, each of which has its advantages and its disadvantages.

Brenner (1935) collated the thickness of the media with the diameter of the external elastic lamina and expressed the result as percentage medial thickness of the diameter of the vessel. Harris and Heath (1962) cast doubt on the accuracy of such values for human pulmonary arteries below 300 microns in diameter and considered the measurements to be too high for that class of vessel.

Kernohan *et al.* (1939), Morlock (1939), Olcott *et al.* (1946) and Dammann and Ferencz (1956) compared the thickness of the wall of the artery with the diameter of the lumen.

O'Neal *et al.* (1955) improved on Brenner's method by measuring the media at a specified level, namely, that of the first respiratory bronchiole although the main disadvantage of the procedure lay in the difficulty of finding a sufficient number of vessels cut in the proper plane.

Naeye (1961a) related the area of the media to that of the intima by projection and planimetry, which practice appeared to give satisfactory results although the technique involved was laborious.

Wagenvoort (1960) measured the amount of arterial muscle per unit of lung tissue and claimed that such a method helped to distinguish between contracted and thickened vessels.

Other workers, e.g. Welch and Kinney (1948) and Scratchard and Wright (1961), applied a visual mode of grading which is acceptable under some circumstances but is not sufficiently critical, especially when changes are of marginal kind.

Towards a decision as to which method was most applicable to the cat, the following factors were taken into consideration:

(1) The method should be as accurate as possible.

(2) Because in some of the pathologically affected arteries excessive changes were found to be associated with dissolution of the external elastic lamina, that structure should not be used as a basis for measurement.

(3) Since in some affected lungs abnormal tortuosity of the pulmonary arteries tended to increase the amount of arterial muscle per unit of lung, Wagenvoort's method was open to error.

(4) With regard to the pathological changes known to occur in the pulmonary arteries of the cats, it was considered sufficient to treat the arterial wall as an entity rather than to stress the differences in the various layers.

The ultimate conclusion reached was that, for the purposes of the investigation under report, the most practical and informative method was that in which the thickness of the arterial wall was compared with that of the diameter of the lumen.

3. MATERIALS AND METHODS.

Fifty-two healthy cats, consisting of 9 kittens (1 to 6 months of age), 18 young females and 25 young males (7 months to 2 years of age), were used to obtain normal values for the pulmonary arteries. As in all cats sacrificed for the purposes of this thesis, euthanasia was induced by means of intra-peritoneal injection of an over-dose of pentothal and, immediately after death, the lungs of each animal were removed and a small quantity, approximately 5 ml., of 10.0% formol-saline solution was introduced via the trachea to assist in fixation of the tissues. The organs were then immersed overnight in a bath of the same fluid and, when fixation was complete, transverse sections - two to four from each lobe - were excised and embedded in paraffin wax. Three such blocks of tissue from each lung, to be used for the identification of lipoidal material, were also taken for sectioning by the freezing microtome. Portions of kidney and myocardium were similarly treated, following which, sections of the latter organs and of the lungs were cut to a thickness of five microns and stained by haematoxylin and eosin or by the Sudan IV method for neutral fat. In the case of several of the animals, further study was made of those tissues by use of Lawson's elastic stain, Gomori's aldehyde-fuchsin, Van Gieson and the periodic acid-Schiff methods of staining.

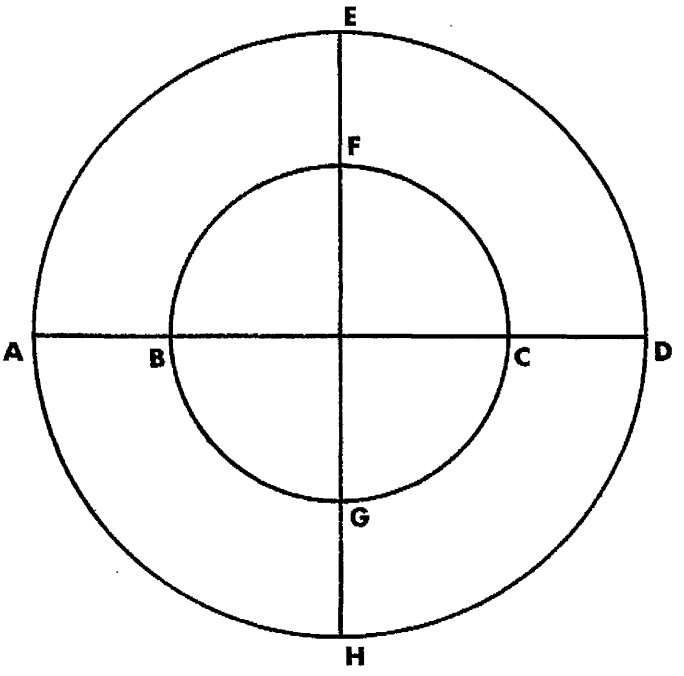
The mode of measurement of the pulmonary arteries was as that described by Kernohan et al. (1929), Morlock (1939), Olcott et al. (1946) and Baumann and Ferencz (1956). With the aid of an ocular micrometer calibrated to a binocular microscope at a magnification of 480 diameters, measurements as illustrated in Fig. 1 (p. 11) were made. Only vessels cut at right angles to their course were heeded and the distances A-B, C-D, E-F and G-H were determined, added and the average value for the thickness of the wall calculated. The distances B-C and F-G were similarly found, the average diameter of the lumen ascertained and from those figures the wall-to-lumen ratio of the artery computed. In each lung, ten arteries were investigated in the above manner in sections stained by haematoxylin and eosin.

At the close of the investigation 520 arteries from 364 lobes of 52 different cats had been measured. The results and conclusions of the exercise are presented and discussed in the course of the following pages.

Fig. 1

THICKNESS OF WALL :

AVERAGE OF AB; CD; EF; GH;



DIAMETER OF LUMEN :

AVERAGE OF BC and FG .

4. RESULTS.

The preceding investigation revealed that the mean wall-to-lumen ratios for the arteries measured varied from 0.1537:1 to 0.2074:1, giving an extreme difference of 0.0537. For each mean in each group, the standard deviation was calculated and, as Tables 1 and 2 (p. 15 and 16) show, in every case a high percentage of the individual measurements were found to fall within the standard deviation. Ninety four to 100% of the measurements lay within twice the standard deviation and in only three groups out of the ten did a small percentage lie beyond three times the standard deviation. From those figures, it was concluded that the distribution around each mean figure was satisfactory.

The average of the wall-to-lumen ratios of pulmonary arteries of differing diameters in the kittens, older males and older females, was compared in turn with members of the same, and of the other, groups. To test both the variability and the validity of the mean figures use was made of the formula

$$\sqrt{\frac{aA^2}{nA} + \frac{aB^2}{nB}}$$

where a = the standard deviation, n = the number of individuals and A and B are the groups under comparison (Hill, 1961).

The results (Tables 3, 4 and 5, p.17 , 18 and 19) show that, when those wall-to-lumen ratios were compared, not on any occasion did the difference between means exceed the standard error by a significant margin. Accordingly, it was concluded that the mean wall-to-lumen ratios of pulmonary arteries of varying sizes, in animals of the age groups exemplified by kittens and young adults of both sexes, did not differ significantly.

It was thought necessary further to investigate whether any difference obtained in the wall-to-lumen ratios of pulmonary arteries in different lobes of the lungs. That aspect was considered by Harris and Heath (1962) to be important in lung biopsies since they found that arteries of the lingula pulmonis possessed a thicker media than did those of other parts although such a view had been earlier rejected by Wagenvoort (1960). In the case of seven of the original cats, therefore, ten arteries from each pulmonary lobe were measured in the manner already described and the mean wall-to-lumen ratios calculated. Table 6 (p. 20) presents those results which indicate that the ratios lie within a comparatively narrow range.

In summary, it may be stated that the findings failed to reveal any significant differences among the mean wall-to-lumen ratios of the pulmonary arteries of:

1. male and female young adult cats,
2. young adult cats of either sex and kittens up to six months old,
3. any group, i.e., young adult male or female and kittens, in respect of size of artery, and
4. different lobes of the lungs.

Those facts ascertained, it was decided that in subsequent investigations any animal with a mean wall-to-lumen ratio of 0.35:1, or more, should be considered abnormal. That figure was chosen because it was virtually twice the lowest normal mean ratio of the series (0.1537, Table 1, p.15), and when compared with the highest and lowest mean figures (0.2074 and 0.1537 respectively, Table 1, p. 15), a significant difference between the values was established on each occasion.

TABLE I.

MEAN WALL-TO-LUMEN RATIOS TOGETHER WITH THE STANDARD DEVIATIONS RECORDED IN PULMONARY ARTERIES OF VARYING SIZE FROM 52 NORMAL CATS OF DIFFERING AGE AND SEX

	ADULT MALES			ADULT FEMALES			KITTENS		
Diameter of vessels (microns)	No. of Arteries	Mean wall/lumen ratio	S.D.	No. of Arteries	Mean wall/lumen ratio	S.D.	No. of Arteries	Mean wall/lumen ratio	S.D.
50-100	145	0.2074	± 0.0095	108	0.1705	± 0.1104	73	0.1946	± 0.0045
100-150	60	0.1920	± 0.1060	42	0.1678	± 0.0925	18	0.1755	± 0.1044
150-200	28	0.1700	± 0.1088	20	0.1753	± 0.1210	-	-	-
200+	19	0.1713	± 0.0980	10	0.1537	± 0.1245	-	-	-

S.D. = STANDARD DEVIATION.

TABLE 2.

STANDARD DEVIATION AND DISTRIBUTION AROUND THE MEAN OF THE WALL-TO-LUMEN RATIOS ENCOUNTERED IN PULMONARY ARTERIES OF VARYING SIZE FROM 52 NORMAL CATS OF DIFFERING AGE AND SEX.

Diameter of vessels (Microns)	ADULT MALES				ADULT FEMALES				KITTENS			
	S.D.	± 1	± 2	± 3	S.D.	± 1	± 2	± 3	S.D.	± 1	± 2	± 3
50 - 100	0.0995	69%	96%	100%	0.1104	89%	96%	98%	0.0943	91%	95%	95%
100 - 150	0.1060	80%	98%	100%	0.0925	95%	95%	100%	0.1044	92%	100%	100%
150 - 200	0.1032	75%	100%	100%	0.1210	91%	95%	100%	-	-	-	-
200 +	0.0980	84%	94%	96%	0.1245	90%	96%	100%	-	-	-	-

S.D. = STANDARD DEVIATION.

TABLE 3.

COMPARISON OF MEAN WALL-TO-LUMEN RATIOS OF PULMONARY ARTERIES, 30 - 200 IN DIAMETER, FROM KITTENS WITH ARTERIES OF VARYING SIZE FROM ADULT MALE AND FEMALE CATS.

Diameter of Vessels (Microns)	KITTENS			ADULT MALES			ADULT FEMALES		
	No. of Arteries	M.D.	S.E.	No. of Arteries	M.D.	S.E.	No. of Arteries	M.D.	S.E.
30 - 100	78	-	-	145	0.0123	0.0136	108	0.0155	0.0152
100 - 150	12	0.0101	0.0320	60	0.0026	0.0175	42	0.0253	0.0197
150 - 200	-	-	-	26	0.0246	0.0240	20	0.0208	0.0177
200 +	-	-	-	19	0.0233	0.0250	10	0.0499	0.0498

M.D. = DIFFERENCE BETWEEN MEANS

S.E. = STANDARD ERROR.

TABLE 4.

COMPARISON OF MEAN WALL-TO-LUMEN RATIOS OF PULMONARY ARTERIES, 50 - 200 DIAMETER, FROM ADULT FEMALE CATS WITH ARTERIES OF VARYING SIZE FROM ADULT MALE CATS AND FROM KITTENS.

Diameter of vessels (microns)	ADULT FEMALES			ADULT MALES			KITTENS		
	No. of Arteries	M.D.	S.E.	No. of Arteries	M.D.	S.E.	No. of Arteries	M.D.	S.E.
50 - 100	168	-	-	145	0.0500	0.0154	78	0.0155	0.0158
100 - 150	42	0.0115	0.0185	60	0.0127	0.0173	12	0.0048	0.0319
150 - 200	20	0.0055	0.0270	26	0.0095	0.0233	-	-	-
200 +	10	0.0256	0.0403	19	0.0080	0.0248	-	-	-

M.D. = DIFFERENCE BETWEEN MEANS

S.E. = STANDARD ERROR.

TABLE 5.

COMPARISON OF THE MEAN WALL-TO-LUMEN RATIOS OF PULMONARY ARTERIES, 30 - 100 DIAMETER, FROM ADULT MALE CATS WITH ARTERIES OF VARYING SIZE FROM ADULT FEMALE CATS AND FROM KITTENS.

Diameter of vessels (Microns)	ADULT MALES			ADULT FEMALES			KITTENS		
	No. of Arteries	M.D.	S.E.	No. of Arteries	M.D.	S.E.	No. of Arteries	M.D.	S.E.
30 - 100	145	-	-	108	0.0300	0.0154	78	0.0128	0.0136
100 - 150	60	0.0154	0.0159	42	0.0396	0.0178	12	0.0319	0.0313
150 - 200	26	0.0304	0.0228	20	0.0336	0.0313	-	-	-
200 +	19	0.0361	0.0239	10	0.0574	0.0402	-	-	-

M.D. = DIFFERENCE BETWEEN MEANS

S.E. = STANDARD ERROR.

TABLE 6.

MEAN WALL-TO-LUMEN RATIO OF PULMONARY ARTERIES OF INDIVIDUAL LOBES IN SEVEN NORMAL CATS.

Lobe	Number of Vessels Measured	Mean Wall/Lumen Ratio
Right apical	10	0.1807
Right cardiac	10	0.1708
Right diaphragmatic	10	0.1818
Right mediastinal	10	0.1852
Left apical	10	0.1771
Left cardiac	10	0.1866
Left diaphragmatic	10	0.1981

5. DISCUSSION.

There is little recorded information concerning arterial mensuration in cats but Olcott *et al.* (1946) found, in respect of 24 arteries from the lungs of eight such animals, a mean wall-to-lumen ratio of 0.1731:1 which closely approximates the findings reported above. By similar metrical means applied to human material, Dammann and Ferencz (1956) established values for normal pulmonary arteries that varied from a mean wall-to-lumen ratio of 1:1 in the instance of babies, a few weeks old, to 0.14:1 in the case of adult persons. Although those authors stressed the difference in the ratio that they found to be associated with age, the present investigation did not serve to reveal a similar state in the cat for the reason that it did not extend to animals under one month of age.

PART TWO.

SPONTANEOUS PULMONARY ARTERIAL DISEASE OF THE CAT.

1. A REVIEW OF THE LITERATURE.
2. A SURVEY OF PULMONARY ARTERIAL DISEASE OF THE CAT.
   a. Materials and Methods.
   b. Incidence and Association with Age.
   c. Association with Sex.
   d. Association with Other Morbid Conditions.
3. CONCLUSION.

1. A REVIEW OF THE LITERATURE.

Hypertrophy, and in some cases hyperplasia, of the medial coat of pulmonary arteries of the cat has been recorded in the literature on several occasions. The first documented reference was by Campbell (1927) who noted, in two cats suffering from oxygen deficiency, hypertrophy of the tunica muscularis of the pulmonary arteries and of the plain muscle of the inter-alveolar septa and regarded those changes as a physiological adaptation to lack of oxygen.

Ettinger (1932) described constriction of arteries and arterioles as a result of the intravenous injection of the dye, Jan us green. Moreover, in an unspecified number of cats he found that, in half-grown animals, the dye served to reduce the perfusion-rate by 25.0% and, in the case of the fully-grown animal, to cause vasoconstriction that was sufficient to obstruct completely the flow of blood.

Pritchett (1938) described arterial changes in the lungs of a six-months-old cat which had died of lungworm disease.

Rubarth (1940) recorded a focal hyperplastic process associated with intimal proliferation and fibrosis in the pulmonary arteries of five cats, four of which were seven years, or more, old. The author did not come to any

conclusion regarding the aetiology of the condition although he did state that the latter was not found in many young cats and that it was of more severe type in the oldest of his experimental animals. The lesion was considered to be post-natal in onset and probably of idiopathic origin or even, in the worst of his cases, to border on neoplasia.

Marcato (1940) discussed the arterial lesion which he encountered in 12 out of 30 cats the majority of which were of an older age group. The changes occurred in arteries of 100 to 500 microns in diameter and were characterized by fragmentation of the elastic layers with conspicuous fibro-elastic intimal proliferation in addition to hypertrophic changes of the media. Comparing the lesions with those of pulmonary arteriosclerosis of man, notably with regard to age-distribution, the author concluded that the condition was one of senile arteriosclerosis.

Neumann et al. (1942), using cats to assay the effects of insulin and of metrazol, found that two out of nine animals treated with insulin suffered from what they described as "a peculiar condition" in which considerable thickening of the walls of the pulmonary vessels was accompanied by proliferation of the endothelial cells and, in some cases, there was also marked infiltration of the adventitia and intima by neutrophilic and eosinophilic leucocytes. After the administration of metrazol, the

authors found that five out of 11 animals had similar pulmonary lesions while of seven control cats one was comparably affected. In the case of neither group was any extra-pulmonary arterial change described, the ages of the animals were not given and the authors did not explain the pulmonary arterial lesions.

Olcott et al. (1946), in a study of the lungs of more than 150 cats, discovered only three cases of pulmonary arterial hypertrophy and hyperplasia. All the animals showed a degree of medial change but the elastic layers and the endothelium were intact and, in at least one cat, all the pulmonary arteries of the section were affected. Of the three cats one was 23½ years old, one had reached adulthood and the other was a large male cat of unstated age. Examination of the arteries from a large selection of organs, and from one heart, failed to reveal any change comparable with that of the pulmonary vessels and the conclusions reached were that the process was of chronic nature and not referable to either inflammatory or arteriosclerotic disease. It was suggested that the lesions might be associated with the dependent position of the lungs in those animals, although the available information was insufficient to substantiate the hypothesis. In five further control cats, of unknown age, pulmonary lesions were not found.

Hoff et al. (1951) stimulated the cerebral cortex of cats by means of electrical impulses passed through the intact skull and found that, when such excitation was maintained over a period of one to six weeks, pathological changes in the glomeruli and tubules of the kidney resulted. According to Kell et al. (1956), the former authors also observed medial hypertrophy of the pulmonary arteries and arterioles.

Blaisdell (1952), in a thesis, remarked on the presence of arterial thickening in cats infested by Aelurostrongylus abstrusus, the lungworm of the cat.

Arteriosclerosis of the cat was reviewed by Lindsay and Chaikoff (1955) but reference was not made to the pulmonary vasculature.

Kell et al. (1956) explored in detail the pulmonary lesions that they found to be associated with excitation of the cerebral pressor mechanisms by various stimuli and further attempted to establish whether, or not, the condition occurred spontaneously in the cat. The authors examined 28 animals, eleven of which were from three months to four years old but the remaining 17 were of unknown age. Of the latter only four showed minimal change of the media while not one of the younger animals proved to be affected, from which findings it was deduced that the spontaneous condition in cats was uncommon. By the use of metrazol, the authors

stimulated the vasomotor centres of the brain of 19 cats (including three 4-months-old kittens) and found that 15 showed pulmonary arterial lesions of varying severity. A final group of 10 cats was subjected to electrical impulses transmitted to the brain via electrodes attached to the skin. Three of the animals were given the stimuli alone; one animal was treated with epinephrine as soon as the impulses were terminated while the remaining six were bled to varying amount immediately after stimulation. Two of the first four animals showed slight alteration of the pulmonary arteries while all of the cats, which were subjected to bleeding in addition to stimulation, were found to have developed medial hypertrophy and hyperplasia of moderate to extreme degree. Moreover, two of the latter animals also showed some intimal proliferation. Because of the absence of pulmonary oedema, the possibility that the lesions were secondary to cardiac failure was discounted.

From their experiments the authors concluded that the observed changes in the pulmonary vessels were not incidental but represented a reaction to repeated, widespread and massive vasomotor stimulation. Such a response might arise from vasoconstriction of neurogenic origin and/or as a result of generalized peripheral vasoconstriction caused by pressor substances resulting from cerebral stimulation and leading to accumulation of the blood in the

lesser circulation. Other than that it may have potentiated the arterial lesion, the import of induced haemorrhage was not explained. Mention was not made of any of the extrapulmonary arteries.

Martin (1959) described the condition in two cats which had died from hepatic failure and gastro-enteritis, respectively. The presence of hypertrophy of the medial muscle fibres, intimal fibrosis, atrophy of the elastic laminae, endarteritis and periarteritis led him to believe that the changes were comparable with those found in pulmonary arteriosclerosis of man.

Dahme (1960), in a critique of the literature and his own findings, did not report any evidence of cardiac disease to be associated with the pulmonary arterial lesions. The latter were of focal distribution in which the medial musculature was mainly affected although musculo-elastic thickening of the intima attended by the formation of longitudinal muscle was from time to time encountered. He considered the lesion to be a phenomenon per se and suggested that the hypertrophic and hyperplastic condition represented a reflex vasomotor response to functional overloading, similar to the "vasospastic arteriosclerosis" that was described by Barnard (1957). The view was also advanced that hormonal or nervous factors may also enter into the aetiology of the disease.

McKenzie (1960) discussed arterial lesions in two 12 weeks-old-kittens infested by lungworms. He declared the small pulmonary arteries to be outstandingly affected and, in some cases, to be accompanied by intimal proliferation and fibrosis. Mild leucocytic infiltration of the thickened intima was frequently present and imparted the appearance of endarteritis obliterans. The author related the arterial lesions to the parasitic condition.

Medial hypertrophy and hyperplasia of the pulmonary arteries of the cat was reported by Scratchard and Wright (1961) who examined sections of lungs from 111 cats. By means of an arbitrary system of classification in which the severity of the lesion was denoted by plus symbols, the authors estimated that 36.0% of the cats suffered from some degree of the abnormality. At least 50 were adult animals but the ages of the other 61 cats were not specified. The authors also found that, if the lesion was present in one lobe, it occurred in all the others and, in the majority of cases, the changes were well distributed throughout each lobe. The main abnormality was a hypertrophy and hyperplasia of the medial coat of the arteries although mild intimal fibrosis frequently was noted. The presence of hypertrophic smooth muscle elsewhere in the lung was also observed and was considered to have originated from blood vessels and bronchioles. A factor in the production of the condition was thought

to be repeated waves of emboli of a parasitic nature from the intestine since, according to Barnard (1953 and 1957), injections of gas and particulate material were found, experimentally, to produce some degree of thickening of the medial coat of the muscular pulmonary arteries together with intimal changes.

Hamilton (1963) reported a case-incidence to 9.6% of lungworm infestation in domestic cats in the West of Scotland and described hypertrophy and hyperplasia of arteries along with intimal proliferation and occasional fibrosis. Quoting Cameron (1929 and 1932), the author suggested that the parasite may cause irritation to the blood vessels either during migration or after localization. Again, like Blaisdell (1952), Hamilton (1963) conceived that the vascular architectural changes were provoked either by a product of parasitic origin or in response to an increase in pulmonary arterial pressure caused by the physical presence of the parasites.

Jubb and Kennedy (1963) mention the arterial disorder of cats and suggest its close correlation with lungworm infestation.

2. A SURVEY OF PULMONARY ARTERIAL DISEASE OF THE CAT.

a. Materials and Methods.

The need for a fresh investigation destined to ascertain the true incidence of spontaneous arterial disease in the cat was prompted by the lack of recorded evidence coupled with the conflicting statements by Kell et al. (1956), who reported that pulmonary arterial lesions were rare, and the arbitrary testimony of Scratcherd and Wright (1961) who claimed that there was an apparently high incidence of the condition. Towards that end, a survey of a random collection of cats was made and by the application of the methods previously employed to normal cats, 256 cases were examined. The animals were received from veterinary practitioners, from other animal houses in the University and from the local Cat and Dog Home and were representative of different ages and both sexes.

Euthanasia was induced in animals obtained alive and, after each cat became unconscious, a sample of blood was withdrawn into a tube containing sequestrene as an anti-coagulant and thereafter subjected to the following examinations. The total white cell count was estimated in an haemocytometer on a sample of blood diluted 1/20 with 2.0% (v/v) acetic acid while the differential white cell count was performed on an air-dried film stained by the method of Leishman. The concentration of haemoglobin was

determined by the oxyhaemoglobin method in which a 1/200 dilution of blood in 0.04% (v/v) ammonium hydroxide was examined in a spectrophotometer at a wave-length of 540 millimicrons. Packed cell volume was ascertained in haematocrit tubes which were centrifuged at 3,000 revolutions per minute for 30 minutes. The method of Wintrobe was used to assess the erythrocyte sedimentation rate and was carried out at room temperature and the results read after a period of 60 minutes.

On all the animals a comprehensive post-mortem examination was carried out and, as formerly, the lungs together with the myocardium and kidneys were removed and processed. The wall-to-lumen ratios of the pulmonary arteries were assessed by methods similar to those which had been applied to normal animals. Additional staining methods employed were Masson's and Mallory's connective-tissue stains, Alcian blue, Gordon and Sweet's method for reticulin and Best's carmine stain for glycogen. Those methods were applied to sections of the pulmonary, myocardial and renal tissues of animals, the pulmonary arteries of which displayed a wall-to-lumen ratio of 0.35:1, or more. In addition, portions of liver, gastro-intestinal tract, lymph-nodes, spleen, pancreas, adrenals, thyroids and pituitary were embedded in paraffin-wax and cut into sections of five microns in thickness to be stained by

haematoxylin and eosin. Sections of adrenals were treated also by Schultz's method for the demonstration of cholesterol.

b. Incidence and Association with Age.

Of the 256 animals examined, 89 were found to have suffered from some degree of pulmonary arterial hypertrophy and hyperplasia, to a case-incidence of 34.7%. That rate becomes more interesting when it is related to age groups, as has been done in Table 7 (p. 34). For simplicity and convenience, the ages have been divided into four groups, namely: old animals, aged nine years and over; adult animals, aged three to eight years; young adults, seven months to two years old and kittens, from one to six months of age. The ages of rather more than half of the animals were ascertained from the owners with a fair degree of accuracy while those of the rest were broadly assessed on anatomical grounds, such as the condition of the teeth and the thickness of the skull bones. Animals of the younger age groups were comparatively easy to recognise.

Just over half of the members (52.4%) of the old group were found to be affected while adult and young adult animals together with kittens were afflicted to a percentage of 39.3, 23.4 and 15.0, respectively. Thus, Table 7 (p.34) indicates that the incidence of cases was highest in the old age group and tended to drop as age decreased, although the

TABLE 7.

AGE DISTRIBUTION OF THE PULMONARY ARTERIAL LESIONS ENCOUNTERED IN 69 CATS.

	Old Cats (9 yrs. & Over)	Adult Cats (3-9 yrs.)	Young Adult Cats (7 mths. - 3 yrs.)	Kittens (1-6 mths.)
Number Examined	65	89	64	40
Number Affected	33	35	15	6
Percentage	52.4	39.3	23.4	15

number of younger animals involved was not insignificant.

Table 8 (p. 36) shows the morbid process as it has been distributed over five grades of severity. It is to be observed that in all the groups, excepting kittens, roughly similar proportions fall within the zone of maximal severity. Such a finding is at variance with the usual concepts of senile change which assume that the most severe lesions supervene in older organisms.

The age-incidence of pulmonary arterial hypertrophy of cats reported in the available literature may be summarized as follows. In respect of a group of 12 out of 30 animals, Marcato (1940) reported that all but two cases occurred at an age of four to five years and upwards, while Rubarth (1940) did not recognise the condition in young experimental cats but only in those over seven years of age. Olcott et al. (1946) cited cases in three cats of which latter one was given as $23\frac{1}{2}$ years old but the other two were of undetermined age. Scratchord and Wright (1961) did not specify age groups although their estimated total incidence of cases (36.0%) approximates the figure of 34.7% experienced by the author of this thesis. Neumann et al. (1942) did not mention age in their report and the experimental animals used by Kell et al. (1956) were comprised of a mixture of age-groups. Pritchett (1938) described arterial changes in an animal of six months of age affected with lungworm

TABLE 8.

SEVERITY OF THE PULMONARY ARTERIAL LESIONS IN DIFFERENT AGE GROUPS.

Age Group	No. of Affected Animals	Grade of Lesion					Percentage of Animals in Grades 3, 4 and 5.
		1	2	3	4	5	
Old Animals	35	5	14	6	6	2	42.4
Adults	35	13	10	9	3	1	37.1
Young Adults	15	7	3	1	2	2	33.3
Kittens	6	3	2	1	-	-	16.6

disease and McKenzie (1960) reported the condition in two kittens three months old. Hamilton (1963), in a record of pulmonary arterial lesions in 12 cats afflicted by lungworm, gave the ages as old (three animals), adult (one animal), young adults (five animals) and kittens (three animals).

Thus, throughout the literature on the subject, emphasis has been laid on the fact that the spontaneous condition usually occurs as a senile change, although it has also been reported in several kittens and young adults. The results quoted above demonstrate, however, that the condition is not unknown in the younger age-groups and that the severity of the lesion is not to be related to advancing years.

Such observations cause doubt to be cast on the hypothesis that pulmonary arterial hypertrophy and hyperplasia in the cat is purely an ageing process.

c. Association with Sex.

The percentages of 34.5, 35.5 and 33.3 presented in Table 9 (p. 38) in relation to male, female and neuter animals fail to establish any marked difference in the overall incidence in the three categories of animal. Further study of the figures pertaining to sex and age, (Table 10, p. 39), suggests that enhanced sex incidence is not characteristic of any age group. Hence, sex does not

appear to play any part in the aetiology of the pulmonary arterial hypertrophy, a fact which contrasts strikingly with the state of affairs in the human being, in whom arterial disease is generally more prevalent in males.

TABLE 9.

SEX DISTRIBUTION OF THE PULMONARY ARTERIAL LESIONS IN THE CAT.

	MALE	*FEMALE*	*MOTHER*
TOTAL NO. OF ANIMALS	*116*	*104*	*36*
NO. AFFECTED	*40*	*37*	*12*
PERCENTAGE	*34.5*	*35.5*	*33.3*

TABLE 10.

SEX INCIDENCE OF THE PULMONARY ARTERIAL LESIONS ACCORDING TO AGE GROUP.

	OLD			ADULT			YOUNG ADULT			KITTENS		
	No. Exam-ined.	No. Aff-ected.	%	No. Exam-ined.	No. Aff-ected.	%	No. Exam-ined.	No. Aff-ected.	%	No. Exam-ined.	No. Aff-ected	%
Male	25	11	42.8	30	17	45.5	26	7	27	29	5	17.2
Female	25	16	52	43	16	38	30	7	23.3	11	1	9.1
Neuter	15	9	60	8	2	25	8	1	12.5	-	-	-

d. Association with Other Morbid Conditions.

Tables 11, 12, 13 and 14 (p. 41 to 45) present the various diseases that in each age-group were found in association with pulmonary arterial hypertrophy, in comparison with those encountered in animals in which the arterial lesion did not exist.

The first important point to emerge is the considerable number of animals in which a comprehensive anatomical and histopathological examination failed to reveal the presence of any morbid process other than the pulmonary arterial lesion. Such was the case among 42.4% of the aged animals, in the adult group to 65.7%, in 53.3% of the young adult group and in 50.0% of the kittens.

Secondly, the variety of diseases present in the affected group was much the same as that observed in non-affected animals, with one exception namely, lungworm disease. Thus if Table 11 (p. 41) be examined with special reference to old cats, members of both groups will be found to have suffered from chronic nephritis and from the same number of neoplasms. Even the types of tumour were not dissimilar and included lymphosarcoma, alimentary carcinoma and meningioma. The only neoplastic growths not represented in both groups are skin carcinoma, mammary carcinoma, hepatoma and osteosarcoma, none of which seem likely to have inhibited or promoted the pulmonary arterial condition.

TABLE 11.

DISEASES ENCOUNTERED IN OLD CATS WITH, OR WITHOUT, PULMONARY ARTERIAL LESIONS.

WITH PULMONARY ARTERIAL LESIONS		WITHOUT PULMONARY ARTERIAL LESIONS	
1. Nephritis	5	1. Nephritis	5
2. Neoplasms	8	2. Neoplasms	8
a Lymphosarcoma	4	a Lymphosarcoma	4
b Intestinal Carcinoma	1	b Tonsillar Carcinoma	1
c Meningioma	1	c Meningioma	1
d Squamous Carcinoma	1	d Mammary Carcinoma	1
e Hepatoma	1	e Osteosarcoma	1
3. Other Lung Disorders	8	3. Other Lung Disorders	2
a Focal Necrosis	1	a Localized Pneumonia	1
b Diaphragmatic Hernia	1	b Bacterial Pneumonia	1
c Pleurisy	1		
4. Enteritis	1	4. Enteritis	1
5. Lungworm Infestation	4		
6. Without Additional Disease	14	5. Disease-Free	14
Total Number	33	Total Number	30

Other disorders of the lung appear to have had little effect since, with the exception of the diaphragmatic hernia, examples of inflammatory lesions occur in both groups as, too, does enteritis. Lungworm disease was noted only in the animals with the arterial abnormality. Save for a few morbid processes, Tables 12, 13 and 14 (p. 43 to 45) present a fairly similar picture that includes the presence of lungworm disease only in the group displaying arterial lesions. The occurrence of lungworm infestation only in the animals affected with pulmonary arterial lesions assumes greater importance in the younger age-groups in which it is seen in 50.0% and 33.3% of kittens and young adults, respectively. Even among adults it remains the most prevalent individual disease and it also occurs to not insignificant incidence among old cats.

TABLE 12.

DISEASES ENCOUNTERED IN ADULT CATS WITH, OR WITHOUT, PULMONARY ARTERIAL LESIONS.

WITH PULMONARY ARTERIAL LESIONS		WITHOUT PULMONARY ARTERIAL LESIONS	
1. Nephritis	2	1. Nephritis	2
2. Neoplasm	1	2. Neoplasms	3
a Bronchial Carcinoma	1	a Intestinal Carcinoma	1
		b Oesophageal Carcinoma	1
		c Lymphosarcoma	1
3. Other Lung Disorders	3	3. Other Lung Disorders	1
a Pleurisy	2	a Upper Respiratory Infection	1
b Focal Pneumonia	1		
4. Enteritis	1	4. Pyometra	1
5. Lungworm Infestation	5	5. Mastitis	1
6. Without Additional Disease	23	6. Disease-Free	46
Total Number	33	Total Number	54

TABLE 15.

DISEASES ENCOUNTERED IN YOUNG ADULT CATS WITH, OR WITHOUT, PULMONARY ARTERIAL LESIONS.

WITH PULMONARY ARTERIAL LESIONS			WITHOUT PULMONARY ARTERIAL LESIONS		
1.	Virus Pneumonitis	2	1.	Virus Pneumonitis	4
2.	Lungworm Infestation	5	2.	Virus Enteritis	3
			3.	Lymphosarcoma	1
			4.	Hepatic Cirrhosis	1
			5.	Paraplegia	1
3.	Without Additional Disease	6	6.	Disease-Free	39
	Total Number	15		Total Number	49

TABLE 14.

DISEASES ENCOUNTERED IN KITTENS WITH, OR WITHOUT, PULMONARY ARTERIAL LESIONS.

DISEASES ENCOUNTERED IN KITTENS WITH, OR WITHOUT, PULMONARY ARTERIAL LESIONS.

WITH PULMONARY ARTERIAL LESIONS			WITHOUT PULMONARY ARTERIAL LESIONS		
1.	Lungworm Infestation	5	1.	Pneumonia	9
			2.	Virus Enteritis	14
			3.	Cystic Lung Lesion	1
			4.	Peritonitis	1
			5.	Paraplegia	1
2.	Without Additional Disease	5	6.	Disease-Free	8
	Total Number	6		Total Number	34

3. CONCLUSION.

The results, so far given, do not indicate any close association with age or sex. However, they have demonstrated that, while a large proportion of the affected animals was not found to suffer from any other disease, in the remainder there occurred a variety of conditions which in distribution was almost identical with that manifested by the unaffected group. To that statement lungworm infestation is the solitary exception, a finding that may be purely coincidental, but the fact that the condition comprised a substantial ratio of the disease present and that there was not any instance of it to be found in animals free from the pulmonary arterial disorder suggests that that form of parasitism is peculiarly associated with the development of pulmonary medial hypertrophy and hyperplasia of the cat. That statement supports the view of McKenzie (1960) and that of Jubb and Kennedy (1963) who suggested that the parasite and the arterial lesions were causatively related.

It appears, therefore, that animals suffering from the arterial lesions together with the muscular hypertrophy of the walls of the bronchioles and of the alveolar ducts, fall into the following three categories:

Group 1. Those infested with lungworm.

Group 2. Those without any other morbid condition.

Group 3. Those afflicted by diseases other than lungworm infestation.

In Part 3 of this work each of those divisions of animals will be examined with special reference to the pulmonary alterations.

PART THREE.

FURTHER INVESTIGATION OF THE CIRCUMSTANCES SURROUNDING THE OCCURRENCE OF PULMONARY ARTERIAL DISEASE OF THE CAT.

1. INVESTIGATION OF ANIMALS SUFFERING FROM LUNGWORM INFESTATION. (GROUP 1).
   - a. A Review of the Literature.
   - b. The Parasite and its Life Cycle.
   - c. Clinical Manifestations.
   - d. Haematological Findings.
   - e. Morbid Anatomy.
   - f. Histopathology. (1) The Lung Substance
     (2) The Vasculature
   - g. Discussion.
2. INVESTIGATION OF ANIMALS WITH PULMONARY ARTERIAL LESIONS IN THE ABSENCE OF OTHER MORBID CONDITIONS. (GROUP 2).
   - a. Morbid Anatomy.
   - b. Histopathology.
3. INVESTIGATION OF ANIMALS WITH PULMONARY ARTERIAL LESIONS IN ASSOCIATION WITH VARIOUS DISEASES. (GROUP 3).
   - a. Morbid Anatomy.
   - b. Histopathology.
4. ASSOCIATION OF PULMONARY ARTERIAL HYPERTROPHY AND HYPERPLASIA WITH GENERALIZED HYPERTENSION.
   - a. Normal Mean Wall-to-Lumen Ratios of Myocardial and Renal Arteries of the Cat.
   - b. Mean Wall-to-Lumen Ratios of Myocardial and Renal Arteries in Animals of Groups 1, 2 and 3.
   - c. Conclusion.
5. DISCUSSION.
6. CONCLUSION.

1. INVESTIGATION OF ANIMALS SUFFERING FROM LUNGWORM INFESTATION (GROUP 1).

a. A Review of the Literature.

Since circumstantial evidence suggests that lungworm disease in the cat is related to the muscular hypertrophy that is conspicuous in the pulmonary arteries, the bronchiolar walls and the alveolar ducts, a review of the condition together with a description of the findings encountered in spontaneous cases, now follows.

Infestation of the cat by the lungworm, Aelurostrongylus abstrusus, has been recognised in Great Britain by Cameron (1926, 1927, 1928, 1929 and 1932), by Lewis (1927), by McKenzie (1960) and by Hamilton (1963). The condition has also been reported from other parts of the world, e.g. the United States by Robmaier and Robmaier (1935a and 1935b), by Fry and Stewart (1932), by Pritchett (1938), by Bailey and Williams (1949), by Bailey and Lowman (1952), by Blaisdell (1952), by Newberne (1953) and by Sudduth (1955); France by Baron (1946); the Netherlands by Baudet (1933); Portugal by da Cruz and de Freitas (1948); Denmark by Christensen et al. (1946); Palestine by Gerichter (1949); Brazil by Cristi and Auyuanet (1947) and Australia by Gordon (1933), by Seddon (1947) and by MacKerras (1957).

Information concerning the degree of infestation is sparse except that Robmaier and Robmaier (1935a) recorded

an incidence of 2.0% among 500 cats in San Francisco, Daudet (1933) of 5.0% of cats in Utrecht, Christensen et al. (1946) to about 1.0% in Copenhagen and Gerichter (1949) of 26.0% of 73 stray cats in Palestine. In Britain, Lewis (1927) reported that 20.0% of 155 cats were affected while Cameron (1927) suggested that the condition was common. More recently, Hamilton (1963), in a survey of 125 randomly selected cats in the West of Scotland, stated that the number infested by Aelurostrongylus abstrusus was 12, or a case-incidence of 9.6%. The number of cats examined has since increased to 256 among which were found 17 cases of lungworm disease, yielding a case-incidence of 6.6%.

b. The Parasite and its Life Cycle.

The adult male worms are very small and slender averaging 5.2 mm. in length by 0.07 mm. in breadth and the female 9.3 mm. long by 0.1 mm. broad (McKerras, 1957).

It is now generally agreed (Hobmaier and Hobmaier, 1935a and 1935b), (Gerichter, 1949), (Blaisdell, 1952) and (MacKerras, 1957) that the adult worms live in the substance of the lung and there deposit their ova. Within the alveoli the latter develop into first-stage larvae which are coughed up to be swallowed and ultimately passed out in the faeces. Once in the soil the larvae enter a large variety of slugs and snails in which further development to third-stage larvae takes place. The latter forms are infective

for the cat which becomes infested as a result of eating a slug, a snail or an auxiliary host, such as a rat, mouse, bird, toad or reptile, that has fed on infected gasteropods and may harbour the third-stage larvae for some time. Such hosts are thought to play an important part in the survival and spread of Aelurostrongylus abstrusus infestation of the cat. After third-stage forms have entered the cat, they quickly pass through the mucosa of the upper alimentary tract, to reach the lungs by way either of the lymphatic or the blood stream. In the lungs the final development to adulthood takes place and, within 35 to 39 days, first-stage larvae are recoverable from the faeces of an infected cat.

c. Clinical Manifestations.

There are few recorded references to the clinical aspects of the disease but Blaisdell (1952), in a thesis on the experimental condition, stated that overt illness rarely ensued although occasional or frequent coughing occurred in a few instances and three of the worst cases were characterized by loss of body weight, depression, increased pulse and respiratory rates, dyspnoea and eosinophilia. Bailey and Lowman (1952) described two cases which presented abnormal respiratory signs. Sudduth (1955) reported eczema, diminished appetite, loss of weight and dyspnoea in association with six cases of feline lungworm disease in

which eosinophilia was not found. McKenzie (1960) stated that, in two 12-weeks-old kittens in which lungworms were found at post-mortem examination, slight unthriftiness was the only clinical feature. Brown (1962) demonstrated the presence of the larvae of Aelurostrongylus abstrusus in the faeces of four out of 12 apparently healthy cats. As far as the present survey is concerned, and this includes the previous findings of Hamilton (1963), there were 17 cases of lungworm infestation out of a total of 256 animals, from only a proportion of which clinical histories were available. Five cats were found to have suffered from other morbid conditions, namely: lymphosarcoma, facial abscess, carcinomatous involvement of the cranium, feline enteritis and pericarditis, whereby it was impossible to ascribe any particular clinical sign to the pulmonary condition. Three animals were without history at all and of nine animals with a medical record, two died after a chronic illness that was associated with a capricious appetite and loss of body weight. In six of the remaining seven instances, the clinical manifestations comprised occasional to frequent coughing, worsened by handling, fitful appetite and gradual loss of bodily condition over a period of months. In addition, several of the animals were seized by fits of sneezing and also exhibited an oculo-nasal discharge. The solitary residual cat almost certainly died as a result of lungworm infestation. It was six months old and had exhibited signs

of respiratory disease over a period of three months prior to death, during which time coughing and sneezing were accompanied by a muco-purulent nasal discharge. The animal became progressively dyspnoeic, was averse to food as well as emaciated and developed marked hydrothorax before it died.

In sum, the main clinical changes encountered were coughing of varying frequency, uncertain appetite, decline of bodily weight together with depression and, in several instances, an oculo-nasal discharge. Such findings are similar to those which have been reported by other workers. It seems, therefore, that the disease is usually of mild character but may sometimes lead to death or to a chronic wasting state with inappetance. The severity of the condition is probably related to the number of infecting larvae which, if small, is likely to be overcome and spontaneous recovery ensue. On the other hand, massive infestation may be associated with respiratory disturbance and, if the animal lives long enough, with a chronic illness lasting for some months before death results.

Lungworm infestation was encountered in all age-groups, from two months to nine years of age, or more, and in both sexes the incidence was balanced in as much as nine males and eight females were affected. The disease was not seasonal in incidence and was encountered in almost every month of the year.

d. Haematological Findings.

It was possible to examine a sample of blood from six of the 17 animals affected with lungworm disease and the results of the examinations are given in Table 15 (p. 55). Of several points which emerge, the first is that haemoglobin (Hb), packed cell volume (P.C.V.) and mean corpuscular haemoglobin concentration (M.C.H.C.) were within normal range, which tends to rule out any interference with erythropoiesis. In each case erythrocyte sedimentation rate (E.S.R.) was increased and values from 6 to 20 mm. per hour were recorded. The only noteworthy aberration in the white cell count was eosinophil leucocytosis which was found in five out of six animals but, as eosinophilia is commonly associated with metazoan parasitic conditions, that feature is not really extraordinary. Blaisdell (1952) mentioned eosinophilia in her list of clinico-pathological findings but Sudduth (1955), in his six cases, stated that eosinophilia did not occur.

e. Morbid Anatomy.

Lesions were confined to the thoracic cavity but varied in character from animal to animal according to the phase of the infestation. In mild or early cases, multiple lesions, of 1 to 2 mm. in diameter, or smaller, and often visible only with the aid of a hand-lens, were found scattered throughout the substance of the lungs. At a later stage of

TABLE 16.

RESULTS OF HAEMATOLOGICAL EXAMINATION IN SPONTANEOUS LUNGWORM DISEASE.

Case No.	1	2	3	4	5	6
E.S.R. (mm./hr.)	15	8	6	6	18	20
P.C.V. (%)	49	43	56	40	46	43
Hb. (gm./100 ml.)	11.9	13.7	16	15	14	13.5
M.C.H.C. (%)	29.9	31.5	29.1	32.5	30	33
W.B.C. (cu.mm.)	14,800	16,700	6,350	10,000	10,200	15,000
Neutrophils (%)	60	68	57	68	48	52
Lymphocytes (%)	25	30	35	28	39	37
Eosinophils (%)	15	2	8	10	13	11

the disease widely distributed larger foci, up to 10 mm. in diameter, were observed and frequently projected from the surface of the lung to impart a nodular appearance to the unopened organ (Figs. 2 and 3, p.57). Confluence gave rise to large protusive nodules which occupied considerable areas of individual lobes and such lesions were fairly firm, somewhat crumbly in consistence and yellowish in colour and in the more severe cases contiguous pulmonary consolidation was such that, little unaffected lung tissue remained. When lesions were squeezed, a milky and viscid fluid was expressed and proved to be particularly rich in ova, larvae, eosinophils, lymphocytes and macrophages and in one animal the pleural cavity was found to be filled with thick, whitish fluid and the visceral pleura was thickened, roughened and partly adherent to the parietal layer. In many instances bronchi contained a muco-purulent exudate and, especially in more severe cases, the bronchial lymph-nodes were enlarged, white and homogeneous on section.

McKenzie (1960) reported congestion, oedema and patchy consolidation of the lungs in both of his cases with, scattered throughout the pulmonary substance, discrete foci that had sometimes coalesced to form larger lesions. In one animal, only one lobe was affected but in the other cat all the lobes were involved but changes in the bronchial lymph-nodes were not recorded. Sudduth (1955), in three out of six animals, found induration of the lungs to be associated

Figures 2 and 3. **Gross appearances of the lungs with parasitic infestation showing the distribution and the coalescence of the elevated, whitish lesions.**

Fig. 2

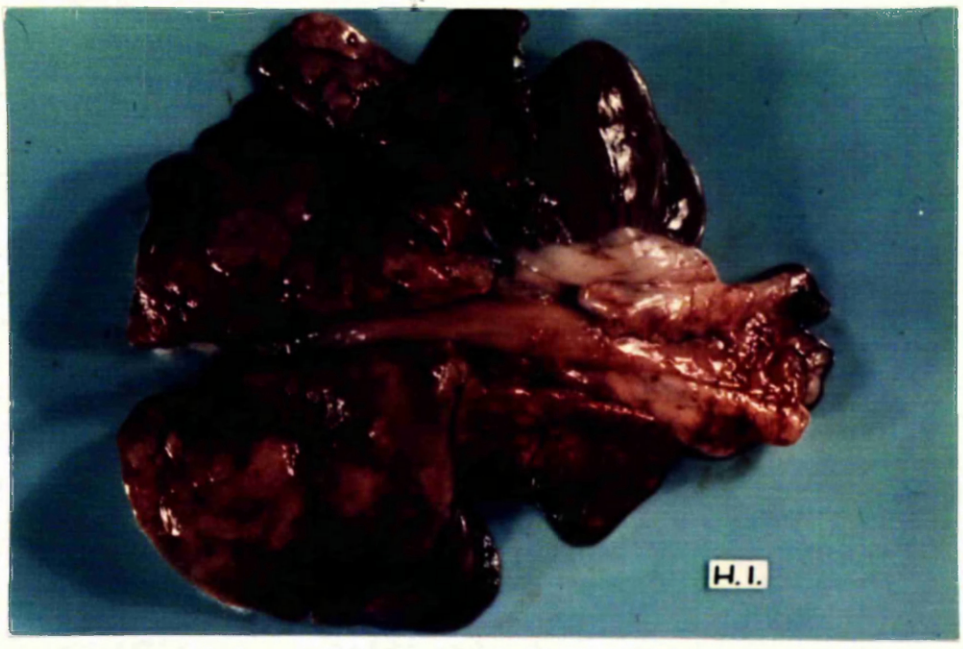
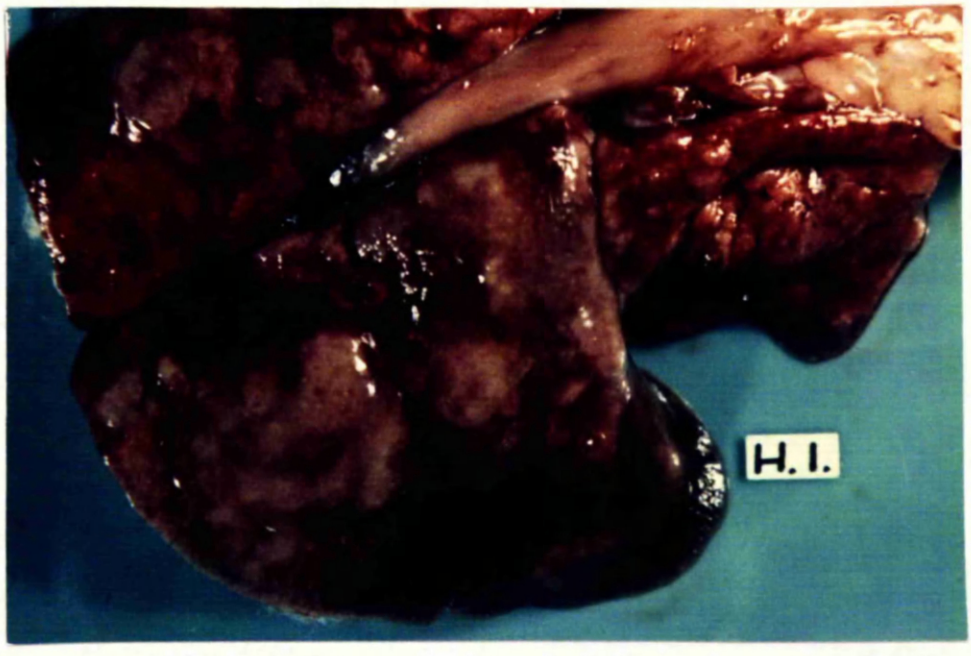


Fig. 3.



with "minute encapsulated spots" together with the presence of thick exudate in the bronchial system. MacKerras (1957) described similar lesions and declared that the extent of the damage was in proportion to the number of worms present.

In short, there is little difference to be noted in the lesions that have been described by the various authors.

f. Histopathology.

Conveniently, the morbid histological changes may be divided into those (1) concerning the lung substance and (2) pertaining to the vasculature.

(1) The Lung Substance.

At an early stage of the condition, some lobes presented few signs of eggs or larvae but manifested a cellular reaction that consisted of lymphocytes, macrophages and eosinophils together with numerous multinucleated giant-cells. Often the centre of such a lesion was necrotic and closely simulated the tuberculous follicle until microscopical examination revealed the presence of the parasite. Additionally, there was commonly present a peribronchial and peribronchiolar lymphocytic reaction which was often diffuse around the circumference of the vessel but at other times was more nodular in form. Moreover, some infiltration of the bronchial and the bronchiolar walls by eosinophils, lymphocytes and plasma cells was associated with mild proliferation of the related mucous membrane.

As the disease progressed, the larvae developed into adult parasites that laid numerous eggs which were associated with the production of more severe lesions and, in the one animal, there were to be found lesions at all stages of development. The following description refers to the main findings characteristic of the later stages of the disease.

Clusters of eggs, some starting to morulate and some already hatched into first-stage larvae, were surrounded by a marked cellular reaction that was comprised of large numbers of eosinophils, together with lymphocytes, some neutrophils and plasma cells and was usually accompanied by numerous multinucleated giant-cells (Figs. 4 and 5, p. 60). Occasionally, the presence of ova did not evoke any response and, in the majority of cases in which adult worms were present, the cellular reaction was predominantly eosinophilic in nature with some infiltration with macrophages (Fig. 6, p.61). Areas of necrosis were not uncommon and in one case calcification was noted. Such cellular accumulations spread beyond the immediate zone of the eggs and larvae to coalesce with similar lesions and so cause quite considerable damage to lung tissue. Thickening of the septa in consequence of vascular and cellular reaction, epithelialization of the alveoli and vesicular emphysema associated with areas of collapse were other changes frequently to be seen.

In the affected parts, the alveoli together with the bronchioles and bronchi contained large numbers of ova,

Figure 4. Section of lung with arterial thickening and periarterial lymphocytic reaction. Developing ova and first-stage larvae with a mixed cellular reaction are evident.
Haematoxylin and Eosin. X150.

Figure 5. The same reaction as above in higher magnification, to demonstrate the eggs, first-stage larvae, leucocytic and giant-cell reactions.
Haematoxylin and Eosin. X330.

Fig. 4.

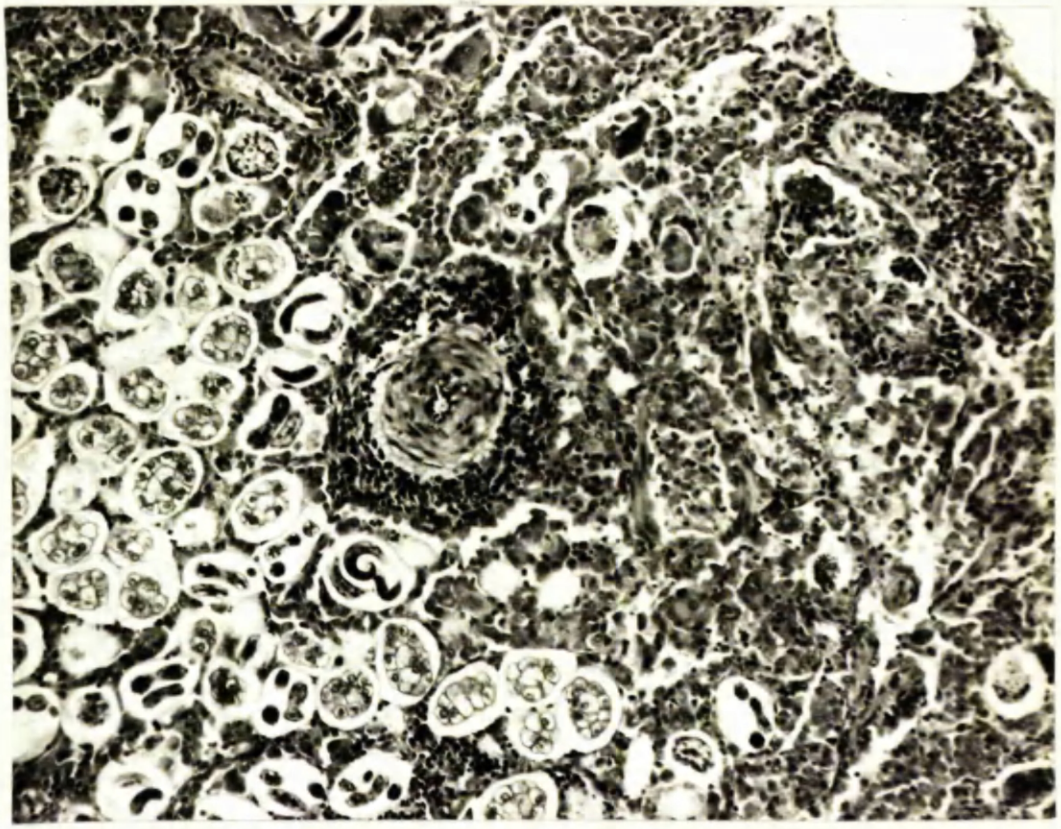


Fig. 5.

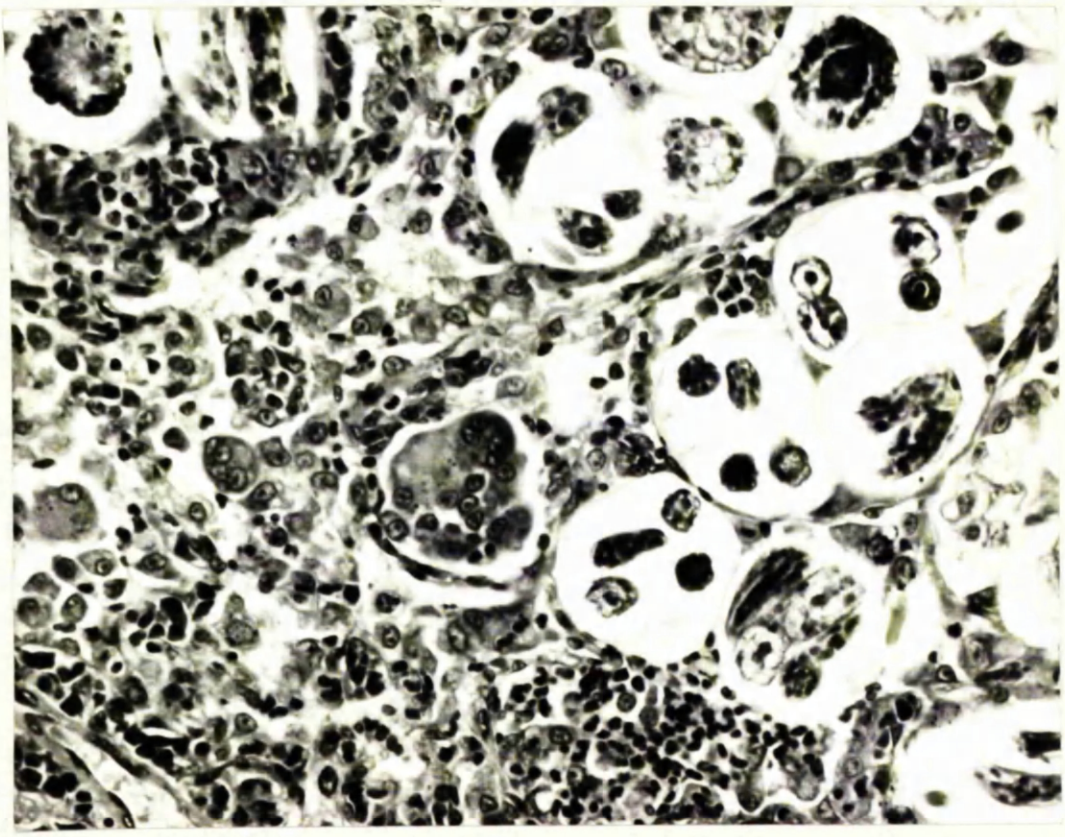


Figure 6. Adult parasite in section surrounded by a predominantly eosinophil leucocytic reaction. Strands of hypertrophic bronchiolar and alveolar duct muscle are also present.
Haematoxylin and Eosin. X150.

Figure 7. Ova, larvae and exudate in a bronchiole.
Haematoxylin and Eosin. X150.

Fig. 6.

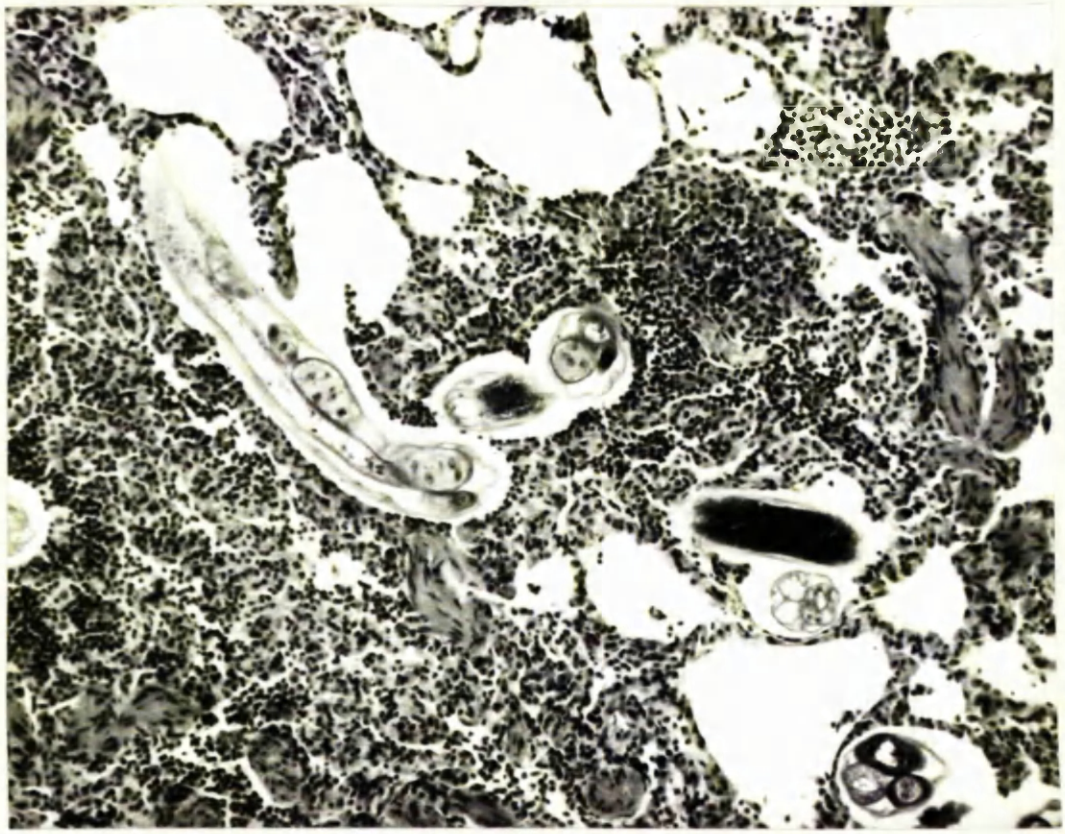
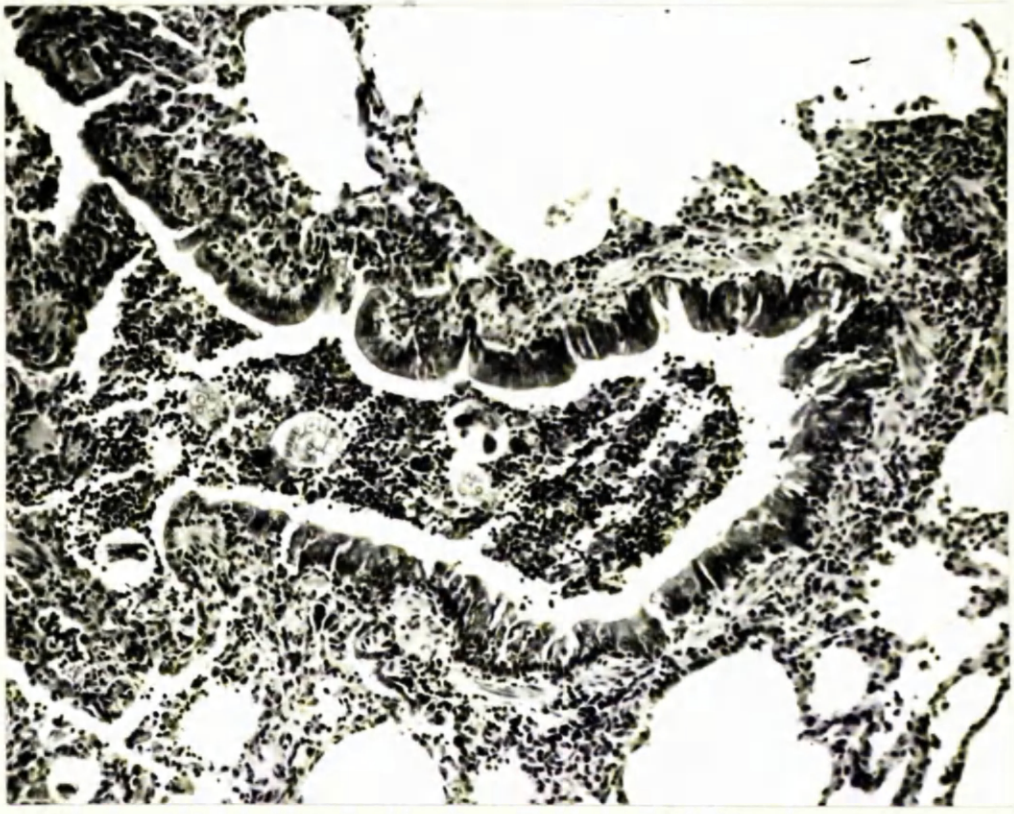


Fig. 7.



larvae and cellular material (Fig. 7, p.61) while peribronchial and peribronchiolar aggregations of lymphocytes were common and often marked. Infiltration of the bronchial and bronchiolar walls by eosinophils, lymphocytes and plasma cells was evident and larvae were sometimes observed on their way through those structures. Proliferation of the epithelium, productive of a multi-layered epithelial covering to bronchi and bronchioles, was frequently noted along with grossly increased production of mucus, which latter was mixed with parasites, ova and cellular exudate in the lumina.

In the cat, the peribronchial mucous glands are well developed and extend further down the bronchial tree than is the case in most species of animals so that they may be found even in the bronchiolar walls. In lungworm infestation, those glands undergo hyperplasia (Fig. 8, p.63) with the production of excess of mucus and, occasionally, show cystic abnormality. Bundles of smooth muscle were commonly seen as strands that were often very thick and sometimes haphazardly distributed throughout the lung substance. (Fig. 9, p. 63). Serial sections served to demonstrate that the main site of origin of that muscle was the walls of bronchioles and alveolar ducts. In areas where the amount of muscle was considerable, reticulation imparted to the lung substance a honey-comb appearance.

Figure 8. Hyperplasia of the peribronchial glands and proliferation of bronchial epithelium. Haematoxylin and Eosin. X150.

Figure 9. Strands of hypertrophic bronchiolar and alveolar duct muscle. A hypertrophic pulm onary artery is also recognisable. Haematoxylin and Eosin. X150.

Fig. 8.

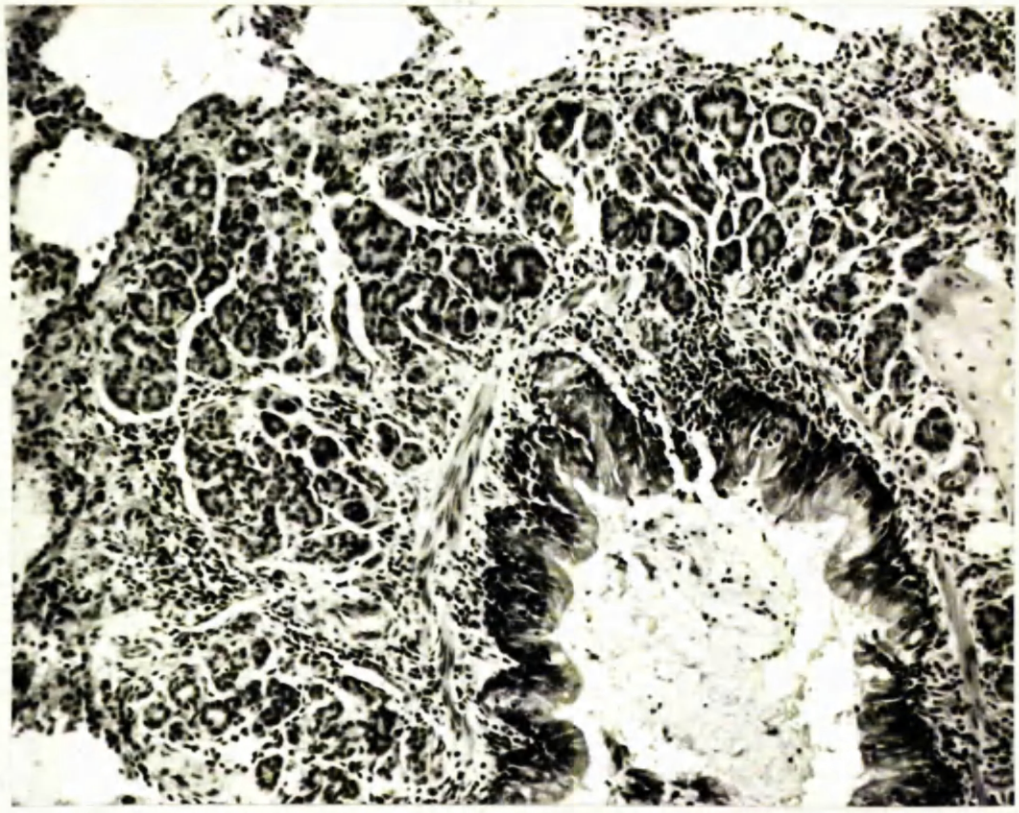
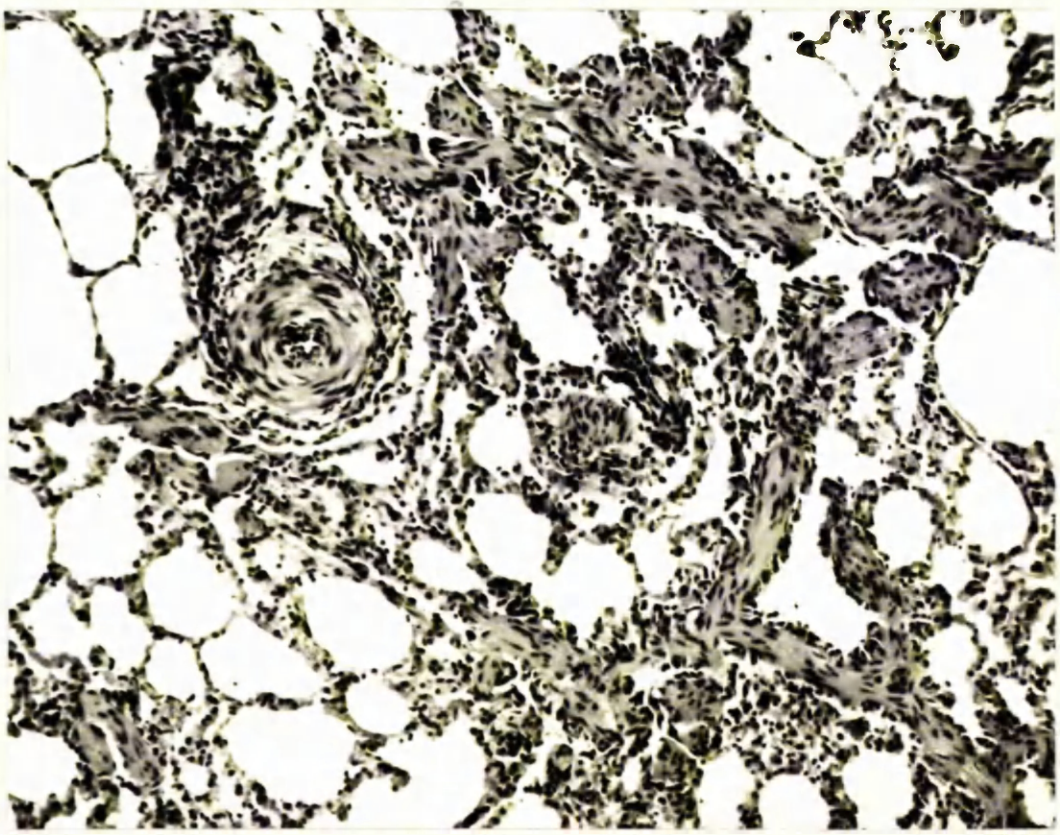


Fig. 9.



(2) The Vasculature.

Vascular lesions were found to fall into five grades of severity which were related to the mean wall-to-lumen ratios of the arteries as follows:

Grade 1 0.35:1 to 0.50:1,

Grade 2 0.51:1 to 1.00:1,

Grade 3 1.10:1 to 2.00:1,

Grade 4 2.10:1 to 3.00:1, and

Grade 5 3.10:1 and upwards.

Not every branch of the pulmonary artery was affected and the main lesions tended to occur in muscular arteries which gave rise to an arteriopathy which was of focal distribution. Whereas the vessels of the zones of maximal infection were widely affected many of the more distant ones were altered to a lesser degree. Minute examination of the lungs showed that the thickening sometimes occurred gradually in one of the arterial branches and, often, it began at the origin of a vessel from an apparently normal larger branch. Perivascular lymphocytic reaction was common and usually surrounded the vessel entirely but was sometimes nodular in its distribution. The elastic arteries, the bronchial arteries and the pulmonary veins were unchanged.

Grade 1.

In this first stage of pathological change there was merely hypertrophy of the vascular smooth muscle. The

Figure 10. Normal muscular pulmonary arteries from a young adult cat.
Haematoxylin and Eosin. X150.

Figure 11. Grade 1 hypertrophy in a muscular pulmonary artery.
Gomori's aldehyde-fuchsin. X150.

Fig. 10.

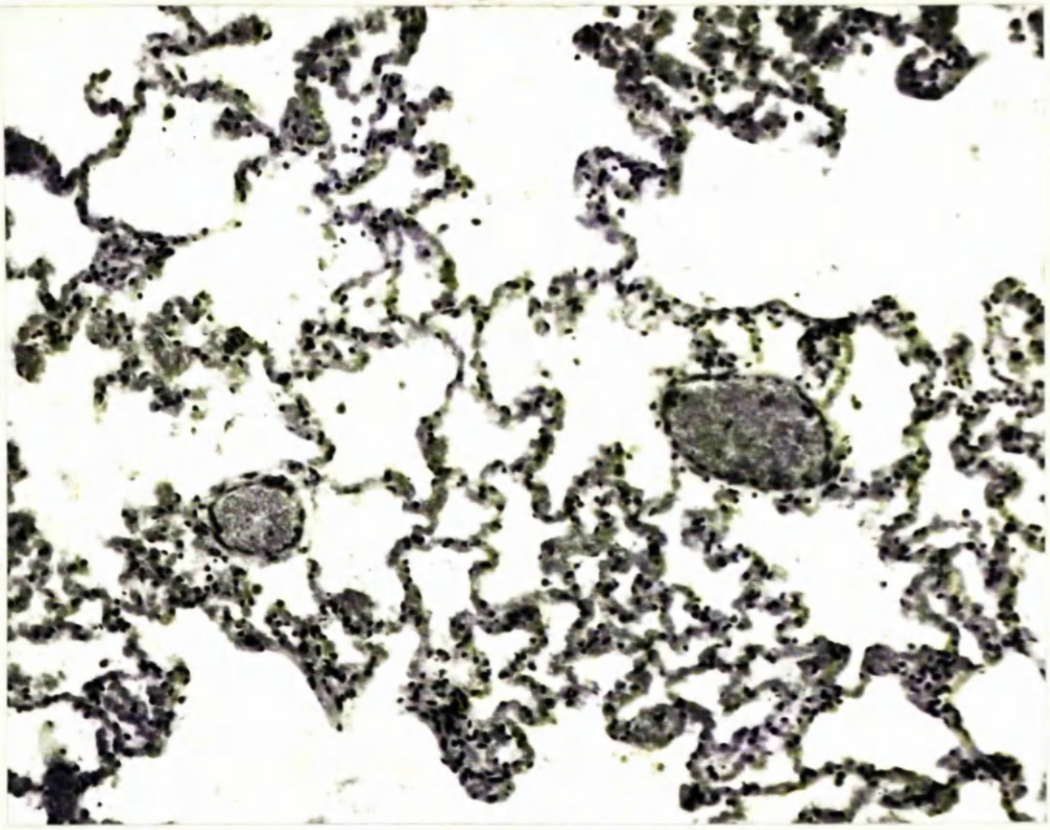
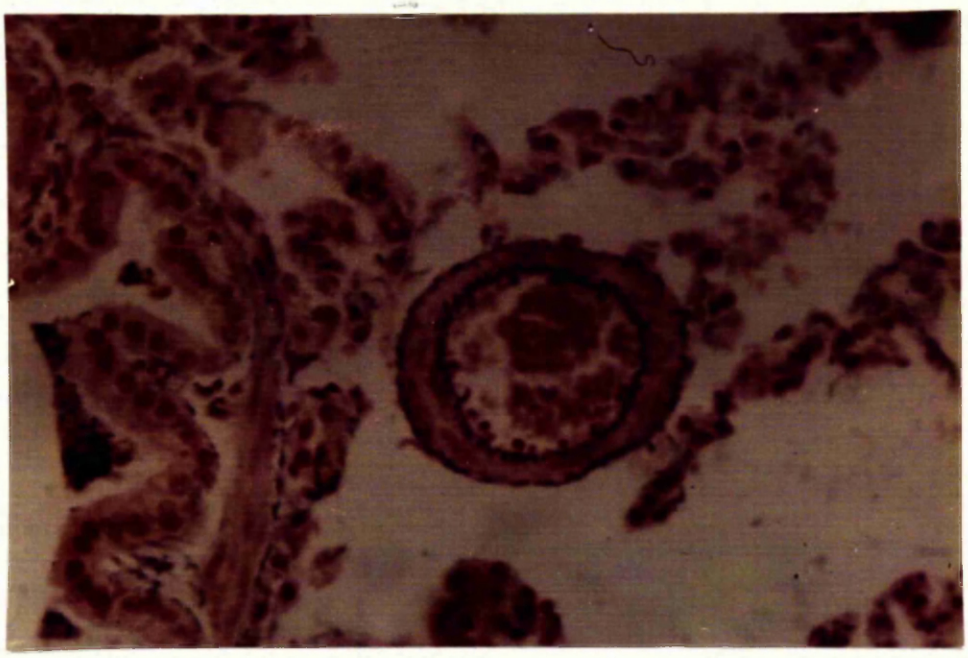


Fig. 11.



swollen myofibrils gave a thickened appearance to the vascular walls which amounted to two to three times that normally estimable (Fig. 11, p. 65). Lesions of the lungs were neither widespread nor severe and excess of bronchiolar muscle was not present.

Grade 2.

The mean thickness of the arterial wall was three to five times the normal whereby the vessels appeared markedly thickened as a result of hypertrophy supplemented by hyperplasia, which latter change was revealed by the presence of mitotic figures in the myofibrils. In three members of the group, fibrosis of the intima was observed but was minimal and considered to be of little, if any, significance.

Ordinarily, in histological preparations, contraction of the vessel wall causes the elastic laminae to appear corrugated instead of stretched as is normal during life. In the second stage, however, muscular hypertrophy was more pronounced and the elastic layers were stretched although in some vessels there was occasionally encountered a break in the continuity of the latter laminae. (Fig. 12, p. 67). In only one animal was there any endothelial reaction which took the form of swelling and proliferation and was accompanied by infiltration by eosinophil leucocytes into the intima. Also observed was a vacuolation of the hypertrophic myofibrils and similar sub-endothelial change gave

Figure 12. Grade 2 hypertrophy in a muscular pulmonary artery, stained to demonstrate the elastic laminae which are beginning to degenerate.
Gomori's aldehyde-fuchsin. X320.

Figure 13. Sub-endothelial vacuolation of a hypertrophied artery of Grade 2.
Haematoxylin and Eosin. X170.

Fig. 12.

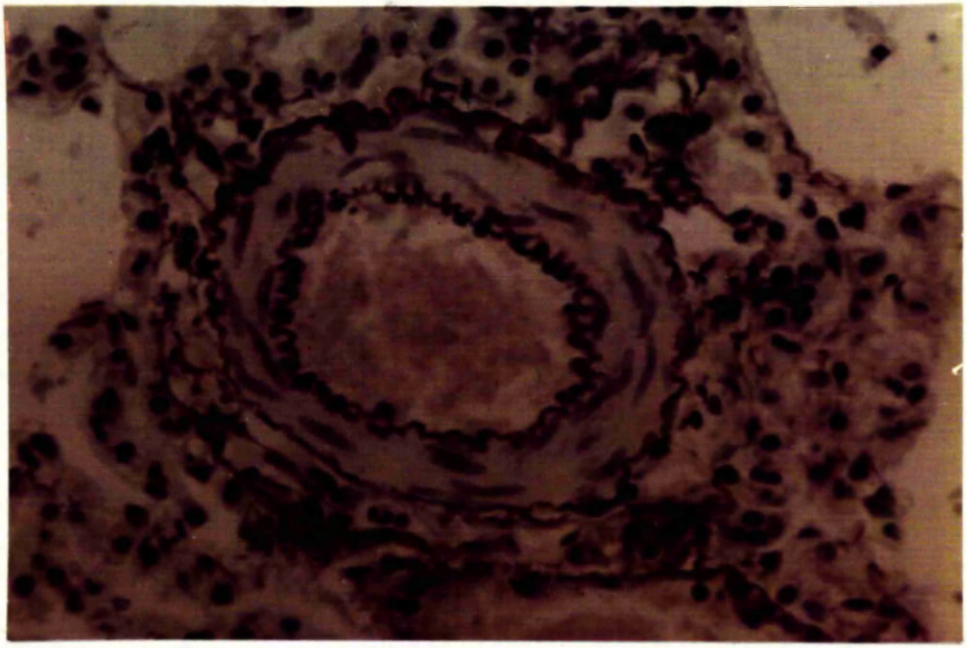
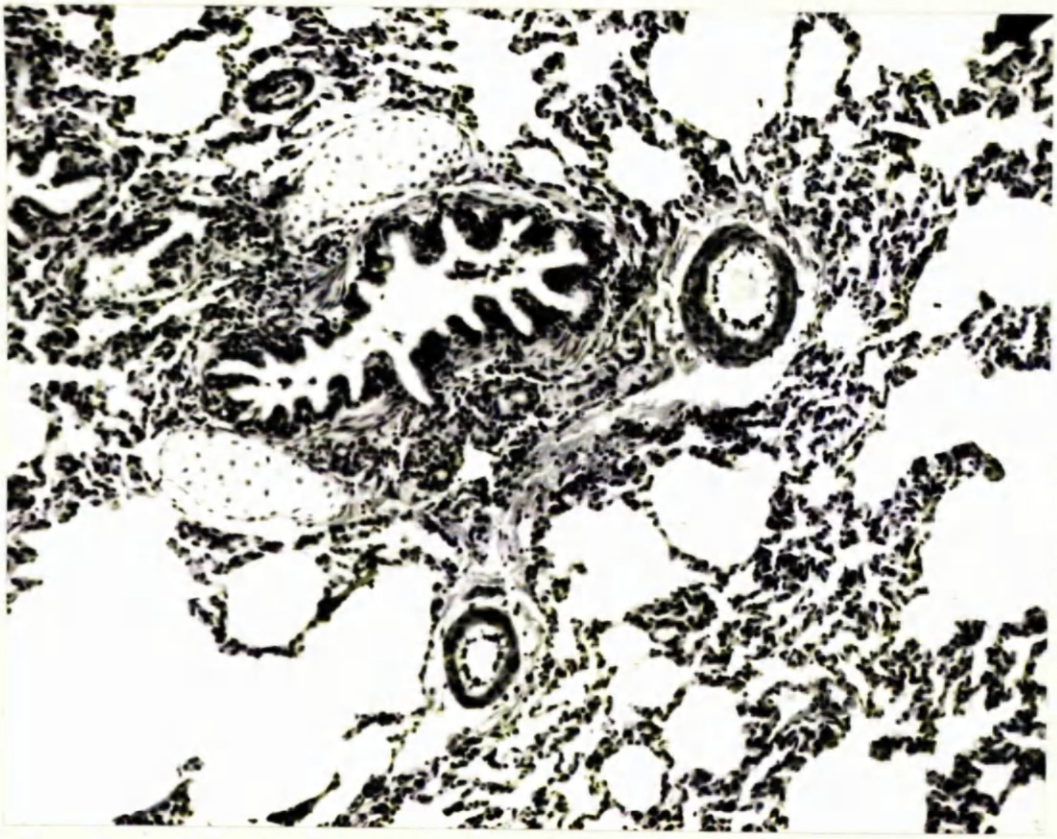


Fig. 13.



the appearance of accumulation of lipoidal material (Fig. 13, p. 67). The tissue responses of the animals in this grade of the disease were more pronounced and at this stage, too, hypertrophy of the muscle of the bronchioles and alveolar ducts was first noticed in all of the animals.

Grade 3.

Typical of this phase was an exaggeration of the hypertrophic and hyperplastic processes that rendered the arterial walls from six to ten times thicker than normal. In all but one animal, in which it was moderately severe, intimal fibrosis was minimal. In one case there was slight endothelial proliferation accompanied by infiltration of eosinophil cells into the intima.

Both the internal and the external elastic laminae showed marked changes. Fragmentation of the layers occurred in all four cats of the group and, although in the majority of the affected arteries, the circumferential pattern of the original structures was traceable, in quite a number of the vessels there was almost complete dissolution of one, or both, layers. Here and there, a portion of lamina remained as proof that it had existed but, in extreme cases, there was not a vestige of either membrane (Fig. 14, p. 69). It was at this stage of the disease that the longitudinal muscle of the arterial wall was first noted in two out of the four animals. In several of the affected arteries, that muscle

Figure 14. Fragmentation of the elastic laminae in association with hypertrophic and hyperplastic changes in a pulmonary artery.
Lawson's elastic stain. X430.

Figure 15. Fasciculi of longitudinal muscle on both sides of the external elastic laminae observable in a grossly thickened pulmonary artery.
Picro-Mallory. X260.

Fig. 14.

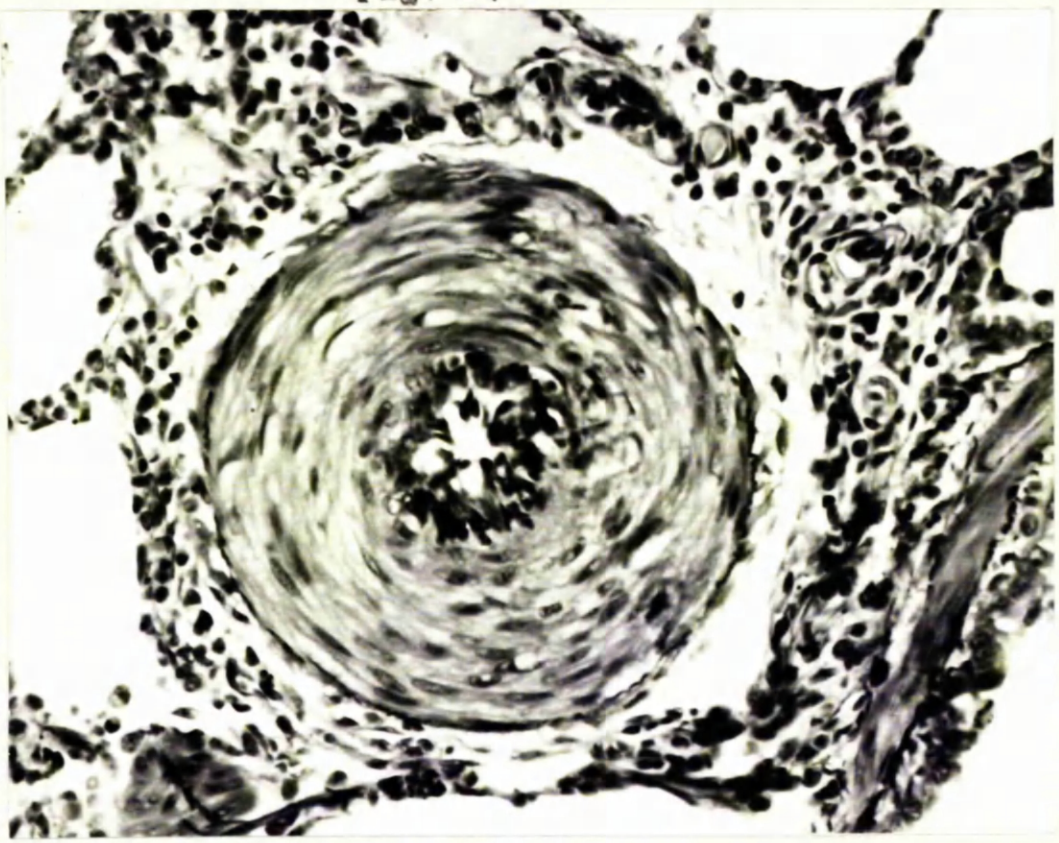


Fig. 15.

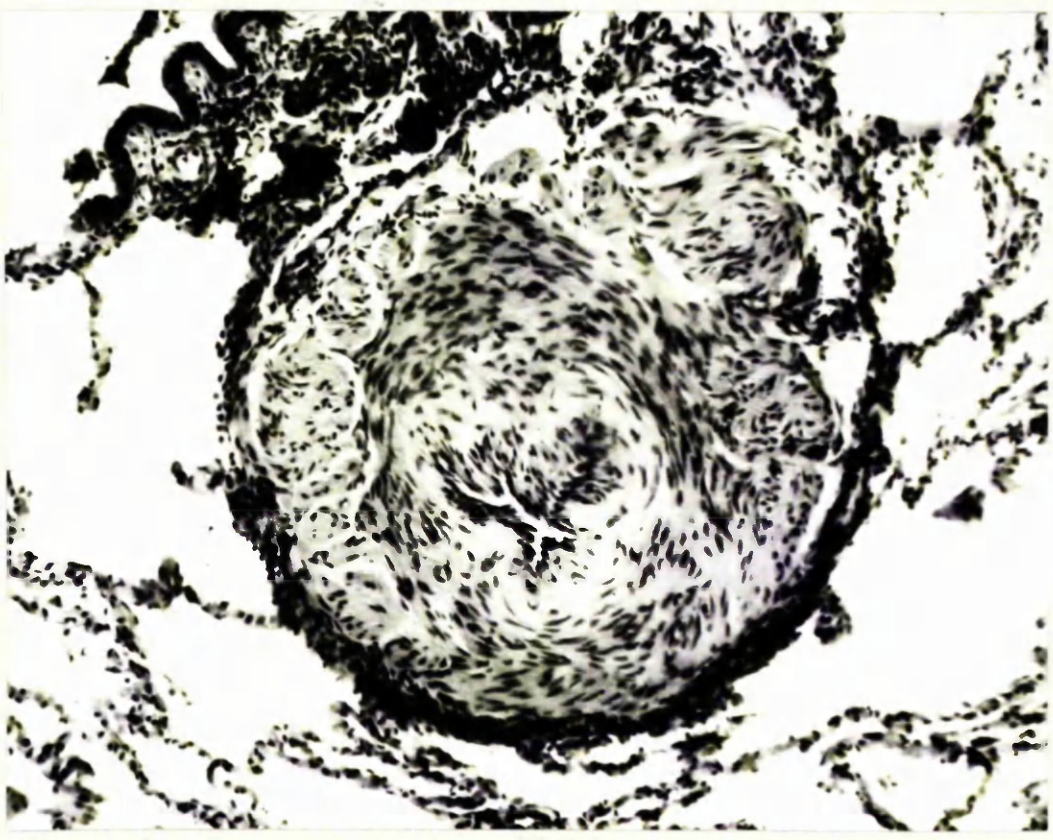


Figure 16. Vacuolation of hypertrophied longitudinal muscle in the intima of branches of the pulmonary artery.

Van Gieson. X150.

Figure 17. The same section as above at a higher magnification to accentuate the vacuolation of the muscle cells.

Van Gieson. X380.

Fig. 16.

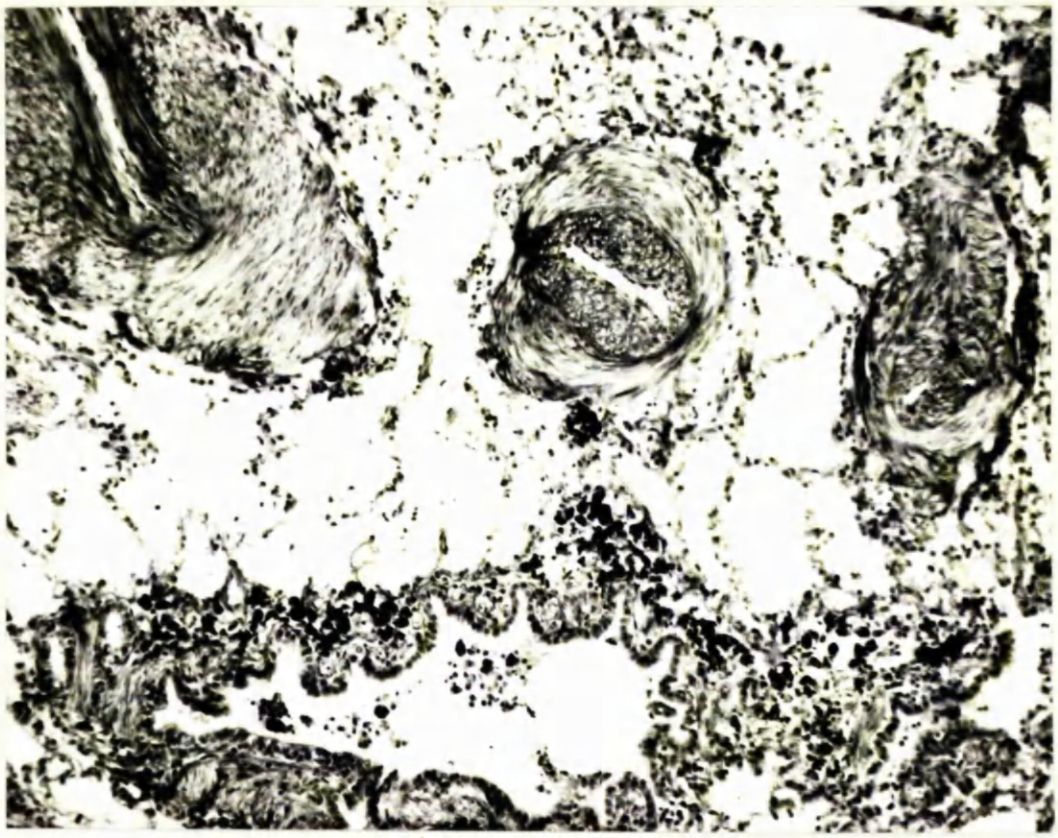


Fig. 17.

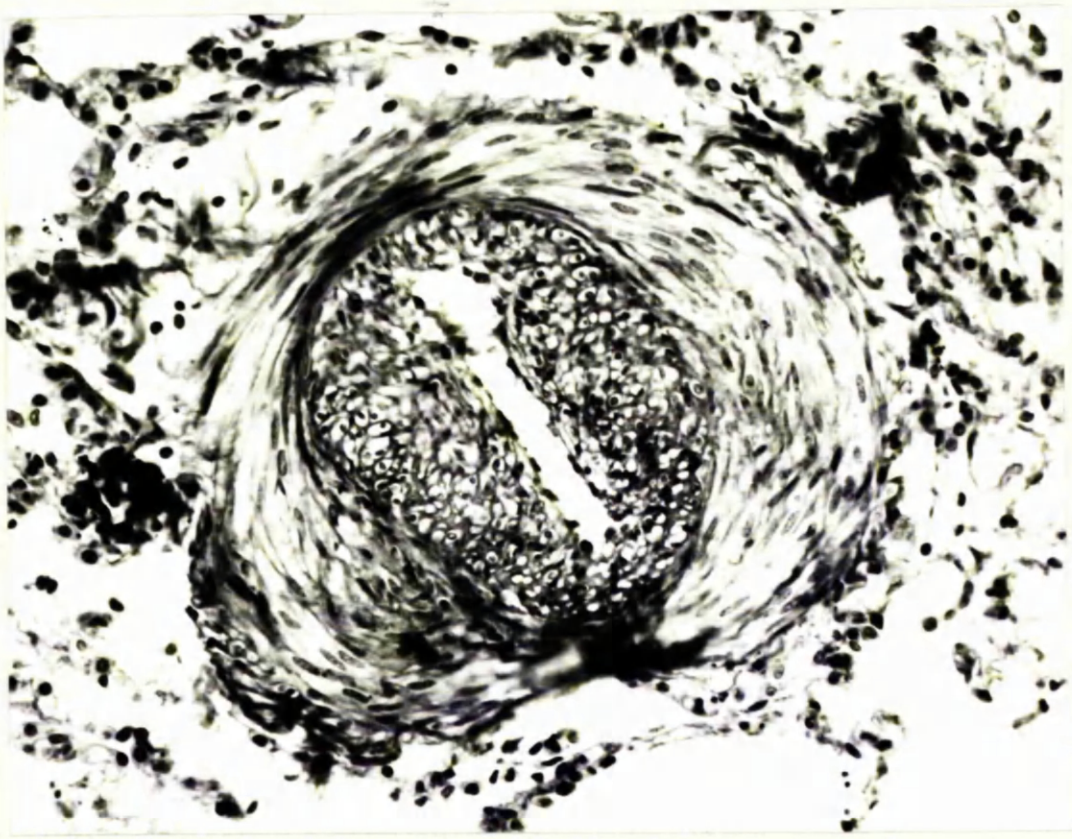


Figure 18. The same lung section, demonstrated in Figs. 16 and 17, stained to show the vacuolated muscle and collagenated matrix of the intima.

Van Gieson. X480.

Figure 19. Almost complete dissolution of the elastic laminae in a pulmonary artery which has undergone hypertrophic and hyperplastic changes.

Lawson's elastic stain. X430.

Fig. 18.

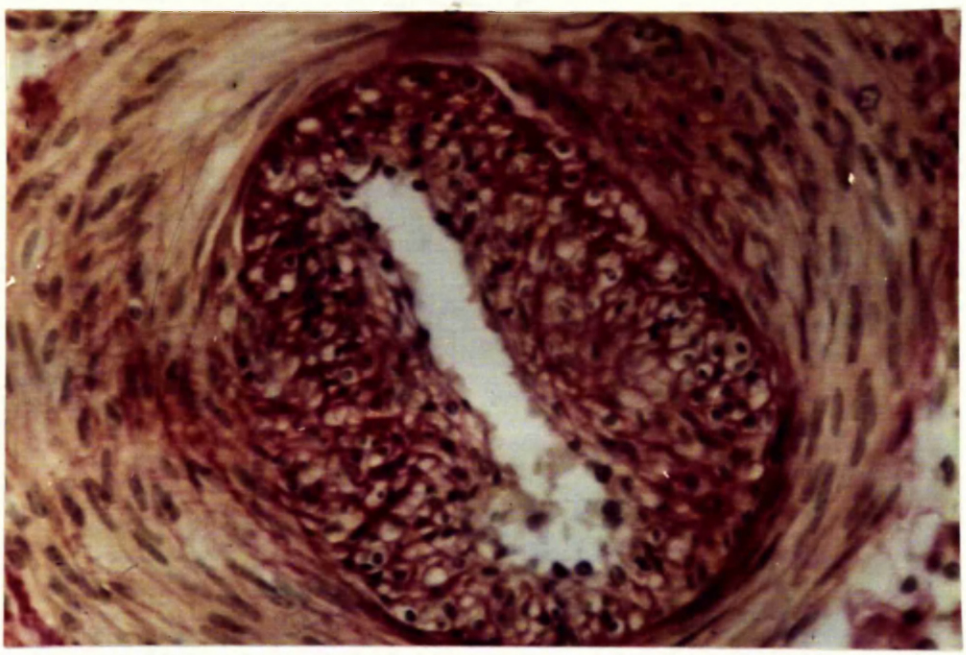
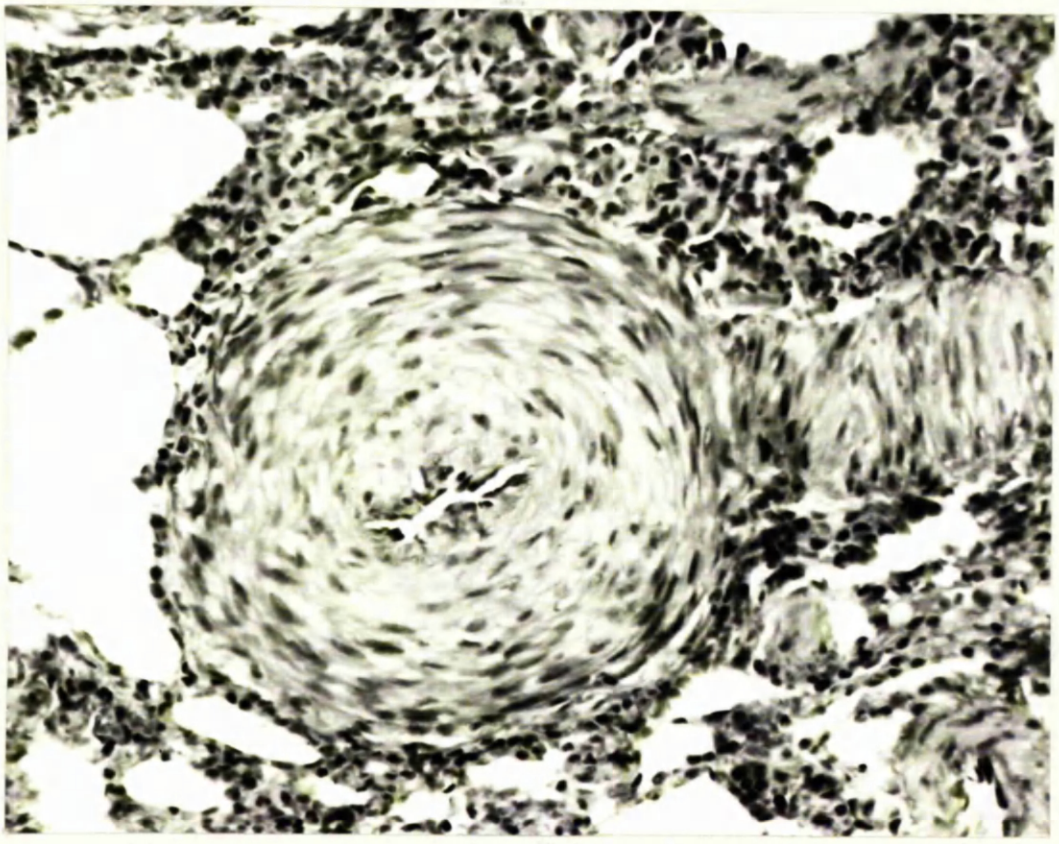


Fig. 19.



was found to lie inside the internal elastic layer but, in some instances, it also occurred in both the medial and adventitial coats (Fig. 15, p. 69). In many cases, the amount of longitudinal muscle accounted for the greater part of the thickening. The muscular tissue consisted of large vacuolated cells, supported by a ground-work of collagenated fibres, which formed a complete ring around the endothelial lining of the artery (Figs. 16, 17 and 18, p. 70 and 71). Where the longitudinal muscle was external to the elastic laminae it lay in fasciculi that were dispersed throughout the hypertrophic circular muscle or the adventitia. The longitudinal muscle was appreciable only in a percentage of the pulmonary muscular arteries of all sizes. In many affected arteries, vacuolation was conspicuous in the sub-endothelial tissues, in the hypertrophic circular muscle and, especially, in the longitudinal myofibrils. The contents of the vacuoles did not respond to staining methods for neutral fats, for cholesterol, for mucopolysaccharide or for glycogen.

In the tissues of the lung other than the arteries, the changes were pronounced and myo-hypertrophy in the walls of the bronchioles and alveolar ducts was even more prominent.

Grade 4.

Quite the outstanding feature was the increased thickness of affected arterial walls which varied from

11 to 15 times that of the normal. The thickening arose from the two processes of hypertrophy and hyperplasia of the myofibrils. In two animals, the longitudinal muscle was distributed in a fashion similar to that of the preceding group but, in some arteries, the muscle had become separated from the overlying media. The elastic laminae were affected as before but, in rather more of the arteries, were either reduced to small fragments or were entirely lacking (Fig. 19, p.71). Intimal fibrosis was fairly well marked in one animal but was of mild type in the remaining three while slight endothelial proliferation and some infiltration of the intima by eosinophil leucocytes occurred in two cases. Vacuolation of the hypertrophied muscle-cells was of type and staining propensity similar to that already noted.

Grade 5.

This, the most advanced stage of the disease, showed medial thickening in which hypertrophy and hyperplasia of the circular muscle-fibres gave rise to considerable narrowing of the vascular lumina. In one of the animals, however, marked endothelial proliferation together with infiltration of the media by eosinophilic cells was present and, in association with the hypertrophic reaction, caused almost total occlusion of the vessel (Figs. 20 and 21, p.74). Generally speaking, a large percentage of the arteries was affected. In both animals the longitudinal muscle was

Figure 20. Endothelial proliferation in a thickened artery associated with infiltration of the intima and the media by eosinophil leucocytes. Haematoxylin and Eosin. X150.

Figure 21. Part of the field in Fig. 20 magnified, to demonstrate more clearly the intimal reaction. Haematoxylin and Eosin. X430.

Fig. 20.

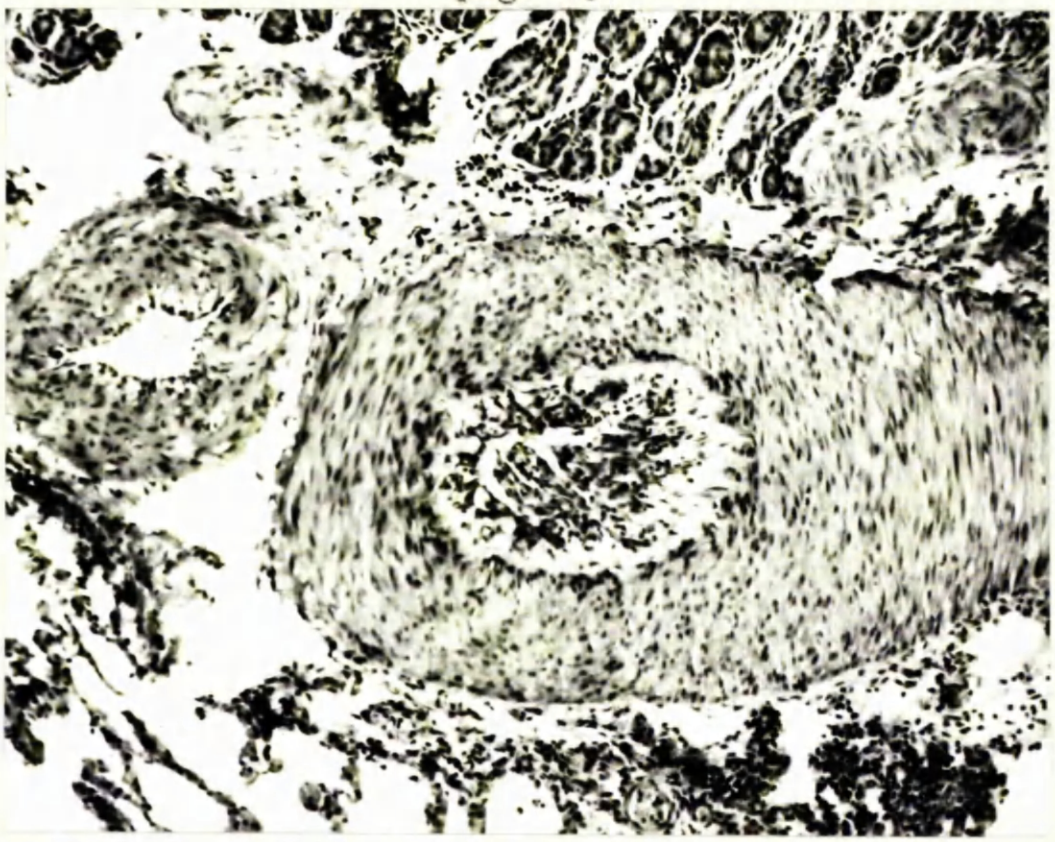


Fig. 21.

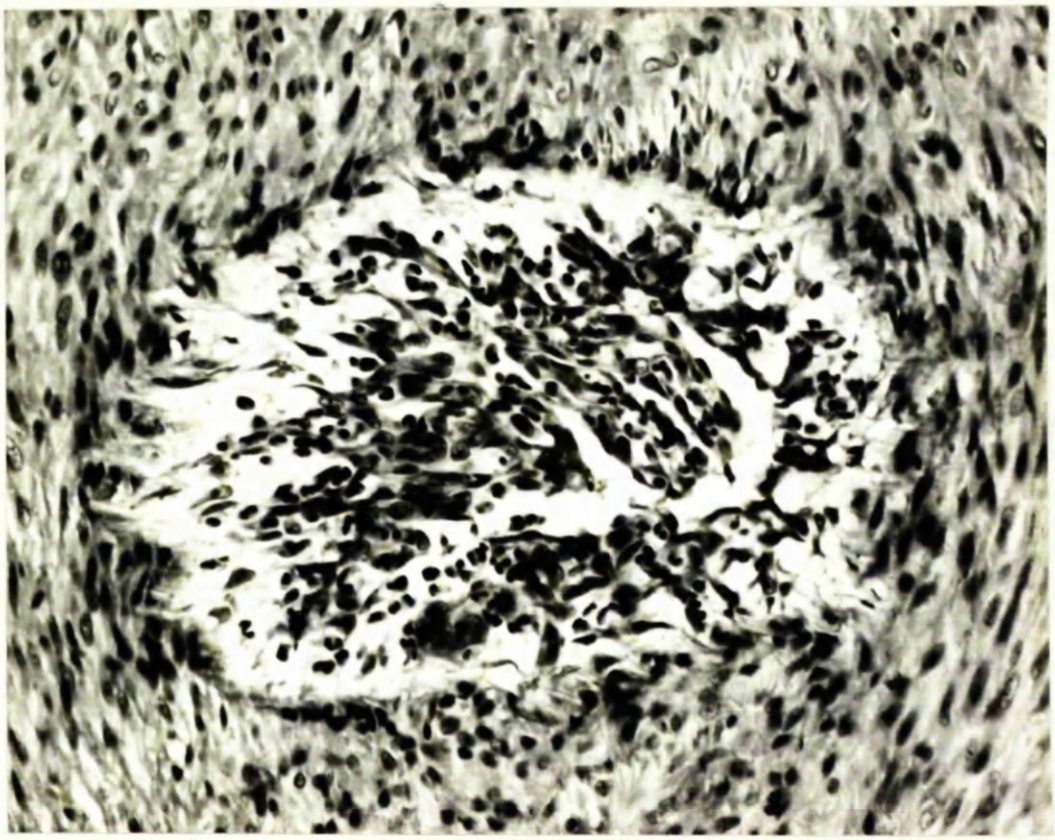


TABLE 16.

SYNOPSIS OF PATHOLOGICAL FINDINGS IN CATS WITH LUNGWORM DISEASE.

Grade of Lesion	Case No.	Intimal Fibrosis	Fragmentation of Elastica	Longitudinal Muscle	Bronchiolar Muscle	Endothelial Proliferation
1	282	-	-	-	-	-
	93	-	-	-	-	-
2	18	-	-	-	+	-
	40	Minimal	-	-	+	+
	73	Minimal	-	-	+	-
	47	Minimal	-	-	+	-
	471	-	-	-	+	-
3	21	Minimal	+	+	+	-
	49	Severe	+	+	+	-
	197	Minimal	+	-	+	+
	464	Minimal	+	-	+	-
4	235	Severe	+	+	+	-
	271	Minimal	+	-	+	+
	440	Minimal	+	+	+	+
	293	Minimal	+	-	+	-
5	283	Minimal	+	+	+	+
	285	Minimal	+	+	+	-

distributed as formerly noted while intimal fibrosis was of minimal degree. The elastic laminae were strikingly altered often to the point of complete dissolution, while vacuolation of the sub-endothelial intima and of the circular and longitudinal muscle fibres was prominent.

In both the grades 4 and 5 the lesions in the other tissues of the lungs were similar to those already described, and included marked hypertrophy of the muscle of the bronchioles and alveolar ducts as well as the changes associated with the presence of the parasite.

g. Discussion.

In the literature on infestation by Aelurostrongylus abstrusus, the only detailed report of histopathological kind is that of McKenzie (1960) pertaining to two kittens. His description of the lesions did not refer to either such features as aggregations of eosinophils,in the tissues, or proliferation of the bronchial and bronchiolar mucosae or hyperplasia of the peribronchial glands or the presence of adult worms in the lungs. Furthermore, although slight hypertrophy of smooth muscle was noted, that change was not stated to relate to the muscle of bronchioles or alveolar ducts, nor was reference made to any peribronchial or peribronchiolar lymphocytic reaction. As far as the vasculature was concerned, mention was made of hypertrophy and hyperplasia of the medial coat of the arteries together

with endothelial proliferation, intimal infiltration and fibrosis and vacuolation of muscle cells but there was not any report of the presence of longitudinal muscle or changes in the elastic laminae. Such omissions may have arisen from the small number of animals that was examined.

Cameron (1929 and 1932) stated that the adult worms live in the smaller pulmonary arteries, where they lay their eggs, and in all probability cause irritation of the vessel. McKenzie (1960), by reason of the absence of peribronchial and peribronchiolar, and the presence of perivascular, lymphocytic reaction, considered that a more intimate relationship between the parasite and the vessel obtained in the cat than in other domestic species. However, since it is now generally accepted that the adult worms reside in the tissues of the lung rather than in the blood vessels and it is clear that peribronchial and peribronchiolar lymphocytic reaction does occur, the view that the adult worm provokes the arterial lesion in consequence of habitation in the vessel has lost support. Precisely how the third-stage infective larvae reach the lungs is still uncertain but invasion may take place via the lymphatic stream or by way of the circulating blood and, if the parasite is to exert any change on the arterial wall, it is the migratory third-stage larvae that are likely to cause damage.

Blaisdell (1952) suggested that a product of some stage of the parasite may act upon the vessels and result in medial

hypertrophy. Hamilton (1963) postulated that an increase of pulm onary blood pressure, culminating in conspicuous alteration of the blood vessels, was attributable to resistance to the flow of blood that was occasioned by the presence of the various forms of the parasite together with the related cellular reactions.

The presence of longitudinal muscle is of special interest and has not been hitherto recorded in the pulmonary arteries in association with feline lungworm infestation. In all, six cats man ifested the abnormality to an appreciable percentage of affected arteries but the alteration was found to occur only in lesions of the third grade and upwards, i.e. cases in which the thickness of the media was six, or more,times that of normal. Since the lesion was observed in animals of differing ages, that factor did not appear to be of any importance in the development of longitudinal muscle.

In the intima of cats affected with pulmonary arterial hypertrophy, Rubarth (1940) described the presence of fibro-muscular tissue that was always longitudinal in direction but did not comment upon its distribution in individual animals or upon the number of cats affected. Dahme (1960), in a review of a similar condition, also remarked on the occurrence of intimal longitudinal muscle but was not specific anent the distribution of the tissue in the individual animal. Quoting Töndury and Weibel (1958), Dahme suggested that the

production of longitudinal muscle was an expression of extreme stress on the artery by an external force and that it had little in common with the proliferative process characteristic of pulmonary arteriosclerosis.

In the human lung, Heath (1963) described seven cases in which a considerable amount of longitudinal muscle appeared in the intima, the media and the adventitia of all classes of pulmonary arteries. The distribution varied from isolated bundles to complete coats around the lumen of the vessel and the myofibrils were interspersed mainly with elastic fibres and, rarely, by collagenated ones. Other pulmonary arteries showed varying degrees of hypertensive change and, because the precipitating cause was different in six of the instances, it was concluded that the development of longitudinal muscle was associated with intravascular hypertension, the underlying cause of which was unimportant. To support this statement, Heath (1963) quoted the work of Turnbull (1914) who had described longitudinal muscle attended by mitral stenosis and cited the reports of Wade and Ball (1957) and Spencer (1962) who had found similar tissue in cases of idiopathic pulmonary hypertension. Heath expressed the opinion that the longitudinal muscle arose from a few pre-existing cells, although such structures are not mentioned in histological studies of normal muscular pulmonary arteries made by Brenner (1935) and by Best and Heath (1961).

In 11 of the 17 cats investigated by the author, intimal fibrosis of the pulmonary arteries was minimal. In two instances the condition was severe but, as the animals were quite old, it may be that the fibrosis was not uninfluenced by age. Fragmentation of the elastic layers became more pronounced as the arterial walls increased in thickness and was regarded to be a simple overstretching of the existing laminae. The contents of the vacuoles of the sub-endothelial region and of the hypertrophied muscle were not identifiable, which led to the suggestion that some form of hydropic degeneration was present. A feature of note was the focal distribution of the pathological changes in the branches of the pulmonary artery.

McKenzie (1960) did not encounter hypertrophy of the muscle of the bronchioles or of the alveolar ducts but he did describe a slight degree of that state to be present in the smooth muscle of the parenchyma of the lung. Pei-Lin-Li (1946) reported hypertrophy of the bronchiolar system in association with infestation by lungworms of sheep and goats and suggested that the condition arose from gradual, but incomplete, obstruction of the bronchiolar system by ova, larvae and inflammatory exudate. Such a concept seems as applicable to the cat as it is to the other species of animals named.

2. INVESTIGATION OF ANIMALS WITH PULMONARY ARTERIAL LESIONS IN THE ABSENCE OF OTHER MORBID CONDITIONS, (GROUP 2).

As indicated in Tables 11 to 14 (p. 41 to 45) more than half (53.9%) of the 89 cats suffering from pulmonary arterial hypertrophy and hyperplasia were not affected by other disease. Of 14 animals, for which a clinical history was obtainable, only one displayed signs attributable to disorder of the respiratory tract.

a. Morbid Anatomy.

Only in the more severely affected animals, examination of the cut surface of the lungsrevealed the thickened arteries in the form of whitish circular tubes that extended throughout the substance of the organ and felt like small thickened cords. Lesions of any other kind were not appreciable in the lungs of the cats.

b. Histopathology.

The histological findings for each grade of the condition are summarized in Tables 18, 19 and 20 (p. 91 to 93) and, for convenience as well as clarity, the lesions have been graded in a fashion similar to that applied to animals with lungworm disease. Such grading together with the distribution and the severity of the lesions related to the various age-groups is given in Table 17 (p. 82). The latter indicates primarily that there was little difference in the distribution and severity of the changes encountered in adult

TABLE 17.

AGE DISTRIBUTION AND SEVERITY OF PULMONARY ARTERIAL LESIONS IN ANIMALS OF GROUP 2.

AGE GROUP	GRADE OF LESION.				
	1	2	3	4	5
OLD	2	5	2	4	1
ADULT	8	9	5	1	0
YOUNG ADULT	5	1	1	1	0
KITTEN	3	0	0	0	0
TOTAL	18	15	8	6	1

and old animals and that lesions up to, and including those of grade 4, were found even in young adults. In comparison with lungworm disease (Table 16, p. 75) it will be noted that more severe arterial change occurred in association with lungworm infestation in as much as 10 out of 17 (58.8%) cases of the latter possessed arterial lesions which were classifiable into grades 3 to 5. By contrast, only 15 of the present group of 48 cats (31.2%) displayed similarly severe arterial change. The main pathological alterations of each grade are outlined below.

Grade 1.

In this, the mildest form, there was slight hypertrophy of the muscular arteries of the lungs with, in just over half of the cases (10 out of 18), a similar response on the part of the bronchiolar and alveolar duct smooth muscle. In a few instances a relatively mild perivascular and peribronchial lymphocytic reaction was present. Although the hypertrophied arteries were scattered widely throughout the lungs, normal vessels were never difficult to recognise.

Grade 2.

Hypertrophy of increased severity was found to be associated with a hyperplastic response of the arteries together with hypertrophy of the muscle of the bronchioles and alveolar ducts which was prominent in 10 out of 15 animals. Slight intimal fibrosis was appreciable in two

cats and, in three out of the 15 animals, fragmentation of the elastic laminae occurred in a small proportion of the more severely affected arteries. In only one instance was longitudinal muscle recognisable as a ring investing the lumen of the vessel. One other case was characterized by a mild proliferation of endothelial cells that was noted in a small number of arteries. Again, although normal vessels were always to be found, the hypertrophic process was fairly well distributed. In a number of instances, vacuolation of affected myofibrils as well as of the intima was evident and sub-endothelially the change appeared as a clear, fairly well demarcated area that encompassed the vascular lumen. Since the contents of the vacuoles did not respond to staining methods for the demonstration of mucopolysaccharide, glycogen, neutral fat and cholesterol, it was concluded that a form of hydropic degeneration was present.

In five of the animals peribronchial and peribronchiolar lymphocytic "cuffing" was prominent and, on four occasions, was accompanied by a similar lesion of perivascular situation. The latter cases showed further change of the lung substance, namely, infiltration of some bronchial and bronchiolar mucosae by lymphocytes and plasma cells associated with a degree of proliferation of the mucosaeand of hyperplasia of adjacent mucous glands together with focal accumulations of macrophages and lymphocytes and, occasionally, a few giant-cells. Restricted areas of bronchitis and bronchiolitis

characterized by the presence of eosinophils were also observed. In general, the pathology of the lung noted in those four animals bore a striking resemblance to that encountered in the cases of lungworm disease, but evidence of the presence of the parasite was completely lacking.

Grade 3.

As the third phase of the condition was reached, so the severity of the lesions increased. Slight intimal fibrosis (Fig. 22, p. 86) was present in all but one animal in which it was of more severe type (Fig. 23, p. 86) and fragmentation of the elastic laminae was common (Figs. 24 and 25, p. 87). Hypertrophy of the muscle of the bronchioles and the alveolar ducts, of varying severity in individual animals, was regularly apparent. In six out of the eight cats of the group longitudinal muscle, of wholly intimal location, was conspicuous and formed a fibro-muscular layer around the lumina of the vessels and was always associated with appreciable thickening of the circular muscle. In two cases, there was proliferation of endothelial cells which was, however, of irregular distribution. In five out of eight animals, peribronchial, peribronchiolar and perivascular lymphocytic reaction was evident although never prominent and two of the five cases showed foci of lymphocytes and macrophages together with a few giant-cells, which changes were fairly widely distributed throughout all lobes.

Figure 22. A muscular pulmonary artery showing hypertrophy and hyperplasia of the medial musculature associated with a minimal degree of intimal fibrosis.
Van Gieson. X480.

Figure 23. An example of the most severe type of intimal fibrosis observable in altered pulmonary arteries.
Masson. X320.

Fig. 22.

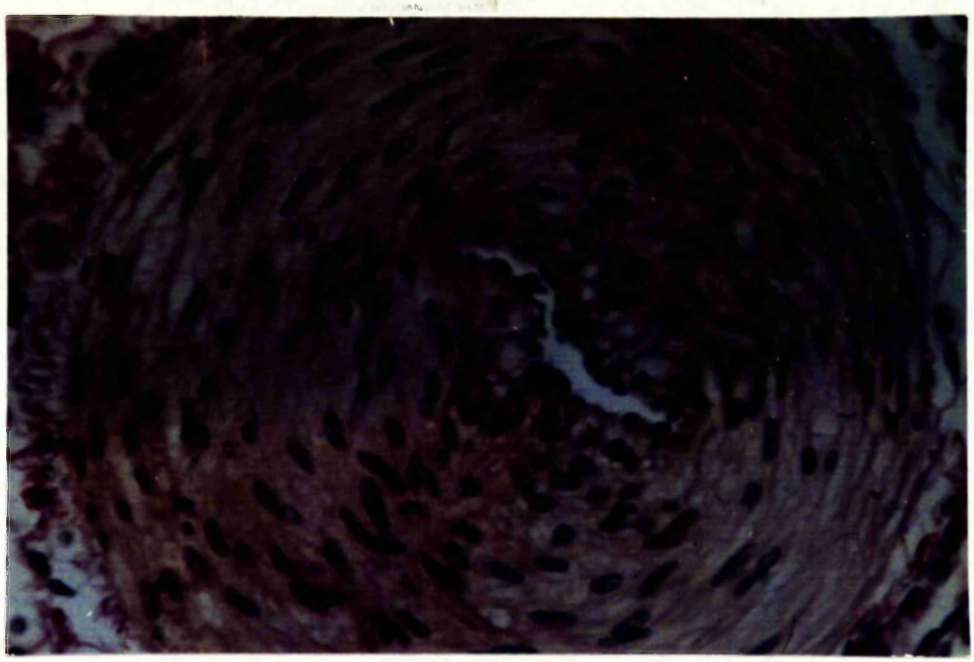


Fig. 23.

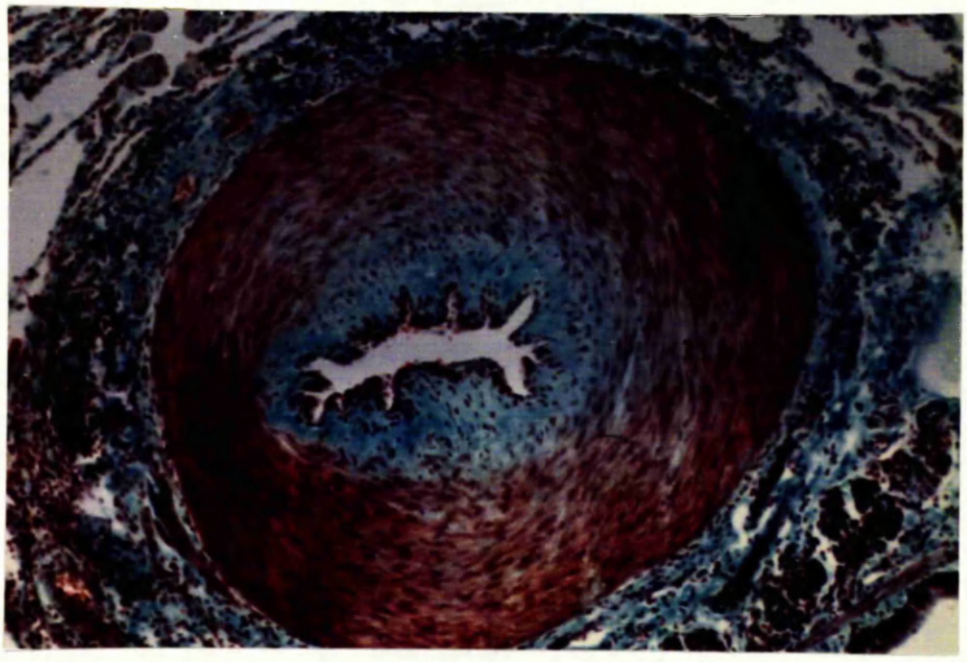


Figure 24. Fragmentation of the elastic laminae together with intimal longitudinal muscle in a markedly thickened pulmonary artery.
Lawson's elastic stain. X150.

Figure 25. The same section of lung as in Fig. 24 at a higher magnification, to show the reactions in greater detail.
Lawson's elastic stain. X330.

Fig. 24.

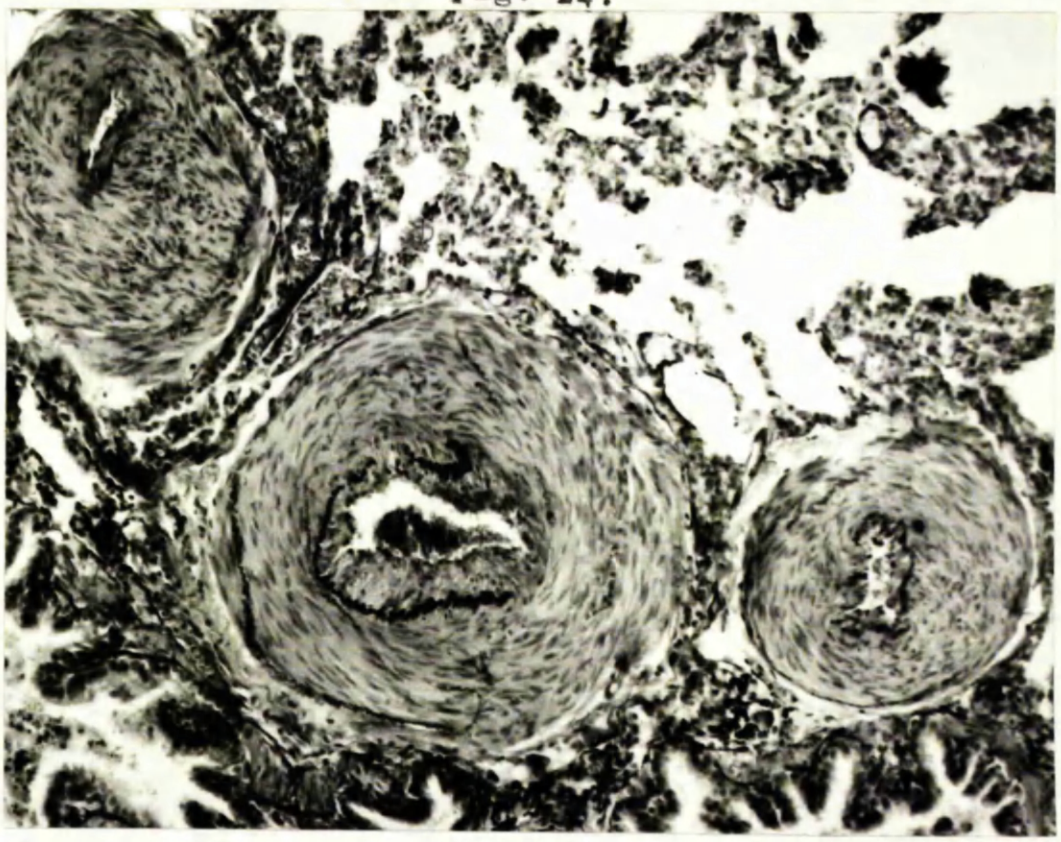
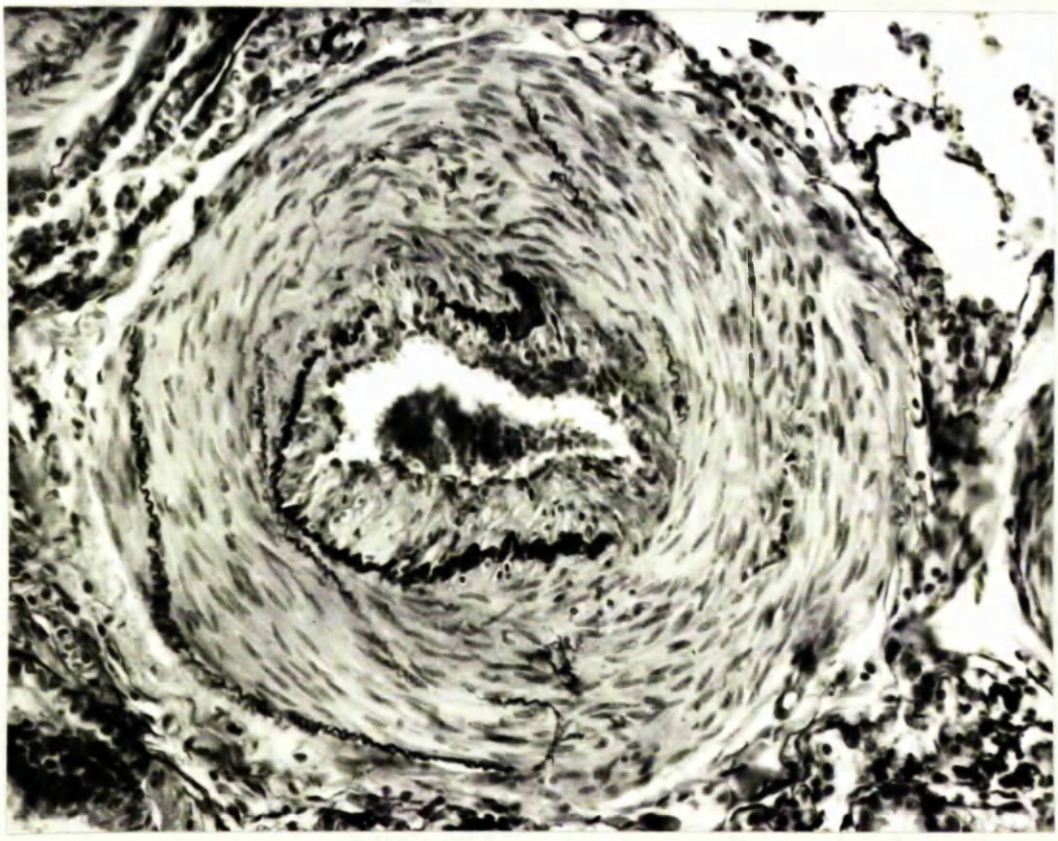


Fig. 25.



Vacuolation of the hypertrophied muscle was of greater degree than that of the previous grade and, in three out of the eight cats, sub-endothelial vacuolation was noticeable. The nature of the material of the vacuoles was not established.

The lesion did not affect all branches of the pulmonary artery to the same extent and, indeed, some vessels appeared normal.

Grade 4.

This penultimate grade of severity was associated with lesions similar to those seen in the preceding stage with a few additional features. The distribution of affected arteries was somewhat similar but the hypertrophic and hyperplastic processes were more marked and longitudinal muscle in an intimal position appeared in five out of six animals to give rise, in conjunction with the altered circular muscle, to considerable narrowing of the vascular lumen (Fig. 26, p. 89). Hypertrophy of the muscle of the walls of the bronchioles and alveolar ducts was prominent in all but one animal but endothelial proliferation occurred in only one instance. The elastic laminae were fragmented and had undergone partial or complete dissolution. Intimal fibrosis was of a pattern similar to that already described and was of minimal degree in all but one case. There was only one instance in which perivascular and peribronchial lymphocytic

Figure 26. A grossly hypertrophied pulmonary artery showing the formation of longitudinal muscle in the intima.

Haematoxylin and Eosin. X380.

Figure 27. A branch of the pulmonary artery manifesting considerable thickening of the wall and increased tortuosity.

Haematoxylin and Eosin. X150.

Fig. 26.

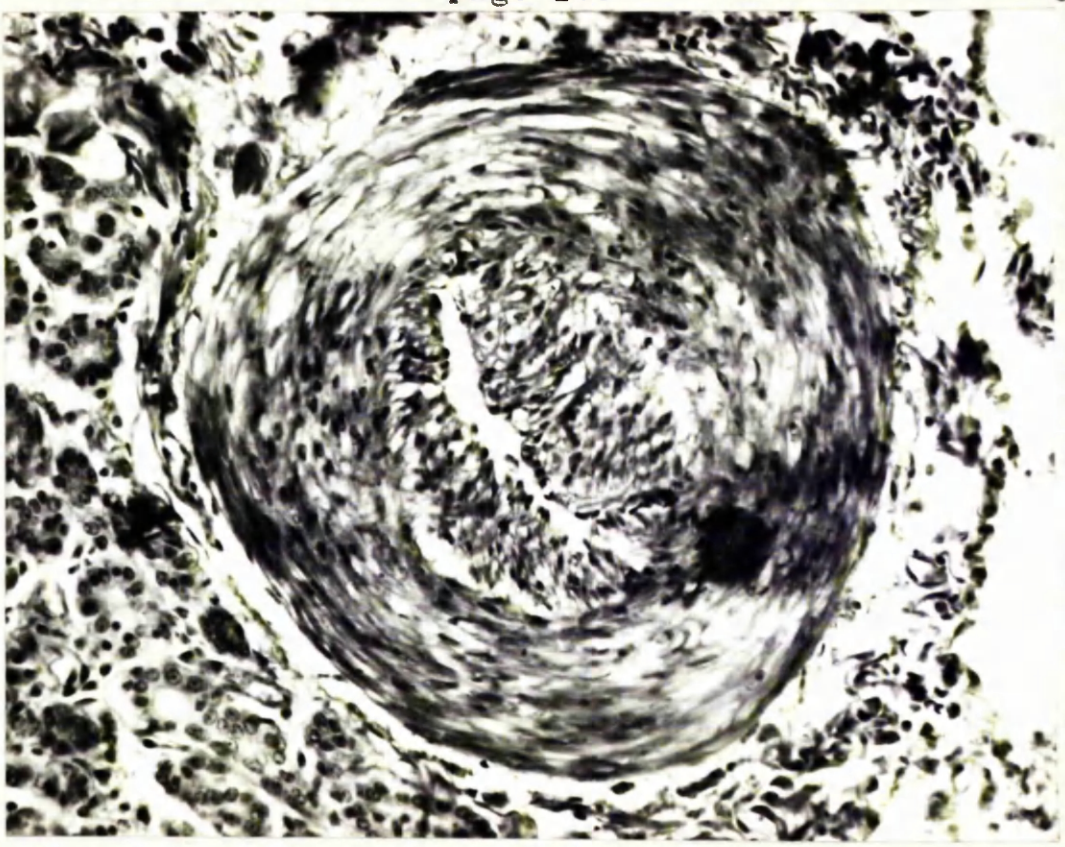
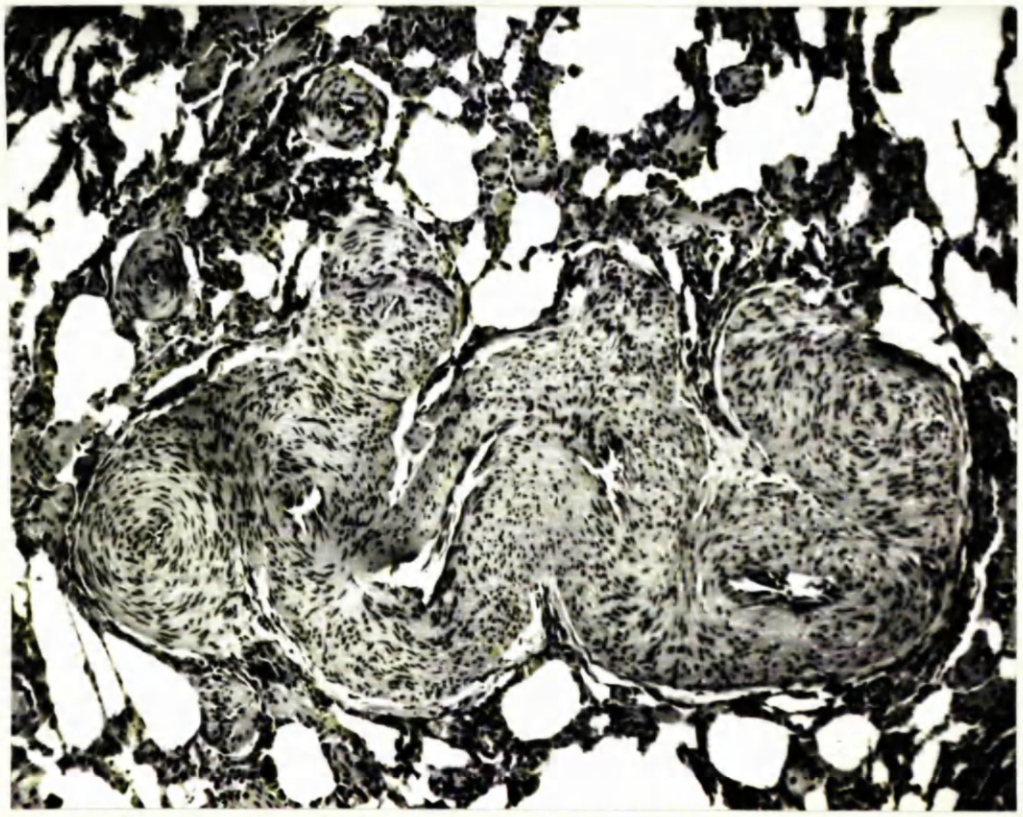


Fig. 27.



reaction was singularly outstanding.

Grade 5.

Into this last grade fell one animal which exhibited marked thickening of the arterial media associated with the presence of longitudinal muscle together with hypertrophy of the muscle of the bronchioles and alveolar ducts and a severe intimal fibrosis. Many of the arteries displayed considerable tortuosity (Fig. 27, p.89).

TABLE 18.

SYNOPSIS OF PATHOLOGICAL FINDINGS IN ANIMALS OF GROUP 2.

Grade of Lesion	Case No.	Age Group	Intimal Fibrosis	Fragmentation of Elastica	Longitudinal Muscle	Bronchiolar Muscle	Endothelial Proliferation	Perivascular "cuffing"	Peribronchial "cuffing"
1	6	K	-	-	-	-	-	-	-
	41	A	-	-	-	+	-	-	-
	63	O	-	-	-	-	-	-	-
	100	A	-	-	-	-	-	-	-
	177	A	-	-	-	+	-	-	-
	209	A	-	-	-	-	-	+	+
	233	Y.A.	-	-	-	-	-	-	-
	241	A	-	-	-	-	-	-	-
	273	A	-	-	-	+	-	-	-
	274	O	-	-	-	+	-	-	-
	335	A	-	-	-	+	-	-	-
	337	Y.A.	-	-	-	+	-	+	-
	360	A	-	-	-	+	-	-	-
	366	Y.A.	-	-	-	-	-	-	-
	395	Y.A.	-	-	-	+	-	+	-
	410	K	-	-	-	-	-	-	-
	411	K	-	-	-	+	-	+	+
	412	Y.A.	-	-	-	+	-	-	-

O = Old A = Adult Y.A. = Young Adult K = Kitten

TABLE 19.

SYNOPSIS OF PATHOLOGICAL FINDINGS IN ANIMALS OF GROUP 2.

Grade of Lesion	Case No.	Age Group	Intimal Fibrosis	Fragmentation of Elastica	Longitudinal Muscle	Bronchiolar Muscle	Endothelial Proliferation	Perivascular "cuffing"	Peribronchial "cuffing"
2	56	O	-	+	-	-	+	-	-
	88	O	Mintmal	-	-	+	-	-	-
	92	O	-	-	-	-	-	-	-
	120	A	-	-	-	+	-	-	-
	170	A	-	-	-	-	-	-	-
	226	A	-	-	-	-	-	-	-
	352	O	-	-	-	+	-	-	-
	373	O	Mintmal	+	+	+	-	+	+
	394	A	-	-	-	+	-	+	+
	409	A	-	-	-	+	-	+	+
	445	A	-	-	-	-	-	-	-
	456	Y.A.	-	-	-	+	-	-	-
	482	A	-	+	-	+	-	+	+
	485	A	-	-	-	+	-	-	-
	488	A	-	-	-	+	-	-	+

O = Old A = Adult Y.A. = Young Adult K = Kitten

TABLE 20.

SYNOPSIS OF PATHOLOGICAL FINDINGS IN ANIMALS OF GROUP 2.

Grade of Lesion	Case No.	Age Group	Intimal Fibrosis	Fragmentation of Elastica	Longitudinal Muscle	Bronchiolar Muscle	Endothelial Proliferation	Perivascular "cuffing"	Peribronchial "cuffing"
3	51	O	Minimal	+	+	+	-	-	-
	128	A	Minimal	+	+	+	-	+	+
	349	O	Minimal	+	+	+	+	+	+
	379	A	Minimal	+	+	+	-	+	+
	374	A	Severe	+	+	+	-	+	+
	425	A	Minimal	+	-	+	-	+	+
	426	Y.A.	Minimal	+	+	+	-	-	-
	459	A	Minimal	+	-	+	+	-	-
4	67	O	-	+	+	-	-	-	-
	248	O	Minimal	+	-	+	+	-	-
	329	O	Minimal	+	+	+	-	-	-
	344	A	Minimal	+	+	+	-	-	-
	438	Y.A.	Minimal	+	+	+	-	+	+
	466	O	Minimal	+	+	+	-	-	-
5	262	O	Severe	+	+	+	-	-	-

O = Old A = Adult Y.A. = Young Adult K = Kitten

3. INVESTIGATION OF ANIMALS WITH PULMONARY ARTERIAL LESIONS IN ASSOCIATION WITH VARIOUS DISEASES. (GROUP 3).

Tables 21 and 22 (p. 95) show the distribution and the severity of the pulmonary lesions according to age and associated morbid entities, respectively. Although the group was composed of more of the older animals, it will be noted that the severity of the lesions proved independent of either age or a particular complex of disease. In greater detail, Tables 11 to 14 (p. 41 to 45) present the variety of attendant pathological conditions which, here, may be summarized as follows: nephritis (5 cases), neoplasms (9 cases), other pulmonary conditions (8 cases) and enteritis (2 cases). Previously, it has been pointed out that such diverse pathological processes are difficult to relate causatively to the pulmonary arterial hypertrophy and hyperplasia, especially as they were found commonly to occur without any change in the pulmonary vasculature.

In respect of this group, clinical histories were of little value because they clearly referred to the concomitant disease rather than to the respiratory condition.

a. Morbid Anatomy.

Gross post-mortem findings were masked by the accompanying morbid state particularly in those cases in which the lungs were involved. In animals not affected by pulmonary disease, instances of severe hypertrophic

TABLE 21.

SEVERITY OF PULMONARY ARTERIAL LESIONS RELATED TO AGE IN ANIMALS OF GROUP 3.

Age-Group	Grade of Lesion				
	1	2	3	4	5
Old	4	7	3	1	1
Adult	2	2	2	0	1
Young Adult	1	0	1	0	0
Kittens	0	0	0	0	0
TOTAL	7	9	5	1	2

TABLE 22.

SEVERITY OF PULMONARY ARTERIAL LESIONS ENCOUNTERED IN VARIOUS DISEASES AFFLICTING ANIMALS OF GROUP 3.

Disease	Grade of Lesion				
	1	2	3	4	5
Lung Disorders	3	2	1	0	2
Nephritis	2	2	1	0	0
Neoplasms	2	3	3	1	0
Enteritis	0	2	0	0	0
TOTAL	7	9	5	1	2

arterial change were recognisable by the presence of thickened vessels, which latter were appreciable only on close examination and, often, by palpation of the cord-like arteries.

b. Histopathology.

Tables 23, 24 and 25 (p. 98 to 100) summarize the histopathological findings that were based, as before, on grading of the lesions into five groups of severity of the arterial change. In comparison with those shown by the group of disease-free animals, the results are essentially similar. Again, the arterial lesions were mainly focal in distribution but, in several cases, they were quite widespread. One animal showed advanced intimal calcification. Five cats presented marked perivascular, peribronchial and peribronchiolar lymphocytic reaction together with lymphocytic infiltration of the bronchial mucosa and small interstitial accumulations of macrophages and lymphocytes that contained a few giant-cells and a few eosinophil leucocytes. Vacuolation of hypertrophied muscle cells was common in lesions of grade 2 and upwards, but sub-endothelial vacuolation was noticeable in only one instance. Slight intimal fibrosis was encountered in the majority of the animals, except those of grade 1, but there were three occasions when the lesion was severe. In two cases of grade 2 and in all but one instance from grade 3 upwards,

longitudinal muscle was to be found in the intima in much the same distribution as already described. The changes in the elastic laminae and in the muscle of the bronchioles and of the alveolar ducts differed little from those previously noted.

Briefly, it may be stated that almost identical pulmonary arterial lesions were encountered in the animals displaying a variety of intercurrent disease and in those without any other morbid condition. It is suggested, therefore, that concomitant processes of disease had little, if any, relation to the pulmonary arterial lesions.

TABLE 23.

SYNOPSIS OF PATHOLOGICAL FINDINGS IN ANIMALS OF GROUP 3.

Grade of Lesion	Case No.	Age Group	Intimal Fibrosis	Fragmentation of Elastica	Longitudinal Muscle	Bronchiolar Muscle	Endothelial Proliferation	Perivascular "cuffing"	Peribronchial "cuffing"
1	5	O	-	-	-	-	-	-	-
	14	A	-	-	-	-	-	-	-
	44	Y.A.	-	-	-	+	-	-	-
	66	O	-	-	-	-	-	-	-
	114	O	-	-	-	+	-	-	-
	369	A	-	-	-	-	-	+	+
	379	O	-	-	-	+	-	-	-

O = Old A = Adult Y.A. = Young Adult

TABLE 24.

SYNOPSIS OF PATHOLOGICAL FINDINGS IN ANIMALS OF GROUP 3.

Grade of Lesion	Case No.	Age Group	Intimal Fibrosis	Fragmentation of Elastica	Longitudinal Muscle	Bronchiolar Muscle	Endothelial Proliferation	Perivascular "cuffing"	Peribronchial "cuffing"
2	70	O	Minimal	+	-	-	-	-	-
	83	O	-	-	-	-	-	-	-
	94	O	-	-	-	-	-	-	-
	97	O	-	-	-	+	-	-	-
	113	A	Severe	+	+	+	-	-	-
	136	O	Minimal	+	-	+	-	+	+
	162	O	Severe	+	+	+	-	-	-
	387	O	Minimal	+	-	+	-	-	-
	429	A	-	-	-	+	-	-	-

O = Old A = Adult

TABLE 25.

SYNOPSIS OF PATHOLOGICAL FINDINGS IN ANIMALS OF GROUP 3.

Grade of Lesion	Case No.	Age Group	Intimal Fibrosis	Fragmentation of Elastica	Longitudinal Muscle	Bronchiolar Muscle	Endothelial Proliferation	Perivascular "cuffing"	Peribronchial "cuffing"
3	16	O	Minimal	+	+	+	-	-	-
	28	O	Minimal	+	+	+	-	-	-
	222	Y.A.	Minimal	+	-	+	-	+	+
	419	A	Minimal	+	+	+	-	-	-
	435	A	Minimal	+	+	+	-	+	+
4	225	O	Severe	+	+	-	-	-	-
5	292	O	Minimal	+	+	+	-	-	-
	446	A	Minimal	+	+	+	-	+	+

O = Old A = Adult Y.A. = Young Adult

4. ASSOCIATION OF PULMONARY ARTERIAL HYPERTROPHY AND HYPERPLASIA WITH GENERALIZED HYPERTENSION.

a. Normal Mean Wall-to-Lumen Ratios of Myocardial and Renal Arteries of the Cat.

Since pulmonary hypertension may be a concomitant of a generalized hypertensive state, it was decided to re-investigate all the cases with special reference to the latter condition. To that end, examination of the myocardial and renal arteries was undertaken. As in the case of the pulmonary arteries, normal values had first to be established by the same methods as had been applied to the lungs. From the kidneys and myocardium of 21 of the normal cats ten arteries, cut at right angles to their course, were measured in the manner prescribed for the pulmonary arteries and the wall-to-lumen ratios ascertained.

Table 26 (p. 103) presents the mean values for the wall-to-lumen ratios obtained for the myocardial and renal vessels together with that calculated for the lungs, and the related standard deviations. From those figures it is apparent that the normal means are acceptable but that in the case of both the myocardium and kidneys such values are sufficiently greater than those for the lungs to indicate a significant difference between the wall-to-lumen ratios of the pulmonary and the systemic vessels. Table 27 (p. 103) shows the comparison of the three means according to the

formula $\sqrt{\frac{aA^2}{nA} + \frac{aB^2}{nB}}$

where a = the standard deviation, n = the number of individuals and A and B are the groups under comparison (Hill, 1961).

The results betoken a significant difference between the means of the pulmonary arteries and those of the vessels of the kidneys and myocardium. Collation of the figures pertaining to the kidneys and the myocardium (Table 28, p.104) does not reveal any significant difference to exist between the means of the wall-to-lumen ratios of those organs. It appears, therefore, that in the cat the pulmonary vessels differ from the systemic ones by reason of a smaller wall-to-lumen ratio. In order that a reasonable margin of safety attach to those findings, a mean wall-to-lumen ratio of 0.6:1, or above, was taken to be abnormal for the arteries of the kidneys and a ratio of 0.5:1 was similarly taken in the case of the myocardium. It is to be noted that both figures are twice the lowest mean values that were recorded for each organ and had been proved to differ significantly from the normal means.

TABLE 26.

NORMAL MEAN VALUES OF WALL-TO-LUMEN RATIOS TOGETHER WITH STANDARD DEVIATIONS OF ARTERIES OF THE MYOCARDIUM, LUNGS AND KIDNEYS.

Organ	Mean Wall-to-Lumen Ratio	S. D.	± 1 S.D.	± 2 S.D.	± 3 S.D.
Myocardium	0.2032	0.0963	80.9%	95.2%	100%
Lungs	0.1735	0.0716	91.0%	100.0%	-
Kidneys	0.3237	0.0629	91.0%	100.0%	-

S.D. = STANDARD DEVIATION.

TABLE 27.

COMPARISON OF NORMAL ARTERIAL WALL-TO-LUMEN RATIOS.

1. PULMONARY WITH MYOCARDIAL AND RENAL ARTERIES.

Organ	Mean	M.D.	S.E.
Lungs	0.1735	-	-
Myocardium	0.2032	0.1000	0.0293
Kidneys	0.3237	0.1400	0.0240

M.D. = DIFFERENCE OF MEANS.

S.E. = STANDARD ERROR.

TABLE 29.

COMPARISON OF NORMAL WALL-TO-LUMEN RATIOS.

2. RENAL AND MYOCARDIAL ARTERIES.

Organ	Mean	M.D.	S.E.
Kidneys	0.3237	-	-
Myocardium	0.2958	0.0400	0.0249

M.D. = DIFFERENCE OF MEANS

S.E. = STANDARD ERROR.

b. Mean Wall-to-Lumen Ratios of Myocardial and Renal Arteries in Animals of Groups 1, 2 and 3.

Result of Group 1.

The arteries of the kidneys and myocardium of the 17 cases of lungworm infestation were examined and Table 29 (p. 106) presents the relevant findings. Of the 17 animals, one had to be rejected because of lack of suitable microscopic sections of the tissues required. Of the remaining 16 cats, two (Nos. 271 and 283) appeared to have suffered from hypertension of more generalized type which, perhaps not altogether co-incidentally, was associated with lungworm infestation of a widespread and severe nature. One cat (No. 96) exhibited a degree of renal arterial hypertension but without any myocardial change, while another (No. 47) was found to have a fairly high myocardial mean wall-to-lumen ratio that was unaccompanied by any renal aberration. Of the 12 residual animals, all presented hypertensive changes in the pulmonary arteries alone.

It seems reasonable to conclude, therefore, that in the majority of animals suffering from lungworm disease the pulmonary arterial changes arose independently of a generalized hypertensive state.

TABLE 20.

MEAN WALL-TO-LUMEN RATIOS OF RENAL, MYOCARDIAL AND PULMONARY ARTERIES OF CATS WITH LUNGWORM DISEASE.

CASE NUMBER	AGE GROUP	LUNGS	MYOCARDIUM	KIDNEYS
18	Kitten	0.5538	0.3235	0.3559
21	Kitten	1.2690	0.3531	0.4573
40	Old	0.9250	0.4640	0.3868
47	Old	0.9335	0.5005	0.3100
49	Old	1.9315	0.2406	0.3375
72	Kitten	0.7169	0.3205	0.4560
96	Adult	0.5510	0.3250	1.0060
187	Adult	1.1687	0.4730	0.2870
235	Old	2.1011	-	-
271	Adult	2.6250	0.5602	0.7540
282	Young Adult	0.4020	0.3405	0.3560
283	Young Adult	4.8900	0.5050	0.7410
285	Young Adult	5.1780	0.2400	0.2900
299	Young Adult	2.1940	0.2417	0.2962
440	Adult	2.4909	0.2550	0.5141
464	Adult	1.0945	0.3005	0.5207
471	Young Adult	0.6126	0.3303	0.4556

Results of Group 2.

Of 48 animals with pulmonary arterial lesions alone, only 8 (16.6%) proved to suffer from a degree of myocardial and/or renal arterial hypertrophy (Table 30, p. 109). If values for the myocardial and renal mean wall-to-lumen ratios of 0.5:1 and 0.6:1, respectively, be rigidly applied, only two animals would appear to have been afflicted by generalized hypertension. But, if the figures be less strictly interpreted because of the presence of border-line cases, all eight animals would seem to have suffered from some degree of the generalized condition. Both histological and metrical evidence failed to establish a close association between the severity of the arterial change in the lung and that in either the myocardium or the kidney in the majority of the animals.

Results of Group 3.

Of 24 animals which suffered from intercurrent disease, only 5 (20.8%) were considered to show changes indicative of generalized hypertension (Table 31, p. 109). On a basis of an almost normal rating for the myocardial vessels, three of the animals may have been omitted were it not that marked alteration of the renal vessels, allied with elevated wall-to-lumen ratios in the lung, suggested that a generalized hypertensive state may have prevailed during life. The severity of either the myocardial or the renal change was

not referable to that of the pulmonary lesion nor was any particular process of disease involved. That there were three neoplasms of entirely different nature and distribution and that only one of five cases of nephritis was represented served further to suggest that the concomitant diseases were of little consequence in the aetiology of the pulmonary arterial lesion.

c. Conclusion.

From the above findings, it was concluded that the vast majority of cats suffering from pulmonary arterial hypertrophy and hyperplasia did not concurrently manifest a generalized hypertensive state.

TABLE 30.

MEAN WALL-TO-LUMEN RATIOS OF PULMONARY, RENAL AND MYOCARDIAL ARTERIES IN ANIMALS OF GROUP 2.

CASE NUMBER	LUNGS	KIDNEYS	MYOCARDIUM
413	0.4970	0.7972	0.4310
228	0.5536	0.5804	0.4570
352	0.7747	0.5075	0.5620
409	0.6041	0.6475	0.6459
445	0.5539	1.1111	0.3750
458	0.5707	0.6734	0.5997
349	1.3440	0.9459	0.4111
370	1.3784	0.7211	0.5713

TABLE 31.

MEAN WALL-TO-LUMEN RATIOS OF PULMONARY, RENAL AND MYOCARDIAL ARTERIES IN ANIMALS OF GROUP 3.

CASE NUMBER	LUNGS	KIDNEYS	MYOCARDIUM
379	0.4566	1.4000	0.4638
429	0.4935	1.3333	0.3777
387	0.9038	1.5166	0.2510
455	1.6270	1.3670	0.4951
225	2.3470	0.6069	0.3333

5. DISCUSSION.

If cats suffering from pulmonary arterial lesions alone, be compared with those afflicted also by lungworm disease or by various other processes of disease, it emerges that the pulmonary pathology is essentially similar in all three groups of animals. Grade 1 of the condition was characterized by simple hypertrophy of the arterial media which, in grades 2 and 3 was further complicated by muscular hyperplasia and, from grade 3 onwards, also by the production of longitudinal muscle as well as by exaggeration of the changes in the circular muscle. In animals of all three groups, vacuolation of the hypertrophied muscle was observable while intimal fibrosis was commonly of minimal degree although some members of each group manifested a more severe reaction. Fragmentation and dissolution of the elastic laminae were fairly frequent. Proliferation of endothelial cells together with cellular infiltration of the endothelium and the sub-endothelial tissues was prominent and occurred to quite greatest degree in animals affected by lungworm disease. Focal distribution of the arterial lesions and widespread hypertrophy of the smooth muscle of the bronchioles and of the alveolar ducts was common. Peribronchial, peri-bronchiolar and perivascular lymphocytic reaction was more often to be seen in association with lungworm infestation although it appeared also in 17 of the 72 animals not

apparently affected by the latter condition.

The similarity of the lesions strongly suggested that a common aetiological factor was at work.

Harris and Heath (1962) listed the main causes of pulmonary hypertension of man as follows:

1. Enhanced pulmonary blood-flow occasioned by a large left-to-right shunt into the systemic venous stream before the latter enters the right ventricle, e.g. all forms of inter-atrial communication.
2. Passage from the left ventricle or the aorta into the right ventricle or the pulmonary artery, e.g. patent ductus arteriosus.
3. Marked and persistent increase of left atrial pressure leading to rise of pressure in the pulmonary artery, e.g. in mitral atenosis.
4. Recurrent pulmonary embolism.
5. Severe forms of emphysema, bronchiectasis and pulmonary fibrosis.
6. Impaired diffusion of oxygen across the alveolar capillary membrane, as happens in occupational chest diseases.

Post-mortem examination of the cats failed to reveal evidence of the presence of any of the above conditions, which finding agrees with the observations of Rubarth (1940) and Dahme (1960) both of whom did not encounter any cardiac abnormality. Furthermore, the arterial lesions of the cats were not of the degree of severity that was described for man

by Harris and Heath (1962). Although the early stage of medial hypertrophy was essentially similar in both man and the cat, the feline lesion did not manifest, to any extent, either the intimal proliferation or the fibrosis or, in any case, the final stages of arterial dilatation and necrotizing arteritis that occur so commonly in man. In human-beings the latter changes were considered to be a concomitant of very high arterial pressure and the reason why they did not occur in the cat would appear to be associated with the focal distribution of the arterial lesions.

In the majority of the cats the pulmonary arterial changes were not accompanied by hypertensive alterations in the kidneys or the myocardium. Campbell (1927) reported pulmonary arterial hypertrophy and hyperplasia in two cats which suffered from anoxia while Ettinger (1932) recorded a similar lesion, in a number of cats, following the injection of the dye, Janus green. The lesions which were described by both authors appeared to be similar to those encountered in the affected animals of the present survey. That fact, allied with the knowledge of the natural incidence of the condition, leads to the suggestion that the animals had been previously suffering from the arterial abnormality.

Marcato (1940) and Martin (1959) considered that the pulmonary arteriopathy represented a senile change. The results of the above survey, however, showed that the condition occurred in cats of all age-groups and that the

severity of the lesions did not increase with advancing years so that the change is not one that is ascribable to senility. Nor was there any suggestion of enhanced incidence in either sex.

Scratchard and Wright (1961) hypothesized that intestinal parasites en route to the lungs were causatively involved and based their claim on the work of Harrison (1948), of Muirhead and Montgomery (1951) and of Barnard (1953 and 1957). Those workers had demonstrated that pulmonary arteriosclerotic changes were inducible in rabbits in response to injection of either fragments of blood clots or bullae of oxygen, nitrogen or air. Generally speaking, the resultant alterations consisted of partially organised adherent thrombi that were found in the larger arteries. In smaller arteries and arterioles, varying degrees of fibro-elastic hyperplasia of the intima were recognized together with proliferation of the endothelium and occasional fibrosis of the medial coat.

The pulmonary arterial lesions of lungworm disease are difficult to explain on the basis of thrombo-embolism since the outstanding change is mainly medial in distribution and is accompanied by intimal lesions that are of lesser import. Again, as third-stage larvae ingested by the cat usually migrate to the lungs within a few hours, frequent waves of emboli are unlikely to be produced and finally, evidence of the presence of parasitic emboli within pulmonary vessels

was never found.

It seems improbable that the dependent position of the lungs of the cat alone leads to the arterial disorder, as was suggested by Olcott et al. (1946). If that were true the lesion ought to have occurred in all cats, and that certainly was not so.

Neumann et al. (1942) and Kell et al. (1956) reported pulmonary arterial lesions in cats in which stimulation of the cerebral centres had been effected by various means. In respect of a control group of 28 animals, the latter authors reported that minimal change of the media was present in only four of the cats, which finding was considered to be of little significance and to justify the conclusion that the spontaneous condition was rare. According to the same authors, of 19 cats treated with metrazol, 15 showed lesions of the pulmonary arteries. Such a proportion of afflicted animals appears to be of some significance since, approximately, seven cats are likely to become affected if an incidence of 36.0% and 34.7% in the cat population given by Scratchard and Wright (1961) and by the author of this thesis, respectively, are taken into consideration. In another group of 10 cats subjected to other forms of vasomotor stimulation, Kell et al. (1956) found eight animals to be similarly affected, that was again too great an incidence to have been attributable to chance.

With the singular exception of lungworm infestation, the pulmonary arterial lesion was not referable to any particular disease. In regard to the role of lungworm in the production of the arterial abnormality, it is remarkable that investigators, such as Scratchard and Wright (1961), Olcott et al. (1946) and Marcato (1940) did not find any evidence of the parasitic state in the 111, 150 and 30 cats, respectively, which they examined. That experience is all the more surprising in relation to the incidence of infestation by Aelurostrongylus abstrusus reported to be 1.0% in Copenhagen, 5.0% in Utrecht, 26.0% in Palestine, 20.0% in Britain and 6.6% in the West of Scotland. As revealed by the present survey, 19% of cats suffering from the pulmonary arterial disorder were found to have lungworm disease and not one case of lungworm infestation failed to show the arterial changes. Pritchett (1938), Blaisdell (1952), McKenzie (1960) and Jubb and Kennedy (1963) are authors who have associated pulmonary arterial hypertrophy and hyperplasia with parasitic infestation of the cat.

It is still uncertain whether the pulmonary arterial abnormalities are a direct result of infection by the lungworm or are connected incidentally with the presence of the parasite. The former view is strongly supported by circumstantial evidence, however, and affords a feasible explanation for the high incidence of spontaneous pulmonary arterial hypertrophy and hyperplasia in the cat.

6. CONCLUSION.

It has been shown that 34.7% of cats suffer from spontaneous pulmonary arterial hypertrophy and hyperplasia together with hypertrophy of the smooth muscle of the bronchioles and alveolar ducts. A relationship has not been proved to exist between that condition and the age or sex of the animals or with any pathological process other than that of infestation by the lungworm Aelurostrongylus abstrusus. Search of the relevant literature, however, has revealed that a similar arterial change has been produced by stimulation of the vasomotor centres of the cerebral cortex either by galvanic methods or by appropriate chemical substances.

It is proposed, therefore, to devote the next part of this thesis to experimental reproduction of the arterial lesions, in consequence firstly, of infestation by the lungworm and, secondly, by the administration of the drug, metrazol, which is known to excite the vasomotor centres of the brain.

PART FOUR.

THE EXPERIMENTAL PRODUCTION OF PULMONARY ARTERIAL LESIONS IN THE CAT.

A. EXPERIMENTAL LUNGWORM DISEASE.

1. THE PARASITE, ITS LIFE-CYCLE AND ITS HOSTS.

   a. Stages of the Parasite.
   b. Intermediate and Auxiliary Hosts.
   c. Development of Larvae in Intermediate Hosts.
   d. Infection of the Mammalian Host.

2. THE EXPERIMENTAL PRODUCTION OF LUNGWORM INFESTATION IN THE CAT.

   a. Care, Cultivation and Infection of the Intermediate Host.
   b. Experimental Infestation of the Mammalian Host by the Parasite.
   c. Methods of Examination of the Infested Host.

3. RESULTS OF THE EXPERIMENTAL INFESTATION.

   a. Clinical Findings.
   b. Haematological Results.
   c. Descriptive Pathology of the Disease.
   d. Discussion.
   e. Conclusion.

B. EXPERIMENTAL VASOMOTOR STIMULATION.

1. THE PRODUCTION OF PULMONARY ARTERIAL LESIONS BY THE USE OF METRAZOL.

   a. A Review of the Literature
   b. Materials and Methods.
   c. Results of the Administration of the Drug.
      (1) Morbid Anatomy.
      (2) Histopathology.
   d. Discussion.
   e. Conclusion.

C. FINAL DISCUSSION.

D. FINAL CONCLUSION.

E. BIBLIOGRAPHY.

A. EXPERIMENTAL LUNGWORM DISEASE.

1. THE PARASITE, ITS LIFE-CYCLE AND ITS HOSTS.

a. Stages of the Parasite.

While some reference has been already made to Aelurostrongylus abstrusus, it is now necessary to elaborate on the parasite and its life-cycle.

The adult male is, on average, 5.2 mm. long and 0.07 mm. broad. Eggs are laid by the female, which latter measures 9.3 mm. in length by 0.1 mm. in breadth, and each ovum is a delicate structure with a clear protective membrane within which all stages of segmentation, from two cells to fully formed larvae, may be seen.

Unfixed FIRST-STAGE larvae from the faeces of the cat were found to measure 0.36 mm. long by 0.018 to 0.02 mm. broad (MacKerras, 1957) and are recognisable by their J-shaped form together with a ventrally turned tail which bears a distinct double notch. The larvae are eliminated in the faeces of the cat and are then taken up by an intermediate host, the precise nature of which has been the subject of some controversy.

Outside the body, the larvae may persist for at least 11 days according to Cameron (1927) and for 18 days according to Fry and Stewart (1932). The latter authors found that, in teased lung maintained at 20° C., the survival time was only two days while out-of-doors in January it was five days. Hobmaier and Hobmaier (1935a) kept larvae alive in water at

room temperature for five weeks. Blaisdell (1952) sustained larvae for 11 days in tap-water at 37°C. and for 26 to 43 days in cat-serum that contained antibiotic. The same author found larvae to survive in tap-water for 34 days at room temperature, for 12 to 13 days at 4°C. and for five days at -8°C. When faeces were allowed to dry at room temperature, all the larvae were killed with the exception of a few at the centre of the mass. Blaisdell (1952) concluded that the larval forms were likely to persist within a thermal range of 19°C. to 43°C. inasmuch as larvae were still active at the former temperature and, at the latter, a few sluggishly motile larvae were appreciable. A temperature of 52°C. was found by Cameron (1927) to be larvicidal as was freezing, although the latter was contradicted by Fry and Stewart (1932) as well as by Blaisdell (1952).

b. Intermediate and Auxiliary Hosts.

According to Cameron (1927), first-stage larvae enter mice to encyst in muscle and sub-cutaneous tissues. The mouse becomesinfective for the cat after about three weeks and may remain so for, at least, one year. As a result of eating an affected mouse, the cat is infected and within it the larvae are liberated to develop into mature worms which are present in the lungs in six weeks. Experiments by Cameron (1927), based on the feeding of infected mice to cats, were successful but passage from cat to cat was not achieved.

Hobmaier and Hobmaier (1935a) repeated the investigation of Cameron but were unable in a series of four experiments to infect mice. Similarly unsuccessful were Baudet (1933), Gerichter (1949), Blaisdell (1952) and MacKerras (1957). However, both Hobmaier and Hobmaier (1935b) and MacKerras (1957) proved that mice may act as auxiliary hosts inasmuch as third-stage larvae introduced into mice encyst and so may remain infective for the cat for some time. Hobmaier and Hobmaier (1935b), after unsuccessful attempts to infect a large variety of vertebrates and insects with first-stage larvae of Aelurostrongylus abstrusus, finally achieved positive results by the use of molluscs. A diversity of slugs and snails proved serviceable but results were found to vary among different species since in some molluscs third-stage larvae developed to considerable number but in others were produced scarcely, if at all, despite heavy infestation. Snails were superior to slugs, in which latter the final numbers of third-stage larvae was always restricted, the time required for their development varied and the span of larval life appeared to be shortened. The most suitable species was Epiphragmophora followed, in order of utility, by Helminthocypta, Helix and Agriolimax.

Gerichter (1949) experimentally infected a large variety of molluscs, of which Helicella, Monacha and Agriolimax were the intermediate hosts of choice.

Blaisdell (1952) made use of seven types of snail and

three types of slug and found that all were efficient intermediate hosts. From one slug of the Limax species 2,500 larvae were recovered over a period of 25 days.

Hobmaier and Hobmaier (1935b) demonstrated that animals including frogs, toads, lizards, snakes, birds (such as sparrows, ducklings and chickens) and small mammals (rats and mice) may act as AUXILIARY HOSTS should they be infected by third-stage larvae. Observations revealed the larvae to be alive after 100 days in frogs, to be degenerate after one month in rats and mice and to be dead after 11 weeks in dogs and that, in all those instances, the larvae occurred as small cyst-like structures located mainly around the alimentary tract. Since some of those hosts are more acceptable as food to cats, they probably play a more important part in the spread of the condition than do molluscs.

c. Development of Larvae in Intermediate Hosts.

According to Hobmaier and Hobmaier (1934) first-stage larvae in contact with molluscs bury themselves in the furrows of the sole and a few hours later may be seen to enter the adjacent epithelial lining whence they migrate into the muscular and connective tissues of the foot. Such invasion is facilitated by the pores of the pedal glands and may take place over the entire area of the plantar furrows although, when they are present,

longitudinal sulci are also favourable sites of entry. Within the mollusc, two moults take place and development to the second stage is complete in, approximately, 11 days after infection. That stage lasts for four days (Gerichter, 1949) and is followed by up to two days of quiescence before third-stage infective larvae evolve. Under optimal conditions, the whole process of intra-molluscan development takes 18 days, measured from the time of infection. Hobmaier and Hobmaier (1935a) gave approximately 10 days as necessary for the first moult and five to six weeks for the emergence of infective larvae while MacKerras (1957) suggested that the first moult occurred at six days and the second at nine days after infection and that infective larvae were forthcoming in about 18 days. The differences in the time of development are probably referable to the diverse species of molluscs employed as well as to variation in seasonal factors. Further maturation of larvae does not occur in the molluscs but viable forms were reported by Hobmaier and Hobmaier (1935a) to have been recovered after six months from species of Epiphragmophora and Helix although, by that time, larvae had disappeared from, or were found to be extinct in, other molluscan hosts. Gerichter (1949) and Blaisdell (1952) obtained living third-stage larvae at the end of 17 and 4½ months, respectively.

Gerichter (1949) reported that the optimal temperature for the development of larvae in molluscs was 30°C. and that,

even in the best of intermediate hosts, larval growth declined with fall of temperature until, at 8°C., it had completely ceased. In infected molluscs maintained at a temperature of 4°C. to 8°C., larval maturation was suspended for a period of four months but was resumed when the temperature was again raised. Blaisdell (1952) stated that larvae grew more rapidly in snails kept at room temperature and that 14 days were required for the production of infective larvae whereas at a temperature of 12°C. to 15°C. a period of 36 days was necessary for maturation.

d. Infection of the Mammalian Host.

The cat becomes infected after it has eaten either an auxiliary host or it has consumed a mollusc which has been infested by first-stage Aelurostrongylus larvae. Infective third-stage larvae are liberated into the upper alimentary tract of the cat as a consequence of the mechanical process of chewing together with the effect of gastric ferments. The larvae are actively motile and enter the mucosa and underlying muscularis of the alimentary tract within one day after infection by which time, too, some larvae may be found in the lungs. Localization of larvae results in the formation of small nodules that occur in the omentum and, occasionally, the mesentery and the peri-oesophageal loose tissues where, however, progress to adulthood does not take place. Hobmaier and Hobmaier (1935b) considered that

localization was a result of forced feeding of larvae since, under natural conditions, cats often vomit and re-ingest their food several times, which habit, in conjunction with the careful chewing characteristic of the species, allows ample opportunity for the release of larvae and their subsequent passage through the alimentary wall. Blaisdell (1952) reported that larvae penetrate the stomach wall within three hours after infection and pass via the lymphatics to the lungs. She failed to isolate any larvae from the liver, peritoneal cavity, urine or blood 18 hours after infection.

When larvae reach the lungs, they remain dormant for a time but, by the fifth or the sixth day after infection, fourth-stage larvae emerge and are followed, up to five days later, by fifth and final stage larvae, after which time young adults are to be found. Both larvae and adults inhabit the lung substance, where sexual maturity is reached by the fourth week, and thereafter eggs in various stages of development occur throughout the lung substance. First-stage larvae are detectable in the faeces from 35 to 39 days following infection, presumably, after they have been coughed up and swallowed by the cat. On the other hand, Blaisdell (1952) found it difficult to discover larvae in swabs taken from the mouth, pharynx or oesophagus but succeeded in recovering them from the trachea of anaesthetized cats.

Adult worms may persist in the lungs for a considerable time and the foregoing author cited two years as an extreme example of that survival. It is now generally accepted that, in the majority of cases, the production of eggs and larvae ceases in from 8 to 13 weeks. Blaisdell (1952), however, declared that there was an inactive phase as well as an active stage of the disease and that, during the former, larvae were absent from the faeces, and eggs and larvae were missing from the lung, despite the fact that adult worms were still present in the latter organ. The female forms, however, did not have any eggs in the reproductive tract, which finding was considered to be the result of an immunological response on the part of the host. The same author also found that, if the resistance of the host was lowered, e.g. by feeding a restricted diet, the infection was exacerbated whereupon ova and larvae were again produced. In the case of eight out of sixteen animals which had recovered from a primary infection, re-infestation was unsuccessful as were also attempts to produce a state of artificial immunity by the use of first-stage larvae.

2. THE EXPERIMENTAL PRODUCTION OF LUNGWORM INFESTATION IN THE CAT.

a. Care, Cultivation and Infection of the Intermediate Host.

Snails of the species, Helix aspersa were collected and kept in the laboratory at room temperature for several months throughout the autumn and winter. They were accommodated in plastic bins, 12" by 9" x 6" deep, over the bottom of which was placed a layer of coarse gravel covered by a mixture of chalk, soil, decaying leaves and vegetable matter and pieces of rotting wood. The snails were confined to the bin by means of wire-gauze. The soil was kept moist, the snails were fed on cabbage alone for a period of five months during which time they appeared healthy, resisted fluctuations in temperature and even produced large numbers of eggs. According to Blaisdell (1952), the likelihood of collecting naturally infected snails is remote since, in the course of examination of a large number of molluscs, she never found third-stage larvae.

Since it is one of the larger species of snails, Helix aspersa is eminently suitable for studies on infection. From a cat severely infested by Aelurostrongylus abstrusus, material was obtained in the form of first-stage larvae which were collected after the infected lungs had been macerated and teased in water. The larvae were allowed

Figure 28. Snails (*Helix aspersa*) along with a sixpenny bit for comparison of size.

Fig. 28.

to sediment and the supernatant fluid was decanted to leave a deposit that proved to be rich in those immature forms.

In all, 24 large snails of the species, Helix, were individually infected with recovered larvae which were deposited by means of a Pasteur pipette into the shell aperture. Additionally, the snails were placed in a covered dish containing larvae-bearing fluid and allowed to stay there for several hours, which treatment did not appear to have any adverse effect. As has been already stated, development to third-stage larvae takes 14 to 18 days under optimal conditions and, since Helix aspersa was recommended as a favourable host by Hobmaier and Hobmaier (1935a) and was kept at room temperature, maturation was thought likely to have occurred in that time, but, to make certain, the snails were not fed to cats until at least 28 days after exposure to infection.

b. Experimental Infestation of the Mammalian Host by the Parasite.

Studies on transmission were pursued in 12 kittens, all of which had been born in the animal house and were used for experiment when they had reached the age of 12 weeks and were of average weight, 650 grammes. Other six kittens, of similar age and weight, were kept under identical conditions to provide control material. The infected snails were removed from their shells and cut into small pieces

which were intimately mixed with small amounts of a proprietary cat food, and fed in equal quantity to the 12 experimental kittens on two occasions. The animals readily ate the mixture but within ten minutes almost all of them became sick although some of the regurgitated material was later eaten. At the second feeding a smaller amount of molluscan material was offered and sickness did not ensue. Blaisdell (1952) found difficulty in persuading cats to accept mollusc-containing food which often caused vomiting. She attributed the latter sickness to the irritative effect exerted by the larvae as they invaded the gastric wall since cats fed free larvae became ill after the same lapse of time as those given molluscan material. In respect of the present experiment, it remains uncertain whether the molluscan material or the larvae were accountable for the emesis and, after the initial vomiting, none of the cats exhibited any other signs of illness. The main disadvantages of the foregoing method of feeding are (a) that the infecting dose cannot be accurately measured and (b) that evidence of individual infection is difficult to establish.

c. Methods of Examination of the Infested Host.

Development of third-stage larvae to adulthood, with subsequent production of eggs and larvae and ultimate appearance of the latter in the faeces, is generally agreed to take 35 to 39 days, so that early infection is detectable

only by means of autopsical and histopathological examinations. In order that initial reactions as well as the pathogenesis of the condition might be ascertained, over a period of six months, one infected cat was sacrificed each fortnight and one control cat was killed monthly. To ensure that all of the animals had been successfully infested, the faeces of each experimental cat, excepting the first two, were examined for the presence of first-stage larvae. For that purpose a small amount of faeces was mixed with water and left overnight at room temperature to allow the larvae to emerge before the extract was centrifuged and the resultant deposit examined microscopically. The clinical progress of each animal was noted and, in due time, euthanasia was effected by intra-peritoneal administration of pentothal. From the unconscious cat a sample of blood was taken and subjected to the following procedures: total and differential white cell count, estimation of packed cell volume and erythrocyte sedimentation rate as well as determination of haemoglobin concentration by means of the methods that have been described in Part 2. Bone-marrow preparations were made and stained by the method of Jenner-Giemsa. Immediately after death, the lungs and other tissues were removed and grossly examined before they were fixed, embedded and cut into sections which were stained by the methods already detailed in Parts 1 and 2 of this work.

3. RESULTS OF THE EXPERIMENTAL INFESTATION.

a. Clinical Findings.

Increased rate of respiration was noted in only one of the experimental animals but, from the eighth week after infection onwards, the majority came to be affected by coughing which was exacerbated by handling. Appetite remained good while the cats were lively and in fair bodily condition. It is difficult, however, to assess the precise clinical import of lung disease in caged animals which are permitted little movement and are not subject to undue stress.

b. Haematological Results.

The main haematological findings have been recorded in Table 32 (p.162) and will be later discussed along with the pathological findings that were encountered at each stage of the experimental disease.

c. Descriptive Pathology of the Disease.

The results of examination of cats killed at fortnightly intervals are detailed below.

At Two Weeks after Infection.

Morbid Anatomy.

The lungs appeared normal but closer examination revealed the presence of minute,whitish lesions that occurred in appreciable numbers throughout all the lobes.

Bronchial lymph-nodes were slightly enlarged, felt firm and were homogeneously white in colour but all the other organs were not grossly altered. Examination of the gastro-intestinal tract for the presence of parasites resulted in the finding of two round worms.

Histopathology.

The lesions were found to be referable histopathologically to the presence of focal collections of cells, which latter consisted mainly of eosinophils, lymphocytes and macrophages. The foci were located in bronchioles and alveoli, occasionally exhibited central necrosis and often incorporated portions of hypertrophied smooth muscle derived from the walls of the bronchioles and the alveolar ducts (Fig. 29, p.134). In a few instances, transverse sections of young adult parasites, again surrounded by a like cellular reaction, were found in respiratory tissue (Fig. 30, p.134). There was also a more diffuse infiltration of the interstitium by the same types of cell that spread outwards from the focal lesions but parts of affected lobes remained free from the cellular reaction. Especially in the more cellular regions, peribronchial, together with peribronchiolar and perivascular, accumulations of lymphocytic and eosinophilic cells were conspicuous and frequently those cells were to be found in contact with the vascular endothelium on their way through the vessel wall. Invasion of the walls

Figure 29. Two weeks after infection. The muscle of the walls of the bronchioles and alveolar ducts has undergone hypertrophy.
Van Gieson. X.138.

Figure 30. Two weeks after infection. A young adult worm embedded in pulmonary tissue and invested by a cellular reaction mainly of eosinophilic cell type.
Haematoxylin and Eosin. X138.

Fig. 29.

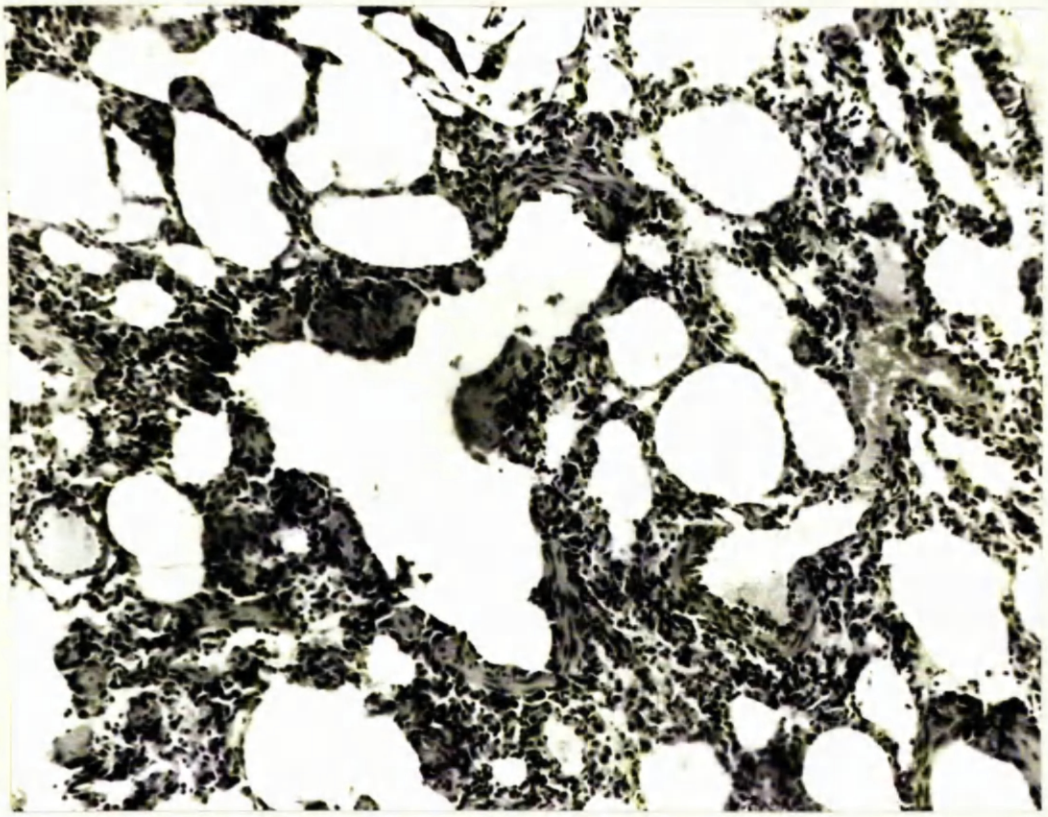
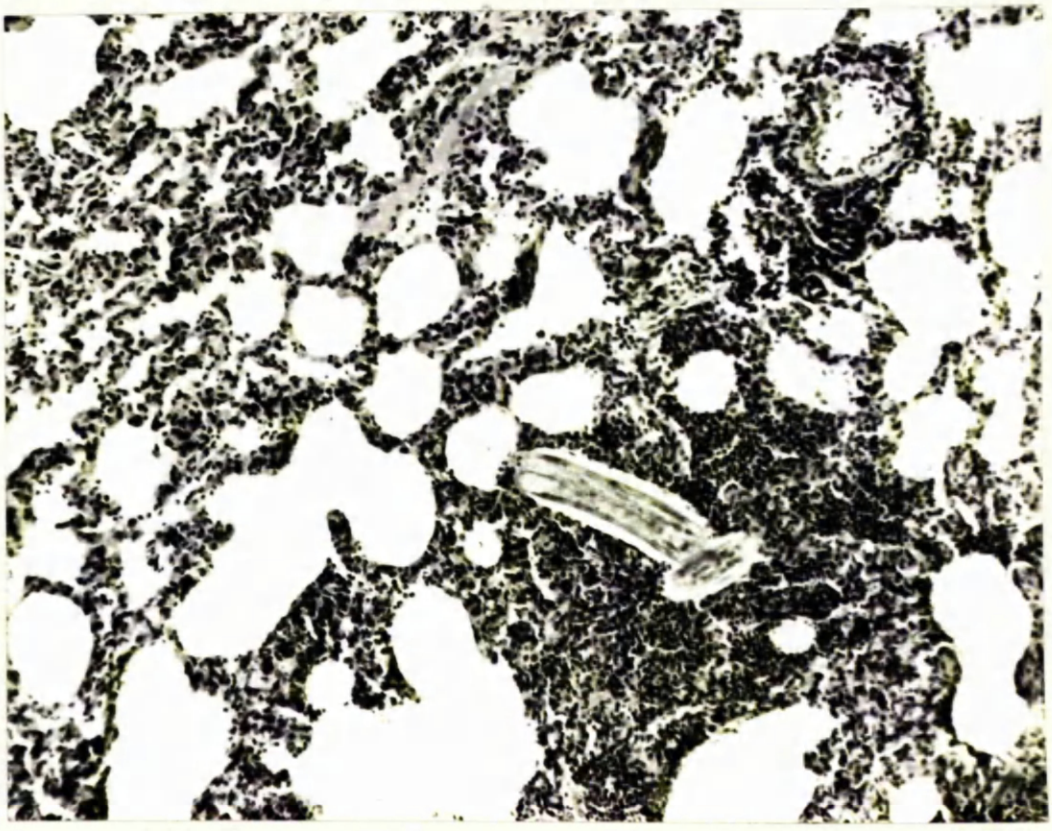


Fig. 30.



and the lumina of bronchi and bronchioles by similar cells was also noted.

In a number of the pulmonary arterial branches, hypertrophy of the smooth muscle of the tunica media was observable and the associated mean wall-to-lumen ratio proved to be of the order of 0.4222:1 (Table 33, p.163), which figure is significantly higher than that recorded for normal arteries (Table 1, p.15). In the case of both the frankly parasitized and the highly cellular areas, the distribution of the affected vessels was remarkable in that it was pronounced and even diffuse whereas away from the lesions the change was less common although just as prominent when it did occur.

Apart from eosinophilia (Table 32, p.162), the only haematological feature of note was a markedly elevated erythrocyte sedimentation rate (E.S.R.) of 20 mm. per hour compared with a value of 1 to 5 mm. per hour which is considered normal for the cat. Preparations of bone-marrow were found to show an increase in the numbers of eosinophil myelocytes and meta-myelocytes.

The bronchial and mesenteric lymph-nodes manifested a degree of lymphocytic hyperplasia but did not show any evidence of the passage of parasites. The amount of lipid in the zona fasciculata of both adrenals was reduced and imparted to the affected cells a more compact appearance but, histopathological aberration of other organs was not found.

At Four Weeks after Infection.

Morbid Anatomy.

Throughout the pulmonary substance were scattered numerous cream-coloured opalescent foci, 1 to 2 mm. in diameter, which had occasionally coalesced to form larger and more irregular lesions. Superficial foci were raised above the surface of the lung and all affected zones were rather caseous in nature (Fig. 31, p. 137). The bronchial lymph-nodes were slightly enlarged, homogenoously white and firm in consistency while inspection of the myocardium revealed the presence of widely distributed, small, pale areas less than one millimetre in diameter.

Histopathology.

Despite careful search of serial sections of lung tissue, adult parasites were hard to find and, when discovered, were found to be seldom attended by much cellular reaction. Invariably they were located in the bronchioles, the alveolar ducts or in the alveolar cavities. At this stage of the disease, oögenesis had begun and evident were multiple foci comprised of cellular material and of ova at various stages of development. As yet, however, the ova were few in number and did not contain any larval forms (Fig. 32, p.137). The cellular reaction consisted mainly of eosinophils, lymphocytes and many

Figure 31. Four weeks after infection. Widespread, multiple small lesions together with occasional coalescence in the lungs of an experimentally infected animal.

Figure 32. Four weeks after infection. A few ova are surrounded by a mixed cellular reaction. Muscular hypertrophy is prominent in the walls of the bronchioles and alveolar ducts. A branch of the pulmonary artery towards the left of the picture shows medial hypertrophy together with some degree of periarteritis.
Haematoxylin and Eosin. X138.

Fig. 31.

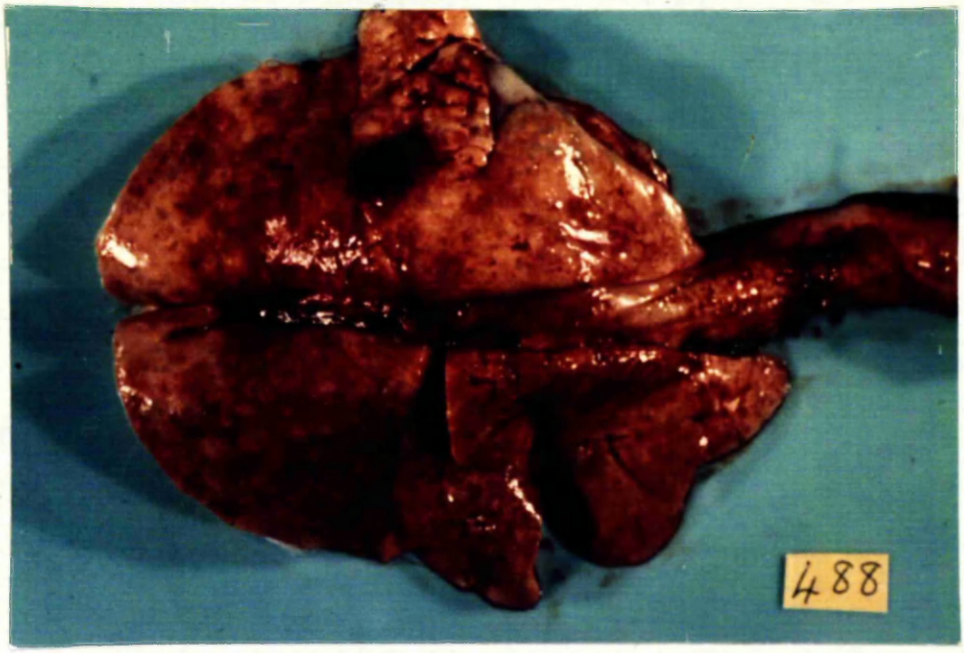
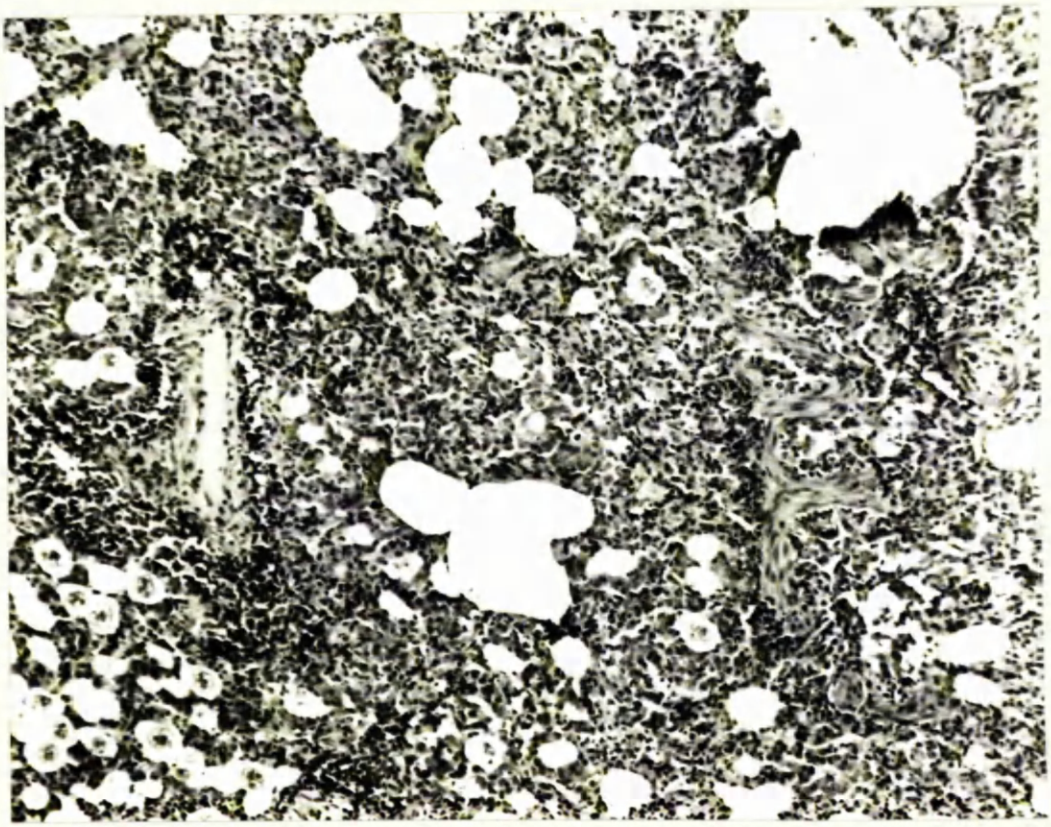


Fig. 32.



macrophages, some of which latter had coalesced to form large multinucleated giant-cells. In certain parts, eggs surrounded by the latter cells had undergone degeneration, a state that was presumed to be indicative of a defensive reaction on the part of the host. Away from the main areas of disturbance, there was slight, but definitely increased, cellularity of the interstitial tissues of the lung.

There was marked hypertrophy of the smooth muscle of the walls of bronchioles and alveolar ducts and occasional foci of peribronchial and perivascular lymphocytic reaction were noted as were, too, penetration of the bronchial, bronchiolar and arterial walls by eosinophils and lymphocytes (Figs. 33 and 34, p.139). Slight proliferation of the bronchial and bronchiolar epithelium was associated with an increased amount of mucus and lymphocytic hyperplasia was also to be seen in the lymph-nodes.

Measurement of the mean wall-to-lumen ratio of the pulmonary arterial branches gave a figure of 0.3704:1 which is slightly below that established for the first animal but still significantly higher than the normal value. As before, the alteration was found to result from simple hypertrophy of the medial smooth muscle. All arteries were not affected and, even in the same section of tissue, many were of normal structure. Histologically, the myocardial lesion proved to consist of focal infiltration of mononuclear cells together with a few granular leucocytes but, the presence

Figure 33. Four weeks after infection. Bronchiolitis, periarteritis and endarteritis in which eosinophil leucocytes are mainly involved.
Haematoxylin and Eosin. X138.

Figure 34. Four weeks after infection. A higher magnification of part of the section illustrated in Fig. 33, to demonstrate the migration of eosinophil leucocytes through the arterial wall and consequent periarteritis.
Haematoxylin and Eosin. X312.

Fig. 33.

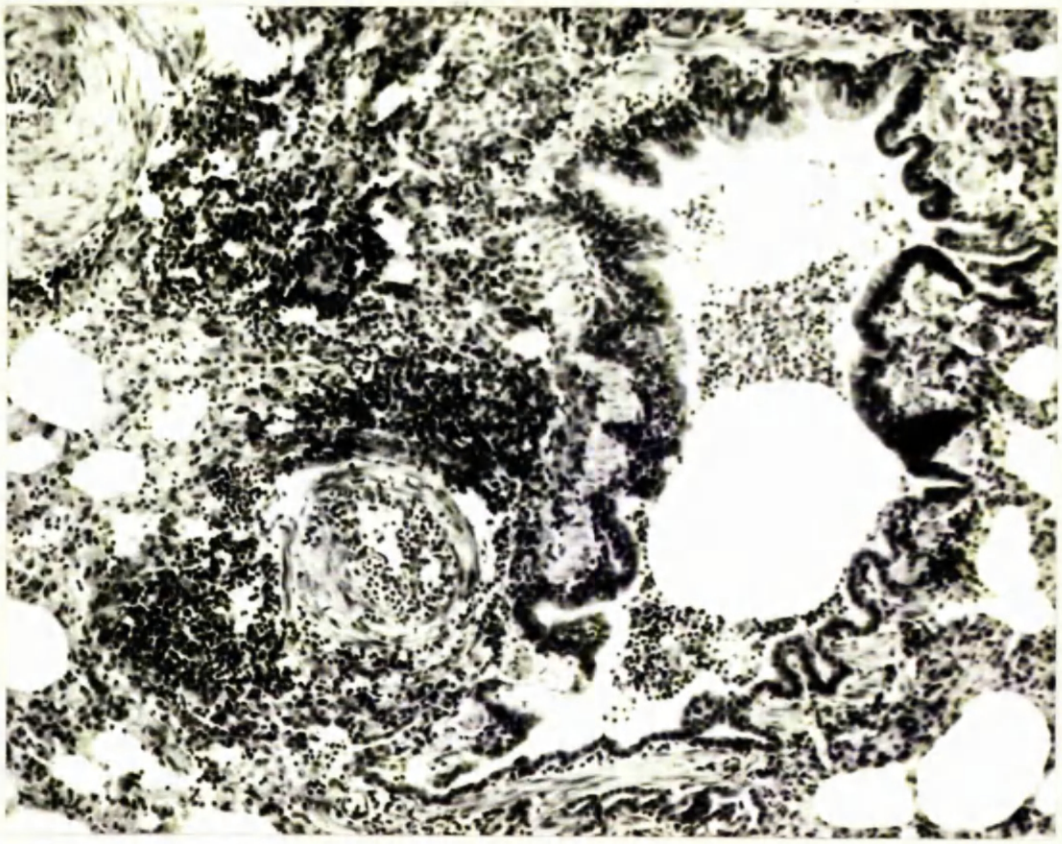
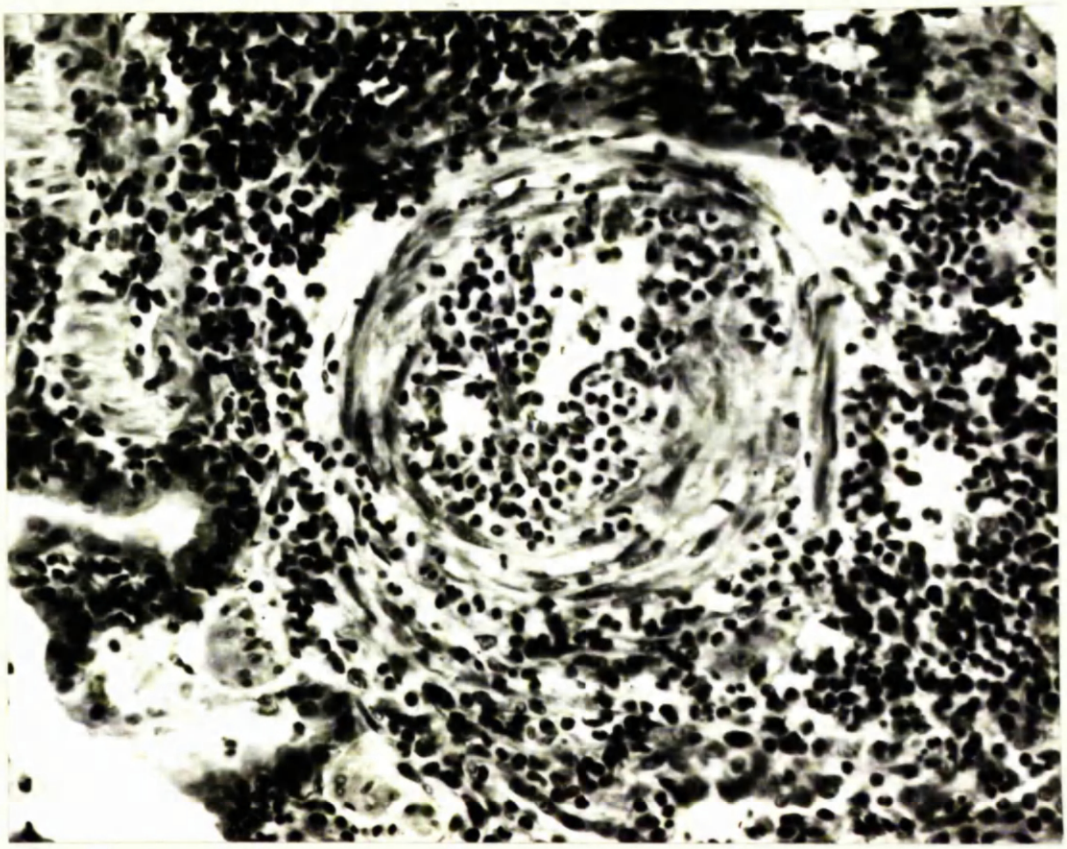


Fig. 34.



of parasitic elements was not demonstrable. The only other organs changed in any way were the adrenal glands in which depletion of lipid in the fasciculate zone was once again evident.

Haematological examination disclosed an increase of the total white cell count to 25,000 per cu. mm. which was ascribable to polymorphonuclear and eosinophilic leucocytosis. The erythrocyte sedimentation rate was raised to 22 mm. per hour and examination of bone-marrow preparations showed prominent hyperplasia of eosinophil-producing cells.

At Six Weeks after Infection.

Morbid Anatomy.

Both lungs were severely affected, especially along the dorsal margins of the diaphragmatic lobes. The lesions consisted of multiple, whitish nodules, a few millimetres in diameter, but in many areas they had coalesced to form foci, up to ten millimetres in diameter, that projected from the surface of the lung (Fig. 35, p. 141). They were of fairly firm consistency and, because of their number and widespread distribution, imparted to the lung a distinctly rubber-like feeling. On section, some of the larger nodules yielded a viscid milky fluid. The bronchial lymph-nodes were considerably enlarged, up to 3 cm. by 0.4 cm., were homogeneously white in colour and were rather firm to the touch.

Figure 35. Six weeks after infection. A close-up view of a lobe of the lung of an experimental subject, to show the widespread distribution and coalescence of the parasitic lesions.

Figure 36. Six weeks after infection. Developing larvae surrounded by a cellular reaction which includes many multinucleated giant-cells. Haematoxylin and Eosin. X138.

Fig. 35.

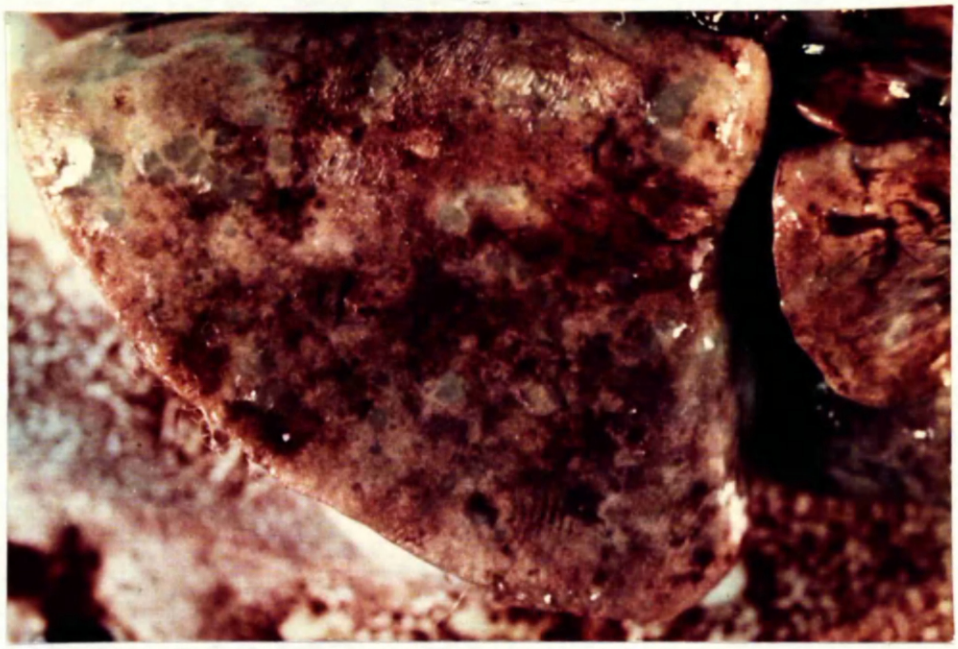
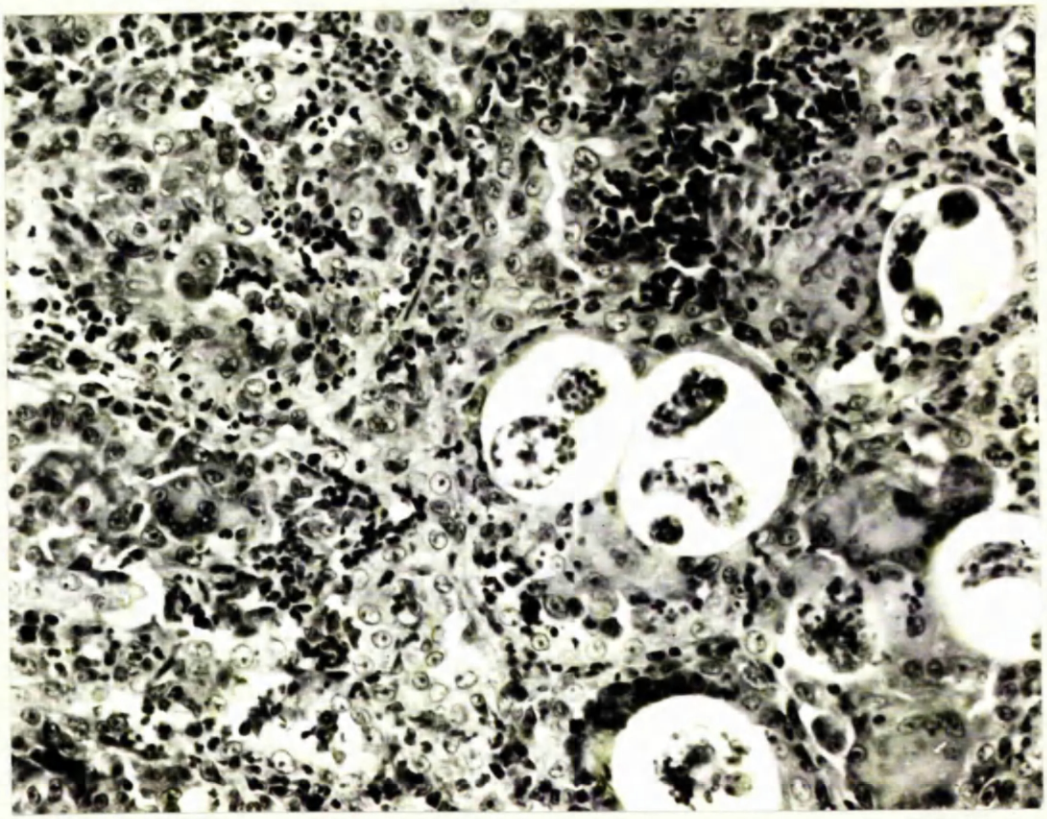


Fig. 36.



Histopathology.

Damage to the organ was widespread and severe. In all lobes, there were to be found large zones of cellular reaction that were located around developing eggs or larvae and, in many instances, exhibited central necrosis (Figs. 36 and 37, p. 141 and 143). Just as the preceding case, the main types of cell embraced eosinophils, lymphocytes and macrophages together with numerous giant-cells. Often, lesions failed to show any sign of the presence of parasitic matter but, after careful examination of serial sections, some evidence of parasitic participation was found in the majority of cases. There were many areas of epithelialization where proliferation of the alveolar lining had given rise to pavement-like sheets of cuboidal cells that together with cellular infiltration of the pulmonary septa, conferred upon the affected part a gland-like appearance (Fig. 38, p. 143). Away from the main foci of activity, there was considerable cellular infiltration into the interstitial tissues and the alveoli while around the bronchi and the bronchioles lymphocytes and eosinophils abounded. In the most affected regions, proliferation of the mucosal cells of bronchi and bronchioles and hyperplasia of the peribronchiolar glands, accompanied by immigration of eosinophils and lymphocytes, were especially prominent. Adult worms were to be found in the bronchioles, the alveolar

Figure 37. Six weeks after infection. A field, similar to that in Fig. 36, chosen to show in greater detail the giant-cell reaction around developing ova.
Haematoxylin and Eosin. X312.

Figure 38. Six weeks after infection. The presence of a marked alveolar epithelialization is to be noted. Also apparent are a few ova and larvae together with a cellular reaction which consists of eosinophils, lymphocytes, macrophages and giant-cells.
Haematoxylin and Eosin. X138.

Fig. 37.

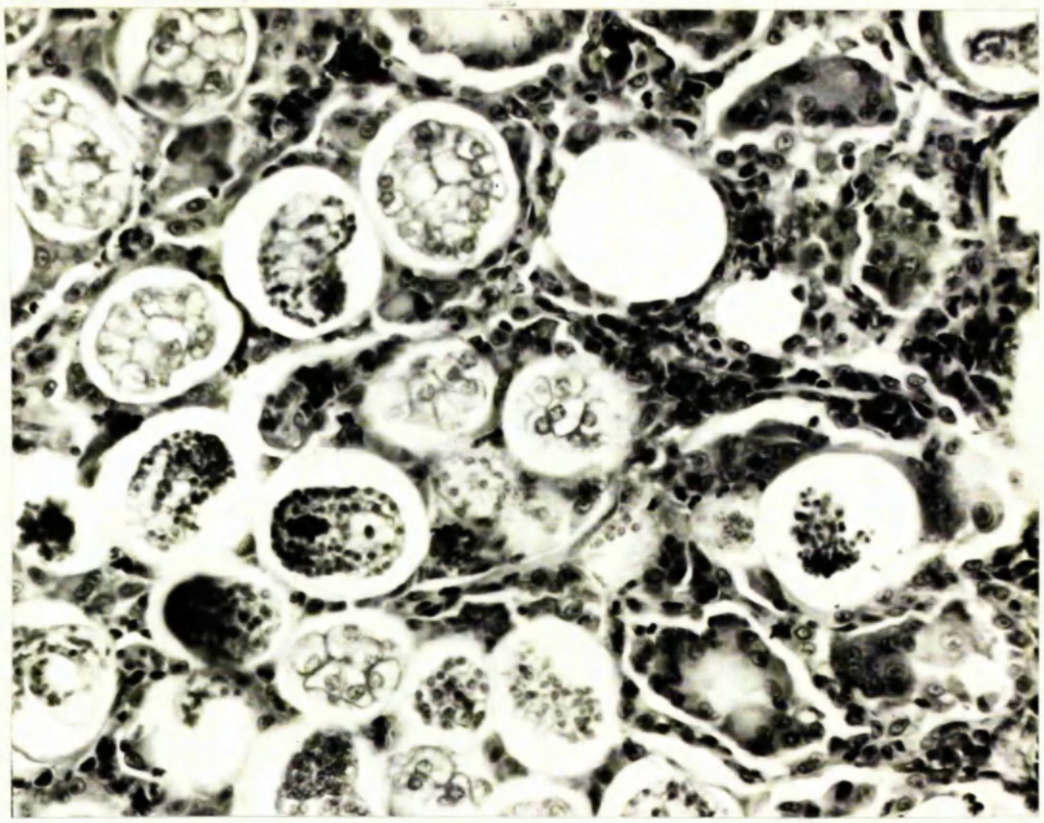
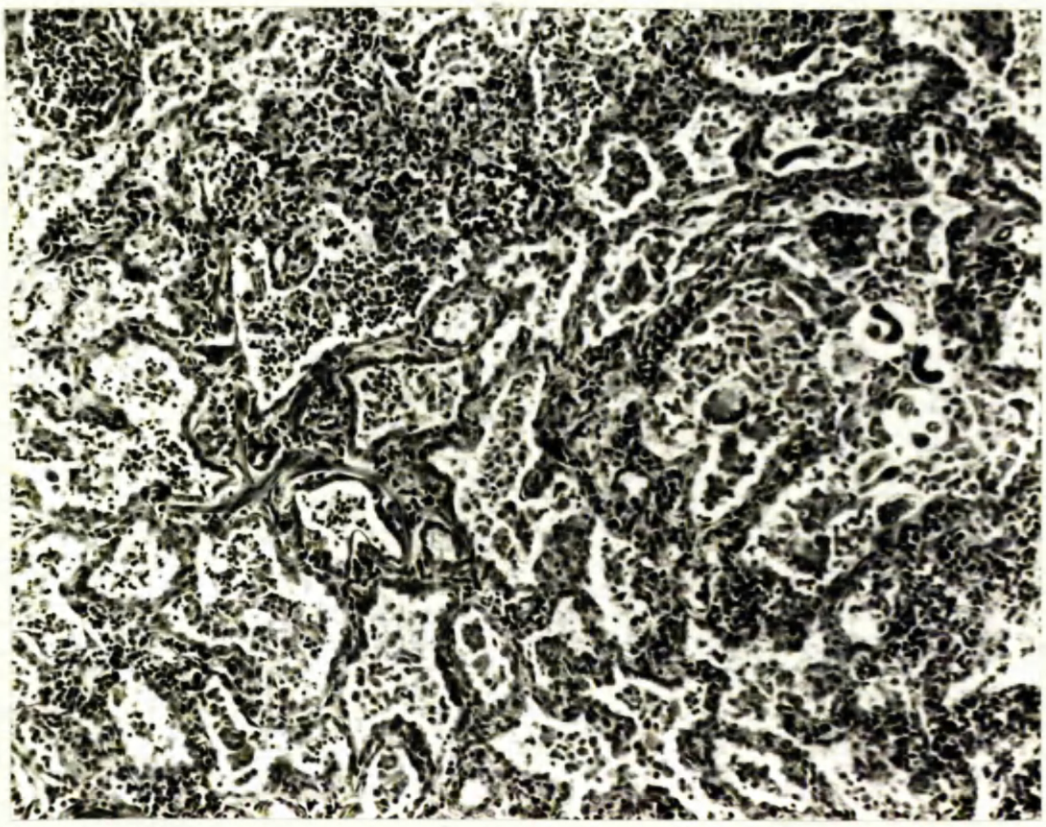


Fig. 38.



ducts and the alveoli where, too, hypertrophic changes of the smooth muscle of the walls were well advanced. Alveolar emphysema was conspicuous in many parts of the lung.

Migration of lymphocytes and of eosinophil leucocytes into the arterial walls and the perivascular tissues was marked and in some vessels endothelial swelling and proliferation was a feature. Hypertrophy of the myofibrils of the medial coat of arteries was more pronounced than that observed in either of the first two animals and was associated with a mean wall-to-lumen ratio of 0.5580:1 but, although the arterial lesions were fairly widespread, normal vessels were always identifiable. Exceptionally, local occlusion of an artery was encountered (Fig. 39, p.145), but, as a rule, affected vessels displayed diffuse thickening of their walls. There was not any evidence of intimal fibrosis but noticeable stretching of the external elastic laminae occurred in some badly affected arteries. The lymphocytic elements of the bronchial lymph-nodes were diffusely increased in number. Elsewhere in the body, the only appreciable alteration was to be seen in the adrenal glands where decrease of lipid in the zona fasciculata was again prominent.

From a haematological viewpoint, there was a diminished white cell count (6,200 per cu. mm.) together with a concomitant eosinophilia of 19.0% and, at 22 mm. per hour, the erythrocyte sedimentation rate was still unduly high.

Figure 39. Six weeks after infection. Longitudinal section of a pulmonary artery displaying a localized area of endarteritis together with perivascular lymphocytic "cuffing".
Haematoxylin and Eosin. X138.

Figure 40. Ten weeks after infection. Prominent pulmonary arterial hypertrophy and hyperplasia accompanied by swelling and proliferation of the endothelial cells of the intima.
Haematoxylin and Eosin. X138.

Fig. 39.

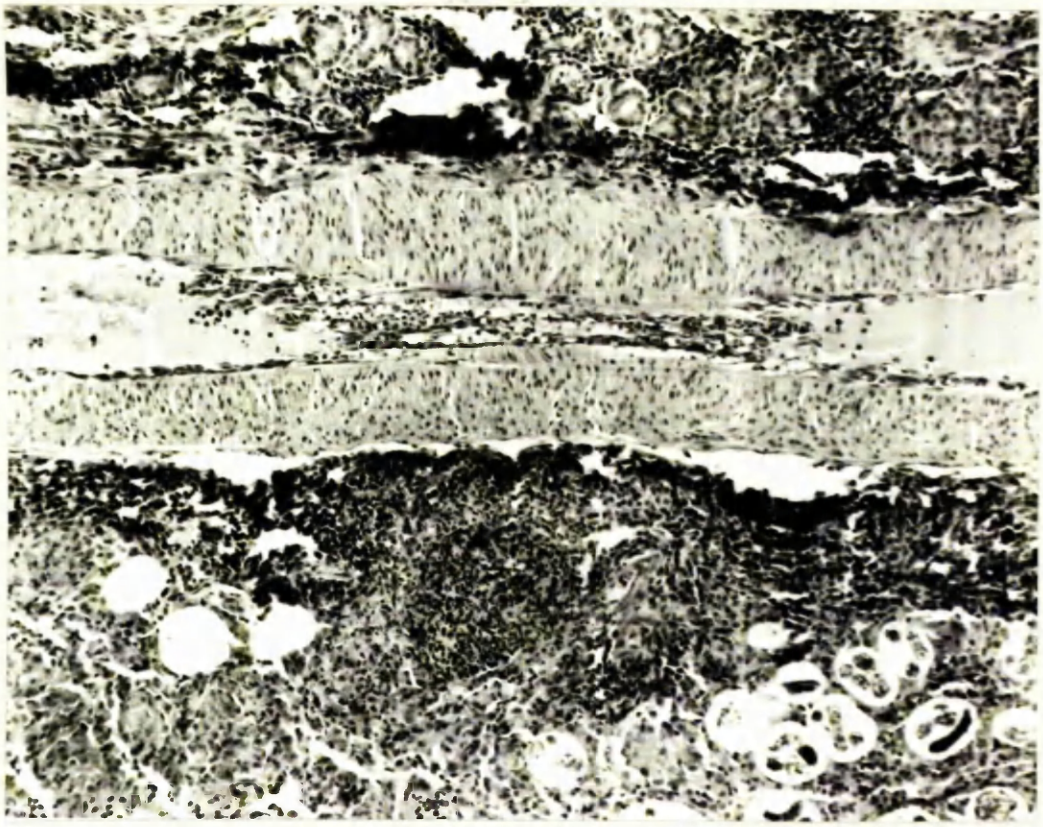
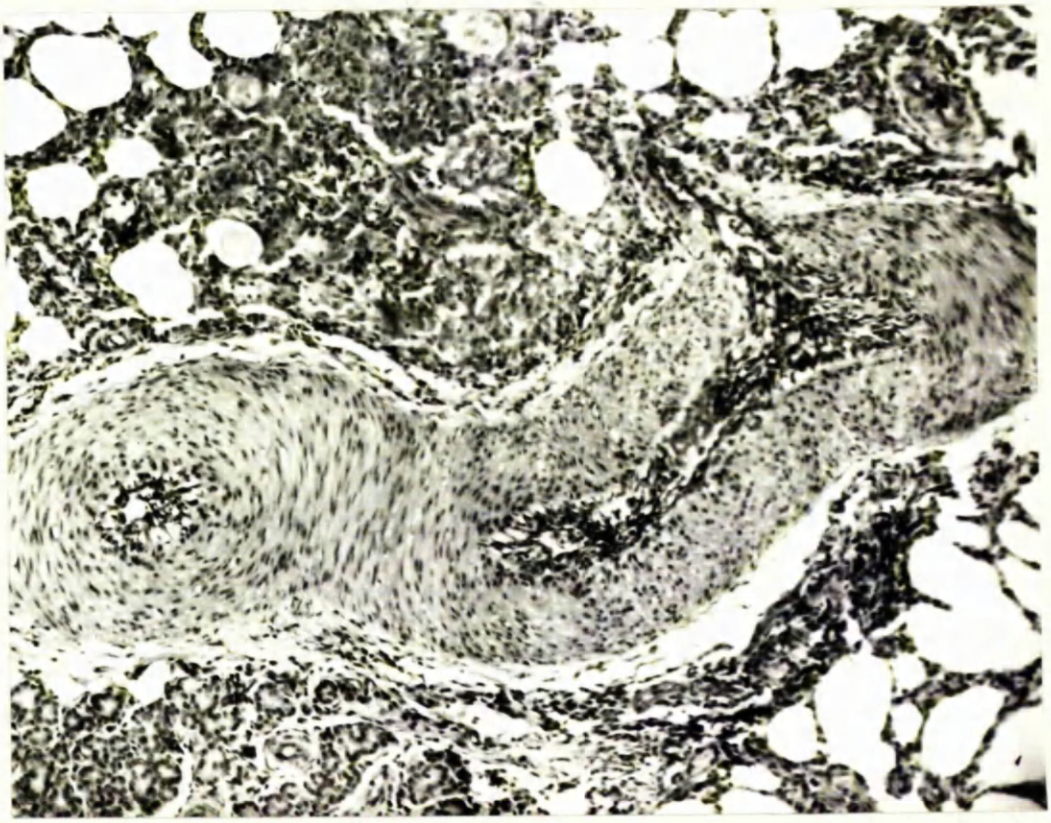


Fig. 40.



Bone-marrow preparations showed hyperplasia of the progenitors of the eosinophil cells.

At Eight and Ten Weeks after Infection.

Morbid Anatomy.

Since the animals killed at both stages of infection displayed gross appearances essentially similar to those found in the animal killed at six weeks after infection, a separate description is unnecessary.

Histopathology.

Ova and larvae were still prominent and the associated cellular reaction was much as that already described save for a greater incidence of multinucleated giant-cells. The reaction around the parasites was of a more densely cellular character and, in some parts, larvae and ova had begun to degenerate, a change that was more obvious in the case of the animal killed at 10 weeks. The large necrotic areas so apparent at six weeks after infection were less common and, overall, the microscopical picture suggested that movement of the parasites had been contained by the defences of the body. In both cases, bronchitis and bronchiolitis was associated with the presence of ova, larvae and eosinophil leucocytes within the affected lumina. Proliferation of the bronchial and bronchiolar epithelium

and enlargement of the peribronchial glands together with zones of epithelialization and emphysema were present. Away from the main foci, the most prominent finding was hypertrophy of the smooth muscle of the bronchioles and alveolar ducts. Adult worms, when present, were found in the bronchioles, the alveolar ducts and alveoli.

Medial hypertrophy of the pulmonary arteries was more extreme and was accompanied by a mean wall-to-lumen ratio of 0.7764:1 in the case of the cat killed at eight weeks and 2.2554:1 for the animal sacrificed at ten weeks. In the instance of the latter, mitotic figures seen in the myofibrils indicated a degree of hyperplasia and, as before, the muscular lesion was mainly accountable for the arterial thickening except when swelling and proliferation of endothelial cells, sometimes quite extensive, had ensued (Fig. 40, p.145). Vacuolation of myofibrils was apparent in a number of the thickened vessels but immigration of cells into the vascular walls was less conspicuous although it was prominent perivascularly. Especially in the animal kept for 10 weeks, fragmentation of both the internal and the external elastic layers was common and, in some vessels, those laminae had partially disappeared. Neither intimal fibrosis nor accumulation of lipid was demonstrable in the altered arteries. Although it involved a great many vessels in all parts of the lung, the arterial thickening was not universal and normal vessels were recognisable.

The bronchial lymph-nodes were the seat of marked lymphocytic proliferation and the only other change of pathological significance, common to both cats, was a deficiency of lipid in the fasciculate zone of the adrenal glands (Fig. 41, p.149). From the intestines of both animals a small number of tapeworms was recovered.

In the eight and ten weeks animals, respectively, the total white cell counts were rather low, at 6,100 and 6,250 per cu. mm., but there was an eosinophilia of 22.0% and 27.0%. Erythrocyte sedimentation rates were elevated to 32 mm. per hour in the eight week, and to 40 mm. per hour in the ten week, animals. Bone-marrow preparations showed proliferation of the eosinophil meta-myelocytes and myelocytes.

At Twelve and Fourteen Weeks after Infection.

Morbid Anatomy.

Although the animal killed at twelve weeks proved to be rather more lightly infected, the pulmonary lesions of both cats were fairly similar. There were pale foci, mainly of 1 to 2 mm. in diameter, scattered throughout the lobes of the lungs although there were also several larger, more irregular, firm and protusive nodules especially, in the animal killed at fourteen weeks after infestation. In addition, other lesions occurred as large, whitish, less

Figure 41. Ten weeks after infection. A section of an adrenal gland stained to demonstrate lipid-depletion of the zona fasciculata. Haematoxylin and Eosin. X138.

Figure 42. Twelve weeks after infection. A few pale foci may be seen on the ventral surface of the lung. Two considerably enlarged bronchial lymph-nodes are also apparent.

Fig. 41.

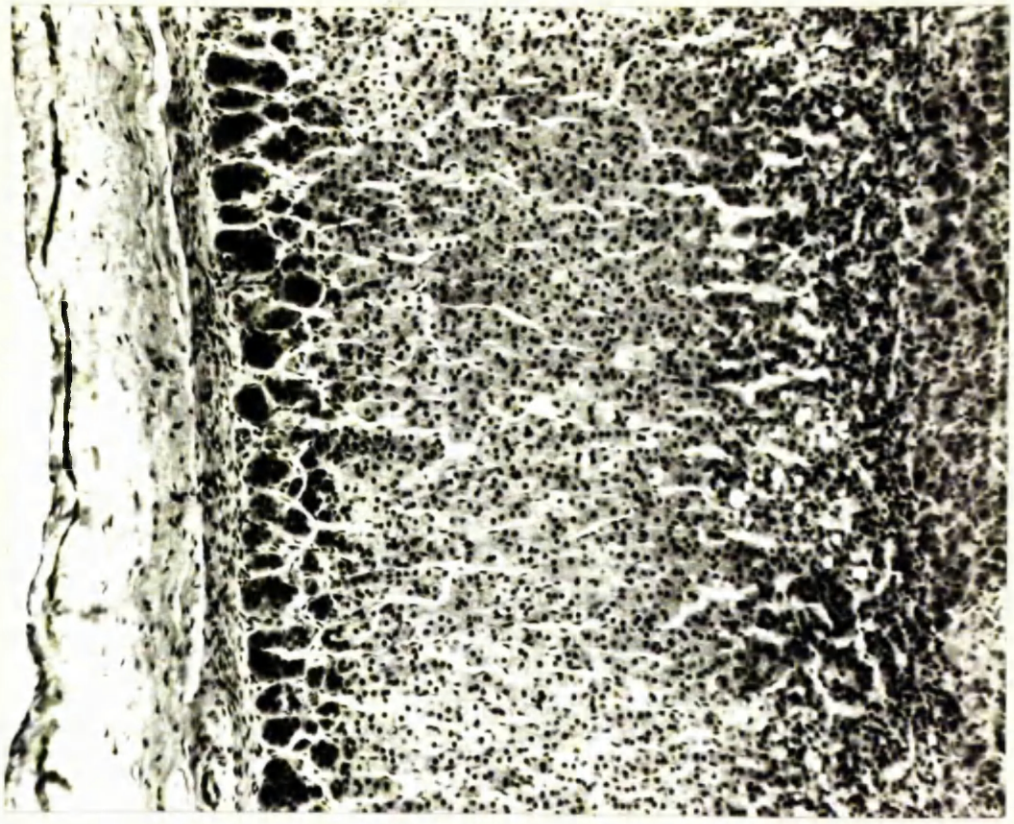
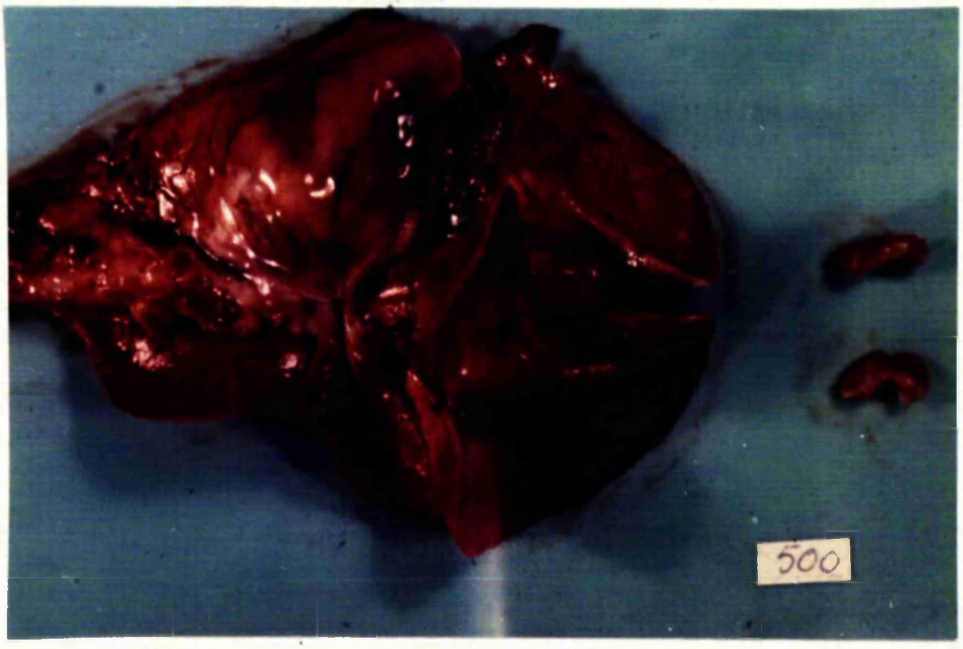


Fig. 42.



well-defined zones which were not elevated and were only slightly firmer than the normal tissue. Enlargement of the bronchial lymph-nodes was still apparent (Fig. 42, p.149).

Histopathology.

Both sets of organs were characterized, above all, by large clear areas of pulmonary tissue and, the parasites were limited in the main to sharply demarcated, highly cellular foci. The second most striking feature was the reduced number of larval forms and, not infrequently, the presence of ova was the sole indication of parasitic infestation. Many larvae and ova were degenerated and, as formerly, were surrounded by eosinophils, lymphocytes, macrophages and giant-cells (Fig. 43, p.151). Also present was peribronchiolar and perivascular infiltration by eosinophils and lymphocytes together with proliferation of bronchial epithelium and hyperplasia of peribronchial glands.

Hypertrophy of the smooth muscle of the bronchioles and alveolar ducts was marked and, in both animals, the pulmonary arteries were considerably thickened and tortuous (Fig. 44, p.151). In the animals killed at 12 and 14 weeks, the mean wall-to-lumen ratios were 2.4000:1 and 1.1906:1, respectively and, as in the preceding cases, the mural thickening was attributable mainly to hypertrophy and hyperplasia of the medial coat with, in a few instances,

Figure 43. Twelve weeks after infection. A few degenerating ova are surrounded by a densely cellular reaction which consists of eosinophil leucocytes, lymphocytes, macrophages and giant-cells.

Haematoxylin and Eosin. X138.

Figure 44. Twelve weeks after infection. Gross medial hypertrophy and hyperplasia of a branch of the pulmonary artery associated with muscular hypertrophy of the walls of bronchioles and alveolar ducts.

Haematoxylin and Eosin. X45.

Fig. 43.

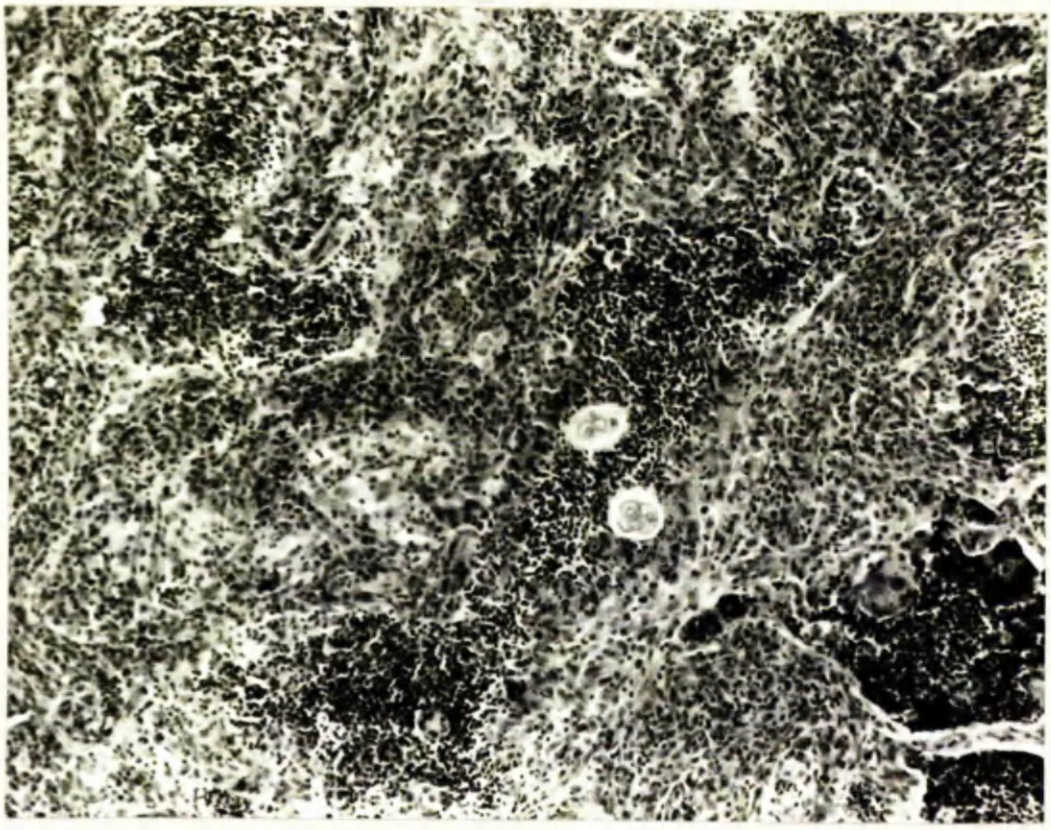
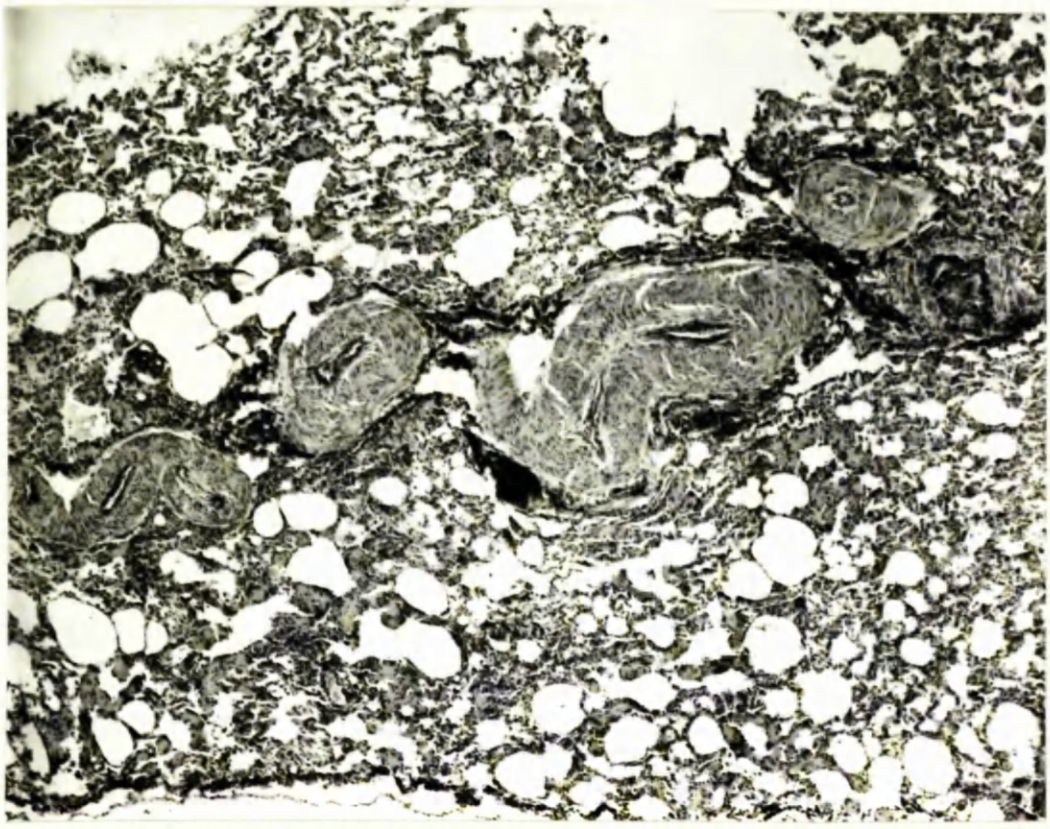


Fig. 44.



slight formation of longitudinal muscle in the intima. Vacuolation of the enlarged muscle cells and degenerative changes, consisting of thinning and fragmentation of both elastic laminae, were widespread. Swelling and proliferation of endothelial cells and eosinophilic infiltration of the vascular walls were less prominent than in the previous cases and the sub-endothelial tissue of a few vessels exhibited a few vacuoles, the contents of which proved negative to methods of staining for lipid, mucopolysaccharide and glycogen. The arteries in the clear zones were similarly affected as was the smooth muscle of the bronchioles and alveolar ducts and such areas appear to have resulted from the removal of ova and larvae by macrophages and giant-cells, thus creating spaces in which disorganised lung tissue and the hypertrophied muscle persisted. Adult worms were difficult to find but some were appreciated in the air passages and alveoli. The bronchial lymph-nodes were diffusely hyperplastic and, once again, the zona fasciculata of the adrenal glands was deficient in lipoidal material.

Haematological investigation revealed a total white cell count of 6,000 and 9,800 cells per cu. mm. of blood, together with eosinophilia of 21.0% and 13.0% and erythrocyte sedimentation rates of 30 and 18 mm. per hour, for the animals sacrificed at 12 and 14 weeks, respectively. Proliferation of eosinophilic cells was noted in the bone-marrow.

At Sixteen and Eighteen Weeks after Infection.

Morbid Anatomy.

In both cases, all the lobes of the lungs, especially the diaphragmatic, were found to show a few nodules, 1 to 2 mm. in diameter. Such lesions were yellowish in colour, friable, fairly well-demarcated and had coalesced, in some instances, to form larger protrusive masses several millimetres in diameter (Fig. 45, p. 154). Also present were more extensive, ill-defined and whitish areas which did not protrude from the surface of the lung and were only slightly firmer in consistency than normal pulmonary tissue. Otherwise, the lungs were little altered and had lost the rather voluminous appearance characteristic of earlier cases. The bronchial lymph-nodes were markedly enlarged, whitish and firm.

Histopathology.

The bulk of the pulmonary tissue proved to be free from parasitic elements and the outstanding feature was that of haphazardly arranged masses of hypertrophied smooth muscle derived from the walls of bronchioles and alveolar ducts. In places, there was increased cellularity of the septal walls due mainly to the presence of lymphocytes, which latter had occasionally spread into the alveoli. In other more severely affected areas, lesions were more

Figure 45. Sixteen weeks after infection. A few pale nodules, 1 to 2 mm. in diameter, are present on the dorsal aspect of the diaphragmatic lobes. Otherwise the lungs are normal.

Figure 46. Eighteen weeks after infection. A markedly thickened pulmonary artery in which the elastic luminae have entirely disappeared. Intimal fibrosis of minimal type is also present.

Lawson and Van Gieson. X312.

Fig. 45.

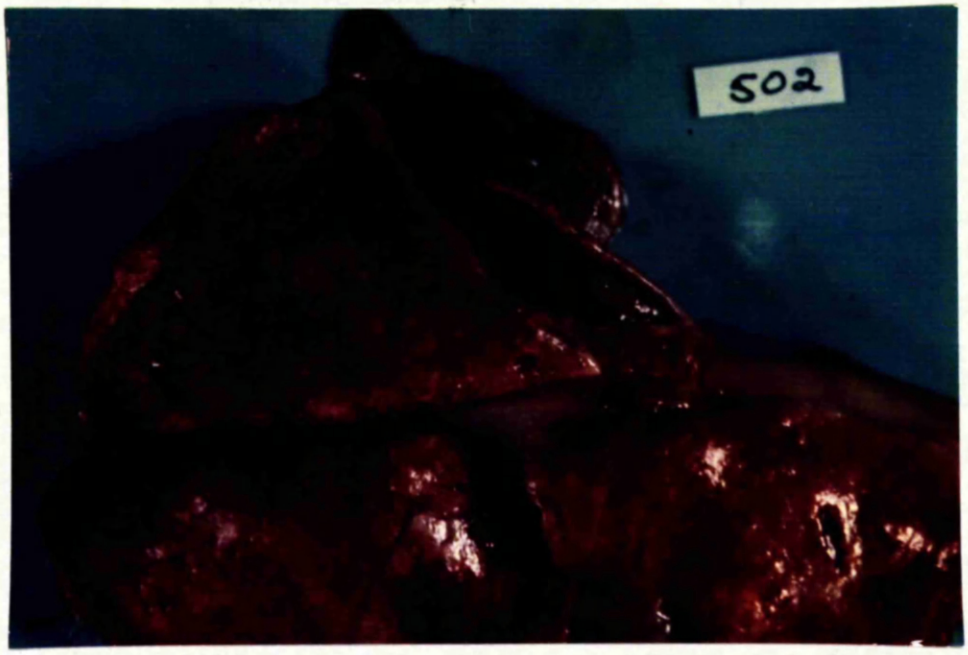
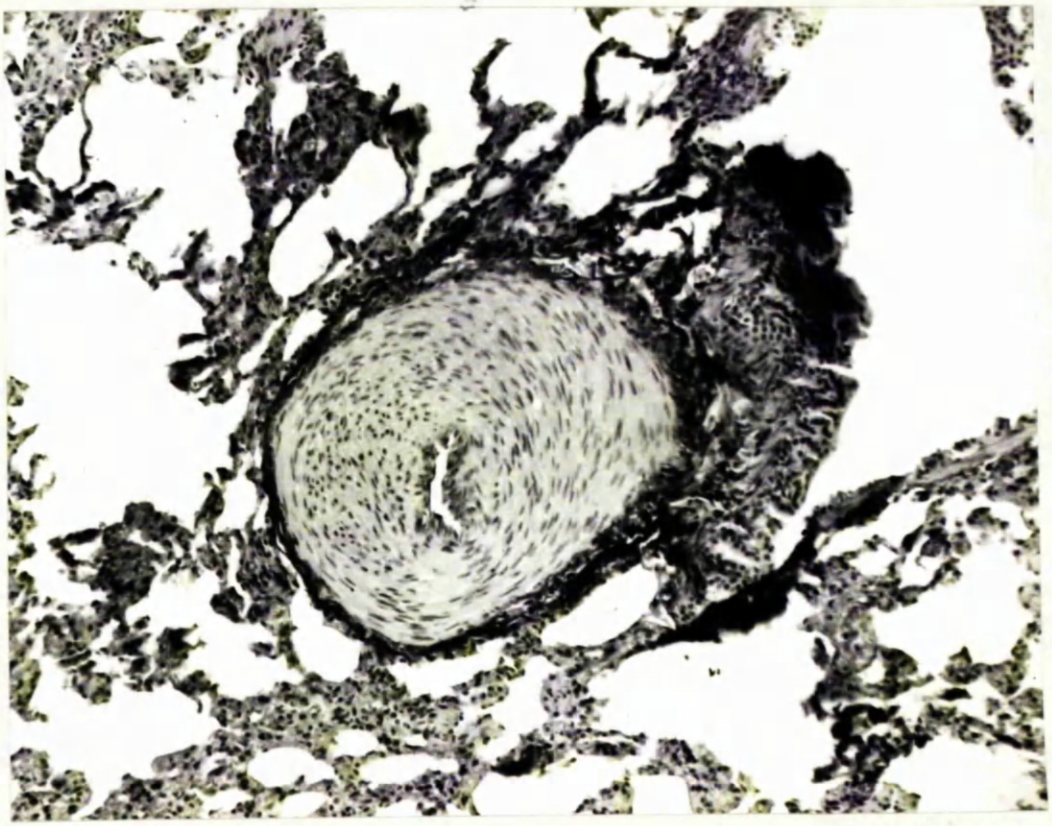


Fig. 46.



solidly cellular and contained lymphocytes, a few eosinophils and macrophages together with some perivascular lymphocytic reaction. Some well-defined foci displayed a few degenerated ova and larvae which were usually widely dispersed and were enveloped by masses of giant-cells associated with a small number of eosinophils and lymphocytes. In animals sacrificed at 16 and 18 weeks, hypertrophied arteries with mean wall-to-lumen ratios of 1.4207:1 and 1.7125:1 ramified throughout the lung tissue. Degeneration of the elastic laminae and slight intimal fibrosis (Fig. 46, p.154) were apparent and a few arteries showed evidence of eosinophil leucocytic immigration and of proliferation of endothelial cells. Peribronchial and peribronchiolar lymphocytic reaction was limited mainly to the affected parts of the lungs and adult worms were increasingly difficult to demonstrate although some female parasites with empty oviducts were noted.

At this stage, therefore, the infestation had begun to regress, which process was associated with removal of debris by macrophages together with some resolution of pulmonary tissue, but the hypertrophic smooth muscle persisted. The bronchial lymph-nodes were hyperplastic, the adrenal glands depleted of lipid in the zona fasciculata but other organs were not altered.

Haematologically, the total white cell counts were 15,000 and 29,500 cells per cu. mm., eosinophilia was 12.0%

and 10.0% and the erythrocyte sedimentation rates were 38 mm. and 2 mm. per hour, for animals sacrificed at 16 and 18 weeks, respectively. Examination of bone-marrow revealed a slight proliferation of eosinophilic cells.

At Twenty Weeks after Infection.

Morbid Anatomy.

The lungs were more severely affected than in the previous case. All lobes were involved and exhibited whitish lesions, of pin-head size, which were scattered throughout the substance or, in several places, had coalesced to form yellowish protrusive nodules, several millimetres in diameter (Fig. 47, p. 157). The organ was distinctly firm to the touch and, on section, the markedly enlarged bronchial lymph-nodes appeared whitish and homogeneous. None of the other organs was visibly altered.

Histopathology.

Several stages of the disease were represented. In some fairly large areas, the only abnormality consisted of extreme hypertrophy of the muscle of the bronchioles and alveolar ducts (Fig. 48, p. 157) together with some vessels that were surrounded by slight lymphocytic reaction or were characterized by proliferation of endothelial cells accompanied by infiltration of eosinophils.

Figure 47. Twenty weeks after infection. Observable in the lung are a number of projecting, yellowish foci, several millimetres in diameter, as well as some smaller lesions of pin-point size.

Figure 48. Twenty weeks after infection. Hypertrophy of the walls of the bronchioles and alveolar ducts is very prominent. A comparatively normal pulmonary artery may be noted towards the left of the picture.

Van Gieson. X138.

Fig. 47.

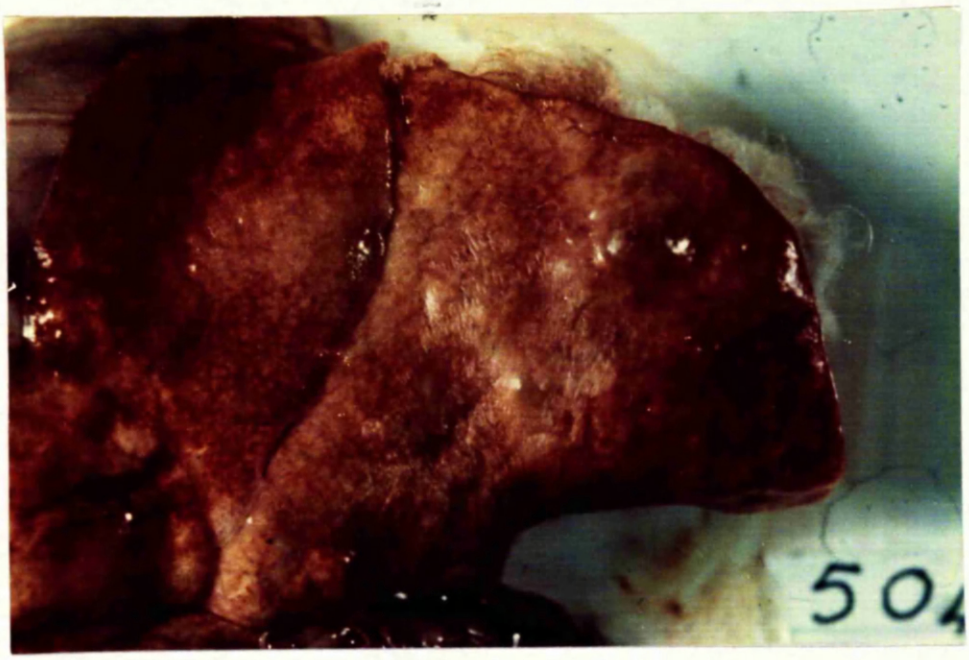
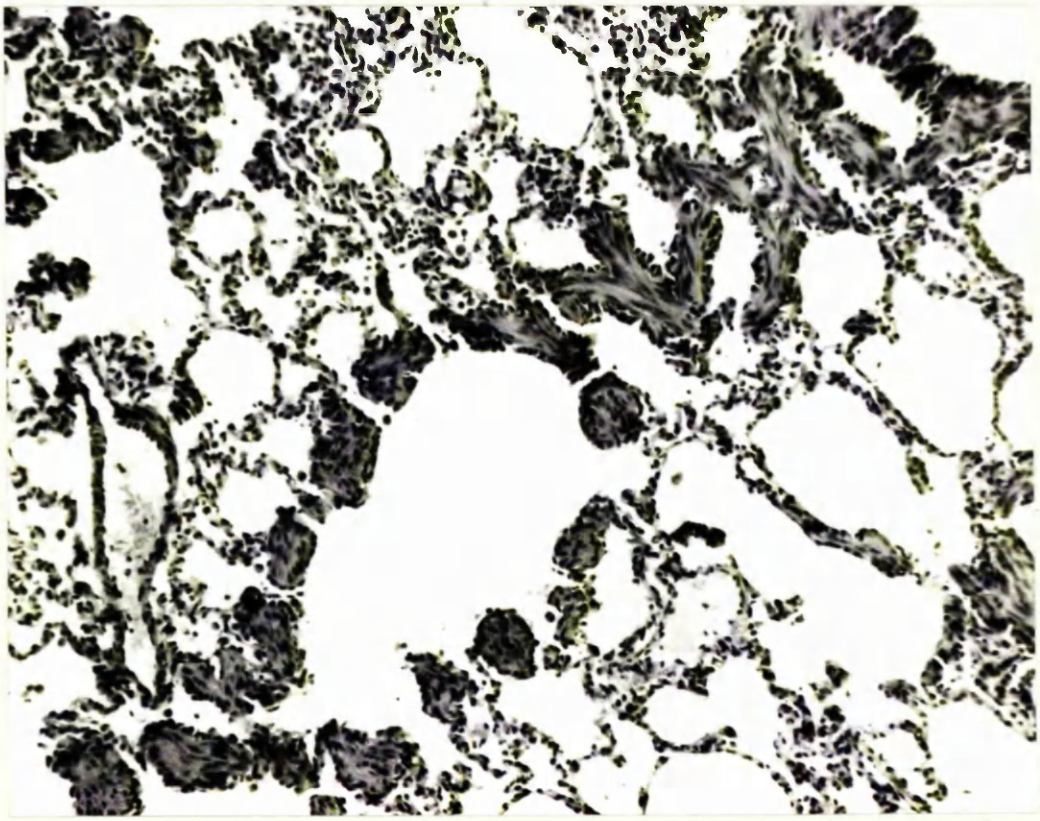


Fig. 48.



Other parts manifested invasion of alveoli and septal tissues by lymphocytes, eosinophils and macrophages, which types of cells in still other parts, enveloped degenerated ova along with occasional larvae. The average wall-to-lumen ratio of the pulmonary arterial branches was found to be 2.0694:1, a value indicative of the presence of the medial lesion, but the latter was not universally distributed throughout the arterial system. Swelling and proliferation of endothelial cells were more apparent in the badly affected regions while degenerative changes of the elastic laminae and slight intimal fibrosis were detectable in the altered arteries. Portions of adult worms were present in the bronchioles and the alveolar ducts and hyperplastic changes were noted in the bronchial lymph-nodes.

The total white cell count was elevated (17,000 cells per cu. mm.) as a result, mainly, of polymorphonuclear leucocytosis although eosinophilia also obtained. The erythrocyte sedimentation rate was within the normal range and preparations of bone-marrow presented a normal histological picture. Changes of pathological significance were not found in any other organ and the adrenal glands carried a full complement of lipoidal material.

At Twenty-Two and Twenty-Four Weeks after Infection

Morbid Anatomy.

Widespread throughout the lungs of both animals were lesions, of almost identical type, which were barely perceptible and consisted of a number of punctiform, non-elevated, whitish follicles which rarely exceeded 1 mm. in diameter. The bronchial lymph-nodes were only slightly enlarged.

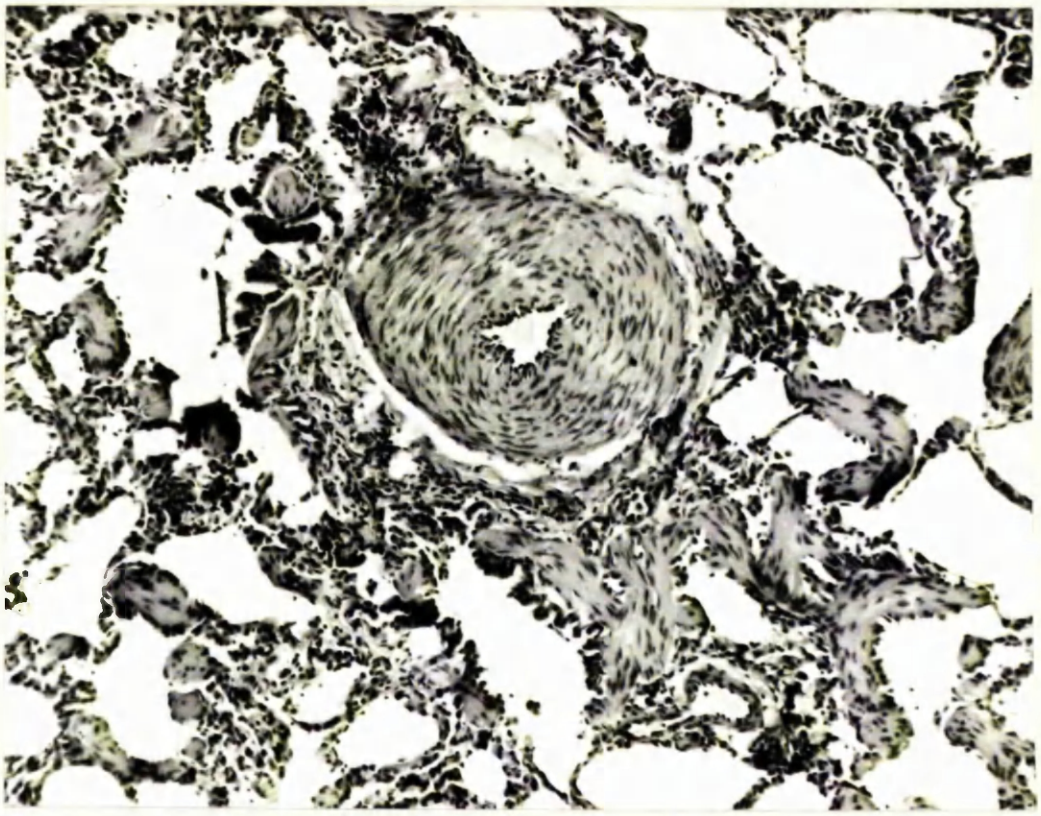
Histopathology.

Focal hypertrophy and hyperplasia of the medial coat of the pulmonary arteries and gross hypertrophy of the musculature of the bronchioles and alveolar ducts constituted the main changes (Fig. 49, p.160). A few slightly cellular foci consisting mainly of lymphocytes and eosinophils were encountered in the lung tissue and in the intima of some hypertrophied arteries occurred an eosinophilic cell infiltration associated with swelling and proliferation of the endothelial cells. In both animals, periarterial lymphocytic hyperplasia and slight intimal fibrosis were observable in the worse affected vessels along with fragmentation of the elastic laminae. In the case of the cat killed at 24 weeks, incipient production of longitudinal muscle, of intimal location, was perceptible. Ova and larvae were completely absent and the only evidence

Figure 49. Twenty-four weeks after infection. Muscular hypertrophy and hyperplasia of the artery and hypertrophic changes in the muscle of the bronchioles and alveolar ducts are still notable. Complete disappearance of the elastic laminae has also occurred.

Lawson and Van Gieson. X138.

Fig. 49.



of parasitic involvement was the finding of portions of adult worms in only three sections out of almost 100 examined.

Haematologically, the total white cell counts were elevated but, despite a reduction in the number of tissue eosinophils, eosinophilia still obtained. Elevation of the erythrocyte sedimentation rate was slight in both animals. Bone-marrow preparations were normal in the case of the cat killed at 24 weeks but showed proliferation of the eosinophilic cells in the instance of the animal sacrificed two weeks earlier.

Pathological changes were not to be found in any other organ of either animal.

Comprehensive examination of the six control kittens, killed after 4, 8, 12, 16, 20 and 24 weeks of observation, failed to reveal any departure from normality.

d. Discussion.

To date there has not been published any detailed account of the pathogenesis of the disease induced by the cat lungworm but a few authors have described, in general terms, the alterations pertaining to the active form of the disease. However, a description of the life-cycle of the parasite, and an account of its pathogenic effects have been given by Robmaier and Robmaier (1935a and 1935b), by MacKerras (1957) and by Blaisdell (1952).

TABLE 32.

HAEMATOLOGICAL FINDINGS IN EXPERIMENTAL INFESTATION BY ANCYLOSTOMOIDES ABSTRUSUS.

Weeks After Infection	Total W.B.C. /cu.mm.	Differential % Poly.	Lymph.	Eos.	Absolute Values /cu.mm. Poly.	Lymph.	Eos.	Hb. Gm/100 ml.	P.C.V. %	MCHC %	E.S.R. mm/hr.
2	11700	51	39	10	5967	4563	1170	14.5	41	35	20
4	25000	67	22	11	16750	5500	2750	13	42	31	22
6	6200	32	49	19	1984	3038	1178	14	45	31	22
8	6100	45	33	22	2745	2013	1342	15	43	35	32
10	6250	40	33	27	2500	2063	1687	16.5	44	37	40
12	6000	40	39	21	2400	2340	1260	15.8	42	37	30
14	9800	48	39	13	4704	3822	1274	14.7	42	36	18
16	15000	38	50	12	5700	7500	1800	14.7	43	35	38
18	20500	44	46	10	12980	13570	2050	17	50	34	2
20	17000	70	23	7	11900	3910	1190	16.6	48	35	5
22	18900	47	41	12	8885	7749	2268	16.5	45	36	10
24	11000	67	27	6	7370	2970	660	15.5	46	33	5

TABLE 53.

MEAN WALL-TO-LUMEN RATIOS OF ARTERIES OF LUNGS, MYOCARDIUM AND KIDNEYS IN EXPERIMENTAL PARASITIC PNEUMONIA.

Weeks After Infection	Lungs	Myocardium	Kidneys
2	0.4222	0.2566	0.2165
4	0.3704	0.1906	0.2772
6	0.5560	0.3286	0.2247
8	0.7764	0.3636	0.3680
10	2.2554	0.2471	0.2225
12	2.4000	0.2738	0.4295
14	1.1905	0.3099	0.3080
16	1.4207	0.1990	0.3060
18	1.7185	0.2241	0.1846
20	2.0694	0.3135	0.2109
22	1.5625	0.3125	0.2655
24	1.8550	0.2555	0.3000

The experimental work peculiar to this thesis did not elucidate the route of migration of the parasite from the alimentary system to the lungs. Lesions were not found in the mouth, stomach, intestinal tract, trachea or in either the mesenteric or the bronchial lymph-nodes. If that aspect of the life-cycle is to be precisely studied, beyond doubt it must be undertaken within a few days after infection in order that regard may be had to the hypothesis of Blaisdell (1952) namely, that spread takes place via the lymphatic vessels after quick penetration of the stomach wall.

According to all the above authors, young adult parasites are produced in the cat lung in approximately 17 days and ova are scantily present by the 28th day, after initial infection. Four to nine days later still, first-stage larvae appear in the faeces. Those findings closely agree with the results of the experimental work herein described. The phase of active infestation is generally accepted to occur from eight to thirteen weeks after infection. Thereafter, larvae are seldom recoverable from the faeces although Blaisdell (1952) reported such a finding for a period up to two years. Moreover, during the course of an experimental infection, MacKerras (1957) obtained larvae seven months after patency.

In the present experiment, it was found that the most active phase of the disease occurred at six to twelve weeks

after infection and that two weeks later the number of first-stage larvae was considerably reduced. Thereafter, regressive changes onsued so that by six months from initial infestation practically all signs of the presence of the parasite had disappeared and only the hypertrophy of the smooth muscle of the arteries, bronchioles and alveolar ducts persisted. Although increasingly difficult to demonstrate, adult worms (the females free of eggs) were encountered in respiratory tissue for up to 24 weeks after infection. It is still unknown how long the parasite may survive in the lung and it also remains to be determined whether, or not, re-activation of the disease is possible, as has been suggested by Blaisdell (1952).

As described in Part 3 of this thesis, the clinical disease noted by most authors took the form of a mild respiratory infection associated, in a minority of cases, with a fatal issue as a result either of heavy infestation or the condition of health of the animal or a combination of both these factors. That general opinion tends to be confirmed by the experimental clinical findings earlier described.

Although it is dangerous to deduce too much from isolated blood examinations, haematological findings were instructive inasmuch as a downward trend in the total white cell counts, due mainly to polymorphonuclear leucopenia, concurred with the most active phase of the disease.

Regression of the parasitic lesions was accompanied by a leucocytosis. Eosinophilia prevailed throughout the course of the infection and was especially marked at the time of the leucopenia when it reached a peak value of 27.0% during the tenth week and did not fall below 10.0% until the twentieth week of the disease. Irfan (1961) has suggested that a high eosinophil count (up to 1000 cells per cu. mm.) is normal for the cat but personal observations inform that such a figure is too high. Even so, the numbers found during the current experiment were generally in excess of the above value.

Archer (1963), in a discursive explication of eosinophilia, implied that the condition was probably more commonly associated with parasitism than it was with any other clinical entity and that the accumulation of eosinophils in tissues invaded by parasites was usually striking. He suggested that the mechanism of eosinophilia was attributable to several factors, probably the most important of which was the release of histamine arising from damage caused by the parasites or as a result of an antigen-antibody reaction where the parasites were antigenic to the particular host. As such injury was usually prolonged, it was likely to exert an eosinotactic effect upon the blood for an extended period and to stimulate the production of eosinophils by the bone-marrow. The author concluded by

emphasizing that the eosinophils function primarily in tissues and not in the circulating blood. Such an explanation of eosinophilia in relation to lungworm disease of the cat is both reasonable and acceptable.

Local tissue-damage with consequent degranulation of the mast-cells and release of their contained histamine is known to cause eosinophils to collect in the injured area (Sheldon and Bauer, 1960). Moreover, Welsh and Greer (1959) found that mast-cell granules are phagocytosed by eosinophils, which observations tend to suggest that a close functional relationship may exist between the two types of cell. However, staining by Gomori's aldehyde-fuchsin and by the periodic acid-Schiff methods failed to reveal any evidence of concentration of mast-cells in parasitized tissue that was massively invaded by eosinophil leucocytes.

The sedimentation rate of erythrocytes is dependent, partly, upon the propensity of those cells to form rouleaux and, partly, upon the number of red cells per unit volume of blood together with certain plasma factors, the most important of which is the concentration of fibrinogen and globulin. In the course of diverse diseases, agglutination of erythrocytes may occur to a degree that is usually commensurate with the severity of the morbid process.

By reason of insufficient available knowledge, Schalm (1961) did not record values for the erythrocyte sedimentation rate pertaining to the feline species but did suggest

that the figure was likely to approach that which had been forthcoming for the dog. Personal observations, however, indicate that normal for the cat is a sedimentation rate of 1 to 5 mm. per hour so that the data registered in Table 32 (p. 162) may be regarded as distinctly abnormal since the values range from 20 mm. per hour at two weeks, to as much as 40 mm. per hour at 10 weeks, after infection.

It may be expected that the lesions arising from infestation by Aelurostrongylus abstrusus would become more severe as the production of eggs and larvae progressed. At two weeks after infection, only young adults were found to be present in the lungs and the associated cellular reaction was both inconspicuous and unmarked by the formation of giant-cells. In contrast, by the end of the fourth, sixth, eighth and tenth weeks of the experiment, the lesions had not only become more extensive but the cellular response was also more pronounced and attended by numerous giant-cells while coalescence of some foci had occurred to produce fairly prominent nodules. Enlargement of the bronchial lymph-nodes, slight at the close of the second week of infection, was considerable by the end of the tenth week but declined steadily from the twelfth week until the end of the experimental period. Prior to the tenth week, lesions appeared to extend, but by the end of the twelfth week they had contracted and were then found to contain the remnants of parasites surrounded by dense accumulations of

cells while the necrotic areas, too, were markedly reduced in extent. Over the next 12 weeks, gradual recession of the cellular reaction together with removal of parasitic detritus took place. Quite the most striking manifestations of the condition were the eosinophilia, as already described, together with the hypertrophic changes encountered in the muscle of the bronchioles and alveolar ducts and the thickening of the arterial walls. Alteration of the muscle of the bronchioles and alveolar ducts was discernable at the earliest recorded stage of the disease but was not wholly limited to the sites of parasitic activity. During the course of the disease the muscular hypertrophy increased and, indeed, had not diminished at the end of the six months period of the experiment.

By the second week of infection, the media of the muscular pulmonary arteries had undergone hypertrophic change consisting of simple enlargement of the myofibrils and, two weeks later, was of similar degree of severity. By the end of the sixth week after infection, exaggeration of the hypertrophic process together with hyperplasia of muscle ensued to persist until the close of the experimental period. The arterial thickening, which was not present in all the muscular arteries of the lung, was fairly symmetrical and was distributed along the length of the vessels, which latter became increasingly tortuous as the lesion progressed. Degenerative changes of the elastic

laminae attended the increase in thickness of the medial coat of the arteries and slight development of longitudinal muscle occurred in only three animals.

Not at any stage of the condition was any form of the parasite to be seen intravascularly but adult worms were found in terminal bronchioles, in alveolar ducts or within alveoli while ova and larvae were encountered in the bronchi as well. Such observations are in agreement with those of Hobmaier and Hobmaier (1935a and 1935b), Gerichter (1949), Blaisdell (1952) and MacKerras (1957) but are in conflict with the opinion expressed by Cameron (1929), namely, that the parasites lived in the pulmonary arteries.

Deficiency of lipid in the zona fasciculata of the adrenal glands is usually associated with a state of stress and is a not unexpected finding in view of the fact that resolution of the gland was noted only in the case of the last three experimental animals.

The data recorded in Table 33 (p. 163) serves to show that the mean wall-to-lumen ratios of the renal and myocardial arteries fall within the normal range, which finding implies the absence of generalized hypertensive change.

If the experimentally produced lungworm disease be compared with the recorded spontaneous condition, in general, the two are quite similar. At least one spontaneous case proved fatal and others may have been more heavily infested

than were the experimental animals, in which event the few minor differences between the two groups are explicable. The spontaneous disease was characterized by more marked proliferation of bronchial and bronchiolar epithelium and by greater enlargement of the peribronchial glands as well as by the occurrence of a larger number of ova and larvae within the bronchi. In respect of the vascular lesions, intimal fibrosis as well as sub-endothelial vacuolation and the development of longitudinal muscle were less evident in the experimental group. Otherwise, the pathological manifestations were similar.

Not without value is the grading utilized in Part 3 of this thesis, whereby the severity of the lungworm condition was related to the degree of arterial medial hypertrophy. In the experimentally produced disease, progressive arterial thickening was recorded up to the tenth week after infestation and, if that aspect of the morbid process be considered in conjunction with other factors, such as the presence of eggs, larvae or adult worms, then it becomes possible thereby to approximately assess the time that has elapsed since infestation.

e. Conclusion.

The experimental evidence offered, leads to the conclusion that hypertrophy and hyperplasia of the muscular pulmonary arteries attended by other changes similar to

those seen in association with spontaneous lungworm disease of the cat are artificially reproducible in consequence of infestation by *Aelurostrongylus abstrusus*.

B. EXPERIMENTAL VASOMOTOR STIMULATION.

1. THE PRODUCTION OF PULMONARY ARTERIAL LESIONS BY THE USE OF METRAZOL.

a. A Review of the Literature.

Metrazol is 1:5 pentamethylene-tetrazol and acts on the medulla oblongata. It is an analeptic, that is, it is invigorating and restorative. It stimulates the respiratory and vasomotor centres of the brain and thereby produces effects on the peripheral circulation and respiration. Metrazol has been used as a respiratory and circulatory stimulant, for instance, to antagonize the cerebrally-depressive effects of poisoning by hypnotic drugs and also to produce convulsions during the treatment of some mental disorders. In human patients, muscular paroxysms are forthcoming within 30 seconds after intravenous administration and last for about 1½ minutes before they are followed by amnesia (Clark, 1955).

Eichler and Hildebrandt (1926) observed that, when metrazol was injected into dogs in a dose of 10 to 20 milligrammes per kilogramme of body weight, it caused a decrease in the volume of the intestine, kidney and limb accompanied by a rise of blood pressure. Contrarious results were reported by Camp (1928).

Maury and Gruber (1939), in spinal as well as anaesthetized dogs and cats, experienced a dual response to the drug in so far as small doses (5 to 10 mg. per kg.)

produced an increase in visceral volume with simultaneous fall of blood pressure whereas larger doses (20 mg. per kg.), after a similar initial effect, caused rise of blood pressure together with splanchnic contraction. The results of administration of large doses to spinal and decerebrate animals indicated that the site of action of the drug was the medulla oblongata.

Woodbury et al. (1941), in an investigation of the effect of metrazol on the blood pressure of man and the dog, found a pronounced variation to exist between the two species. In the human being, the drug stimulated the parasympathetic and sympathetic nervous systems with resulting increase of blood pressure in which vasoconstriction played only a minor role. In the dog, on the other hand, the drug produced considerable and prolonged elevation of arterial pressure in consequence of vasoconstriction that but slightly involved the pulmonary vascular system.

Neumann et al. (1942) employed metrazol to produce convulsions in cats, for which purpose the total amount given over a period of 2 to 99 days lay between 513 and 3,100 mg. administered thrice weekly. The main pathological findings were vascular congestion and stasis of the abdominal and thoracic viscera together with petechial haemorrhages into the lungs, myocardium and kidneys and, in some cases, glomerulo-nephritis and focal round-cell infiltration of the liver. Focal calcification of the adrenal glands was

noted in one animal and was attended by endarteritis, fibrosis and reticulo-endothelial hyperplasia of the spleen. There were several cases of pulmonary endarteritis, of which an explanation was not found.

Kell et al. (1956), pursuing a finding incidental to a previous experiment, conjectured that chronic cerebellar stimulation had an influence upon the pulmonary vasculature. They considered that spontaneous pulmonary arterial hypertrophy of the cat was rare, but found that stimulation of the vasomotor centres of the brain by use of metrazol resulted in an arterial lesion of similar kind in almost eighty per cent of nineteen cats so treated. Dosage varied from 15 to 30 mg., administered twice or four times per day, but the duration of treatment of those animals was not stated.

Several articles concerning the effects of metrazol on the central nervous system of various animal species have been published, thus: in the dog, by Shemano and Nickerson (1959) and by Bircher (1963); in rats, by Manax and Stavraky (1962); in the case of isolated cardiac muscle of the cat, by Covino and Gillen (1962) and, in relation to arteriosclerosis of man, by Kass and Brown (1956). However, search of the literature has failed to reveal any corroborative evidence of the effects of the drug on the pulmonary arteries of the cat.

The purpose of the following experiment was to determine whether, or not, lesions described by Neumann et al. (1942)

and by Kell et al. (1956) were to be reproduced in response to administration of metrazol.

b. Materials and Methods.

Twelve kittens, weaned in the animal house and eight to ten weeks old at the beginning of the experiment, were used for the investigation. On average, the animals weighed 600 gm. and were injected four times per day with a 10.0% solution of metrazol, each dose of which contained 20 mg. of the drug, an amount that was barely subconvulsive since a few paroxysms developed in several animals. In numbers of 3, 3, 2, 2 and 2, from one to five weeks, respectively, after administration, the experimental cats were sacrificed at which times also, for purposes of control, a kitten of the same age and weight was killed. At post-mortem examination, portions of lung, heart, liver, spleen and lymph-nodes, gastro-intestinal tract, adrenals, pituitary, thyroid, kidney and brain were taken for histological examination, by means of paraffin-wax sections stained by haematoxylin and eosin.

The wall-to-lumen ratios of the pulmonary, renal and myocardial arteries were appraised by the procedures that have been already described.

c. Results of the Administration of the Drug.

Table 34 (p. 178) shows the number, and the duration of the period, of injections as well as the total amount of the drug administered to each animal.

Clinical signs were non-existent except for mild incoordination that ensued immediately after injection and disappeared within about 15 minutes. The animals remained healthy, were lively and good appetite was maintained throughout the experiment.

Morbid Anatomy.

Pathological lesions were not appreciable at post-mortem examination.

Histopathology.

Table 35 (p. 179) proffers the wall-to-lumen ratios obtained for the arteries of the lungs, myocardium and kidneys, which values denote that the medial structure of those vessels did not undergo alteration. Histopathological change in other organs of the body was completely indiscernible at all stages of observation.

In the five control kittens abnormality was not detected.

TABLE 54.

NUMBER OF INJECTIONS, DURATION OF ADMINISTRATION AND AMOUNT OF METRAZOL GIVEN TO EXPERIMENTAL KITTENS.

Cat No.	No. of Injections	Duration (Days)	Total Amount (mg.)
1	28	7	560
2	28	7	560
3	28	7	560
4	56	14	1120
5	56	14	1120
6	56	14	1120
7	84	21	1680
8	84	21	1680
9	112	28	2240
10	112	28	2240
11	140	35	2800
12	140	35	2800

TABLE 55.

MEAN WALL-TO-LUMEN RATIOS OF PULMONARY, MYOCARDIAL AND RENAL ARTERIES IN CATS TREATED WITH NETRAZOL.

Cat No.	No. of Weeks	Lungs	Myocardium	Kidneys
1	1	0.2556	0.2962	0.1050
2	1	0.2105	0.3262	0.3445
3	1	0.2005	0.2436	0.2562
4	2	0.1005	0.3225	0.2562
5	2	0.2345	0.3200	0.3560
6	2	0.2145	0.2365	0.2464
7	3	0.1995	0.3665	0.4325
8	3	0.1075	0.2565	0.3225
9	4	0.2356	0.3536	0.2975
10	4	0.1115	0.3425	0.2045
11	5	0.0909	0.2545	0.2365
12	5	0.2335	0.3500	0.2680

d. Discussion.

The total daily dose of metrazol given to each animal was 80 mg. and, even a slight excess of that amount was sufficient to cause convulsions in most of the kittens. It was presumed that, as a result of the injection routine, the vasomoter centres of the medulla oblongata were maintained in a fairly constant state of stimulation and that some bodily changes should develop within the period of the experiment. However, the pulmonary arteries were found not to display any evidence of the muscular hypertrophy and hyperplasia or of the intimal proliferation described by Neumann et al. (1942) and Kell et al. (1956).

If the post-mortem findings catalogued in the report of Neumann et al. (1942) be analyzed, the occurrence of glomerulo-nephritis together with adrenal calcification and focal infiltration of the liver, in some animals, at once leads to conjecture relative to the age and the state of health of the experimental subjects. Personal experience, supported by the work of Howell and Pickering (1964), has revealed that adrenal calcification is to be seen mainly in older animals and that nephritis tends to occur in adults. In addition, the pulmonary arterial lesions were not specific for the animals treated with metrazol but were reported to occur in control and insulin-treated cats. It seems probable, therefore, that Neumann et al. (1942) had made use of unselected animals some of which were affected by

pre-existing pulmonary arterial lesions that were not caused by the drug.

Kell et al. (1956) injected metrazol into 19 cats, and of them 15 developed lesions of the pulmonary arteries. Eleven animals were either slightly or not at all affected, although the authors did not divulge the criteria by which they judged the changes to be slight, and only in the remaining eight cats did the lesions appear to be of moderate or pronounced kind. Such a proportion of afflicted animals would approximate the number which might be expected to suffer from the spontaneous condition if the case-incidence of 36.0% given by Scratchard and Wright (1961), and 34.7% recorded earlier in this thesis, are applicable.

The published description of the arterial lesions furnished by Neumann et al. (1942) and by Kell et al. (1956) is remarkably similar to that recorded previously in this work in the experimental lungworm infestation. The latter information, therefore, strongly suggests that both groups of authors worked with cats which had been in contact with Aelurostrongylus abstrusus.

e. Conclusion.

Pulmonary arterial lesions, similar to those described by other authors as a result of the administration of the vasomotor stimulant, metrazol, were not produced in 10-weeks-old kittens despite comparable dosage of the drug and corresponding duration of treatment.

C. FINAL DISCUSSION.

The work pertaining to this thesis has established that a condition of hypertrophy and hyperplasia of the media of the pulmonary arteries of the cat, in the majority of cases associated with hypertrophy of the musculature of the bronchioles and alveolar ducts, occurred spontaneously in 34.7% of 256 cats. It has been demonstrated, too, that little correlation obtained with age, sex or morbid processes other than infestation by the lungworm Aelurostrongylus abstrusus and that all animals so afflicted were found to exhibit arterial lesions.

Although lungworm disease occurred in an appreciable percentage of the 89 animals that displayed the arteriopathy, slightly more than half (53.9%) of the total number of cases was not associated with disease of any kind. However, comparison of the arterial lesions encountered in the animals of Groups 1, 2 and 3 (i.e. cats infected with lungworm, those affected by pulmonary arterial disease alone and those suffering from a variety of diseases in addition to pulmonary arterial alterations, respectively) revealed a similarity which led to the conclusion that a common pathogenesis was more than probable.

Experimental work consisted of attempts to reproduce the characteristic arterial lesion, firstly, by artificial infestation of young kittens with lungworms and, secondly,

by stimulation of the vasomotor centres of the brain by means of a particular drug. The result of those exercises have been recorded and discussed and, in summary, it may be said that (a) the vasomotor stimulation failed to cause any change in the pulmonary arteries and (b) the disease induced by Aelurostrongylus abstrusus was attended by lesions identical with the spontaneously occurring arterial alterations.

It has been previously remarked that some investigators of natural arterial disease of the cat failed to observe any sign of parasitism despite examination of an appreciable number of animals, e.g. Marcato (1940) investigated 30 cats, Olcott et al. (1946) explored more than 150 and Scratchard and Wright (1961) examined 111. Such results tend to suggest that the animals concerned carried only a light burden of parasites or were in convalescence or had actually recovered from the infestation. The experimental results of the present investigation revealed that, by six months after infestation, little evidence of the presence of parasites was to be found unless examination was made of serial sections obtained from many portions of lung tissue.

Contemplation of the descriptions, photographic as well as printed, provided by the articles of Campbell (1927), Ettinger (1932), Rubarth (1940), Marcato (1940), Neumann et al. (1942), Olcott et al. (1946), Koll et al. (1956),

Martin (1959), Dahme (1960) and Scratcherd and Wright (1961) leads to the conclusion that all those reports related to a late stage of the lungworm disease. The supreme importance of an awareness to the spontaneous existence of the arterial condition becomes evident when the articles of Neumann et al. (1942), and especially of Kell et al. (1956), are considered. The latter authors attributed the vascular changes to the effect of the vaso-stimulant employed whereas, almost certainly, the lesions were already in being. Therefore, when cats are used for experimental investigation, especially that of cardio-pulmonary application, it is essential that they be comprised only of animals which have been born, or at anyrate weaned, on the premises if insignificant results are to be obviated.

The considerable incidence of the spontaneous condition in cats indicates a high rate of infestation and of recovery, both of which accord with the mildness of the clinical disease.

The intimal fibrosis, which figures prominently in the reports of several authors and was also encountered to marked degree in a few spontaneous cases recorded in Part 3 of this thesis, is probably explicable on the grounds of age and the severity of the lesion since the more prolonged the injury, the greater is the likelihood of the production of fibrous tissue.

If it is accepted that lungworm infestation is responsible for the arterial lesions in the cat, the problem of pathogenesis remains. It is generally agreed that, neoplasia apart, excess of muscle tissue is an expression of increased muscular load and that arterial medial hypertrophy is the result, rather than the cause, of arterial constriction. Thus, medial hypertrophy implies an active contraction occurring intermittently or continuously over a prolonged period (Harris, 1955). The mere presence of an excess of muscle, however, is not constrictive but it is also true that the thicker the muscle the more strongly does it contract when stimulated.

According to Harris and Heath (1962), the causation of muscular hypertrophy may be neural or humoral or myogenic in origin although the authors were inclined to disregard the first two on a basis of lack of sufficient proof. The myogenic theory postulates that, in the majority of individuals affected by pulmonary hypertension, the original cause is likely to produce a slight rise of pulmonary arterial pressure as a result of either reflux transmission or increased flow of blood through the lungs. The initial rise may not occur during rest and becomes appreciable only under conditions of stress whereby small, and probably transient, increase of pulmonary arterial pressure leads to distension and to constriction of the medial muscle. At first, the contraction is weak because the amount of medial

muscle is small but frequent or continued stricture causes the muscle to hypertrophy. In turn, enhanced constrictive power tends to exaggerate an originally insignificant function whereby the pulmonary arterial pressure is raised and a vicious cycle of hypertension and constriction is so induced. The production of longitudinal muscle seen in a number of animals has been commented upon in Part 3 and was considered to be part of a process of vascular response to elevated pulmonary pressure.

In the human being, the development of pulmonary hypertension is accompanied by intramural increase in the amount of elastic tissue and the establishment of intimal, and eventually medial, fibrosis, all of which are manifestations of prolonged injury.

Aviado (1960), in an analytical review of the literature pertaining to the effects of anoxia upon the mammalian pulmonary circulation, reported the finding of substantial agreement with the view that anoxia caused constriction of the pulmonary vessels. That effect appears to result from excitation of the chemo-receptive aortic and carotid bodies with subsequent sympathicotonia.

Naeye and Bickerton (1959), in a study of pulmonary hypertension among healthy human beings at high altitudes, considered the arterial change to be an adaptive form of hypertrophy that resulted from increased vasotonus due to chronic anoxia. Naeye also maintained that the arterial

changes, encountered in human beings suffering from chronic hypoxia as a result of damage to the respiratory centre (1961b) or of kyphoscoliosis (1961c) and in rats kept in an hypoxic environment (1959), were the consequence of the same event rather than a sequel of increased pulmonary pressure.

Alexander and Jensen (1963), in relation to High Mountain disease in cattle, considered the medial hypertrophic changes to have arisen from hypoxia leading to vasoconstriction. Further hypertrophy was attributed to a rise of intravascular pressure associated with hypertension, which view seems to combine the theories advanced by Harris and Heath (1962) and by Naeye and Dickerton (1959).

How far those hypotheses are applicable to the cat is debatable and the first problem to be met involves the extent to which the lesion is distributed in the arteries of the lungs. In the papers cited above, the pathological conditions productive of pulmonary hypertension, e.g. mitral stenosis and septal defects, are located outside the lungs and so are likely to affect all the pulmonary arteries to similar degree whereby a diffuse alteration is liable to ensue. Although they were sometimes to be found widely diffused in parts of the lungs, the lesions in the cat were decidedly focal in character and involved branches of the pulmonary artery. In the majority of cases, too, arteries of normal size were always present, sometimes, in the same or different sections of the lungs and, at other times, in

different lobes. In consequence the myogenic theory propounded by Harris and Heath (1962) does not appear to be entirely applicable to the causation of the pulmonary arterial lesions of the cat.

Rosenberg et al. (1963), discussing pulmonary arteries in which the blood-flow was accelerated, declared that hypertrophic changes involved only the number of vessels necessary to maintain homeostasis and that the arteries did not obey the "all or nothing" law. Unfortunately, it was not made altogether clear whether a similar finding applied to a group of patients in whom decreased flow of blood was associated with elevated pulmonary pressure and the production of intimal lesions. Were that so, it would afford a logical explanation of the arterial changes noted in the cat, if only to the extent that a small increase of pulmonary pressure, initially due to the presence of fourth-stage larvae, may lead to adaptive medial hypertrophy in a number of arteries, with, sometimes further progression as visualized by Harris and Heath (1962).

The theory that hypoxia stimulates the vasomotor centres and induces vasoconstriction suffers from the same defect as does the myogenic hypothesis, namely, that the direct cause of the reduced tension of oxygen is of extra-pulmonary location and so is likely to produce diffuse changes in the vasculature of the lungs. Furthermore, the experiment described in an earlier part of this thesis

showed that increased vasomotor stimulation, per se, does not result in pulmonary arterial hypertrophy of the cat so that it is debatable, indeed, that stimulation arising from hypoxia serves to produce arterial lesions. It is also unlikely that hypoxia in a part of the lung substance, where dense cellular infiltration and massive parasitic invasion obtain, would lead to focal hypertrophic change of the arteries.

The theory advanced by Scratcherd and Wright (1961) to the effect that the arterial changes arose as a result of thrombo-embolism has earlier been rejected since it did not seem to offer a suitable explanation for the condition. The findings of the experimental lungworm infestation not in any way alters that decision.

It would be convenient to accept Cameron's view (1929), namely, that adult worms located in the pulmonary arterial system cause local irritation and probably also give rise to partial blockage of the vessels. However, there has not been any confirmation of that theory and, indeed, the evidence furnished by all other workers in the field has been to the contrary.

Blaisdell (1952) suggested that, at some stage of its development, the parasite may produce a substance capable of stimulating smooth muscle. As hypertrophy of the muscle of the bronchioles and the alveolar ducts as well as the arterial muscle was observable within two weeks of

infestation, when only fourth-stage larvae or young adults were present, those are the forms of the parasite most likely to have elaborated such a substance. The idea is attractive, especially, in application to the muscle of the bronchioles and alveolar ducts in which diffuse change occurred early and continued until the end of the disorder. Blaisdell's theory is less acceptable, however, in reference to arterial muscle in which the alteration was progressive and of a focal nature.

Metazoan parasites may produce histamine (Archer, 1963) but that substance has not been demonstrated to cause alteration of pulmonary pressure (Harris and Heath, 1962). Serotonin is a potent vasoconstrictor that is closely allied to histamine but, although it has been claimed to cause pulmonary arterial lesions in rabbits (Ahmed and Harrison, 1964 and Rossi and Zamboni, 1958), it has not been found by the author of this thesis to be similarly active in the cat.

The explanation of the characteristic pulmonary arterial lesion of the cat is not easy. Indubitably, occlusion of arterioles together with disorganisation and even obliteration of areas of the capillary bed, caused by the parasite and the consequent cellular reaction, results in increased resistance to flow of blood in the muscular arteries of the affected regions. Constriction of the arterial myofibrils over a period of time is likely to occasion hypertrophic changes in the media of the vessels

which leads to increase in the intramural pressure. That, in turn, stimulates the production of longitudinal muscle, intimal fibrosis and endothelial proliferation. It is noteworthy, however, that the later stages of hypertensive vascular disease, so commonly seen in man, do not occur in the pulmonary arteries of the cat because of the survival of normal arteries, even, in the most severely affected lungs. That other factors, such as hypoxia or the production of toxic substances by the parasite, may also be involved in the aetiology of the feline arterial lesions is indisputable but adequate proof of their participation has not yet been forthcoming.

Whatever explanation for the development of the arterial changes proves acceptable, the single outstanding fact revealed by the investigations reported in this thesis, is that Aelurostrongylus abstrusus - the lungworm of the cat - is a most important, if not the sole, agent responsible for the initiation of the condition of hypertrophy and hyperplasia so commonly encountered in the muscular pulmonary arteries of the cat.

D. FINAL CONCLUSION.

Hypertrophy and hyperplasia of the pulmonary arterial media has been established to obtain commonly in the cat and its occurrence is independent of either age or sex but it is associated with lungworm disease. The author claims to have correlated, for the first time by facts rather than by impressions, the spontaneously occurring condition with parasitic infestation but acknowledges that many facets of the disease still await elucidation. Thus, it is essential to investigate the early migration of third-stage larvae together with the immunological responses of infested animals as well as the pathogenesis of the arterial lesions and the effects of the disease on the pulmonary and systemic blood pressures. Because of technical difficulties, much of that work has not yet been attempted and it is hoped still to advance the state of knowledge of this important parasitic condition of the cat.

F. BIBLIOGRAPHY.

1. AHMED, F.S. and HARRISON, G.V. (1964). J. Path. Bact. 87. 325.

2. ALEXANDER, A.F. and JENSON, Rue. (1963). Amer. J. vet. Res. 24. 103. 1094.

3. ARCHER, R.K. (1965). The Eosinophil Leucocyte. Blackwell.

4. AVIADO, D.M. (1960). Pharmacol. Rev. 12. 159.

5. BAILEY, W.S. and WILLIAMS, A.G. (1949). Vet. Med. 44. 267.

6. BAILEY, W.S. and LOMAN, C.B. (1952). Auburn Vet. 9. 1.

7. BARNARD, P.J. (1953). J. Path. Bact. 65. 129.

8. BARNARD, P.J. (1957). J. Path. Bact. 73. 17.

9. BARON, J. (1946). Thesis. Alfort, Paris.

10. BAUDET, E.A.B.F. (1933). Tijdschr. v. Diergeneesk. 60. 982.

11. BEST, P.V. and HEATH, D. (1961). Circulation Res. 9. 288.

12. BIRCHER, R.P. (1963). J. Pharmacol. 141. 6.

13. BLAISDELL, K.F. (1952). Thesis. Cornell University.

14. BREMER, C. (1935). Arch. intern. Med. 56. 211.

15. BROWN, V.K. (1962). Vet. Rec. 74. 829.

16. CAMERON, T.W.M. (1926). J. Helminth. 4. 53.

17. CAMERON, T.W.M. (1927). J. Helminth. 5. 55.

18. CAMERON, T.W.M. (1929). J. Helminth. 6. 165.

19. CAMERON, T.W.M. (1929). Brit. vet. J. 85, 97.

20. CAMERON, T.W.M. (1932). J. Helminth. 10. 231.

21. CAMP, J. (1928). J. Pharmacol. 33. 81.

22. CAMPBELL, J.A. (1927). J. Physiol. 63. 25.

23. CHRISTENSEN, N.O., OLSEN, S.J. and ROTH, H. (1946). J. Parasit. 32. 514.

24. Clark's Applied Pharmacology. 8th Ed. Churchill. Edited by Wilson, A. and Schild, H.O. (1955).

25. COVINO, B.G. and GILLEN, H.W. (1962). J. Pharmacol. 135. 136.

26. CRISTI, C.A. and AUYMANET, P. (1947). Anales de la Facultad de Veterinaria Montevideo. 5. 155.

27. DA CRUZ, A.A. and de FREITAS, L.R. (1949). Rev. Med. Vet., Lisbon. 43. 222.

28. DAHMS, E. (1960). Berl. Münch. tierärztl. Wschr. 73. 17. 333.

29. DAMMANN, J.F., Jn., and FERENCZ, C. (1956). Amer. Heart J. 52. 7.

30. ETTINGER, G.H. (1952). Quart. J. exp. Physiol. 22. 167.

31. EICHLER, O. and HILDEBRANDT, F. (1926). Arch. f. exp. Path. Pharmak. 116. 100 and 111.

32. FRY, W. and STEWART, J.T. (1952). J. Parasit. 18. 54.

33. GERICHTER, C.B. (1949). Parasitology. 39. 251.

34. GORDON, H.McL. (1953). Aust. vet. J. 9. 199.

35. HAMILTON, J.M. (1963). Vet. Rec. 75. 417.

36. HARRIS, P. and HEATH, D. (1962). The Human Circulation. E. and S. Livingstone.

37. HARRIS, P. (1955). Brit. Heart J. 17. 65.

38. HARRISON, C.V. (1948). J. Path. Bact. 60. 29.

39. HAURY, V.G. and GRUBER, C.M. (1939). J. Pharmacol. 126. 143.

40. HEATH, D. (1963). J. Path. Bact. 85. 407.

41. HECHT, H.H., LAMKE, R.L., CARNES, W.H., KUIMA, H. and BLAKE, J.T. (1950) Tr. A. Am. Physicians. 72. 157.

42. HILL, D.A. (1961). Principles of Medical Statistics. 7th Ed. Lancet Ltd.

43. HORMAIER, A. and HORMAIER, M. (1954). Science. 2071. 229.

44. HOERLEIN, A. and HOERLEIN, M. (1956a). Proc. Soc. exp. Biol. N.Y. 92. 1641.

45. HOERLEIN, M. and HOERLEIN, A. (1956b). J. Amer. vet. med. Ass. 67. 191.

46. HOFF, E.C., KELL, J.P., HASTINGS, N., SHOLES, D.M. and GRAY, F.H. (1951). J. Neurophysiol. 14. 317.

47. HOWELL, J.McC. and PICKERING, Christine M. (1964). J. comp. Path. 74. 230.

48. IRVAN, H. (1961). Irish Vet. J. 15. 65.

49. JUBB, K.V.F. and KENNEDY, P.C. (1963). Pathology of Domestic Animals. Academic Press.

50. KASS, I. and BROWN, E.C. (1956). Jour. nero. ment. Dis. 123. 57.

51. KELL, J.P. Jr., HENNIGAR, G.R. and HOFF, E.C. (1956). A.M.A. Arch. Path. 61. 239.

52. KERNOHAN, J.W., ANDERSON, E.W. and KEITH, N.M. (1929). Arch. int. Med. 44. 395.

53. LEWIS, E.A. (1927). J. Helminth. 5. 171.

54. LINDSAY, S. and CHAIKOFF, I.L. (1955). A.M.A. Arch. Path. 60. 29.

55. MacKERRAS, M.J. (1957). Aust. J. Zool. 5. 169.

56. McKENZIE, A. (1960). Rec. vet. Sci. 1. 255.

57. McLAUGHLIN, R.F. Jr., TYLER, W.S. and CANADA, R.O. (1961). Amer. J. Anat. 109. 149.

58. MANAX, S.J. and STAVRAKY, G.W. (1962). Canadian J. Biochem. Physiol. 40. 1477.

59. MARCATO, A. (1940). Nuova vet. 18. 75.

60. MARTIN, J. (1959). Mh. Vet. Med. 14. 693.

61. MORLOCK, C.G. (1959). Arch. int. Med. 44. 395.

62. MUIRHEAD, F.E. and MONTGOMERY, P. O'B. (1951). A.M.A. Arch. Path. 60. 89.

63. MAYR, R.L. and RICKERTON, W.A. (1959). Fed. Proc. 18. 407.

64. MAYR, R.L. (1961a). A.M.A. Arch. Path. 71. 121.

65. MAYR, R.L. (1961b). Amer. J. Cardiol. 8. 416.

66. MAYR, R.L. (1961c). Amer. J. Path. 39. 561.

67. NEUMANN, M.A., COHN, R. and KATZENELBOGEN, S. (1942). Amer. J. Psychiat. 99. 668.

68. NEUBERNE, J.W. (1953). Auburn Vet. 9. 5.

69. OLCOTT, C.T., SAXTON, J.A. and MOSELL, W. (1946). Amer. J. Path. 22. 2.

70. O'NEAL, R.M., THOMAS, W.A. and HARTCROFT, P.M. (1955). A.M.A. Arch. Path. 60. 267.

71. PEI-LIN-LI. (1946). J. Path. Bact. 58. 575.

72. PRITCHETT, H.D. (1936). J. Amer. vet. med. Ass. 92. 692.

73. ROSENBERG, H.S., McNAMARA, D.G. and COLN, C.D. (1963). A.M.A. Arch. Path. 75. 177.

74. ROSSI, P. and ZAMBONI, L. (1958). Nature. 4617. 1217.

75. RUBARTH, S. (1940). Skand. Vet. Tidskr. 30. 469.

76. SCHALM, O.W. (1961). Veterinary Haematology. Baltimore, Tindall and Cox.

77. SCRATCHERD, T. and WRIGHT, D.E. (1961). A.M.A. Arch. Path. 72. 111.

78. SEDDON, H.R. (1947). Aust. Dept. Health. Div. Vet. Hyg. Serv. Pub. 2.

79. SHELDON, W.H. and BAUER, H. (1960). J. exp. Med. 112. 1069.

80. SHIMAMO, I. and NICKERSON, M. (1959). J. Pharmacol. 126. 143.

81. SPENCER, H. (1962). Pathology of the Lung. Oxford.

82. SUMUTH, W.H. (1955). J. Amer. vet. med. Ass. 126. 211.

83. TÖNDURY, G. and WEIDEL, E. (1958). Cited by Dahme (1960) Berl. Münch. tierärztl. Wschr. 73. 17. 333.

84. TURNBULL, H.M. (1914). Quart. J. Med. 8. 201.

85. VANE, G. and DALL, J. (1957). Quart. J. Med. 26. 65.

86. WAGENVOORT, C.A. (1960). Circulation. 22. 535.

87. WELCH, K.J. and KINNEY, T.D. (1948). Amer. J. Path. 24. 729.

88. WELSH, B.A. and GREER, J.C. (1950). Amer. J. Path. 35. 103.

89. WOODBURY, R.A., HAMILTON, W.F., CARCKEEY, H.M. and VOLPITTO, P.P. (1941) J. Pharmacol. 72. 421.