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SPONTANEOUS ARTERIOSCLEROSIS IN RABBITS

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INTRODUCTION:

Spontaneous lesions in the cardiovascular system found in small laboratory animals have been studied extensively, (3,9, 11 & 12). Studies performed on human autopsy materials have occasionally revealed marked calcification in media of vascular system, (11 & 13). Many investigators have tried to induce such lesions in experimental laboratory animals expecting to clear out the pathogenecity and real cause of the disease in both laboratory animals and man. In this field those who have tried to start their experiments with impairment of renal function were quite successful in inducing similar lesions in cardiovascular system, (3,4,8,10,12, & 14)

In this communication we report a severe arteriosclerosis (Mönckeberg - Type) and calcification in the cardiovascular, urinary and digestive system in rabbits. The pathogenecity of the disease and histopathological findings have been studied.

THE SUBJECT:

A batch of New Zealand strain rabbits was imported from England to Razi State Institute, in December 1974. Rabbits were fed pellet (Table No 1) ad libitium and bred for new colonies.

In July 1975 rabbits were infested with liver coccidiosis and treated with sulfaquinoxaline 0.1 gr. per 100 ml of drinking water for 7 days. A relapse of coccidiosis was noted three months later and a second treatment of 0.1 gr. sulfaquinoxaline per 100 ml of drinking water was administered for seven days.

In March 1976 a new colony of the rabbits aged 12 – 15 months weighing

3–4 Kg. was employed for an experiment and kept in an isolation unit. They were fed with a new formula pellet (Table No 2) Two rabbits died from this batch 15 days after their being transferred to the new place. The lost rabbits were neceropsied and the prominent change was necrotic foci in liver. Microscopic study of direct smears and histoslides prepared from liver revealed liver coccidiosis. So a third treatment with the mentioned drug in the same dose and duration was administered. But, on the 6th day of treatment two more rabbits died. The rabbits were in cachectic condition and at necropsy there was no sign of liver coccidiosis but the prominent changes of "Mönckeberg - Type" arteriosclerosis of the stem and branches of the aorta and large arteries were noted. Roughness and rigidity of the aorta and its branches and extensive whitish knob formation caused these vessels look like bamboo-stick and resembling trachea. The surface of kidneys was rough and both kidneys and adrenal glands were enlarged, (Fig. 1). There was petechial hemorrhages and ulcers in the mucosa of the stomach. Within a week eight rabbits from a flock of 70 were lost with similar changes. Five rabbits were randomly bled and tested for cholestrol, uric acid, BUN, Ca, P, and creatinine levels. The results are figurated in Table No 3.

In April 1976 the pellet was changed and the rabbits were fed from the first fromula pellets. Simultaneously green alpha alpha was also added to ration. The mortality was reduced to one per month during three months.

MICROSCOPIC FINDING:

Heart: Degenerative myopathy was conspicuous in heart muscle. The cardiac muscle exhibited focal coagulative necrosis in wide zone. Nuclear debries were accompanied by the presence of macrophages, lymphocytes and callium depositions. Persisting endomysial connective tissues were augmented by mild fibrous proliferation. In some places the necrotic foci were completely invaded by calcium depositions, (Fig. 2). The subendocardium specially in the cardiac valves proliferated and there was scattered conspicuous calcium deposition in this layer, (Fig. 3). Coronary walls showed thickness and were edematous. Necrosis progressed in the media of some coronary arteries. There was irregularity of the endothelial counter and spur like protrusion due to increased amount of connective tissue ground substance and calcium deposition in media was noted, (Fig. 4).

Arteries: There was advanced changes in main-stem of the aorta and its branches as well as in other arteries and arteriols throughout the body. The walls were thickened and the lumen showed bizarre protrusion and was widened in large arteries while narrowed in arteriols.

In the media, connective tissue proliferated, elastic membrane splitted and the muscular layer disintegrated. Necrosis and calcium deposition were prominent throughout the medial layer, (Fig. 5). The necrotic calcified materials

sometimes bulged toward both interior and exterior of aortic wall, forming knob like protrusion on both sides. These were responsible for the bamboo-stick appearance of the aorta in the gross.

Kidneys: Prominent and advanced changes were noted in the cortical layer and in this region the glomeruli were shrunken.

Bowman's capsules extended and some contained homogeneous eosinophilic materials. Most of the Bowman's capsules and proximal convoluted tubules were calcified. There was conspicuous calcium deposition throughout the cortex, (Fig. 6).

The vascular lesions in the renal arteiols resembled those observed in the coronary vessels. Calcium deposits and ischemic infarcts due to constricted inelastic arteriols caused some patchy whitish wedged shaped appearance in cortical layer in cut surface in gross, (Figs. 7 & 8). Tubular epithelial cells were hypertrophied and some showed different stages of degeneration up to necrosis. Slight monocytic infiltration was noted. Hyalin casts varying in size and frequency were noted in collecting tubules.

Liver: Few calcified necrotic foci due to previous coccidial infestation that were surrounded by coagulative necrosis and hemorrhages were noted in liver sections. Severe fatty midzonal changes were observed in the parenchymal cells throughout the liver, (Fig. 9).

Stomach: There was ulcers and hemorrhages in gasteric crypts. Conspicuous calcium droplets were deposited in the corium of mucosa. Arteriol in the stomach wall showed a severe mediosclerosis with calcium deposition in the medial layer. The lumen in the calcified arteriol was narrowed, (Fig. 10).

Lung: Severe alveolar edema and congestion were noted throughout the lung tissue. There was marked calcification in the bronchial walls. Connective tissue proliferation, metaplasia of cells, ossification and calcium deposits were noted in peribronchial zone of large bronchi, (Fig. 11). The arteriols and arteries showed the changes that have already been mentioned for the vascular-system.

DISCUSSION:

Rabbits in this case received O.lgr. sulfaquinoxaline in 100ml of drinking water for three 7-day periods with 1-3 months intervals. It seems that excessive dosage of sulfanilamide induced invariably massive and lognlasting intrarenal deposition of sparingly soluble crystals and resulted in obstructive nephropathy and permanent kidney damage, (6,7,12 & 14). This renal damage caused elevation of the level of some toxic substances such as urea, uric acid etc... The high level of different electrolytes and toxic substances in circulating blood that had

been prevented from spilling over into urine might have played an important role in the emergence of mediosclerosis of the arterial tree, (8), Then the inability of cardiovascular system itself presumeably caused ischemic and secondary necrosis which was noted thrughout the body. On the other hand, in the wake of renal dysfunction and due to electrolytes imbalance the parathyroid glands are activated. Then the calcium is mobilized from the body due to high level of parathormone and deposited in necrotized areas, (1,2 & 6)

SUMMARY:

A case of spontaneous arteriosclerosis (Mönckeberg-Type) in New Zealand strain rabbits is reported. Histopatholoical changes and the probable pathogenesis is discussed.

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REFERENCES:

1- BAHARSEFAT, M. & AHOURAI, p. (1972)
Arch. Inst. Razi, **24,** 83

2- GILLMAN, J. & GILBERT, C. (1956)
Exp. Med. Surg., **14,** 136

3- KLEINROK, Z. and ROZYNEK, M. (1973)
COR VASA 15 (2)/146 (Abraviated in Biol. Abst. 1973, No 18375)

4- KOLETSKY, S. (1955)
Arch. Path., **20.** 1

5- LEHR, D. (1944)
Bull. N. Y. Acad. Med., **20,** 424

6- LEHR, D. and MARTIN, C. (1956)
Proc. Soc. Exp. Biol. Med., **93,** 596

7- LEHR, D. and CHURG, J. (1952)
J. Mt. Sinai Hospt., **19,** 106.

8- LEHR, D., CHURG, J. and MILORA, R. (1954)
Proc. Soc. Exp. Biol. Med., **85,** 615

9- NUZUM, F.R. & al. (1930)
Arch. Path., **10,** 697

10- ROTHER, L. (1954)
Proc. Soc. Exp. Biol. Med., **85,** 285

11- RENAUD, S. (1962)
Brit.J. Exp. Path., **43,** 387

12- RIBELIN, W.E. and McCOY, J.R. (1971)
The Pathology of Laboratory Animals, 2nd Ed. Charles C. Thomas, Publishere, Springfield, Illinois, U.S.A.

13- TAGUCHI, J.T. & al. (1974)
J.A.M.A., **228** (6), 733

14- WILGRAM, G.F. and INGLE, D.J. (1959)
Arch. Path., **68,** 690

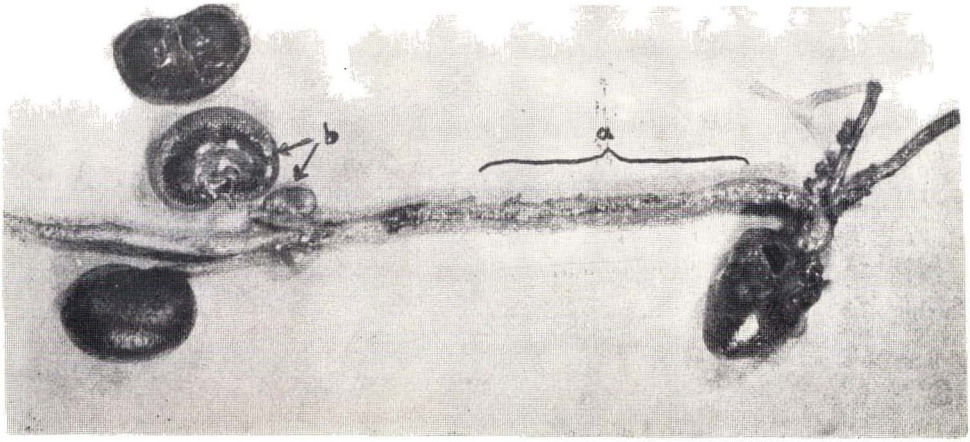

Fig. 1) a: The surface of main trunk of aorta shows roughness.
b: Kidneys and adrenal glands are enlarged.

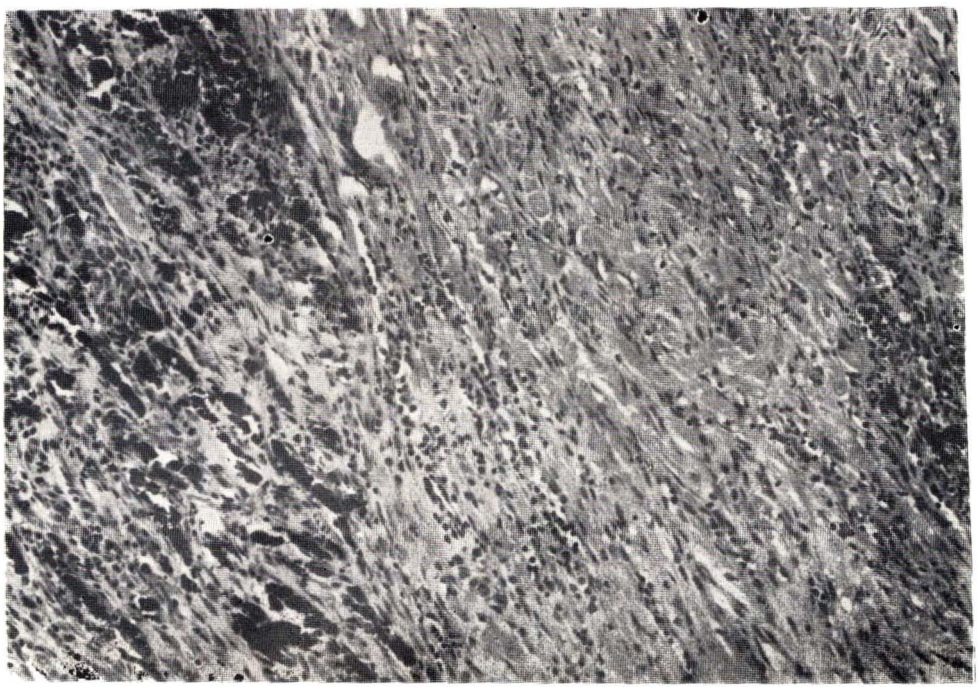

Fig. 2) Myocardium of left ventricle. Note necrotized muscle fibers are replaced by connective tissue proliferation, inflammatory cells infiltration and calcium deposition. X 125

Fig. 3) Note calcium deposition in the endocardium and cardiac valves of left ventricle. X 60

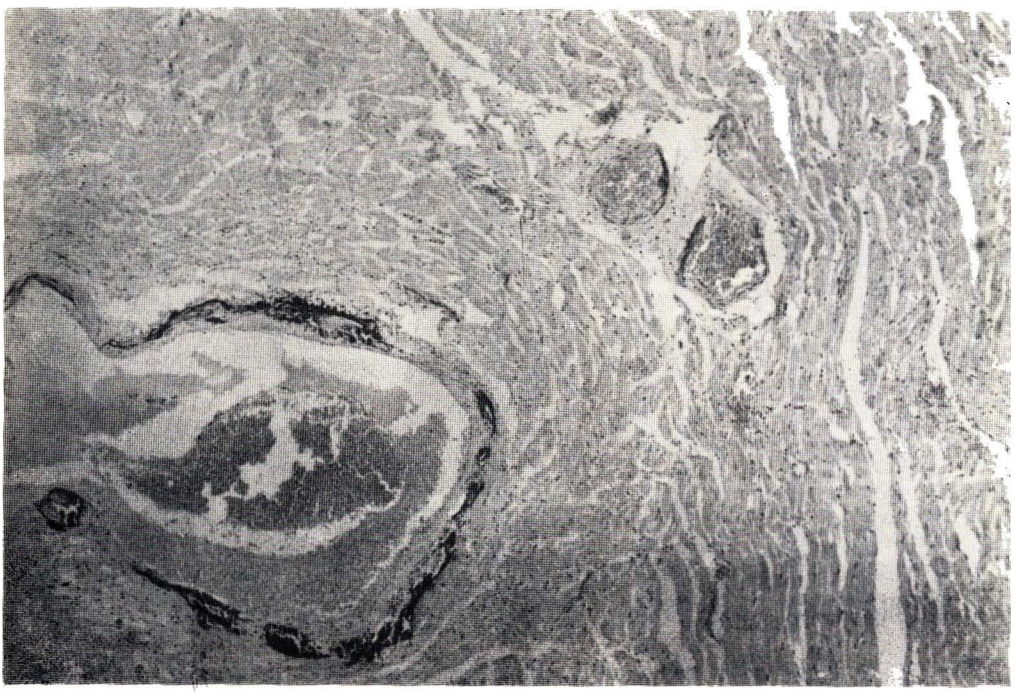

Fig. 4) Necrosis and calcium deposition in the wall of left coronary artery and its branches. (60

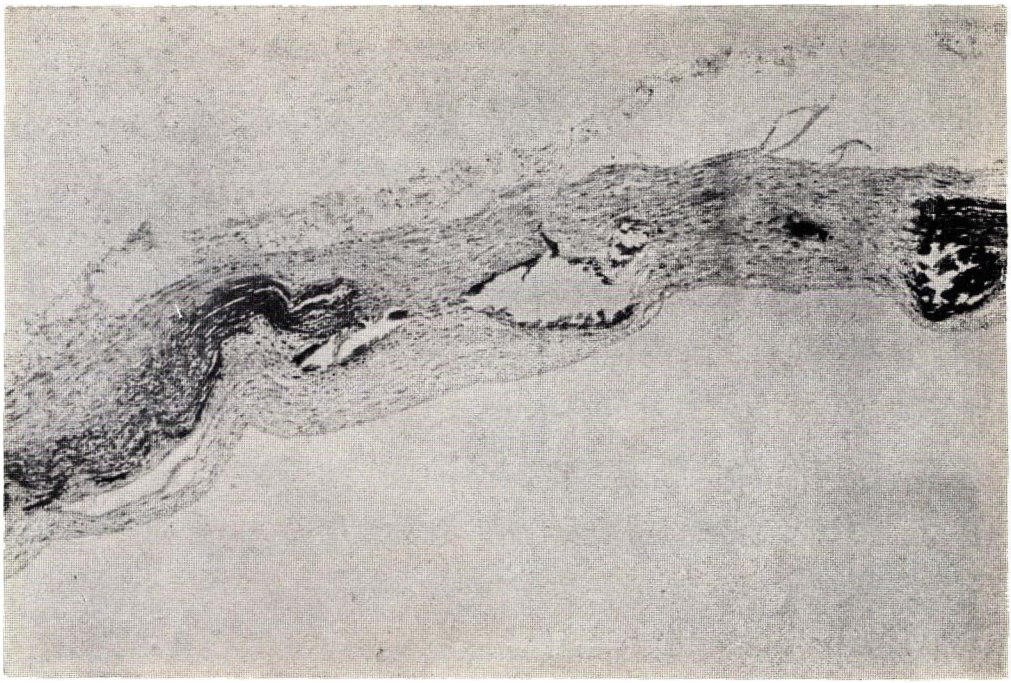

Fig. 5) Aorta wall. Note disintegration of muscular layer, connective tissue prolferatic and calcium deposition. X 60

Fig. 6) Cortical region of the kidneys. Calcium is deposited throughout. X 60

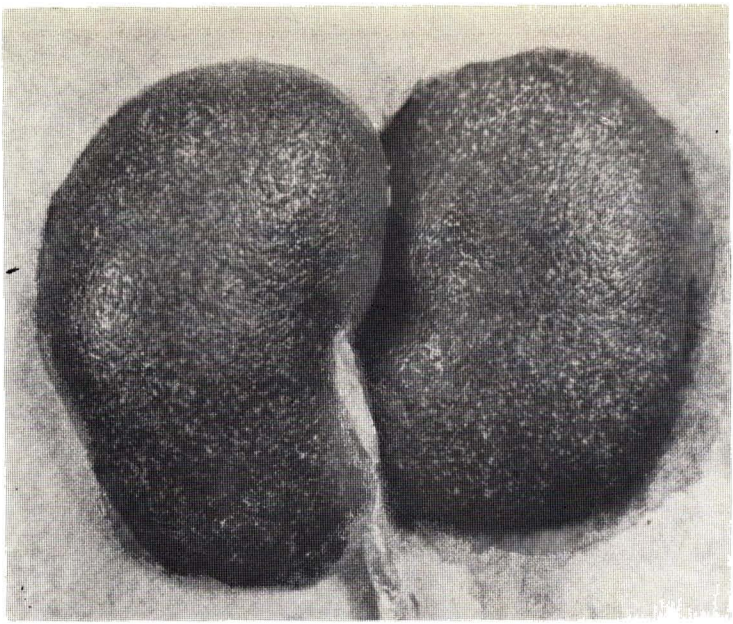

Fig. 7) Note the rough surface of the kidney.

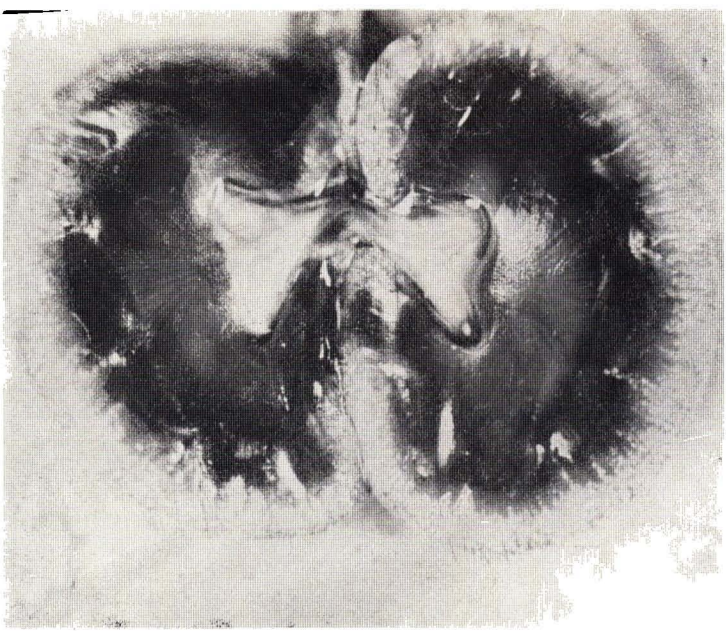

Fig. 8) Note the demarkated cortical zone.

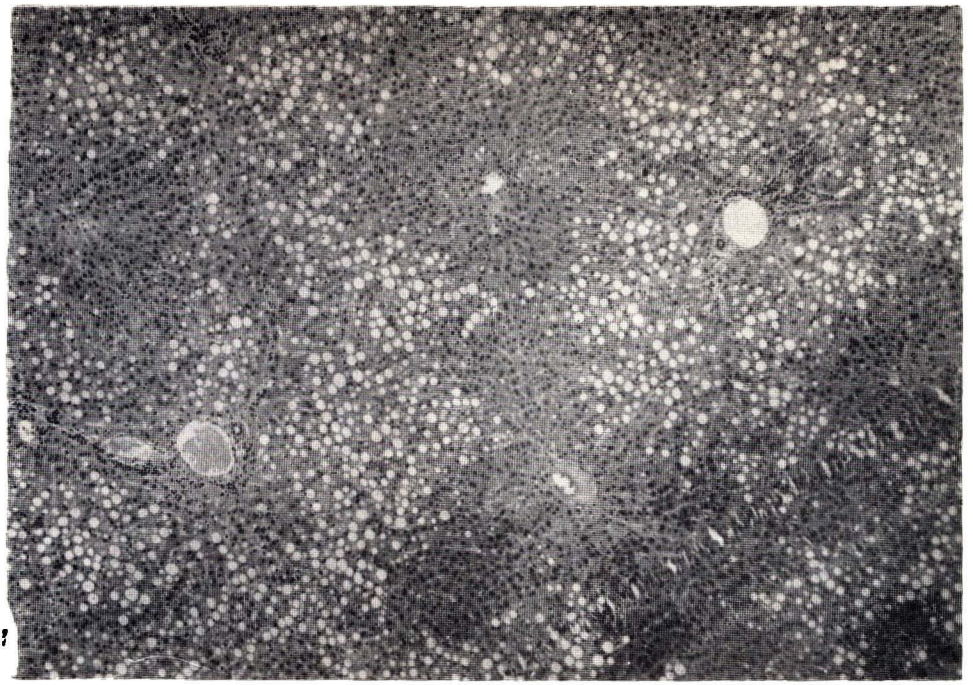

Fig. 9) Fatty changes in the midzonal portion of liver lobule. X 60

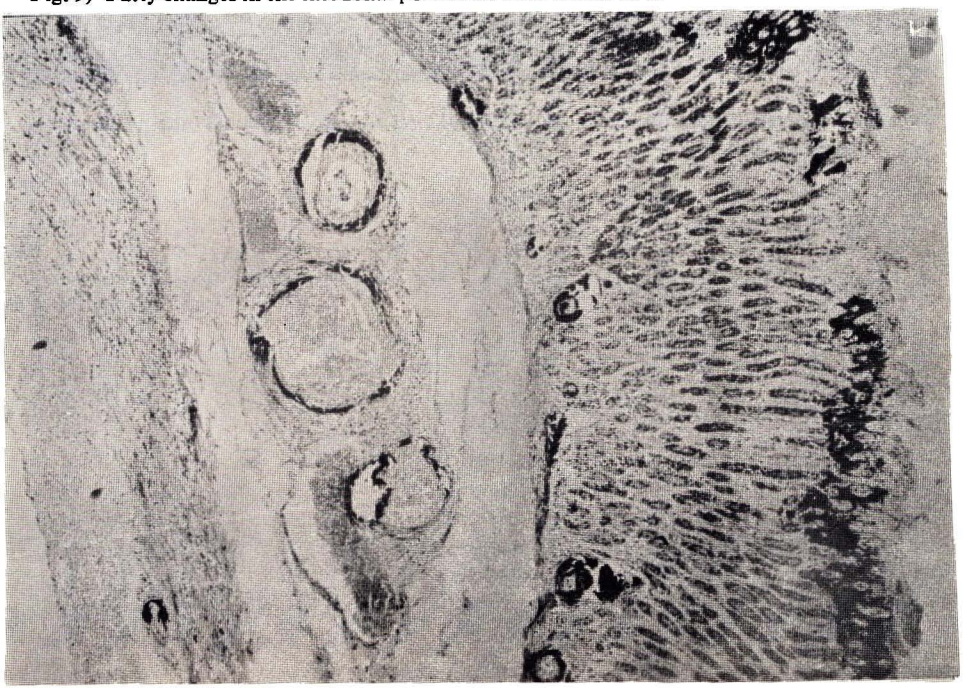

Fig. 10)The stomach wall. Note calcium deposition in the corium of mucosa and arteriol walls. X 60

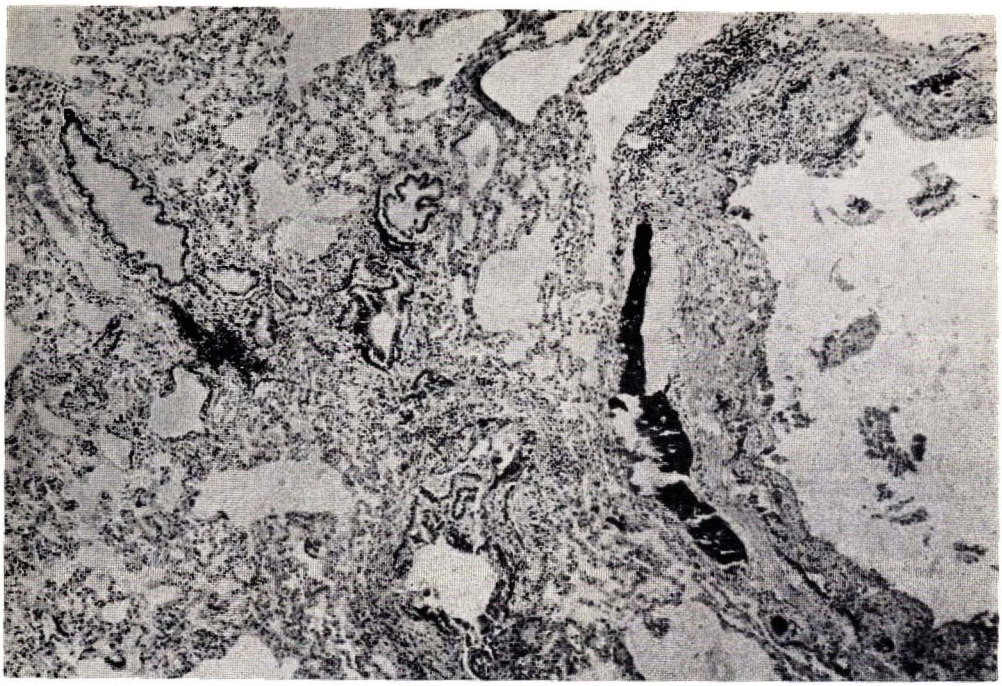

Fig. 11) Note ossification of cells in the bronchial wall and calcification in the peribronchial Zone. X 60

TABLE No 1 = Pellet's Ingridient

Ingridient	Per cent	Convertible energy Kcal/Kg	Raw Protein Gr/Kg	Raw Fat Gr/Kg	Phosphorus Gr/Kg	Calcium Gr/Kg
Wheat	15	2950	115	17	3	0.6
Maize	10	3170	94	47	3.1	0.3
Barely	19	2640	102	19	3.3	0.7
Dried Alpha meal	16	1020	178	25	2.2	13.2
Extracted Soya bean	5	2620	451	8	6.7	2.7
Meat meal	5	2770	579	55	22	59
Bran	19	-	141	39	11.6	2.5
Dried Milk Fowder	6	2750	339	40	10.2	12.7
Vitamin Mineral Supplement	1	-	-	-	-	-
Linsead meal	4	NT	386	19	5	2.5

NT = Not tested

TABLE No 2 = Pellet's Ingridient

Ingridient	Per Cent	Convertible energy Kcal/Kg	Raw Protein Gr/Kg	Raw Fat Gr/Kg	Phosphorus Gr/Kg	Calcium Gr/Kg
Wheat	15	2950	115	17	3	0.8
Maize	10	3170	94	41	3.1	0.3
Barley	19	2640	102	19	3.3	0.7
Dried Alpha meal	16	1020	178	25	2.2	13.2
Soya bean	NT	NT	421	200	6.6	1.8
Meat meal	5	2770	579	55	31	59
Bran	19	NT	141	39	11.6	2.5
Dried milk powder	6	2750	359	40	10.2	12.7
Vitamin Mineral Supplement	1	-	-	-	-	-
Total	100					

TABLE No 3 = Rabbits Serum Analysis

Rabbits No	Uric Acid mg/dl	BUN mg/dl	Cholestrol mg/dl	Creatinine mg/dl	Inorganic Phosphorus mg/dl	Calcium mg/dl
1	1.1	14.8	175	1.64	5.1	17.3
2	1.2	45.9	219	3.8	4.8	16.9
3	1.9	29.2	139	3.5	5.8	18.5
4	1.7	28.9	191	3.14	6.1	19.6
5	2.1	19.6	152	1.76	4.9	16.9