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COMPARATIVE HISTOPATHOLOGICAL STUDIES OF THE LESS COMMON PULMONARY FIBROSES WITH SPECIAL REFERENCE TO THE HAMMAN—RICH SYNDROME

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First in 1935, then in 1944, HAMMAN and RICH described a syndrome with a course some weeks or months in duration, characterized clinically by cough, cyanosis, dyspnoea and moderate fever, and morphologically by exudative changes accompanying diffuse interstitial fibrosis of the lungs. They termed the condition acute, diffuse, interstitial pulmonary fibrosis. Since then a number of similar cases has been observed. According to WHITE and CRAIGHEAD until 1957 the number of reported cases was 46, while CARABASI found 63 cases in 1958. However, some of these have not been verified satisfactorily and the American authors failed to take into account the cases reported from Europe [1, 9, 14, 38, 50, 57, 76, 77, 78]. Among the cases only a few were more or less acute [6, 11, 50, 60, 65, 76]; most of them lasted several years. By now it has become obvious that the acute course is not an essential feature of the condition; also, the morphological changes are often indicative of a protracted course. VANEK and CROSS distinguish between acute, subacute and chronic forms, emphasizing that these are variants of the same disease. The longest duration (15 years) was observed by CARABASI. The disease has been reported to occur in childhood [3, 13] and even in infancy [15, 76]. Earlier, the diagnosis could be established exclusively *post mortem*, but in recent years numerous cases have been identified *in vivo*, by lung biopsy [31, 56, 58, 67, 71, 74].

The cause of the disease is still unknown. Some authors list it among the collagen diseases, and many suggest an allergic aetiology. Although the attempts at isolating a pathogenic agent have thus far failed, virus infection is suggested to be responsible. We had the occasion to observe a chronic case of a diffuse interstitial pulmonary fibrosis [77], and to study rheumatic pulmonary changes, sclerodermal pulmonary fibrosis and virus pneumonias, *i. e.* representants of such conditions as have been claimed to be closely related with the Hamman—Rich syndrome. As the disease groups mentioned usually exhibit characteristic morphological changes, it is thought that a comparative histopathological study might supply some approach to the aetiology of the syndrome

under discussion. In the present paper we have undertaken to analyze the pulmonary changes occurring in the above-mentioned conditions.

Case reports

Case 1. A female patient 39 years of age had fallen ill in April 1952 with increasing dyspnoea, cyanosis and cough as the leading symptoms. Bacteriology had been negative. In the lungs an inhomogeneous density had been revealed in the left upper lobe. At first, pulmonary tuberculosis had been suspected, then, in the autumn of 1956, diffuse interstitial pulmonary fibrosis had been diagnosed (Department of Medicine No. 2 of the MÁV Lung Sanatorium, Budapest). The patient had died May 19, 1957.

At autopsy (record No. 297/57), the lungs were adhering to the chest wall, the pleura was thickened. The lungs were heavy, the superior lobes were shrunk, dense, elastic. Near the pleura and in most of the superior lobe there were homogeneous, greyish cavities of corn to small pea size. The severity of the lesion decreased gradually in the apicocaudal direction. In the right superior lobe there was moderate bronchiectasis. Pea-sized and smaller butter-yellow plaques were visible on the intima of the pulmonary vessels. The heart weighed 400 g, the wall of the right ventricle measured 8 mm, its cavity and that of the right auricle were dilated. The valves were normal. The spleen, liver, kidneys, and the gastrointestinal mucosa exhibited congestive changes.

Histologically, a transformation of lung structure was observable *(Fig. 1)*. The interstitial connective tissue, especially around the blood vessels and bronchi, was increased. The connective tissue, composed mainly of hyaline fibres in some areas and more rich in cells in others, was infiltrated almost exclusively by mononuclear cells, mainly lymphocytes. Plasma cells, histiocytes and eosinophile cells occurred in much smaller numbers. Foreign body giant cells, one by one or in groups, frequently occurred around the cavities similar in shape to cholesterol needles. In orcein-stained sections some areas of the increased connective tissue showed the presence of rough elastic fibres, most of which became rigid and fragmented, while in other, often large, areas no elastic fibres were demonstrable. In some areas there was a conspicuous abundance of dilated capillaries filled with erythrocytes. In some arterioles the intima was slightly thickened; the elastic fibres were mostly intact, but some of them showed thickening and others fragmentation. There were a few compressed alveoli with fibrosed wall; many alveoles had no epithelial lining. In the areas between the fibrosed parts the epithelial cells were swollen, cuboid in shape or reminiscent of cylindrical epithelium. In the lumen of many alveoli epithelial cells of varying size, sometimes very big, and eventually polynuclear, histiocytes and occasionally eosinophile material were visible. In some parts alveolar fibrosis was detected, while in others alveoli with thin

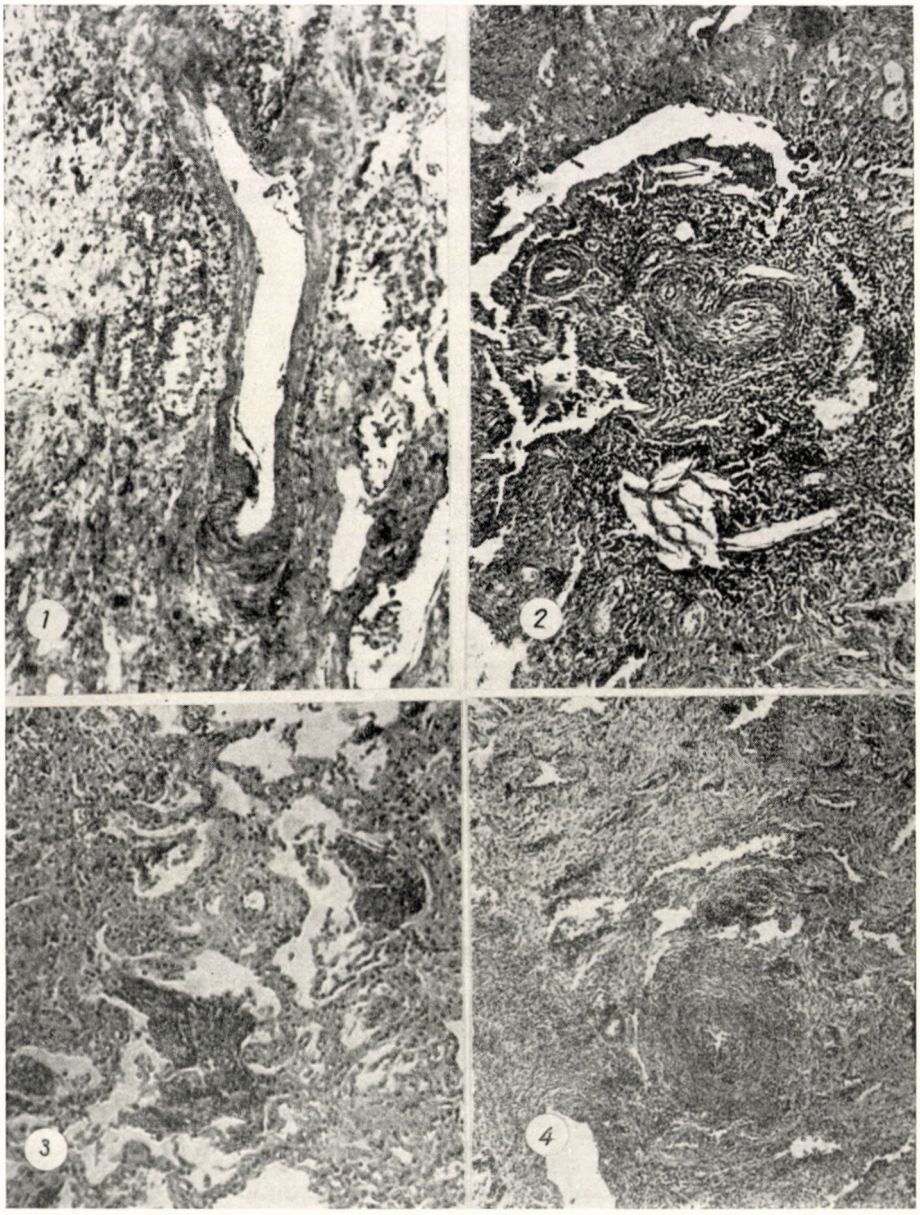

Fig. 1. Hamman—Rich syndrome; pulmonary fibrosis. H. E. ×45

Fig. 2. Scleroderma; pulmonary fibrosis, vascular changes. H. E. ×60

Fig. 3. Rheumatic pneumonitis; intraalveolar exudate. H. E. ×100

Fig. 4. Rheumatic pneumonitis; pulmonary fibrosis, productive arteriitis. H. E. ×30

walls and dilated in varying measure were found. Fibrin was not demonstrated either in the alveoli or in the interstitium. The bronchial epithelium was mostly intact.

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The described pulmonary changes essentially corresponded to those occurring in the Hamman—Rich syndrome. Some other changes usually associated with the syndrome were, however, missing in our case. For example, HOFF, HARRIS et al., as well as LARSEN found an increase of smooth muscle elements in the interstitium; in the cases of WHITE and CRAIGHEAD, and those of WEBER, this was marked especially around the bronchi and small arteries. This change cannot be considered to be characteristic; LIEBOW et al. regard it as common in chronic lung diseases of various types. CARABASI described the presence of granulation tissue with epitheloid-like cells in the interstitium, where WILDBERGER and BARDAY found small bone islets.

HOFF, CARABASI and LARSEN observed hyaline membrane, PEABODY et al., as well as OGILVIE and HULSE found organized exudate, and others [6, 11, 76] in acute cases demonstrated fibrinous exudate. Several authors [7, 11, 14, 38, 76, 81] described metaplasia of the alveolar epithelium. CARABASI, PEABODY et al., DA COSTA and TORRES reported on vascular changes, believed to be secondary, with thickening of the vascular wall. VANEK alone has mentioned the presence of arteriitis, chronic or acute.

Although the pulmonary changes described to occur in collagenoses running an acute or subacute course, periarteritis nodosa or LED [5, 16, 32, 35, 51, 73, 75] owing to the presence of necrosing arteriitis and fibrinoid necrosis of the parenchyma are fundamentally different from the acute Hamman—Rich syndrome, the chronic ones (scleroderma, dermatomyositis) bear resemblance to it in several aspects. On the basis of comparative studies of the pulmonary changes in scleroderma (WILBERGER and BARDAY), scleroderma and dermatomyositis (HINSHAW and GARLAND), rheumatoid arthritis (RUBIN and LUBLINER) and the Hamman—Rich syndrome, it has been suggested that the Hamman—Rich syndrome might be a localized collagen disease.

Case 2. A female patient 56 years of age had been admitted with typical sclerodermal manifestations preceded about 2 years earlier by dyspnoea. Febrile and afebrile periods had alternated, dyspnoea and the skin manifestations had become worse. A chest X-ray had revealed in both lungs diffuse, fine, small, focal, interstitial miliary densities in net-like distribution. Twelve days before death excitation, dysarthria, aphasia, then deepening coma had developed.

At autopsy (608/1955) skin changes corresponding to acrosclerosis were found. The heart weighed 330 g, the right ventricle showed dilatation and hypertrophy. The pleura exhibited fibrous adhesion, there was a recent pleu-

ritis on the left side. The lungs were of subnormal size, increased in weight, dense on palpation. The cut surface was greyish-red, with fine greyish-white bundles, minor bronchial dilatation and an absence of alveolar parenchyma. Spleen and liver were congested. In the brain, in both caudate nuclei there was one small, pea-sized, yellow focus with a haemorrhagic border.

Histologic study showed the pulmonary changes to diminish in severity in the direction of the apices. Diffuse, chronic fibrosis was visible basally. In the alveolar wall and interstitium the connective tissue was increased in amount; it was hypercellular in some areas, but most of it showed hyaline degeneration, and focal infiltration by mononuclear cells, chiefly lymphocytes. The number of alveoli was definitely reduced, some of the remaining ones had narrow, others had dilated lumina. The epithelial alveolar lining was composed of cuboid cells, detached at many sites. The bronchioles were dilated and lined by flat or cuboid epithelial cells. In the small and medium-sized arterioles changes were detectable throughout the lung tissue. The media was thick and showed hyaline degeneration; this, together with the proliferation of the intima resulting in a thickening of the vascular wall and a narrowing of the lumen, nearing obliteration in some areas *(Fig. 2)*. In many blood vessels the elastic fibres were thick, straight or fragmented.

The skin showed the pattern of the final stage of scleroderma. In the myocardium focal fibrosis reminiscent of granulation tissue, in some fine coronary branches minor intimal proliferation were visible. In the oesophagus, the small and large intestine submucous fibrosis invading the muscular layer, and in the oesophageal blood vessels productive endarteriitis were seen. The bone marrow exhibited vascular changes similar to those in the lung. In the cerebral foci necrosing arteriitis, fibrinoid thrombi, mononuclear infiltration in and around the blood vessels were found (For a detailed description, see [46]).

Pulmonary changes similar to those described above have been reported to occur in scleroderma (Bevans, Weiss et al., Orabona and Albano), as well as in a case of dermatomyositis associated with scleroderma (Talbot et al.). In addition to "compact sclerosis" Getzowa found also a so-called cystic sclerosis. Similarly, cystic changes, as well as hyperplasia of the cicatrized connective tissue, fibrinoid in the alveoli, crystalline foreign bodies and foreign body giant cells have been described as occurring in a case of scleroderma complicated by dermatomyositis (Pagel and Treip). Beside these similar features a fundamental difference from the Hamman—Rich syndrome was represented in our case by the severe vascular changes. Essentially similar changes have been described by Bevans, Weiss et al., Pagel, Treif and Kraus. In addition, round cell infiltration of the media was found by Matsui, Deutsch and Ormos. Sharp observed chronic vascular changes, a homogeneous eosinophilic material subendothelially, and at some sites organizing fibrin or hyaline thrombi.

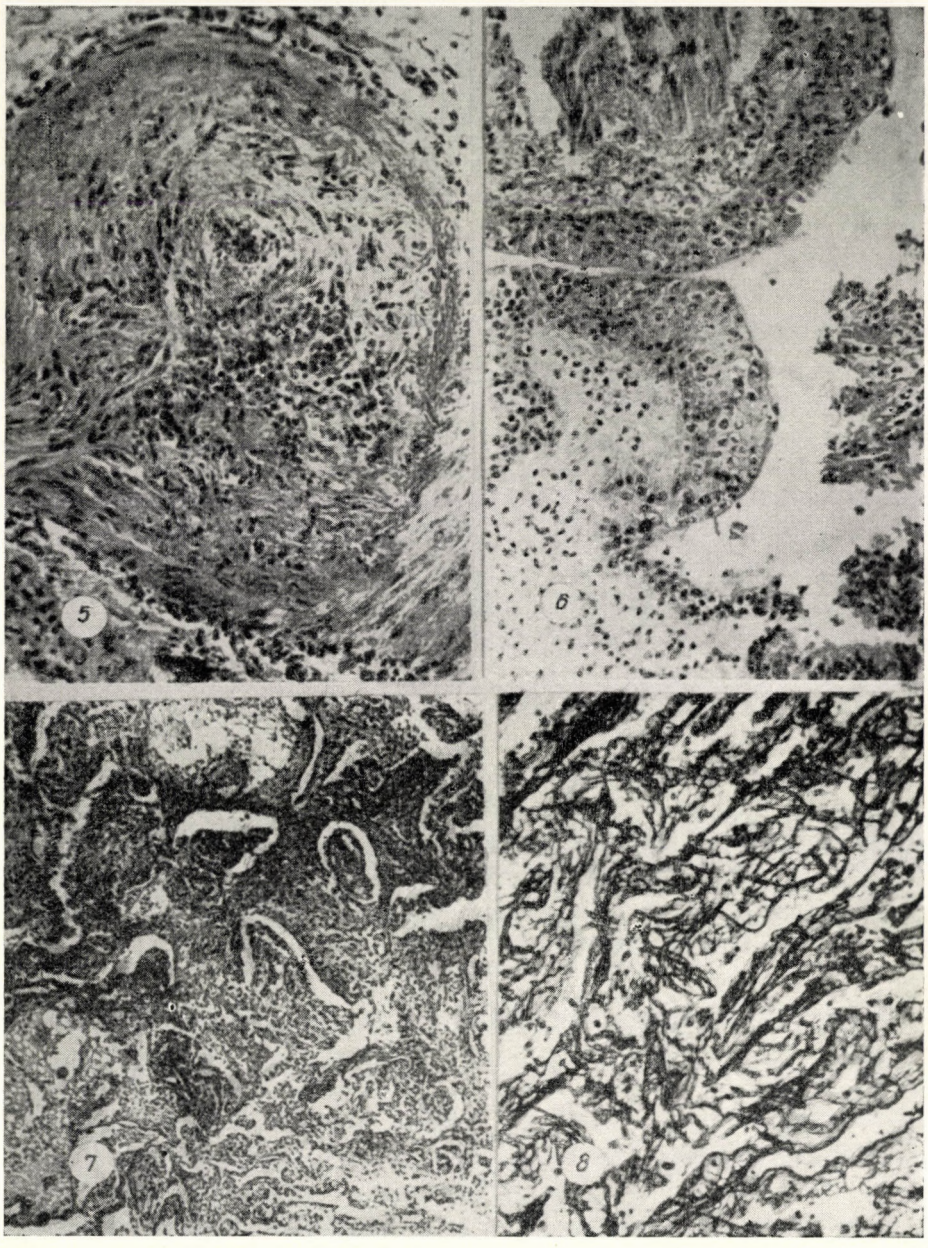

Fig. 5. Rheumatic arteriitis. H. E. ×150.

Fig. 6. Influenza-pneumonitis; metaplasia of flat bronchial epithelial cells. H. E. ×100

Fig. 7. Influenza-pneumonitis; interstitial pulmonary fibrosis, organizing intraalveolar exudate. H. E. ×60

Fig. 8. Influenza-pneumonia; increase of argyrophilic fibres. Gomori's silver impregnation. ×150

The differences in the pulmonary changes (especially those of the pulmonary vessels) between the collagen diseases and the Hamman—Rich syndrome are most clearly illustrated by our case 3.

Case 3. A 42 years old female patient with a 10 year history of rheumatism had been repeatedly hospitalized during the past 3 years because of congestive heart failure. Three days before her death the ESR had been 30 mm in 1 hour and a throat test positive for *St. haemolyticus;* active endocarditis had been suspected.

At autopsy (No. 26/1959) the heart weighed 430 g. It was dilated, especially the hypertrophied right ventricle. The mitral and aortic valves were thick, grown together; the left venous ostium was markedly narrowed. The pleura showed fibrinous adhesions. The lower pulmonary lobes were dense and a diffuse, fine greyish-white pattern was visible on the cut surface. In the major branches of the pulmonary artery several butter-yellow plaques were visible. Bilateral hydrothorax, severe chronic changes indicative of congestion and slight arteriosclerosis were also found.

Histologic study showed in the heart muscle small fibrotic foci, with a few fibroblasts and mononuclear cells. In some minor coronary branches proliferation of the intima caused total obliteration of the lumen. Mononuclear infiltration was found in the adventitia and intima. Marked thickening of the media and adventitia was observed in many small and medium-sized arteries.

The lungs showed congestion and in some alveoli eosinophilic exudat filling the lumen at sites, or adherent to the inner wall in other areas *(Fig. 3)*. The exudate contained als detached alveolar epithelial cells and mononuclear cells. Diffuse fibrosis was visible mainly in the lower lobes, in the interstitium in some, and in the alveoli in other areas. In such areas only a few alveoli lined with compressed cuboid epithelium were found *(Fig. 4)*. In general, the connective tissue was rich in collagen fibres. Silver impregnation according to GOMORI revealed an increase of reticular fibres. The network of elastic fibres was broken up. Infiltration by mononuclear cells was seen in the interstitium, mainly perivascularly; around the alveoli containing exudate, polymorphonuclear leucocytes were also found in some areas. There were intensive endothelial proliferation and variable thickening of the media in the branches of the pulmonary artery *(Fig. 4, Fig. 5)*. In many blood vessels the intima contained a homogeneous, intensely eosinophilic material staining a bright yellow with PTAH; in some areas a fibrinoid substance staining blue appeared between the layers of the media. Every stratum of these blood vessels was infiltrated by many mononuclear cells and a smaller number of neutrophilic leucocytes. The wall of the precapillary arterioles was thick and the lumina were narrowed.

We considered the changes in the heart and lung to be part of the chronic rheumatic disease, which had shown a terminal exacerbation. A wide variety of pathological changes have been described to occur in rheumatic pneumoni-

tis: in the cases with a short course intraalveolar exudate containing mononuclear cells and rich in fibrin and protein [24, 26, 68, 69], hyaline membrane [25], thickening and focal necrosis of the alveolar wall [29, 48], granulation tissue invading the alveoli from the interstitial septa [24, 29, 43], and fibrin thrombi in the small pulmonary blood vessels [24, 63] were observed. Aschoff nodes were uncommon [23]. Focal or diffuse fibrosis due to the organization of the exudate have been suggested to characterize the more advanced stage by SCOTT et al. and GUNN. Most authors emphasize the absence in the lung parenchyma of morphological changes characteristic of rheumatic pneumonitis. In contrast, severe vascular changes similar to those found by us and presumably characteristic have been described by many authors [18, 24, 26, 39, 42, 72]. According to HALL, such changes are common; SOKOLOFF et al. consider rheumatic vascular changes to occur most often in the lungs. Productive vascular changes are found in the lungs also in pulmonary hypertension, but they are fundamentally different from the changes associated with rheumatic arteriitis, owing to the absence of inflammation. Similar changes have been described to occur in rheumatoid arthritis [61].

Using the term viscerocutaneous collagenosis, KUZMA and SHARP emphasize that the pulmonary changes occurring in the various collagen diseases are essentially identical and the histological differences are due merely to variations in the duration of the disease or in the severity of changes. For this reason in scleroderma and chronic rheumatism the pulmonary changes seldom show such acute features as those found for example in LED, but it can hardly be doubted that the fibrosis and chronic vascular changes associated with scleroderma and rheumatism represent a more advanced stage of a pathological process of the same nature. It therefore seems that the Hamman—Rich syndrome is lacking certain fundamental criteria characteristic of the collagen diseases and the vascular changes are different even in the chronic cases. We therefore do not believe that the Hamman—Rich syndrome would constitute a form of collagenosis.

Allergy has been suggested to be responsible for the Hamman—Rich syndrome [9, 50, 56, 62, 65]. The different nature of the pulmonary changes in periarteriitis nodosa and rheumatic fever seems to discredit this view. CHURG and STRAUSS described in the lung of patients with asthma so-called allergic granulomas composed of epitheloid and giant cells, with central necrosis, as well as vascular changes similar to those in periarteriitis nodosa. HOOD et al., as well as GODMAN and CHURG, in Wegener's granulomatosis found necrosing arteriitis and around necrosed foci granulomas whose most characteristic cell types were eosinophilic cells, fibroblasts and giant cells in palisade-like distribution in the lungs. PARKIN et al. in acute glomerulonephritis demonstrated in the lungs necrosing alveolitis, focal fibrinoid necrosis, hyaline membrane and haemorrhages; these changes resulted in cicatrisation of the alveolar wall

and in an increase of connective tissue infiltrated by mononuclear cells. Thus, the pulmonary changes found in these characteristically allergic diseases are entirely different from those encountered in the Hamman—Rich syndrome.

The possibility of viral infection had been suggested by HAMMAN and RICH. It was also considered probable by CALLAHAN, CROSS, DACOSTA, OGILVIE and HULSE, POKORNY and VANEK. During the 1959 influenza epidemic we had opportunity to study the lungs of several patients who had died of influenza pneumonia. Two of these cases are thought to merit particular attention with respect to the problem under discussion.

Case 4. A male patient 47 years of age had fallen ill nine days before his death. The disease had begun with backache, shivers, cough, haemoptoea, dyspnoea. He had died after two days of hospital treatment.

At autopsy (No. 151/1959) the left lung was free, oedematous. The paravertebral areas were dense, dark purple, with pea-sized and smaller yellowish spots. The right lung adhered to the chest wall in its entire length. The upper lobe was dense, the cut surface was dark reddish grey, with a nut-sized cavity filled with pus and many lenticle-sized yellowish foci in it. The lower lobe was somewhat softer, pea-sized small foci were visible on its cut surface. The heart weighed 350 g; it was flaccid, yellow. The spleen was 100 g in weight, soft, and much material could be abrased from its cut surface. The liver weighed 1760 g; it was friable and yellow on its cut surface.

Histologic study showed exudate and detached epithelial cells in some alveoli. In most of them there was a substance staining a bright red with eosin, filling the intraalveolar space or adhering to the inner surface. In the latter case the epithelial lining of the lumen was absent. In some areas the substance contained a few lymphocytes, histiocytes, detached alveolar epithelial cells and eryhtrocytes. One or two of the circumscribed foci were composed of polymorphonuclear leucocytes, with homogenisation of the lung tissue. Many alveoli were lined by swollen cuboid epithelium. The bronchial lumen contained exudate with mononuclear cells and granulocytes. In some bronchi metaplasia of the flattened epithelium with some atypical cells was visible (Fig. 6). The intraalveolar septa were thickened in varying degree due to infiltration by lymphocytes and plasma cells, but mainly to a proliferation of fibroblasts. They were richly vascularized and resembled fresh granulation tissue (Fig. 7). The arterioles and arteries were intact. Van Gieson's stain revealed some scarce connective tissue network, while silver impregnation a marked increase of fine argyrophilic fibres (Fig. 8). By orcein staining a few thickened elastic fibres were demonstrated in the interstitium. In the dilated alveolar wall the elastic fibres were fragmented.

Case 5. A male patient 68 years of age died after 4 weeks' illness. The X-ray had revealed in the right lung a subclavicular homogeneous shadow of indistinct outlines.

At autopsy (No. 44/1959) the lung was soft, swollen. Extensive pleural adhesion was found on the right side. In the right upper lobe, subapically, a dense area of the size of a female fist rather distinct in outlines, dirty red in colour, was seen. The bronchial mucosa was dirty pink in colour. The lumina were filled with much foamy fluid. Other findings included hypertrophy of the left ventricle, sèvere systemic arteriosclerosis, congestive phenomena.

The upper lobe of the right lung showed essentially the same histological changes as those described for case 4. Interalveolar fibrosis was less marked, but fibrosis of the interstitium was more advanced and the connective tissue was richer in fibres. In some arterioles a moderate thickening of the intima was seen.

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The changes described were essentially identical with those encountered in acute or subacute cases of the Hamman—Rich syndrome. In case 4, the only difference was that the fibrosis was in an early stage, owing to the short duration of the disease.

Had the disease lasted longer, the same morphological picture as that found in the Hamman—Rich syndrome would have developed, as in case 5, where death ensued after longer illness. Pulmonary changes identical with those described by us have been reported in connection with the 1918 influenza epidemic by GOODPASTURE, and in cases of virus pneumonia by AUERBACH et al., and GOLDEN. WOLLENMAN and FINLAND observed cases of influenza-pneumonitis superinfected with *Staphylococcus aureus*, with fibrosis of the lungs, organization of the exudate, foreign body giant cells in the organizing areas, or eventually with abscess formation. WOLMAN and GOLDBERG suggested that a thickening of the septa with mononuclear infiltration and fibroblast proliferation, an increase of reticular fibres, a "cuboidal metaplasia" of epithelial cells and parenchymal haemorrhages were characteristic of interstitial pneumonitis. In primary atypical pneumonia PARKER et al. found mononuclear infiltration and oedema of the interstitium, fibrinous, partly organized exudate, hyaline membrane and a cuboid swelling of alveolar epithelial cells. Similar pulmonary changes were described as occurring in psittacosis by LILLIE. CROSS found the pulmonary changes in interstitial pneumonitis and ornithosis to be similar to those occurring in acute Hamman—Rich syndrome. In adenovirus pneumonia NINOMIYA found a thickening of the alveolar wall with an increase of reticular fibres and mononuclear infiltration, excessive capillary dilatation, intraalveolar exudate with swelling and eventual polynuclear transformation of the alveolar epithelium.

Conclusions

In the chronic stage of the conditions analyzed above it is always the advanced diffuse fibrosis that dominates the picture and in spite of some marked differences this makes the morphological patterns closely similar. Examination of acute cases, however, reveals differences in the process responsible for diffuse fibrosis. The pulmonary changes found by us and other authors in viral pneumonia of longer duration are identical in every basic feature with those suggested to be characteristic of the Hamman—Rich syndrome; at the same time, the changes thought to be characteristic of collagenosis and allergic conditions are absent. According to GOLDEN, one of the cases originally described by HAMMAN and RICH was apparently one of interstitial pneumonia. VANEK has pointed out that although the protracted course does not suggest it, the process may be initiated by viral infection and the severe fibrosis may be a result of recurrent infection or incomplete resolution. With respect to this it is important that acute symptoms may appear at the onset of a process lasting several years [13, 38, 59, 78, 81]. Such symptoms often escape recording if the patient fails to remember or attributes no significance to an earlier respiratory infection.

We believe that the above points support the view according to which the Hamman—Rich syndrome actually develops on grounds of viral pneumonia. As according to present knowledge the widest variety of viral infections (primary atypical pneumonia, psittacosis, ornithosis, the various influenza strains, Vaccinia virus, etc.) produce essentially the same pulmonary changes, for the development of chronic pulmonary fibrosis not a specific virus, but some non-specific factor influencing the course and outcome of inflammation and promoting the development of fibrosis should be made responsible, such as a disturbance of fibrinolysis [59] or an impairment of lymph circulation [14, 45, 66, 76, 84].

Summary

The pulmonary changes associated with the Hamman—Rich syndrome, scleroderma, rheumatic pneumonitis and influenza pneumonia, have been discussed. The histopathological changes observed in these conditions suggest that the Hamman—Rich syndrome is apparently neither a collagen disease, nor an allergic condition. The close resemblance of the pulmonary changes with those found in pneumonia due to influenza and other viral infections and the absence of changes characteristic of collagenosis and allergic conditions seem to support the view that the Hamman—Rich syndrome develops on the basis of a viral pneumonia.

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СРАВНИТЕЛЬНОЕ ИССЛЕДОВАНИЕ БОЛЕЕ РЕДКИХ ФИБРОЗОВ ЛЁГКИХ

И. БАРТОК и Ф. БИЛИЦКИ

Авторы излагают на основе своих собственных наблюдений, как и литературных данных, изменения лёгких, возникающие при синдроме Хамман—Рича, склеродермии, ревматическом пневмоните и гриппозном воспалении лёгких. При сравнительном анализе наблюдаемых в этих картинах болезней патогистологических изменений они пришли к тому заключению, что синдром Хамман—Рича нельзя рассматривать ни коллагенным, ни аллергическим заболеванием. Тот факт, что гистоморфологические изменения синдрома Хамман—Рича по существу тождественны с изменениями при гриппозных (и прочих вирусных) пневмонитах, при одновременном отсутствии характерных для коллагеноза и аллергических поражений изменений, подтверждает то предположение, что эта картина болезни развивается на почве вирусной пневмонии.

VERGLEICHENDE UNTERSUCHUNGEN SELTENER LUNGENFIBROSEN

I. BARTÓK und F. BILICZKI

Es wurden die mit Hamman—Rich-Syndrom, Sklerodermie, rheumatischer Pneumonitis und Influenzapneumonie einhergehenden Lungenveränderungen untersucht. Die vergleichende Analyse ergab, daß das Hamman—Rich-Syndrom weder als eine Kollagenerkrankung, noch

als eine allergische Krankheit betrachtet werden kann. Die Tatsachen, daß die Lungenveränderungen bei diesem Syndrom und bei den durch Influenza und andere Viren bedingten Krankheiten praktisch identisch sind und daß gleichzeitig die für Kollagenose und Allergieschäden kennzeichnende Veränderungen fehlen, lassen die Annahme zu, daß das Hamman—Rich-Syndrom als Folge einer Viruspneumonie zu betrachten ist.

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