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Blood vessels and their construction in the cavities of pulmonary tuberculosis

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Abstract

First of all, we investigated the origin, the construction and distribution of the bronchial arteries and veins in adult rabbits, and then observed various changes of the blood veels in experimental cavities and caseous foci and also studied the effects of streptomycin and isoniazide on the blood veels of the cavity wall. The summary findings of the present experiments are described in the following. 1) In ten out of the fifteen rabbits emloyed, the bronchial artery originates from the right supreme intercostal artery; in three cases, in addition to this origin, it originates also from the left supreme intercostal artery; and in another case from the intercostal thoracic artery; while in the remaining one from the arc of the aorta. 2) The bronchial veins are divided into the extra-pulmonary and the intra-pulmonary veins. The former arises from the submucous blood veels located in the proximal part of the third bronchus, and running along with the bronchial artery, finally empties into the superior Vena cava; while the latter, originating from the submucous capillaries in the distal part of the third bronchus, and after anastomosing with one another in the capsule of the bronchus, is communicated with the pulmonary veins. 3) In the caseous foci, although blood veels are obliterated, capillaries are newly formed around the main trunks of the pulmonary artery and vein as well as around their residual branches. 4) These caseous foci are supplied with arterial blood from the bronchial arteries, the blood veels in the bronchial wall, and the newlyformed veels of pulmonary arterial origin. 5) The capillaries in the cavity wall are claified into three types according to their origins; namely, Type I, those regenerating from fine branches of the pulmonary veels; Type Ⅱ, those regenerating from the main trunk of the pulmonary veels; and Type Ⅲ, those regenerating from the bronchial artery situated in the orifice of the drainage bronchus. 6) The tuberculous cavities only in the orifice of the drainage bronchus receive an abundant supply of arterial blood directly from the bronchial artery, but those in other regions receive a scanty blood supply indirectly from the anastomoses between the bronchial artery, its sister veels and the pulmonary artery. 7) The regeneration of blood veels in tuberculous foci has been confirmed to occur not only in the bronchial artery and its sister blood veels but also in the pulmonary artery and vein as well. 8) The constructions of blood veels in the cavities treated with streptomycin or isoniazide present no significant difference from those of the control. 9) The regeneration of blood veels and hyperemia in the cavity wall of the cases treated with streptomycin present no significant difference from those observed in the control, but the cases treated with isoniazide show marked hyperemia, newly-formed veels, and occasional bleedings.

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BLOOD VESSELS AND THEIR CONSTRUCTION IN THE CAVITIES OF PULMONARY TUBERCULOSIS

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As for the blood vessels in the wall of tuberculous cavities, it has for a long time been believed to be poorly distributed due to the occlusion of pulmonary artery caused by endarteritis obliterans and the attention had only been focused mainly on the so-called Rasmussen's aneurysm occurring in the branches of the pulmonary artery, that pass through the cavity wall, as the cause of hemoptysis. Moreover, as regards aftermath of the occlusion of the pulmonary artery, many articles concerning the involvement of bronchial artery with the blood circulation of tuberculous lesions appeared since those of GUILLOT, VIRCHOW, and more recently fairly detailed reports on the subject by WOOD and MILLER, LIEBOW[1,2,3], CUDKOWICZ[4], DELARUE[5,6], YAMASHITA[7], TOKUGAWA[8] and AOKI[9,10] are available, nevertheless, there are still many minute points that remain to be solved.

However, with the advent of anti-tuberculous agents such as streptomycin (SM), para-amino salicylic acid (PAS), isoniazide (INH), and the like, there have arisen new problems which aroused a keen interest; namely, the pathway through which these agents reach the foci and the modus how tuberculous bacilli acquire the resistance against these anti-tuberculous drugs.

In the application of streptomycin SUGIHARA[11] observed regeneration of the vessels and hyperemia or hemorrhages in tuberculous lesions, while TAMAI[12] and KUROBANE[13] in their INH therapy recognized the dilatation, hemangiomatous growths, and hemorrhages per diapedesis in capillaries of tuberculous granulations.

Glancing over the available literatures, most investigators have recognized a stimulating action of INH on the tuberculous lesions or a lytic action on the caseous lesions ; but what are the effects of the two drugs, SM and INH, on the vessels and their construction in the pulmonary cavity wall ? With the purpose to obtain some answers to these questions, we have conducted a series of experiment using adult rabbits and present

herewith some of our findings.

METHODS

Observations of the pulmonary vessels in normal rabbits : After sacrificing the rabbits under urethane anesthesia and dissecting the bronchial artery and vein as well as the pulmonary artery and vein, indian ink solution and 1% Berlin blue solution are gradually injected into these vessels. Then the whole thoracic organs are removed and fixed thoroughly in 10% formalin solution as one block. After the fixation, the whole block is thoroughly dehydrated in alcohol, increasing its concentration by degrees ; and these organs are again passed through benzol ; and finally they are immersed into methyl salicylate to obtain Spaltehotz's translucent specimens. These specimens are observed under a three dimensional microscope.

Preparation of specimens of experimental tuberculous cavities and caseous foci, and their observations : By YAMAMURA'S[14] method using the bovine type tuberculous bacilli (Miwa strain) donated by YAMAMURA, eighteen cavities and eleven caseous foci were obtained (Tables 1 and 2). Then translucent serial specimens were prepared in the similar manner as mentioned in previous paragraph with additional treatment with cinnabar solution. The cinnabar solution can not enter into capillaries but it is suitable for the observation of trunk vessels while indian ink and Berlin blue are suitable for observation of both capillaries and trunk vessels.

The treatment of experimental cavities with streptomycin (SM) and isoniazide (INH) : The sensitivity of the bovine type tuberculous bacilli (MIWA strain) to streptomycin and isoniazide was determined by KIRCHNER's medium with 10% human serum (Tables 3, 4). Fifty days after producing plumonary cavities in rabbits by YAMAMURA's method, the rabbits were treated with the dosage of 50mg (20mg/kg) of SM and 25mg (10mg/kg) of INH daily, respectively for thirty consecutive days ; and obtained the eight cavities treated with SM and the five cavities treated with INH. To these cavities dye was injected and transparent specimens as well as histopathological specimens were prepared for observations.

RESULTS

Bronchial arteries and veins of rabbits : On investigating the origins of bronchial arteries in fifteen rabbits, we found that they might be classified into four types as illustrated in Figure 1.

Table 1 Experimental Cavities

No. of rabbit	site	size (mm)	duration (in days)
KL 6	r l	20×21	60
KL 9	r m	15×15	36
KL 13	r m	12×25	53
KL 15	r m	2× 5	57
KL 18	l l	12.5×13	47
KL 20	r l l l	16×18 32×33	60
KL 21	l u r u r m	12× 8 7×16 20×25	75
KL 31	r m	10×20	43
KL 32	r u l u	14×13 14×16	48
KL 43	r u	10×12	83
KL 56	r m	15×12	73
KL 57	r u r m	22×10 8× 7	73
KL 61	r m	13×16	73

r : right, l : left, u : upper, m : middle, l : lower

Table 2 Experimental Caseous Foci

No. of rabbits	site	size (mm)	duration (in days)
KL 2	r m	8× 6	39
KL 16	r u	6× 4	10
KL 21	l l	6× 8	75
KL 36	l l	8× 9	17
KL 37	r m	12×15	30
KL 38	r u r m	10×12 10×14	41
KL 39	r u r m	12×15 10×12	41
KL 54	r u	6× 4	65
KL 59	r m	12×13	99

r : right, l : left, u : upper, m : middle, l : lower

Table 3 Sensitivity of Bovine Type Tuberculous Bacilli (Miwa strain) to Streptomycin

oγ/cc	0.05	0.1	0.2	0.3	0.4	0.5	1.0	5	10	100
##	+	+	+	+	−	−	−	−	−	−
##	+	+	+	+	−	−	−	−	−	−

Table 4 Sensitivity ot Bovine Type Tubercuous Bacilli (Miwa strain) to Isoniazide

oγ/cc	0.05	0.1	0.2	0.3	0.4	0.5	0.6	0.8	1	5	10
##	+	−	−	−	−	−	−	−	−	−	−
##	−	−	−	−	−	−	−	−	−	−	−

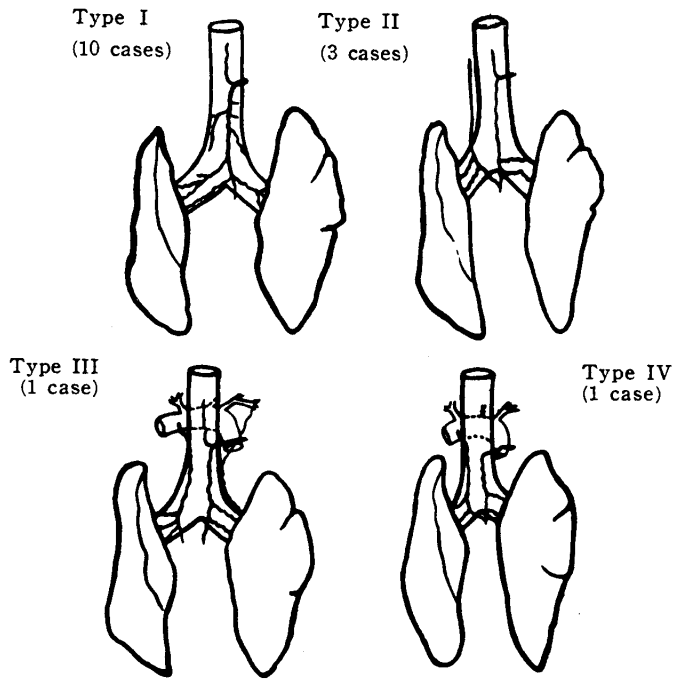


Fig. 1. Schematic Representations of the Origin of the Bronchial Artery in Rabbit (dorsal views)

Type I : To this type are assigned ten out of the fifteen rabbits (66.7 %) in which the bronchial artery originates only from the right supreme intercostal artery arising from the right axillary artery.

Type II (three out of the fifteen cases, 20%) : In this type besides the right bronchial artery observed in Type I, the left bronchial artery arises from the left supreme intercostal artery.

Type III (one out of the fifteen cases, 6.7 %) : In this type besides the branch originating from the right supreme intercostal artery as in Type I, a left bronchial artery branches out from the internal thoracic artery and a small branch, originating from the right internal thoracic artery, is distributed in the right hilum of the lung.

Type IV (one out of the fifteen cases, 6.7 %) : Besides the branch as observed in Type I, a left bronchial artery is seen originating from the posterior surface of the aortic arc.

In the Type I, the bronchial artery branches out from the right supreme intercostal artery on the right side of the spine at the level of the first intercostal space, and running either transversely or diagonally downward and entering between the trachea and the esophagus, they send out ascending branches at once, while the main branch sends out its branches to the walls of trachea and esophagus as it descends along the right posterior wall of the trachea down to the tracheal bifurcation where it is divided into right and left branches each of which is again subdivided into two or three smaller branches. These smaller branches on either side, entering into the hili of the lungs, are finally communicated with terminal bronchi on respective side.

In the Type II aside from the right bronchial artery observed in the Type I, a left bronchial artery descends between the trachea and the esophagus along the left wall of the trachea, and it is mainly distributed to the left bronchi but in some right and left bronchial arteries are seen anastomosed with one another.

In the Type III, the left bronchial artery originates from the left interthoracic artery, and passing down in front of the arc of the aorta oblique-medially to the posterior wall of the bronchus, descends the left and posterior side of the trachea and then enters into the left lung along the left bronchus. The small branch, arising from the right interthoracic artery goes down obliquely at the back of the aortic arc along the right surface of the trachea and reaches the right mediastinal pleura.

As for the Type IV, the left bronchial artery branches out from the posterio-inferior surface of the arc of the aorta, and running down along the rear side of the trachea, its branches enter mainly into the left lung. Some anastomoses of right and left bronchial arteries are seen in this type, too.

The bronchial arteries in rabbits are chiefly distributed to the walls of the trachea, bronchus, and esophagus, and partly to the mediastinal pleura, pulmonary ligaments, lymphnodes, and nerves.

The bronchial veins in rabbits are consisted of the so-called extra-and

Fig. 2. The Pulmonary and Bronchial Arteries in the Center of a Caseous Focus ; Fine vessels in the caseous focus have completely disappeared and the pulmonary, dilated bronchial artery, and newly-formed vessels from them are recognized only around the bronchus.

the intra-pulmonary bronchial veins. The former, derived from the submucous vessel network in the proximal part of the third junction of the bronchus, ascends in parallel with the bronchial artery up to the superior vena cava ; while the latter, originating from the submucous capillaries in the distal part of the third junction of the bronchus, runs through the capillary network of the bronchial capsule and is communicated with the pulmonary vein.

Blood vessels in caseous foci : As small arterial and venous branches in the caseous foci disappear nearly completely, the caseous foci appear to be homogenous ; but when they are fairly large, there may be seen blood vessels remaining around the bronchi, consisting of the stems of the pulmonary arteries and their newly-formed branches, the bronchial arterioles, and the blood vessels in the bronchial wall. Whereas at the periphery of the foci in contrast to the structureless center, the networks of blood vessels are seen left almost intact. In the peripheral region closer to the foci, however, there are the stenoses and the dilatation of arterioles and venules as well as complicated distribution of newly-formed blood vessels (Fig. 3).

The bronchial arteries distributed in the caseous foci are dilatated, and precapillary and capillary anastomoses can be recognized between the newly-formed bronchial arteries and the pulmonary arteries. Around the caseous foci which are beginning to form cavities are seen remnants of the pulmonary arteries and veins along with newly-formed capillaries.

In the wall of cavities, however, new blood vessels originating from

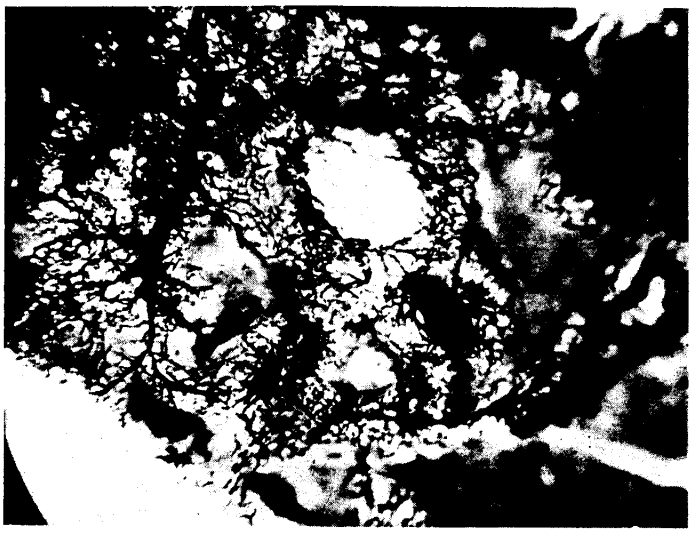


Fig. 3. Blood Vessels in the Periphery of Caseous Focus : In the bronchial wall there can be seen marked dilatation of the bronchial artery and anastomoses of capillaries and precapillaries with the newly-formed vessels of the pulmonary artery.

the bronchial artery are densely packed, which are distinctly different from those of the caseous foci and the networks of these newly-formed vessels are limited in the orifice of the drainage bronchus. These vessles are consisted of precapillaries running in parallel with the cavity wall and capillaries branching out either at right angle or obliquely and reaching beneath the necrotic substances in the cavities and anastomosed with one another in a cage-like formation and then reversing their direction they are communicated with venules (Fig. 4).

Blood vessels in the cavities : The majority of the arterial and venous branches original but not newly-formed are occluded in the cavities. However, in the case where there are main pulmonary arteries on the wall of the cavity, they are compressed by the cavity and are running around the cavity without their capillaries. In the case of multiple cavities where the pulmonary arteries are running through them, the vascular width of these arteries becomes smaller as the arteries approach closer to the cavities but the width recovers its original size as they leave further away from the cavities (Fig. 5). This contraction of the vascular width of the pulmonary artery is due not only to the pressure by the cavity but also due to endarteritis obliterans, and it is truly interesting to note that new growths of capillaries are observed originating from the wall of the pulmonary

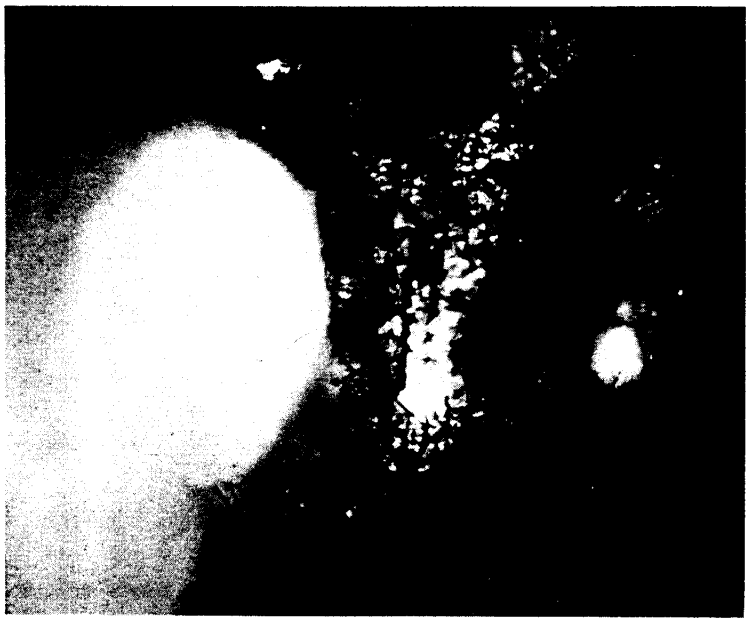


Fig. 4. Blood Vessels in the Orifice of a Drainage Bronchus of a Caseous Focus Beginning to form a Cavity : In the cavity wall in the part of drainage bronchus, there are marked new-growths of blood vessel arising from the bronchial artery. Precapillary and capillary anastomoses are located between these newly-formed blood vessels from the bronchial artery and the branches of the pulmonary artery.

Fig. 5. The Pulmonary Artery of Multiple Cavities : The pulmonary artery is affected by pressure, the stenoses due to endarteritis obliterans and aneurysm-like dilatations. In the stenotic part, blood vessels are newly formed near the cavity wall.

artery and running in the direction of the cavity wall.

The distribution of blood vessels in the cavity wall is much more abundant than that in the caseous foci, and these vessels in the cavity wall can be classified into three kinds according to their origins.

(1) The networks newly growing out of the pulmonary arterioles and venules are consisted of those running along the contour of the cavity wall and those newly-formed centipede-like capillaries running either at right angle or obliquely to those former vessels ; and they make a semi-circular turn immediately under necrotic layer in the cavity wall and are communicated with venules. These newly-formed capillaries are all anastomosed with one another in a cage-like formation. These capillary networks, in our experience, are seen almost all around the cavities (Fig. 6).

Fig. 6. Blood Vessels in the Cavity Wall (Type I) : Newly-formed blood vessel network from the branches of the pulmoary artery.

(2) The networks of branches newly growing out of main arteries and veins are, as shown in Figures 5 and 7, observed in the case where the main pulmonary arteries and veins have approached the cavity or in the case of the multiple cavities. Those peculiar branches that run from the main stem to the cavity are the ones newly-formed from the main trunk that is occluded just before reaching the cavity. The structural pattern of the terminal region is identical with the case mentioned in (1) and these terminal vessels finally reach granulation layer.

(3) Newly-formed blood vessel network arising from the bronchial artery is located in the orifice of the drainage bronchus. This is the

Fig. 7. Blood Vessels in the Cavity Wall (Type II): Blood vessel network newly formed from the stem of the pulmonary artery.

regenerated network derived from the swollen and dilatated bronchial artery and is located only in the orifice of the drainage bronchus (Fig. 8).

Next, the blood flow in the bronchial arteries distributed in the cavities seems to have increased due to the dilatation and the twisting of the vessels. Moreover, on the hilar side of the cavity many anastomoses of precapillaries and capillaries are recognized between the pulmonary and bronchial arterioles regenerated in the proximity of the drainage bronchus. In the pleuritic region of the cavity, pulmonary arterioles and venules are newly formed, while the intercostal, the esophageal, and the pericardiac arteries are seen entering into the region of communication and anastomosing with each other.

The blood vessels in the cavity wall treated with anti-tuberculous agents : In Spalteholz's specimens prepared from the cases treated with INH, the blood vessels in cavities present no significant difference from those of the untreated as well as from those treated with SM, and blood vessels of Types I, II and III can be clearly discerned in the cavity-wall vessels. As for the pathologic changes in the histo-pathologic specimens, capillary hyperemia is in general marked, and particularly capillaries in the granulation tissue are markedly dilatated and proliferated. And he-

Fig. 8. Blood Vessels in the Cavity Wall (Type III) : Blood-vessel network from the bronchial artery, situated in the orifice of a drainage bronchus (left side facing the cavity wall).

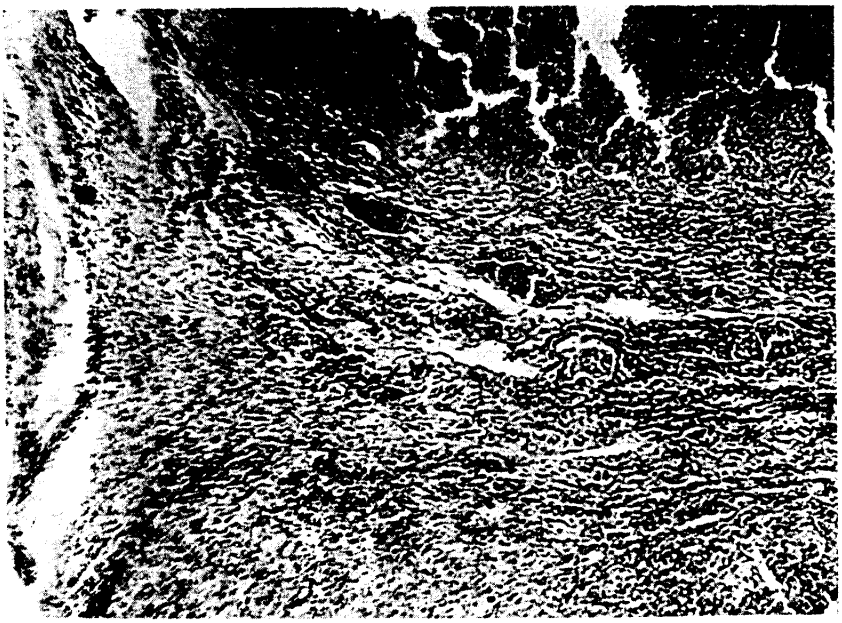


Fig. 9. Cavity Wall of a Case treated with Streptomycin : Blood vessel distribution is poor in the granulation.

morrhages can be recognized in some of lesions, and these are especially more striking in the region close to the thin necrotic layer. These changes are distinctly different from those observed in the control and the cases treated with streptomycin (Fig. 10).

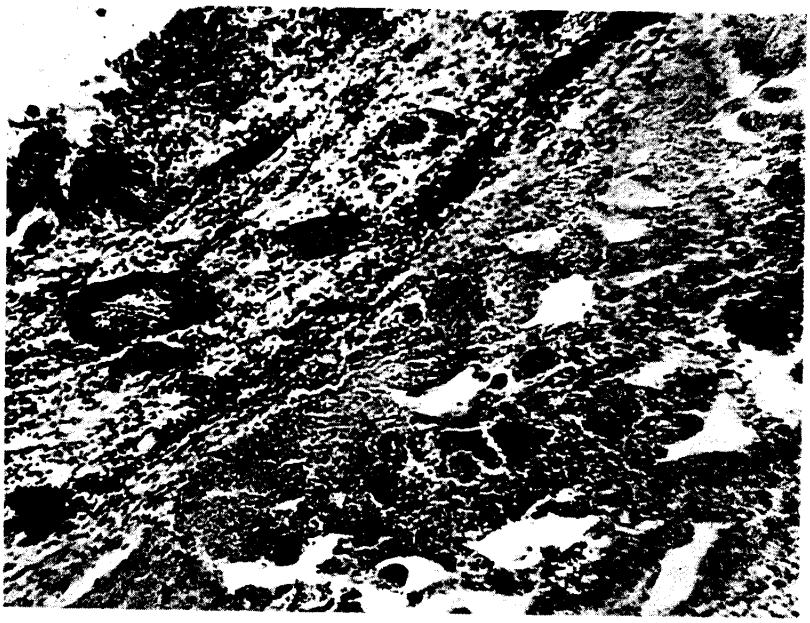


Fig. 10. Cavity Wall of the Case treated with Isoniazide : Marked hyperemia, new-formations of blood vessel and occasional hemorrhages can be recognized in the wall.

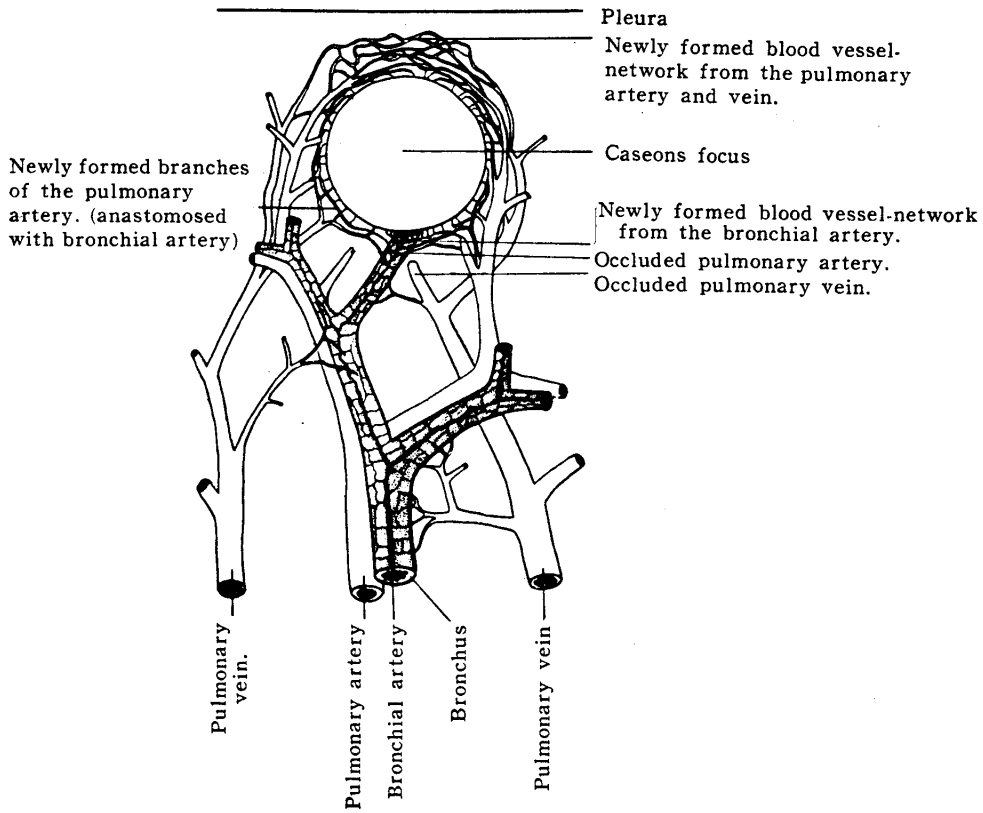
DISCUSSION

Articles dealing with the origin of the bronchial artery in man and dogs are abundant while the same in rabbits are scarce probably because of the difficulties in observing such small animals whose blood vessels are naturally so minute. Reviewing a few articles on this subject, MORI *et al*[15]. claim that the bronchial arteries in rabbits originate from the supreme intercostal artery, while ELLIS and AOKI[9] state that the bronchial arteries branch out from the right interthoracic artery in the majority of cases. In our experiment with fifteen rabbits, the bronchial arteries originate from the right supreme artery in ten cases of the fifteen (66.7%) while in three cases (20%) not only from the right supreme intercostal artery but also from the left supreme intercostal artery ; and besides these we found in one each of the remaining two cases which, in addition

to the above mentioned, the bronchial arteries branch out from both sides of the interthoracic artery or from the aortic arc. In our findings with these rabbits, the origin of the bronchial arteries has been most frequently located in the right supreme intercostal artery, and in no case have we been able to find the bronchial artery originating from the aortic intercostal artery as in the case of man or dog.

Concerning the distribution of blood vessels in caseous foci, MATSUO[16] observed, in his reconstruction models prepared from serial slices of the caseous foci obtained from man, that the caseous foci are supplied with blood vessels from three sources, namely, (A) pulmonry arterial branches that are located close to the foci but escaped pathologic changes, (B) nutrition blood vessels of fairly large pulmonary arteries that are located close to the foci, and (C) indigenous capillary networks in the wall of the bronchus. In our experiment, however, we found two sources of blood supply for the caseous foci as shown in Fig. 11, namely, a) residual

Fig. 11. Diagrammatical Picture of the Blood Vessel Structure in a Caseous Focus :



vessels of pulmonary arteries and newly-formed capillaries arising from these residual vessels, and b) the indigenous bronchial arteries of the bronchus and the capillary networks in the bronchial wall, but we could not recognize any blood supply from the nutrition vessels of the pulmonary artery as mentioned by MATSUO.

Now, turning our attention to the blood-vessel distribution in cavities, CUDKOWICZ contends that those occluded pulmonary arteries are recirculated by Vasa vasorum which is broncho-arterial in its origin and consequently all the vessels in the cavity wall are broncho-arterial in nature; and DELARUE *et al.* likewise claim that the pulmonary arteries are recirculated by the active penetration of broncho-arterial capillaries into those occluded pulmonary arteries. Moreover, in our country, we have reports by NAGAISHI, NAGAZAWA, and YAMASHITA, in which they mention only about the distribution of blood vessels at the orifice of the drainage bronchus, where they find numerous regenerated bronchial arterioles with abundant anastomoses. From these observations of various investigators it seems that the actual structural patterns of blood vessels in the tuberculous cavities has not yet been sufficiently clarified.

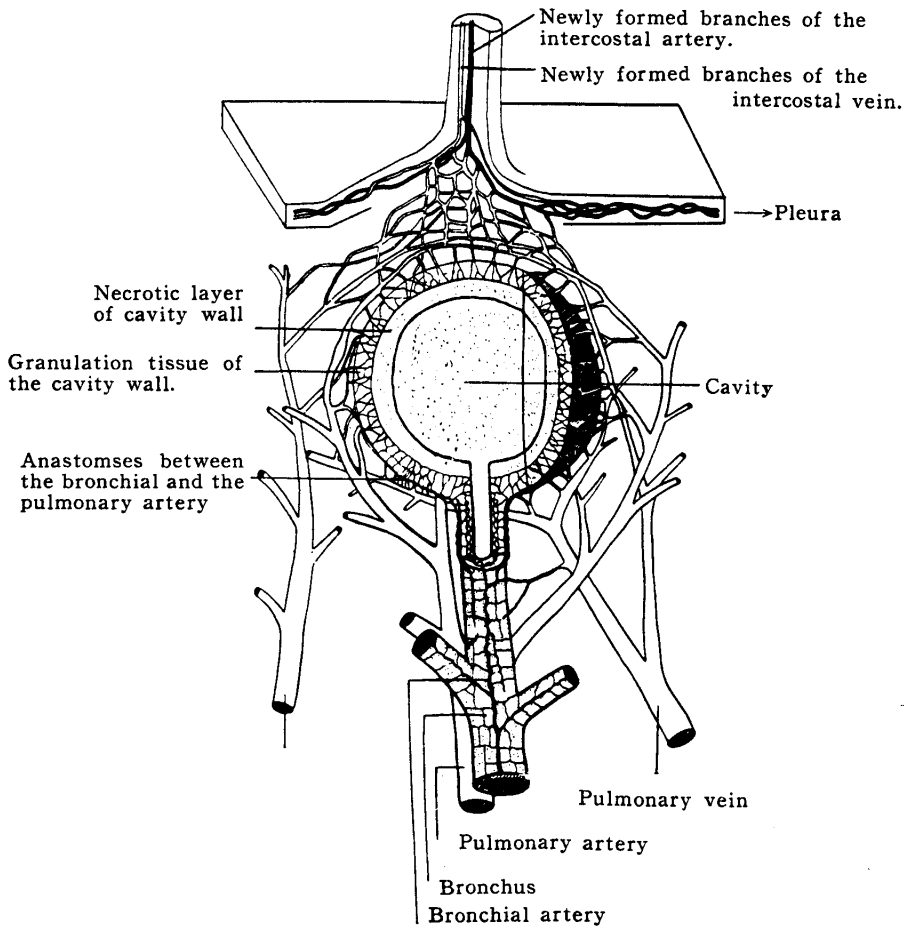
According to the results of our experiment, as shown in Figure 12, the vessels that actually occupy the cavity wall are chiefly pulmonary arterioles, venules, or those capillaries newly formed from the main trunk of the pulmonary artery, namely, of Type I and Type II ; and only the orifice of the drainage bronchus is supplied with newly-formed bronchial arteries. Therefore, the arterial blood for the cavity wall solely at the orifice of the drainage bronchus is abundantly and directly supplied by the newly-formed broncho-arterioles, while all the rest of cavity wall seems to receive the blood supply rather scantily and indirectly from the pulmonary arteries through the anastomoses of bronchial arteries and their sister blood vessels.

As regards the origin of newly-formed blood vessels in the tuberculous lungs, WOOD and MILLER, TOKUGAWA, YAMASHITA, CUDKOWICZ, and DELARUE have thus far recognized the regenerations only in the aortic vessels such as the bronchial arteries and the intercostal arteries. In our experience, however, we found, besides the regeneration of these aortic blood vessels, the regenerations in the main trunks of the pulmonary artery and vein (Cudkowixz has described these as Vasa vasorum of the pulmonary artery) as well as in capillary blood vessels.

Even after the streptomycin or the isoniazide treatment on the experimental cavities, we found no essential changes in the structural patterns of blood vessels of the cavity wall. Concerning the blood vessels

in the tuberculous lungs treated with drugs, SUGIHARA found the proliferation and dilatation of blood vassels and bleedings in the miliary tubercle of the lungs treated with streptomycin, TAMAI and KUROBANE observed the dilatation, hyperemia, bleedings and hemangiomatous proliferation of capillaries in the granulation. In our experiments, however, we could recognize no difference in the cases treated with streptomycin as compared with the untreated, while in the cases given the INH treatment we recognized marked hyperemia, the proliferation of capillaries as well as occasional bleedings. These changes, suggestive of a stimulating action of isoniazide on the blood vessel wall, seem to call for a special clinical consideration.

Fig. 12. Diagrammatical Picture of the Blood Vessel Structure in a Tuberculous Cavity.



SUMMARY

First of all, we investigated the origin, the construction and distribution of the bronchial arteries and veins in adult rabbits, and then observed various changes of the blood vessels in experimental cavities and caseous foci and also studied the effects of streptomycin and isoniazide on the blood vessels of the cavity wall. The summary findings of the present experiments are described in the following.

1) In ten out of the fifteen rabbits emloyed, the bronchial artery originates from the right supreme intercostal artery ; in three cases, in addition to this origin, it originates also from the left supreme intercostal artery ; and in another case from the intercostal thoracic artery ; while in the remaining one from the arc of the aorta.

2) The bronchial veins are divided into the extra-pulmonary and the intra-pulmonary veins. The former arises from the submucous blood vessels located in the proximal part of the third bronchus, and running along with the bronchial artery, finally empties into the superior Vena cava ; while the latter, originating from the submucous capillaries in the distal part of the third bronchus, and after anastomosing with one another in the capsule of the bronchus, is communicated with the pulmonary veins.

3) In the caseous foci, although blood vessels are obliterated, capillaries are newly formed around the main trunks of the pulmonary artery and vein as well as around their residual branches.

4) These caseous foci are supplied with arterial blood from the bronchial arteries, the blood vessels in the bronchial wall, and the newly-formed vessels of pulmonary arterial origin.

5) The capillaries in the cavity wall are classified into three types according to their origins ; namely, Type I, those regenerating from fine branches of the pulmonary vessels ; Type II, those regenerating from the main trunk of the pulmonary vessels ; and Type III, those regenerating from the bronchial artery situated in the orifice of the drainage bronchus.

6) The tuberculous cavities only in the orifice of the drainage bronchus receive an abundant supply of arterial blood directly from the bronchial artery, but those in other regions receive a scanty blood supply indirectly from the anastomoses between the bronchial artery, its sister vessels and the pulmonary artery.

7) The regeneration of blood vessels in tuberculous foci has been confirmed to occur not only in the bronchial artery and its sister blood vessels but also in the pulmonary artery and vein as well.

8) The constructions of blood vessels in the cavities treated with streptomycin or isoniazide present no significant difference from those of the control.

9) The regeneration of blood vessels and hyperemia in the cavity wall of the cases treated with streptomycin present no significant difference from those observed in the control, but the cases treated with isoniazide show marked hyperemia, newly-formed vessels, and occasional bleedings.

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