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Pulmonary vascular changes associated with isolated mitral stenosis in India

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Pulmonary vascular changes were studied in 100 cases of isolated mitral stenosis; these included 90 patients in whom lung biopsies were obtained at valvotomy and 10 patients who came to necropsy. Medial thickness of the pulmonary arteries was measured in each case and in 12 cases was correlated with the haemodynamic data.

Most patients were young, 78 being 30 years of age or less and 42 under 20 years or less. Males predominated 2:1. All patients with mitral stenosis showed varying degrees of vascular and other associated parenchymal changes. The most conspicuous were those observed in the muscular branches of the pulmonary artery in which the media was thickened in all cases, moderately in 44 and considerably in 28 cases. Dilatation lesions representing grade 4 lesions of hypertensive pulmonary vascular disease (Heath and Edwards, 1958), hitherto not described in mitral stenosis, were observed in 4 cases. The intima was found to be frequently abnormal, showing oedema, fibrosis, and, more importantly, variable degrees of muscularization, often suggesting the incipient formation of a second media. Arteries and arterioles were often occluded by thrombi in various stages of organization, and the freshly formed channels tended to acquire a muscular lining. Arterioles were muscularized in all cases, and in many there was a pronounced intimal proliferation. Other changes included medial hypertrophy in the veins and occasional muscularization and dilatation of the lymphatics. A notable feature was hypertrophy of the musculature of the bronchiolo-alveolar system seen in a majority of cases. The alveolar walls showed variable degrees of thickening and fibrosis, intimal proliferation of alveolar capillaries, and 'epithelialization' of alveoli. Haemosiderosis was present in 70 cases. On the whole the more severe changes were observed more often in the younger subjects, further supporting the observation that rheumatic mitral stenosis in India commonly affects the juvenile age groups and is characterized by association with severe pulmonary hypertension. Medial hypertrophy was proportional to the level of pulmonary artery pressure.

Morphological changes in the pulmonary vasculature and lung parenchyma in mitral stenosis are well known (Parker and Weiss, 1936; Larrabee, Parker, and Edwards, 1949; Henry, 1952; Heath and Whitaker, 1955; Heath and Best, 1958; Wagenvoort, 1960; Walton and Heath, 1960; Lendrum, 1960; Roy *et al.*, 1963; Wagenvoort, Heath, and Edwards, 1964; Jordan *et al.*, 1966; Bhayana *et al.*, 1969). There have been several reports on the correlation of histopathological and haemodynamic data in such cases (Ellis *et al.*, 1951; Graham *et al.*, 1951; Clowes *et al.*, 1953; Denst *et al.*, 1954; Heath and Whitaker, 1955; Harris and Heath, 1962; Bhayana *et al.*, 1969). Most of these studies were in adults. In India, mitral stenosis resulting from rheumatic heart disease commonly affects the juvenile age group, and is characterized by association with severe pulmonary hypertension (Mathur, 1960; Padmavati, 1962; Roy *et al.*, 1963).

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The present study is a critical analysis of the qualitative and quantitative changes in the pulmonary vasculature and lung parenchyma seen in these cases. An attempt has been made to correlate these changes with the available haemodynamic data.

Materials and methods

Pathological material was obtained from 90 cases of mitral stenosis at the time of valvotomy, and 10 cases of this disease which came to necropsy. In addition, 15 randomly selected necropsy cases of comparable age, without cardiopulmonary disease, and in which the heart and lungs were grossly within normal limits, were studied to establish baseline data in respect of the normal structure of the lung, with special reference to pulmonary vasculature. Tissue for microscopical sections was obtained from the lingula and lower lobe of the left lung

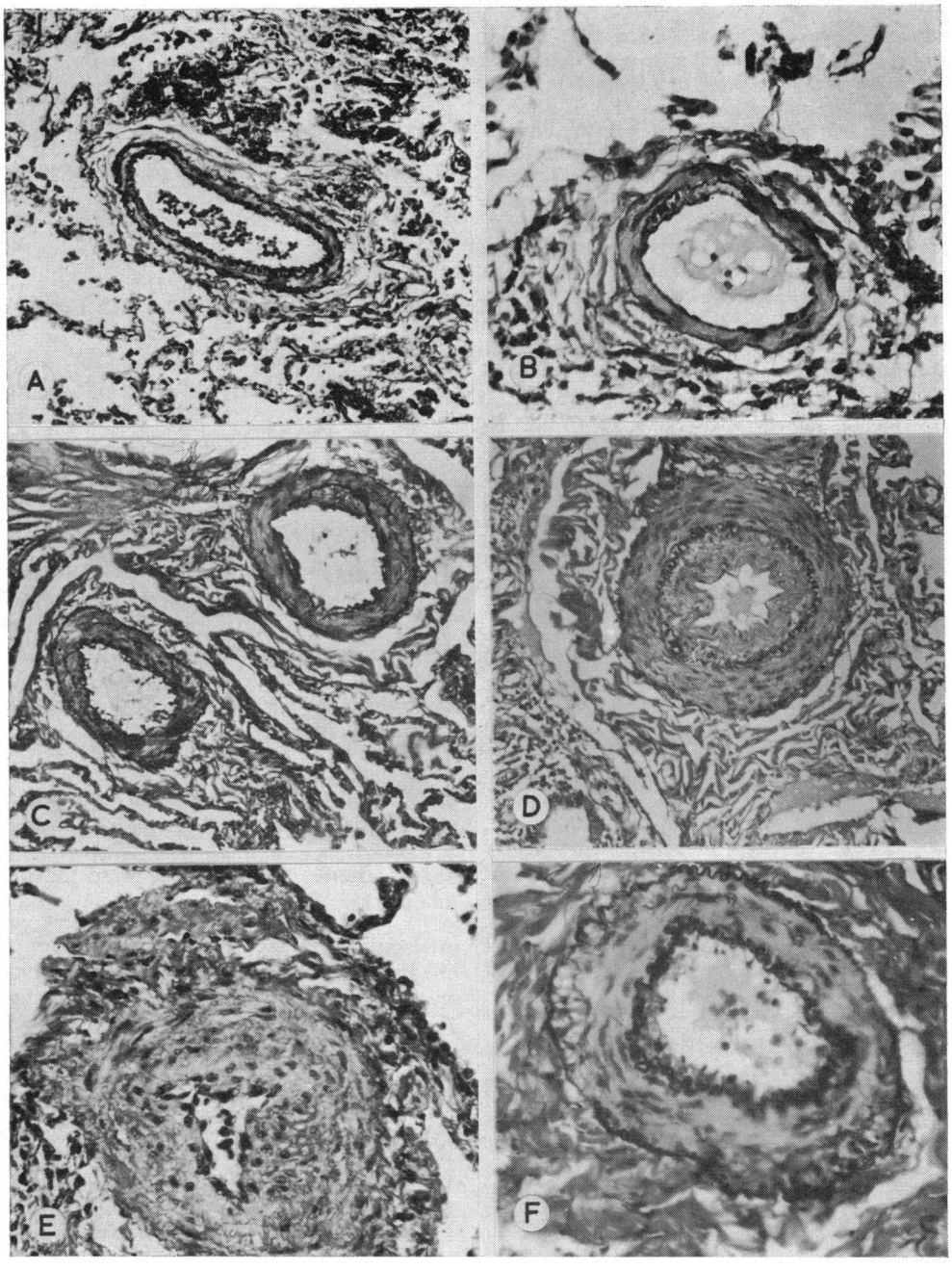

FIG. 1 *Muscular branches of the pulmonary artery showing varying grades of severity of thickening. Medial thickness of each vessel expressed as per cent of external diameter. A) Normal vessel, 3 per cent. (VVG × 260.) B) Mild hypertrophy, 9 per cent. The internal elastic lamina is duplicated in one place. (VVG × 260.) C) Moderate hypertrophy, 14 per cent. (VVG × 260.) D) Severe hypertrophy, 20 per cent. The intima shows early muscularization. (H. and E. × 109.) E) Severe hypertrophy, 50 per cent. (Masson trichrome × 260.) F) Severe hypertrophy, 30 per cent. There is an additional layer of longitudinal muscle in some places beneath the external elastic lamina. (Masson trichrome × 260.)*

in the valvotomy cases and from all lobes of both lungs in the necropsy cases. This was fixed in 10 per cent buffered formalin, and 5 μ thin sections were stained routinely with haematoxylin and eosin (H. and E.), Verhoeff's stain counterstained with Van Gieson's stain for differentiating between elastic and collagenous connective tissues (VVG), Masson's trichrome stain for differentiating between collagenous and muscular connective tissues, Gomori's stains for reticulin (Armed Forces Institute of Pathology, 1960), and Perl's reaction for iron. In addition, sections were stained with Mallory's phosphotungstic acid haematoxylin for fibrin, and Von Kossa's stain for calcium when necessary.

Vascular changes

Blood vessels including elastic and muscular branches of pulmonary artery, pulmonary arterioles, capillaries, and veins were examined with reference to medial thickness and intimal proliferation. The arterial blood vessels were classified by Brenner's criteria (1935), the elastic branches measuring 1000 μ and above, muscular branches between 100 μ and 1000 μ, and arterioles below 100 μ in external diameter.

The diameters were measured by the technique of Wagenvoort *et al.* (1964) using a micrometer eyepiece. In each section a minimum of five vessels of each category was measured and the mean was taken as the final measurement. The medial thickness of the arteries was measured from the external to the internal elastic lamina along diameters at right angles to each other, and the average of these two measurements was expressed as a percentage of the external diameter. The upper limit of normal medial thickness of the muscular branches of pulmonary artery was taken as 7 per cent.

The presence of abnormal muscularized pulmonary arterioles was sought. The criterion for this change was the presence of a distinct muscular media in an arterial vessel less than 100 μ in diameter.

In addition, lymphatics in the pleura, interlobular septa, lung parenchyma, and around the pulmonary arteries were examined for dilatation or other changes.

Pulmonary parenchyma

Fibrous or muscular thickening of the alveolar walls, the degree and site of haemosiderosis if any, the presence of 'epithelialization' of the alveoli, and elastic and reticulin tissue changes, such as mineralization, thickening, reduplication, and fragmentation, were sought. The severity of haemosiderosis was graded 0 to 2+ (Heath and Whitaker, 1956). The severity and extent of changes in the upper and lower lobes were compared.

Haemodynamic studies

Haemodynamic data obtained at right heart catheterization, using standard techniques (Roy *et al.*, 1963), were available from 12 valvotomy cases: these included pulmonary artery and wedge pressures, cardiac output, cardiac index, and pulmonary vascular resistance. The vascular and parenchymal changes were correlated with the haemodynamic data.

TABLE 1 *Age and sex distribution of cases studied by biopsy and at necropsy*

Age range (yr)	*Male*		*Female*		*Total*
	Biopsy	*Necropsy*	*Biopsy*	*Necropsy*	
0–10	1	—	1	—	2
11–20	20	4	14	2	40
21–30	22	3	11	—	36
31–40	14	—	4	1	19
41–50	2	—	1	—	3
Total	66		34		100

Results

The age and sex of the subjects are indicated in Table 1. Seventy-eight patients were 30 years or less, 42 were 20 years or less.

Pathological findings

Elastic arteries Moderately severe atherosclerosis in the pulmonary trunk and the extrapulmonary and intrapulmonary elastic arteries was observed in the 10 cases coming to necropsy; of these 9 were between the ages of 11 and 30 years. Only one of the control series, a subject aged 55 years, had some minimal pulmonary atherosclerosis.

Changes of variable degree were observed in the muscular branches of pulmonary arteries, pulmonary arterioles, veins, and lymphatics, and in the alveolar walls in all cases of mitral stenosis. Changes in the arteries and arterioles were the most pronounced.

Muscular arteries In the normal controls, the media of the muscular branches is thin, sandwiched between two elastic laminae, which show no duplication or fragmentation, or focal changes only (Fig. 1A). The intima is insignificant, usually comprising a single layer of endothelial cells.

In all cases of mitral stenosis, the media of the muscular branches of the pulmonary artery was thickened to a variable degree because of hypertrophy of the circular muscle, with an admixture of small quantities of fibrous connective tissue in advanced lesions (Fig. 1B–F).

Table 2 shows the distribution of cases according to the severity of medial thickening of the muscular pulmonary arteries. The medial thickness in the mitral stenosis cases ranged from 5 to 50 per cent of the external diameter, as compared to 2 to 7 per cent in controls. The largest number of cases had a moderate thickening (10 to 14%). It is noted that a proportionately larger number of cases in the younger age group (20 years or below) belonged to

TABLE 2 *Distribution of cases according to severity of medial thickening of muscular branches of pulmonary artery*

Groups	*Cases*		*Total*	*Medial thickness* (normal 2 to 7)*
	Age 20 years and below	*Age above 20 years*		
1	9	19	28	5 to 9
2	17	27	44	10 to 14
3	16	12	28	15 to 50
	42	58	100	

* Expressed as percentage of external diameter.

groups 2 and 3, with moderate and severe medial thickening, respectively. In a majority of cases in group 3, the medial thickness ranged between 15 and 20 per cent; in 4 it was 21 to 30 per cent, and in 1 it was 50 per cent of the external diameter.

In 5 cases of group 3 with severe medial thickening, there was an additional layer of longitudinal muscle outside the circular layer and beneath the external elastic lamina (Fig. 1F). In association with severer changes, the internal elastic lamina was often thickened, split, reduplicated, or even ruptured. No evidence of vasculitis or fibrinoid necrosis was seen in any case.

Intimal proliferation and a variable degree of fibrosis was observed in 40 cases. The earliest change

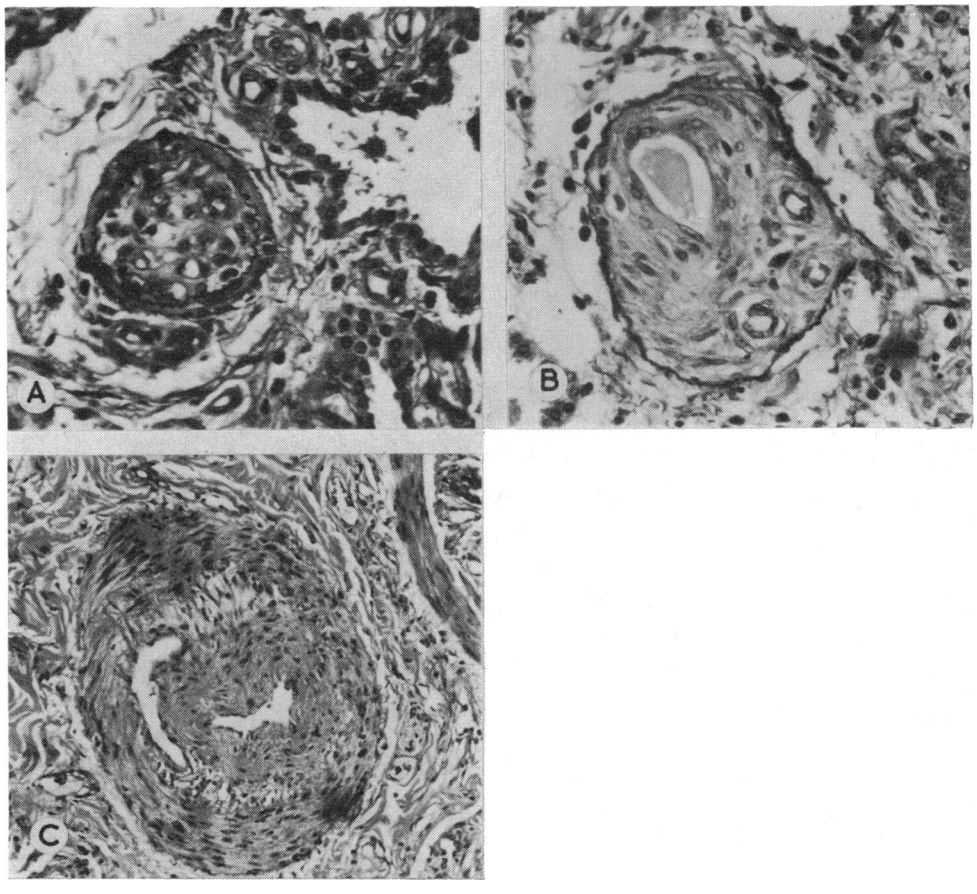

FIG. 2 *Pulmonary arterial channels showing varying stages of recanalization of a thrombus. A) New channels are small and slit-like, lined by a single layer of endothelial cells. (VVG × 273.) B) The thrombus is replaced by fibrous tissue; the new channels have thicker walls, and the largest one has acquired some muscle. (VVG × 260.) C) The lumen is occupied by two well-formed new vascular channels. One of them has a thick fibromuscular wall. The wall of the parent vessel is hypertrophic. (H. and E. × 109.)*

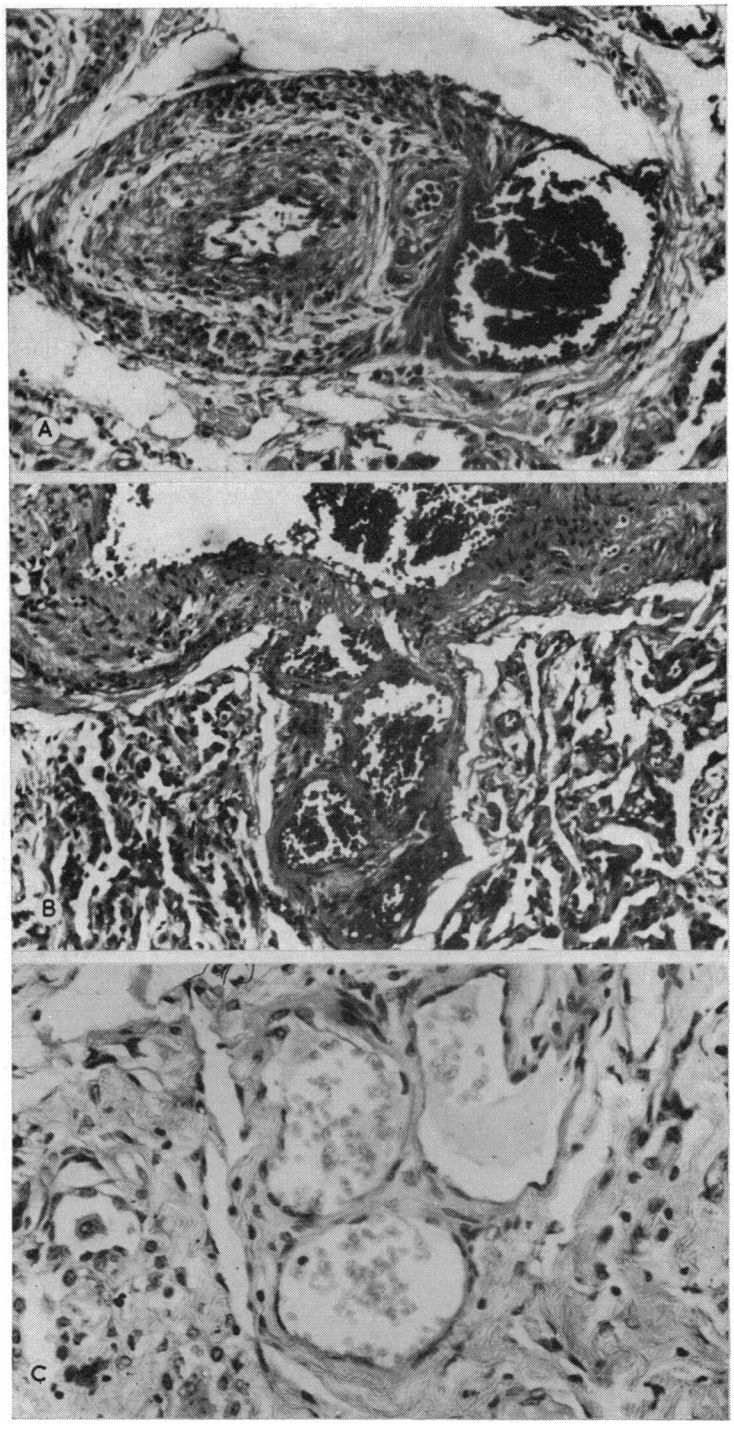

FIG. 3 *Dilatation lesions. A) A vein-like muscular channel is lying adjacent to a muscular pulmonary artery with a thickened media and muscularized intima. Another small independent channel is seen within the wall of the parent vessel. (H. and E. × 109.) B) Vein-like lesion (H. and E. × 109.) C) Angiomatoid lesion. (H. and E. × 218.)*

consisted of a diffuse oedema. Later, proliferating intimal cells embedded in a fibrillar matrix contributed to an eccentric or a generally concentric thickening. This was mostly fibrous connective tissue, but in advanced lesions, there was a variable degree of muscularization of the intima, sometimes resulting in the appearance suggesting the incipient formation of a second 'media' within the boundaries of the internal elastic lamina (Fig. 1D). In 4 cases, all in the younger groups the lumen was almost completely occluded by such a lesion. Three of these 4 cases were 15 years old or less, and one was 27 years old. Two had moderate (9 to 10%), and 2 had severe (15 to 20%) muscular hypertrophy.

In a few cases, the lumina of the muscular pulmonary arteries and arterioles were occluded by what appeared to be an organized and recanalized thrombus (Fig. 2). The newly formed channels tended to acquire a muscular wall, later appearing as complete fibromuscular septa (Fig. 2B and C).

Characteristic dilatation lesions were seen in 4 cases, all in the juvenile age group, and were of two types (Heath and Edwards, 1958).

1) Vein-like branches of hypertrophic pulmonary artery (Fig. 3A and 3B): a vein-like channel is seen arising from, or lying adjacent to, a hypertrophic pulmonary artery.

2) The angiomatoid lesion (Fig. 3C): this consists of a cluster of dilated vascular channels of variable thickness, presumably arising from a pulmonary artery.

Arterioles In the normal controls, the arteriole has a single elastic lamina lined by a single layer of endothelial cells. A thin layer of muscle, often incomplete, is rarely seen only in larger arterioles. In patients with mitral stenosis, arterioles were muscularized in all cases except three. In many cases, they had acquired an internal and external elastic lamina sandwiching a media of circularly disposed fibres (Fig. 4). The medial thickness ranged from 4 to 17 per cent of the external diameter as compared with negligible thickness in normal controls. In the majority of cases, the thickness was 9 to 10 per cent. Intima were generally swollen. In 35 cases, there was a pronounced intimal proliferation, often so severe as almost to obliterate the lumen.

Pulmonary veins Almost all cases showed venous hypertrophy of mild to severe degree. The thickening was largely the result of hypertrophy of circularly disposed muscle fibres, with occasional fascicles of longitudinally disposed muscle. Intimal fibrosis of varying degree was present in 20 cases. In some cases the thickening was so severe as almost to obliterate the lumen. In one case the lumen was completely occluded and was recanalized by slit-like channels resembling an organizing thrombus. In this case similar changes were observed in the arteries and arterioles.

Lymphatics Dilated lymphatics in the pleura and interlobular septa were observed in 40 cases. Dilatation was pronounced in a few cases, and occasionally the lymphatics had acquired a hypertrophied muscular wall (Fig. 5).

Parenchymal changes There was a variable degree of alveolar thickening and fibrosis in most cases. The mildest change was slight thickening of the alveolar septa with reduplication of reticular framework, in 25 cases. The change was moderately severe in 47 and severe in 28 cases. With increasing severity the alveolar septa became thicker, encroaching on the lumen as a result of reduplication and condensation of the reticulin and elastic fibres, variable degrees of collagenization, thickening of the basement membrane of the alveolar capillaries, oedema, and 'epithelialization' of the alveoli. In 5 cases the alveoli had almost a glandular appearance. In some cases with severe changes, the intimal lining of the alveolar capillaries also showed con-

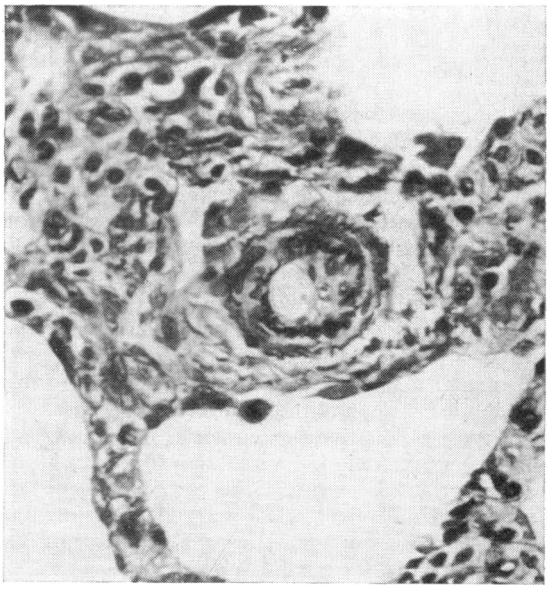

FIG. 4 *Muscularized arteriole. The muscular media is sandwiched between two elastic laminae. (VVG × 380.)*

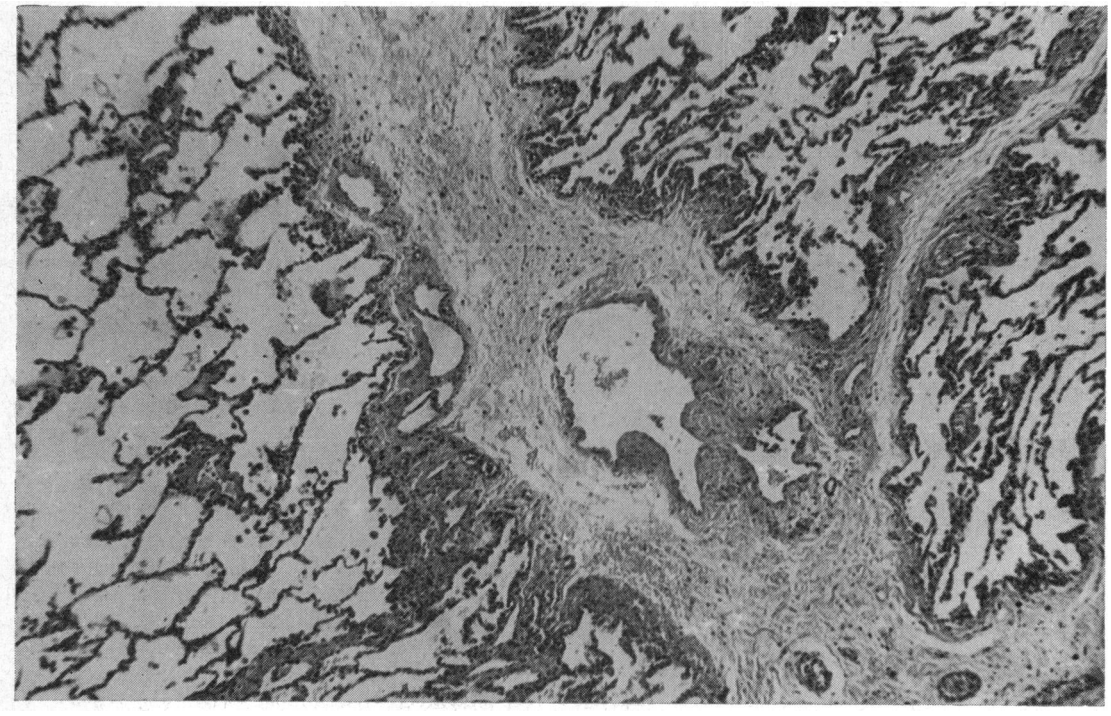

FIG. 5 *The oedematous interlobar septum contains a dilated lymphatic vessel, with irregularly thickened and muscular walls. (H. and E. × 80.)*

centric narrowing caused by intimal proliferation (Fig. 6).

The elastic tissue of the alveolar walls was encrusted with deposits of iron and calcium in 4 cases. In 2 cases, there was a foreign body type of giant cell reaction around degenerated elastica.

Another notable feature was the presence of smooth-muscle hypertrophy in the bronchiolo-alveolar system. Thick strands of muscle often extended into the alveolar septa. This change was observed in 65 cases, and was particularly severe in 16; of the latter, 10 were less than 20 years of age. In some of these cases, the change extended to the interlobular septa and the pleura (Fig. 7).

In 10 cases, the alveolar capillaries showed diffuse aneurysmal dilatation. Five of these subjects were aged 20 years or less, and the rest were 28 to 40 years old. In all these cases except one, the medial thickness of the pulmonary arteries ranged from 10 to 20 per cent of external diameter.

Haemosiderosis The occurrence, degree, and location of haemosiderosis varied widely. Using the grading of Heath and Whitaker (1956), the severity of haemosiderosis was + in 60 cases and + + in 10 cases. Twelve cases had only a few scattered haemosiderin-laden macrophages in the alveolar lumina, mostly adjacent to the interlobular septa and pleura; the remainder had none.

In 67 out of 90 biopsied cases, changes of equal severity were found in the upper and lower lobe sections. This finding has been further substantiated by the observations in cases coming to necropsy, where no striking differences in severity were observed between different lobes.

Haemodynamic and clinical data

Resting pulmonary arterial pressure was raised in all cases. Pulmonary hypertension was mild (20 to 29 mmHg mean pressure) in 5, moderate (30 to 49 mmHg) in 6, and severe (58 mmHg) in 1 case. Pulmonary artery wedge pressure was also raised in all; in all cases except 2, the pressure was between 20 and 28 mmHg. The pulmonary vascular resistance was normal in 8 cases, and increased in 2 cases. The correlation between medial hypertrophy of the pulmonary arteries and the pulmonary artery pressure (Fig. 8) was significant ($P < 0.01$).

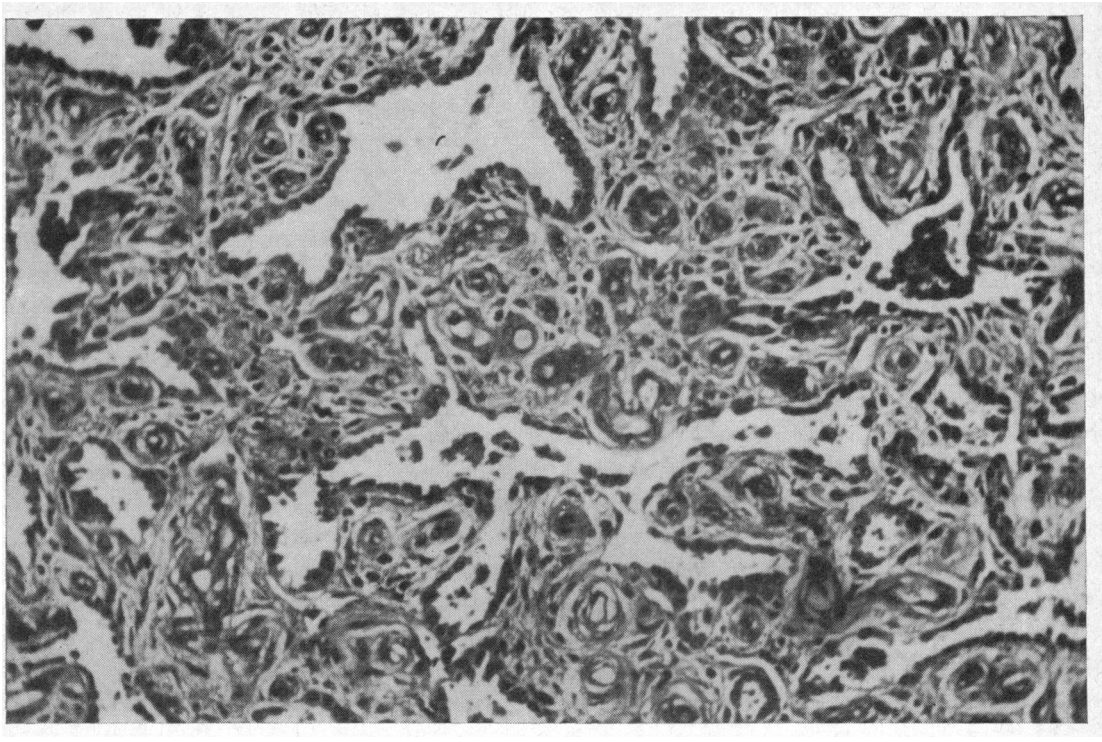

FIG. 6 *The alveolar septa are severely thickened and oedematous. Multiple channels derived from alveolar capillaries are seen, showing concentric narrowing caused by intimal proliferation. The alveolar spaces are 'epithelialized'. (H. and E. × 160.)*

Discussion

In India, isolated mitral stenosis following acute rheumatism commonly affects subjects below 20 years of age. In the series of Vaishnava, Webb, and Cherian (1960) from South India, 26 per cent of the patients were below the age of 13 years. In a series of 754 cases of rheumatic heart disease (Roy *et al.*, 1963), 171 subjects were 20 years of age or younger: of these 108 had pure or predominant mitral stenosis, i.e. 14 per cent of the whole series. Our analysis deals only with cases who were operated upon (90 cases) or came to necropsy. In this group, the proportion of juvenile cases is still higher, 42 per cent being 20 years of age or less and 78 per cent 30 years of age or less. This confirms the increased prevalence of mitral stenosis in younger age groups in India: a large number of cases needing operation were in these groups.

Morphological changes

Qualitative changes in the pulmonary vasculature and parenchyma were seen consistently in almost every case; these changes appeared to be more severe in the juvenile age group. Using the precise and measurable parameter of medial thickening of pulmonary arteries, a larger proportion of young subjects was affected as the lesion became more severe. In group 3 with the severest thickening, 16 out of 28 subjects were 20 years of age or less (Table 2). Furthermore, in 5 cases of group 3 there was an additional layer of longitudinally disposed muscle just inside the external elastic lamina. The severest degree of other changes, e.g. intimal proliferation in the arteries, veins, and arterioles, smooth muscle hypertrophy in the bronchiolo-alveolar system, aneurysmal dilatation of the alveolar capillaries, was observed more often in the young age group.

Dilatation lesions were observed in 4 patients, all of whom were less than 20 years of age. This is a significant finding. Bhayana *et al.* (1969) from India have reported these in 5 of their series of 25 cases, but their photomicrographs do not convincingly show the lesion described by Heath and Edwards (1958). This lesion is believed to be indicative of

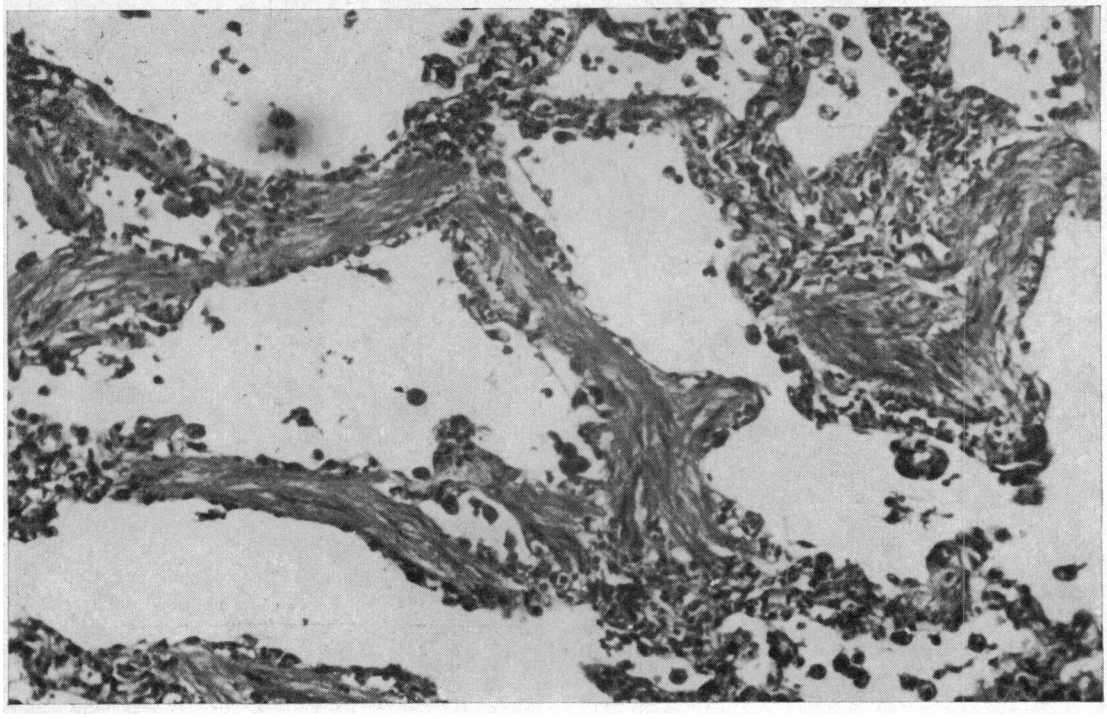

FIG. 7 *Muscular hypertrophy of the bronchiolo-alveolar system. (H. and E. × 160.)*

severe pulmonary hypertension (grade 4 of Heath and Edwards, 1958) and is reported to occur only in idiopathic pulmonary hypertension, congenital heart disease (Wagenvoort, 1959), or schistosomiasis (Brewer, 1955; Naeye, 1961a). Progression of vascular changes to this degree has not been reported in isolated mitral stenosis (Heath and Edwards, 1958; Wagenvoort, 1959), though Heath and Edwards (1958) have reported the development of fibrinoid necrosis of the arteries in a very few cases. The latter change has not been observed in our series or in other Indian series (Roy *et al.*, 1963; Bhayana *et al.*, 1969).

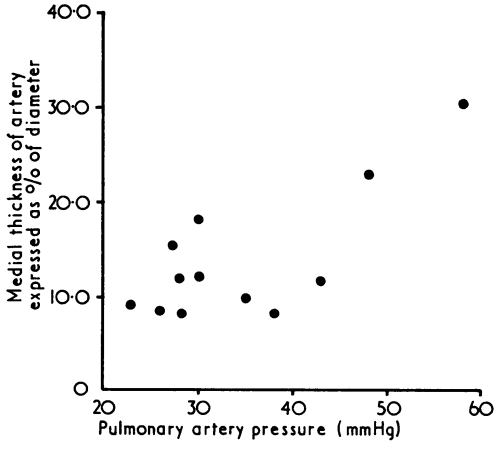

FIG. 8 *Scattergram showing the correlation of pulmonary artery pressures and medial thickness of the pulmonary arteries.*

These observations seem to indicate that pulmonary hypertension is a dominant feature in Indian cases, particularly in the younger age groups. Other workers (Denst *et al.*, 1954; Parker and Weiss, 1936) have also observed that the pulmonary vascular changes observed in the older age groups are less severe compared with those seen in younger subjects. It is possible, therefore, that the higher levels of pulmonary hypertension in the young patients merely reflect an age-related response.

Roy *et al.* (1963) have postulated that the high prevalence of severe pulmonary hypertension associated with the severe vascular changes seen in such cases may indicate a hypersensitive reaction of the pulmonary vasculature to a fulminating rheumatic process, or a tissue response to multiple overt attacks of rheumatic fever, caused by lack of chemoprophylaxis in Indian patients, or continuing low grade rheumatic activity. Denst *et al.* (1954)

have also postulated a direct role of rheumatic fever in the induction of vascular lesions, since changes caused by age or raised pulmonary arterial pressure do not fully explain their pathogenesis.

The most consistent finding was the muscularization of arterioles seen in all but three cases. In the most advanced lesions, the arterioles resembled small arteries with an internal and external elastic lamina, except for their small size. Apart from muscular hypertrophy, the lumen was further narrowed because of intimal proliferation in 35 cases. In the series of Heath and Whitaker (1955) this was observed only in cases with severe pulmonary hypertension (more than 70 mmHg) and was absent in all cases of mild (less than 40 mmHg) and some of moderate (41 to 50 mmHg) hypertension. Such a correlation with the level of pulmonary artery pressure was not evident in our series, since it was observed with varying severity in all the 12 cases whose haemodynamic data were available and whose pulmonary artery pressures ranged from 23 to 58 mmHg.

The figures for medial thickness of the pulmonary arteries are variable in the western studies. In the series of Jordan *et al.* (1966) comprising 20 patients all of whom were 30 to 55 years of age, the maximum medial thickness reported was 17 per cent of the external diameter and was seen in only one case. Heath and Whitaker (1955) on the other hand reported medial thicknesses of 15 per cent or more in 20 of their 31 cases, with ages ranging from 23 to 55 years. These contrast with our figure of 28 out of 100 cases in which the medial thickness was 15 per cent or more. Criteria for measuring the severity of vascular changes used by other western workers are less precise (Denst *et al.*, 1954).

Our observations suggest that medial thickening is probably the result of medial hypertrophy (Wagenvoort, 1960; Naeye, 1961b) though vasoconstriction may be a contributory factor (O'Neal, Thomas, and Hartroft, 1955; Short, 1957). Hyperplastic changes in the muscle constituting the arterial media, muscularization of the arterial intima and of arterioles, and the presence of additional fasciculi of longitudinal muscle in the arterial media reinforce such a theory (Wade and Ball, 1957; Heath and Best, 1958; Wagenvoort, 1960; Walton and Heath, 1960; Heath, 1963). These mechanisms probably result in increased mechanical rigidity of the vessel wall, as postulated by Burton (1954).

Our observations seem to support a speculation by Wagenvoort *et al.* (1964) that at least one of the modes of evolution of the dilatation lesions is by recanalization of the pulmonary arteries. It seems that the recanalized channels acquire a muscular wall of their own, out of a haemodynamic necessity, in response to the high pressure. These may dilate, resulting in a plexus of independent vessels within the adventitial boundary of a large one.

The smooth muscle hyperplasia in the bronchiolo-alveolar system was a conspicuous feature in our cases. It was particularly pronounced in the young subjects. In severity it was related to the changes in the alveolar walls rather than to the medial hypertrophy of the pulmonary arteries. It has been reported by Rodbard (1950) and Liebow, Loring, and Felton (1953) in a variety of pulmonary disorders, and by Roy *et al.* (1963) in cases of juvenile mitral stenosis. The significance of the change is not understood. In some way perhaps it is related to a quick rise in pulmonary vascular pressures in a young person, as postulated by Roy *et al.* (1963).

Correlation of haemodynamic and morphological changes

Our analysis is handicapped by the fact that the number of cases in this series on whom haemodynamic data were available is small, but there was a significant correlation between medial hypertrophy of the pulmonary arteries and the pulmonary artery pressure. Roy *et al.* (1963), from this institute, have published data on 62 cases, and their studies indicate the frequent occurrence of severe pulmonary hypertension particularly in young patients.

Haemodynamic data were obtained from the records of the Department of Cardiology. Assistance provided by Mr. P. Ganguli of the Medical Illustration Unit is gratefully acknowledged.

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