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MORPHOLOGIC ASPECTS OF THE PULMONARY CHANGES ASSOCIATED WITH COLLAGEN DISEASES

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It was chiefly on a morphological basis that KLEMPERER et al. [51] collected into a group the conditions known under the comprehensive name of collagen diseases. As a result of subsequent investigations the group has been widened although some authors still refuse to accept its homogeneity. On the basis of data in the literature and some own morphological and clinical observations we shall attempt in the following to discuss the pulmonary changes associated with certain collagen diseases.

The study of lung changes occurring in collagen diseases has a short history. Although the occurrence in scleroderma of pulmonary changes had been mentioned by FINDLAY [27] in 1891, and lupus pneumonitis by OSLER [68] in 1904, it was only after the report on rheumatic pneumonitis published by MASSON et al. in 1937 [60] that a number of pertaining papers have been published. Especially those of RICH and GREGORY [78, 79] and NEUBERGER [64] regarding rheumatic fever, of RAKOV and TAYLOR [74], further TEILUM and POULSEN [95] concerning disseminated lupus erythematosus (DLE), of ZEEK et al. [102, 103] and ROSE and SPENCER [81], regarding lung involvement in polyarteritis nodosa, of CHURG and STRAUSS [14] further KORNBLUM and FIENBERG [52] on pulmonary changes accompanying necrotizing polyangiitis and granulomatosis, finally of ELLMANN and BALL [20], CAPLAN [10] and RUBIN [83] rheumatoid arthritis have to be mentioned.

In recent years, several papers have dealt with the pulmonary changes occurring in collagen diseases, mostly giving a review of the pertaining literature rather than original observations [5, 7, 41, 54, 63].

The data agree in that in collagen diseases the same phenomena are found in the lungs as in other organs, especially in the vessels, the endocardium and the synovial membranes. It is nevertheless indisputable that, owing to its special structure, the lung parenchyma is capable of histological reactions different from those of other organs; these reactions display a morphological similarity to the allergic changes [78, 79, 58, 5, 84, 9, 14, 19, 83].

Our examinations were made on 35 lung specimens of patients who had died with various collagen diseases. Microscopic or gross changes were revealed

in 30 cases with the following distribution: in 4 cases of rheumatic fever; 3 of disseminated lupus erythematosus; 9 of polyarteritis nodosa; 3 of necrotizing polyangiitis and granulomatosis; 5 of rheumatoid arthritis; and in 6 cases of scleroderma. 5 to 10 sections were prepared from the different parts of each specimen and stained with haematoxylin-eosin, azan, Masson's trichrome, resorcin-fuchsin, resp. Schiff's periodic acid.

Pulmonary changes associated with collagen diseases

Rheumatic fever

Lung involvement was revealed in 4 cases of rheumatic fever. The age of the patients had ranged from 7 to 17 years. Only some of them displayed respiratory symptoms, such as cough, dyspnoea, thoracic pain and, later, cyanosis. At autopsy, the cut surface of the lungs showed beside haemorrhagic areas rust coloured and ochre yellow patches especially at the base and the marginal areas. Histology revealed mucinous oedema in the parenchyma, the connective-tissue septa in particular (Fig. 1); desquamation of the alveolar and bronchial epithelium (Fig. 2); coagulating necrosis of the alveolar walls, and — in one case — a mass of hyalin membranes (Fig. 3); further interstitial infiltration of varying degree. The vessels were congested, their walls showed fibrinoid necrosis and aneurysm-like dilatations. In some instances precipitated fibrin connected with the necrosed vessel-wall extended polyp-like to the alveolar lumen (Fig. 4). Essentially, these changes were identical with those termed "pneumonitic lesions" and "pseudomembranaceous lesions" in the classical description by MASSON et al. [60]. We observed in two instances also the "vegetative lesions", structures composed of young cell-rich connective tissue arising from the organizing exudate, that have been termed "Masson bodies" by NEUBUERGER [64].

Of recent, LUSTOK and KUZMA [54] have reviewed the data concerning the pathomorphologic aspects of rheumatic fever. They regard the following histological features as characteristic of rheumatic pneumonitis: alveolar haemorrhage, necrosis of alveolar walls, hyalin membranes, proliferation of alveolar cells, Masson bodies, necrosis of the wall of bronchioles and vessels, as also the reparative phenomena of all acute changes. Other authors have pointed to the morphological similarity between rheumatic pneumonitis and other diseases, the various kinds of antigenic pneumonitis in particular [78, 79], as also to the common features of pulmonary changes accompanying collagen diseases and allergic syndromes [5]. Again, other authors concerned themselves with the differential diagnosis of chronic congestive lung changes and rheumatic pulmonary lesions [50].

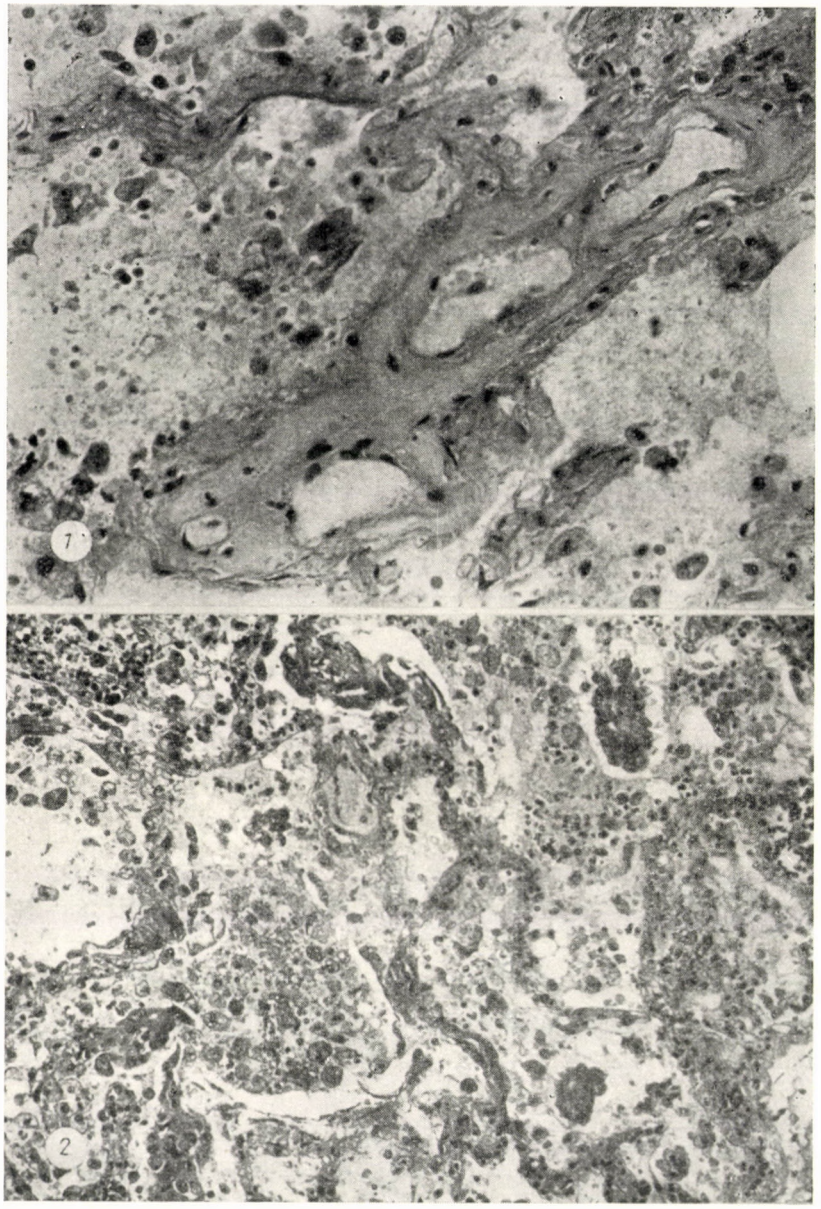

Fig. 1. Rheumatic fever. Oedematous-mucinous swelling of pulmonary interstitium. Moderate exudation and desquamation in the lumen of alveoli. H. E. — ×260

Fig. 2. Rheumatic fever. Amorphous and cellular exudate in alveoli. Occasional groups of alveolar epithelial cells. H. E. — ×180

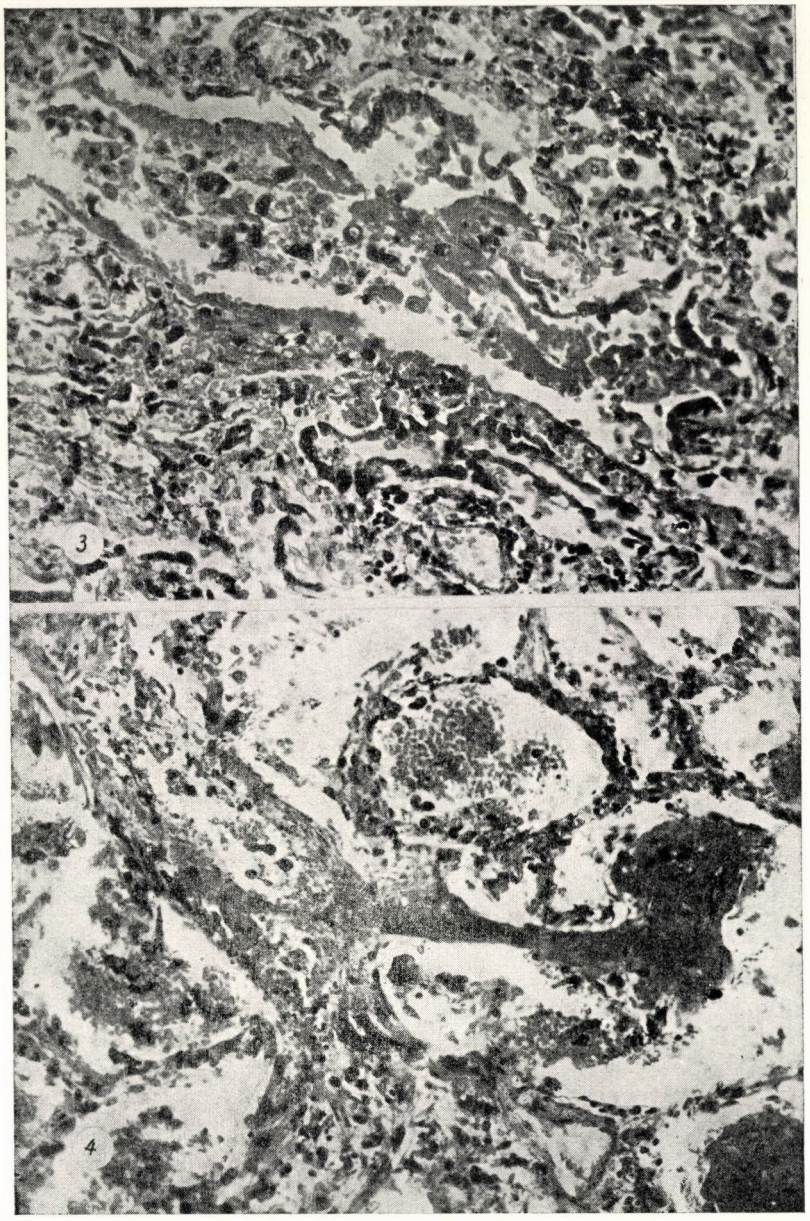

Fig. 3. Rheumatic fever. Note homogeneous hyalin membranes on the wall and in the lumen of alveolar duct. The surrounding alveolar epithelium is cuboidal and proliferating. H. E. — ×220

Fig. 4. Rheumatic fever. Fibrin polyp connected with necrosed vessel-wall and extending into alveolar lumen. H. E. — ×180

The data in the literature as well as our own observations justify, therefore, the statement that acute inflammatory phenomena, the histological picture of pneumonitis, accompanied by a microscopic necrosis of tissues constitute the chief characteristics of pulmonary changes associated with rheumatic fever. The histological picture of such lesions resembles the one occurring with allergic pneumonitis. Symptoms of repair, cicatrization, occur in protracted cases, but such signs are mostly insignificant.

Disseminated lupus erythematosus

We examined the lungs of 4 patients who had of with DLE. Three were females and one was male. Their age waried between 22 and 65 years. One of the present authors (B. R.) has discussed in detail the problem of lung changes in DLE in an earlier paper [44]; those findings have been partly confirmed and partly supplemented by the results of the present examinations. Clinical symptoms had been observed in the terminal stage only: a migrating density above the base which appeared as a coarse patchy shadow on the X-rays, a pattern held to be characteristic by SANTE and WYATT [84]. Additional symptoms had been a dry cough, sputum occasionally tinged with blood, pleuralgia and pleural fluid accumulation. All patients with extensive pulmonary changes suffered from intractable dyspnoea.

Autopsy in part of these cases revealed hyperaemia and oedema; the cut surface showed a characteristic variegated pattern displaying red, haemorrhagic, rusty and greyish yellow areas, suggestive of lipoid pneumonia, side by side with fibrotic patches, especially in the chronic form of the disease (Fig. 6). In one case, there were bronchiectasic portions in the scarred pulmonary areas, displaying a honeycomb structure. The pleura was mostly oedematous, lined occasionally with organizing fibrin.

Microscopic examination revealed essentially the same changes as in the above cases. The most conspicuous phenomena were mucinous oedema, congestion and inflammatory infiltration of the alveolar septa, proliferation and desquamation of the endothelium (Fig. 7), fibrinoid necrosis of the capillary and alveolar walls and the formation of hyalin membranes. Certain portions of the alveolar ducts were filled with exudate composed of blood and fibrin (Fig. 8). We frequently observed the successive phases of the organization of intraalveolar exudate, its complete transformation into connective tissue, and its retraction, *i. e.* the formation of Masson bodies (Fig. 9). Grave changes were displayed by the small pulmonary vessels: their wall was oedematous with occasional signs of fibrinoid transformation, inflammatory infiltration and minute hyaline thrombi. Intimal pads arising from the organization of clots sometimes constricted the lumen, as in Moschcowitz's thrombotic thrombopenic

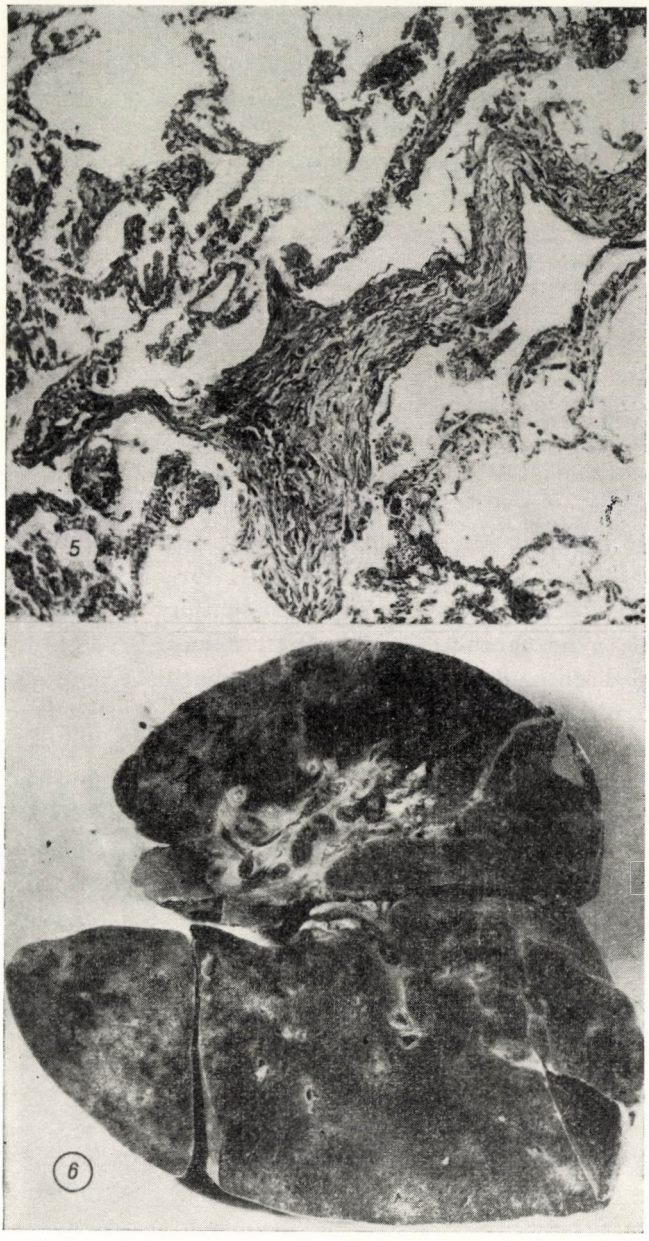

Fig. 5. Rheumatic fever. Fibrous Masson body in the lumen of alveolar duct. H. E. — ×80

Fig. 6. DLE. Cut surface of lung with bright (pneumonitic) and dark (haemorrhagic) areas

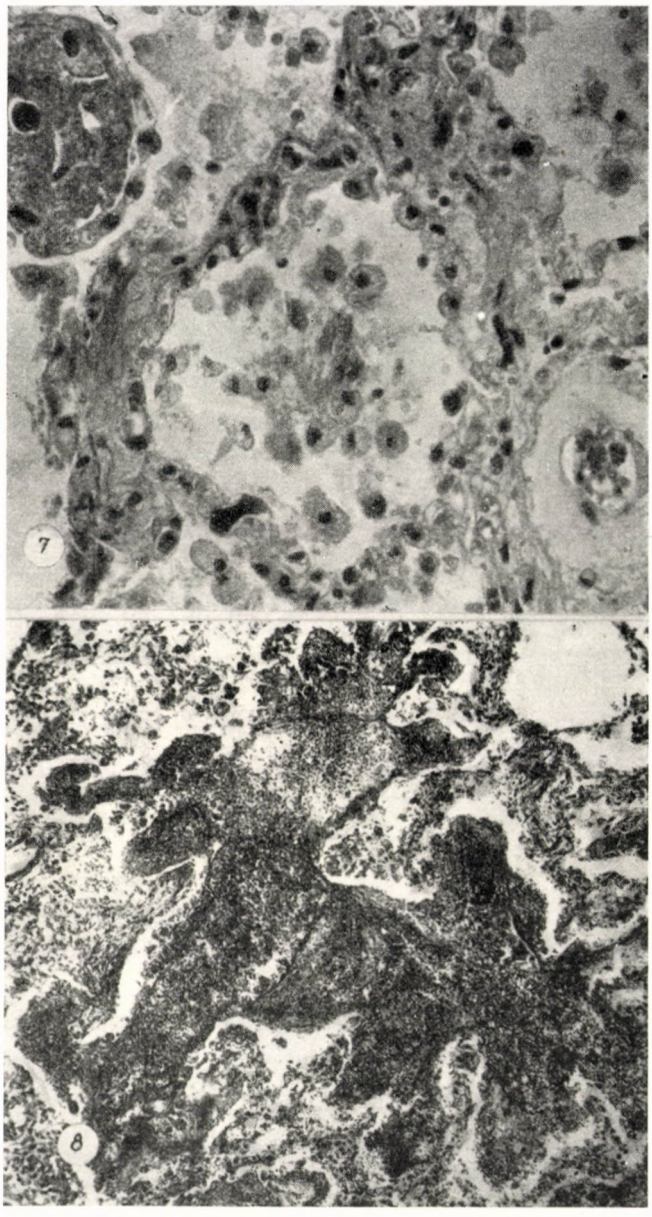

Fig. 7. DLE. Mucinous interstitial oedema, proliferation and desquamation of alveolar epithelium, in early stage of lupus pneumonitis. H. E. — ×340

Fig. 8. DLE. Fibrinous-haemorrhagic cast-like exudate filling alveolar duct. Inflammatory infiltration of alveolar walls. H. E. — ×60

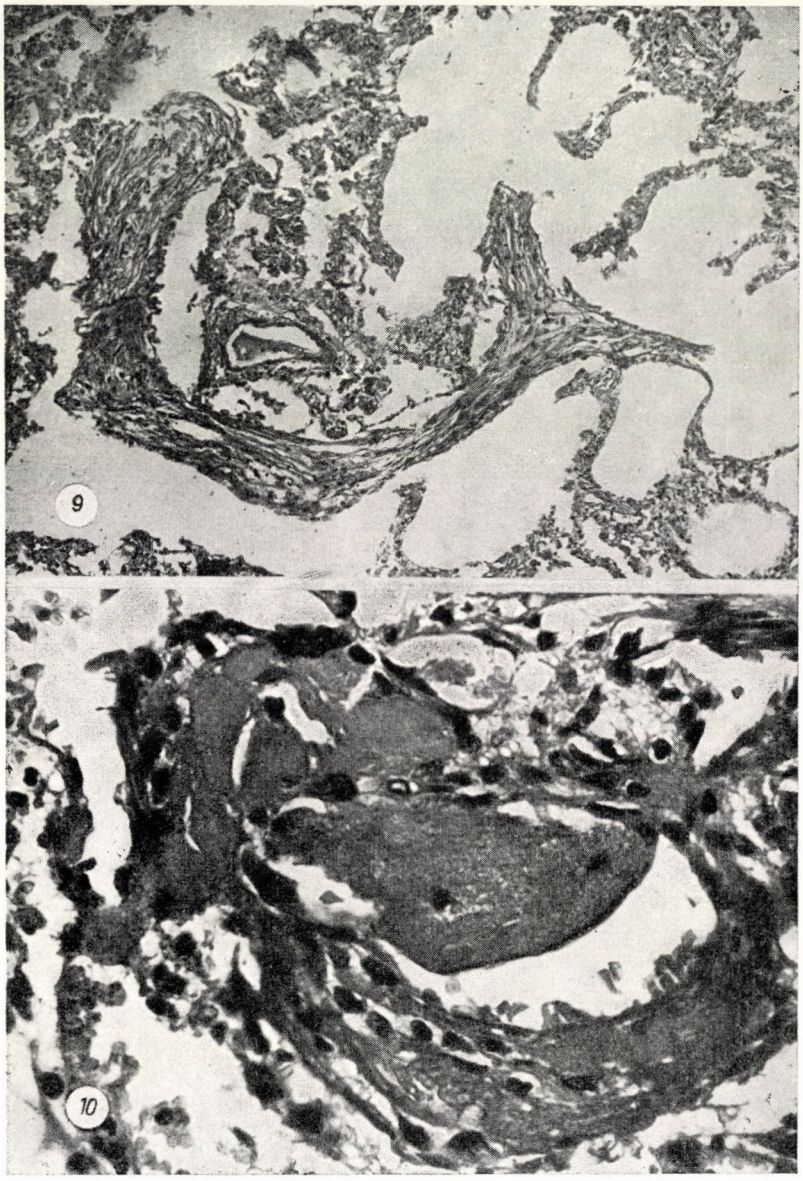

Fig. 9. DLE. Fibrous Masson body in lumen of alveolar duct. H. E. — ×120

Fig. 10. DLE. Areas of hyaline impregnation in arteriolar wall, with adhering hyaline globule. H. E. — ×420

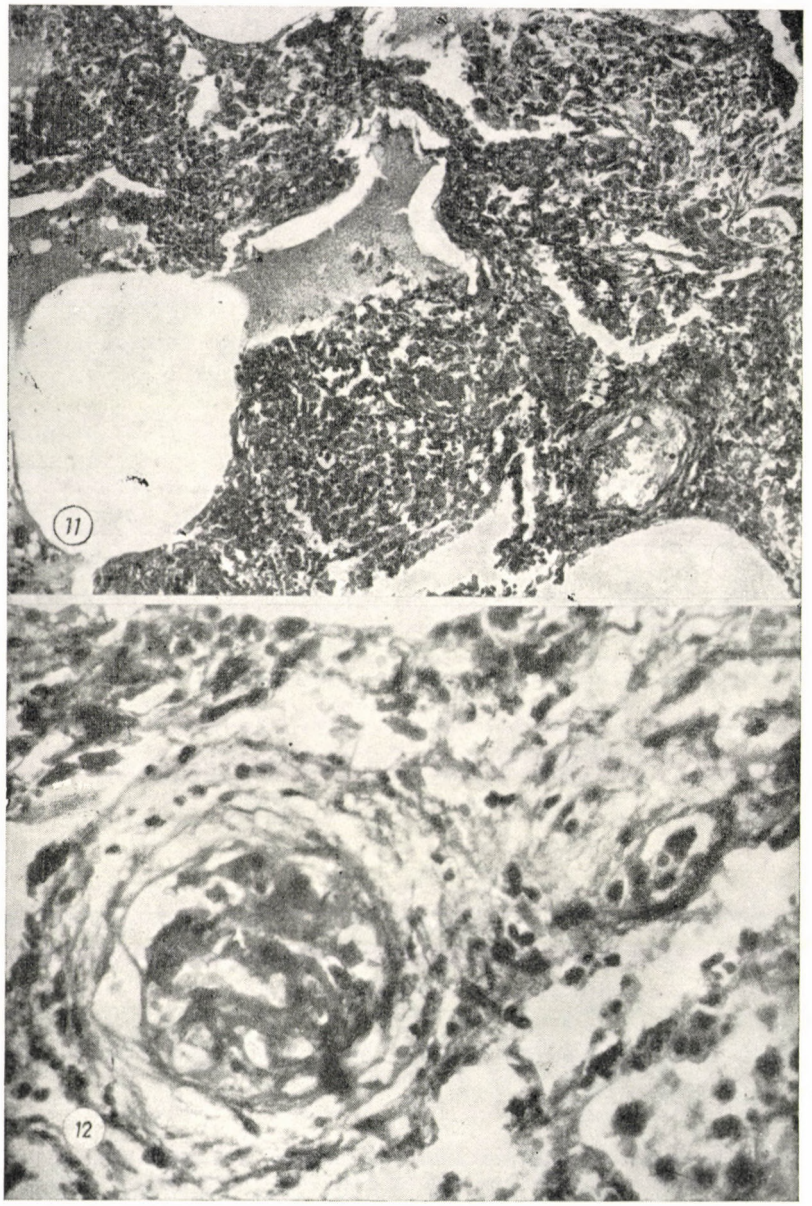

Fig. 11. DLE. Cell-rich granulomata in pulmonary interstitium. H. E. — ×180

Fig. 12. DLE. Oedematous swelling and inflammatory infiltration of pulmonary arteriole; intraluminar hyaline thrombus; signs of recanalization. H. E. — ×360

purpura (Fig. 10). In one case granulomas had formed in the wall of the vessels and the interstitium, a phenomenon regarded by TEILUM [94] as typical of lung involvement in DLE (Fig. 11). To the same category of phenomena belonged the ulcerative granulomatous lesions of the bronchioles observed in another case. Of chronic changes, thickening of arteriolar walls and recanalisation of hyaline thrombi were observed (Fig. 12).

One of the subacute cases of DLE had responded to ACTH treatment with rapid deterioration soon leading to death. Autopsy in this case revealed, beside signs of pneumonitis, fresh necroses and granulomata. We regard this as a morphological confirmation of the observation, according to which steroid therapy may sometimes aggravate the pulmonary process associated with collagen diseases [55, 16, 88].

Our above observations were in good agreement with the pertaining data in the literature. Clinical descriptions [17, 47, 76, 4, 40, 90] are unanimous in affirming that, because of the great variety of symptoms, the clinical picture is often so uncertain as to lead to erroneous diagnosis. The morphological pattern is mostly dominated by acute inflammatory phenomena which have been subsumed under the collective term of lupus pneumonitis [74, 84, 96, 82, 40, 75, 21, 71, 30, 2]. A phenomenon which has been considerably less often observed in connection with DLE is the granulomatous pulmonary lesion [94, 95, 44]: this, like pneumonitis, is an allergic tissue-reaction [36] and corresponds, therefore, to the granulomatous processes occurring in association with polyarteritis nodosa and necrotizing polyangiitis. It is generally accepted that, in contradistinction to the usual pulmonary changes (oedema, bronchopneumonia), the characteristic pneumonitic and granulomatous patterns occur in not more than 20 to 30 per cent of the cases of DLE. A secondary bacterial or mycotic infection is frequently associated with lupus pneumonitis [13].

Polyarteritis nodosa

Before discussing the pulmonary changes associated with them, it seems necessary precisely to define polyarteritis nodosa and necrotizing polyangiitis, and to make an adequate distinction between the two conditions. In our opinion the chief difference lies in the location of the lesions: while they are confined to the vascular system in polyarteritis nodosa, the vascular lesions may be accompanied and sometimes dominated by massive necroses and granulation of other tissues in cases of necrotizing polyangiitis. The organs, including the lung, involved in the two diseases constitute a further difference. Those forms of necrotizing polyangiitis which, beside generalized vascular changes, are confined to the respiratory parenchyma and the renal glomeruli are known under the name of Wegener's granulomatosis. At the same time the two conditions in question form a close pathomorphologic and clinical entity.

We examined 9 cases of polyarteritis nodosa accompanied by pulmonary changes. All the patients were males, from 21 to 57 years of age. The clinical symptoms of the pulmonary process were uncertain: cough, copious sputum, occasional asthmatic complaints. X-rays showed partly miliary and partly large, irregular, sometimes confluent patches which often disappeared with striking rapidity. Autopsy revealed yellowish purple spots suggestive of bronchopneumonia, and frequently also haemorrhagic infarctions. In chronic cases scarring and bronchiectasis occurred. Histological analysis revealed acute necrosis of vessel-walls, granulation and constriction scarring of the blood vessels. Beside haemorrhagic infarctions the pulmonary parenchyma displayed primary lesions, such as exudative, desquamative inflammation, hyaline membranes and even focal fibrinoid necrosis of the alveolar wall (Fig. 13), in short, the well-known symptoms of acute pneumonitis. Masson bodies originating from organized exudate were found in 5 cases; foci of fibrosis seemed to surround these bodies in the interstitial space. In one instance, formations resembling Masson bodies were observed to occupy the dilated lumen of bronchioles in a polyp-like manner (Fig. 14). No tissue necroses or granuloma formation could be seen.

Literary data concerning the pulmonary changes associated with polyarteritis nodosa are contradictory. While certain authors observed them frequently, other regard them as rare occurrences. We attribute this incertitude to the fact that a number of authors refuse to accept necrotizing polyangiitis as a separate disease and consider it a form or polyarteritis nodosa. This may explain the view of Rose and Spencer [81], who distinguished between two types of polyarteritis nodosa according to the presence or absence of lung involvement. We are of the opinion that the first type belongs to the category of necrotizing polyangiitis so that only cases without lung involvement should be regarded as genuine instances of polyarteritis nodosa. According to earlier observations [15, 66, 102, 92, 53, 34, 90] and our own findings while a whole range of phenomena from acute necrotizing processes through granulation to constrictive cicatrization may occur in the pulmonary vessels, the parenchyma reveals — apart from secondary lesions or vascular origin — only mild acute and chronic changes corresponding to those of rheumatic pneumonitis. Contrary to the observations of Rose and Spencer, we failed to observe necrosis or granulation independent of vascular changes.

Necrotizing polyangiitis and granulomatosis

The clinical and morphological features of necrotizing polyangiitis have been discussed by us in connection with two earlier cases [45]. Only one of them had pulmonary lesions. Since then, we had occasion to observe two more cases of this nature. Of the three patients, two were male and one female.

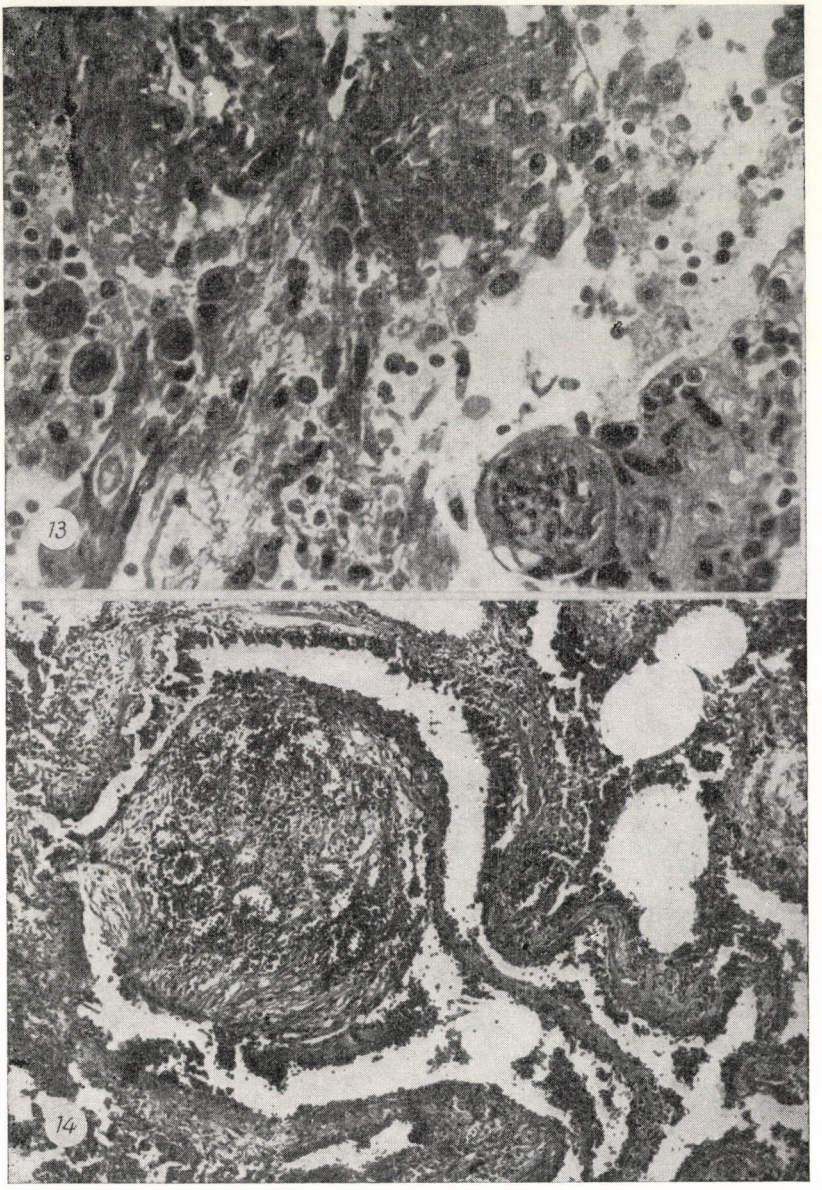

Fig. 13. Polyarteritis nodosa — Fibrinoid necrosis of inflamed capillary and alveolar wall, with connected fibrinous polyps. H. E. — ×360

Fig. 14. Polyarteritis nodosa. Intrabronchiolar Masson body-like structure. H. E. — ×80

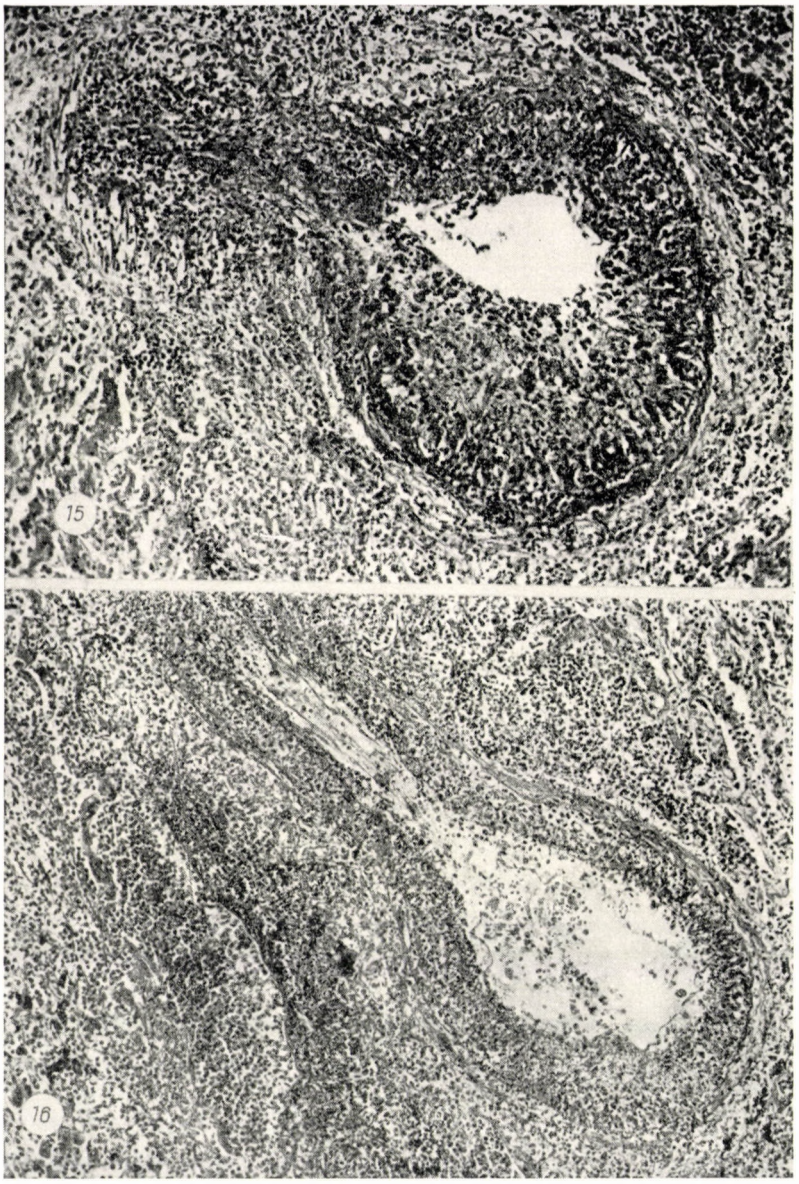

Fig. 15. Necrotizing polyangiitis. Granulation tissue with radial structure, composed of fibroblasts and inflammatory cells in pulmonary artery, constricting the lumen. H. E. — ×180

Fig. 16. Necrotizing polyangiitis. Granulating inflammation in the wall of pulmonary arteriole and adjacent bronchiole; inflammatory ulceration of bronchiolar epithelium. H. E. — ×150

Their age ranged from 45 to 52 years. The pulmonary symptoms were at first as uncertain as in polyarteritis nodosa; they became, however, more and more pronounced with the advance of the disease and were in some cases misleadingly similar to those seen in acino-nodular tuberculosis. In one of the patients especially in the basal portions of the lung the X-rays revealed loose snow-flake-like shadows with blurred edges, similar to that described by KORNBLUM and FIENBERG [52].

At autopsy the lungs had a variegated appearance, displaying pneumonitic areas, infarctions and yellowish grey compact necrotic masses of plum size and containing cavities resembling caseous tuberculous foci. The microscopic picture was likewise variable. Vascular lesions were restricted to the small arterioles and veins, part of which revealed signs of fibrinoid necrosis and pronounced granulation constricting the lumen. The granulation tissue had a characteristic radial structure composed of fibroblasts, round cells and eosinophils (Fig. 15). The neighbouring bronchioles displayed a similar necrotic granulation tissue (Fig. 16). The parenchymal lesions consisted of focal pneumonitis, larger or smaller necrotized areas and granulomata. The necroses were not as pronounced as in the case of tuberculous caseation, the pulmonary structure was not completely destroyed and these areas were surrounded by granulation tissue containing fibroblasts, histiocytes, lymphocytes and a few eosinophils and in one case also a great number of Langhans type giant cells (Fig. 17). The absence of tubercle bacilli was sometimes the only difference against tuberculosis.

The pattern essentially agreed with the one described in recent years under the name of necrotizing polyangiitis and allergic granulomatosis [89, 19, 14, 26, 52, 58, 99, 59, 87]. On the evidence of its morphological features, we regard also those of ROSE and SPENCER's cases [81], in which polyarteritis nodosa was associated with pulmonary changes as belonging to this category. Likewise in this group belongs a part of the cases described as Wegener's granulomatosis [24, 34, 9], atypical polyarteritis nodosa [93, 18], eosinophil granuloma or Löffler's syndrome. The pattern being a separate nosological entity can hardly be contested if we consider the clinical and morphological features of the condition, for which the term necrotizing polyangiitis seems to be the most comprehensive one. All processes in this group are characterized by more or less massive necroses of the vessels and other tissues and the associated granulation.

Rheumatoid arthritis

Pulmonary changes were revealed in five patients with rheumatoid arthritis, all of them females between 36 and 70 years of age. Clinically, the moderate changes had been accompanied by the usual symptoms such as

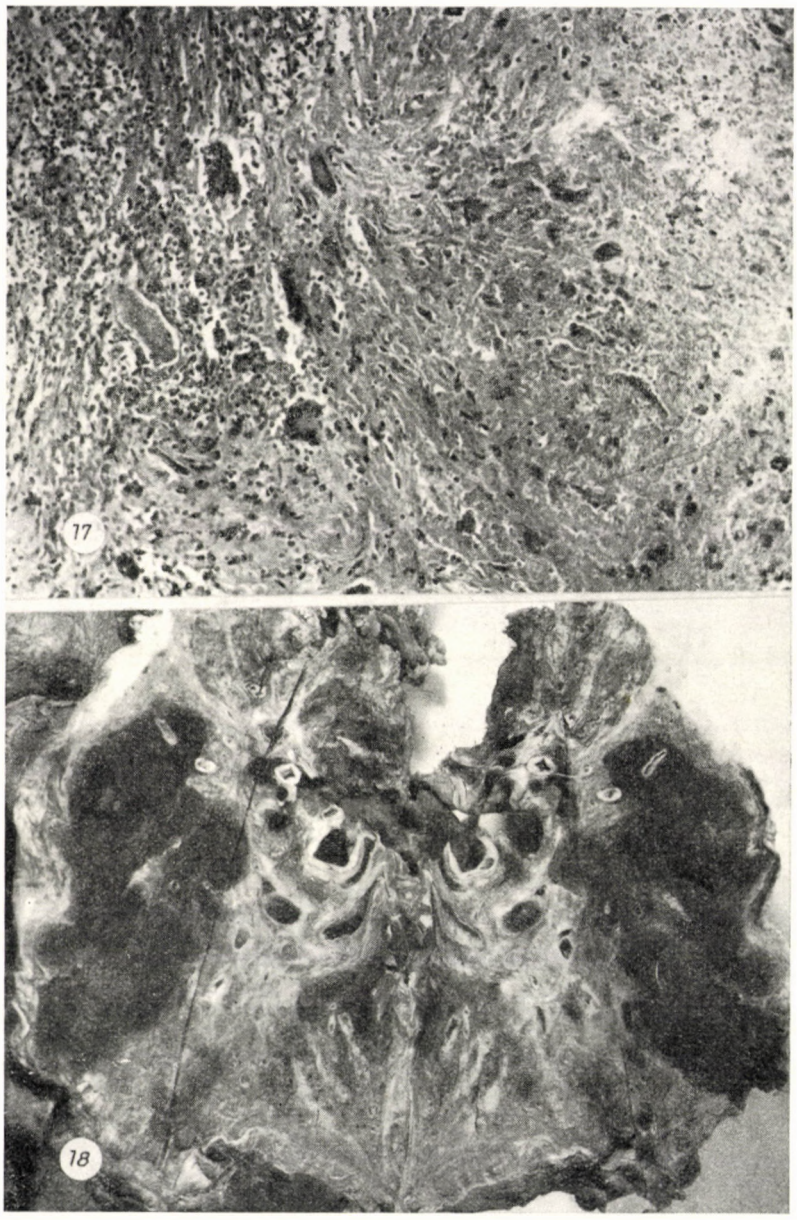

Fig. 17. Necrotizing polyangiitis. Necrotizing granulation with giant cells, resembling tuberculous granulation tissue. H. E. — ×180

Fig. 18. Rheumatoid arthritis. Grave scarring in apex and base of lung, with bronchiectases and pleural callus

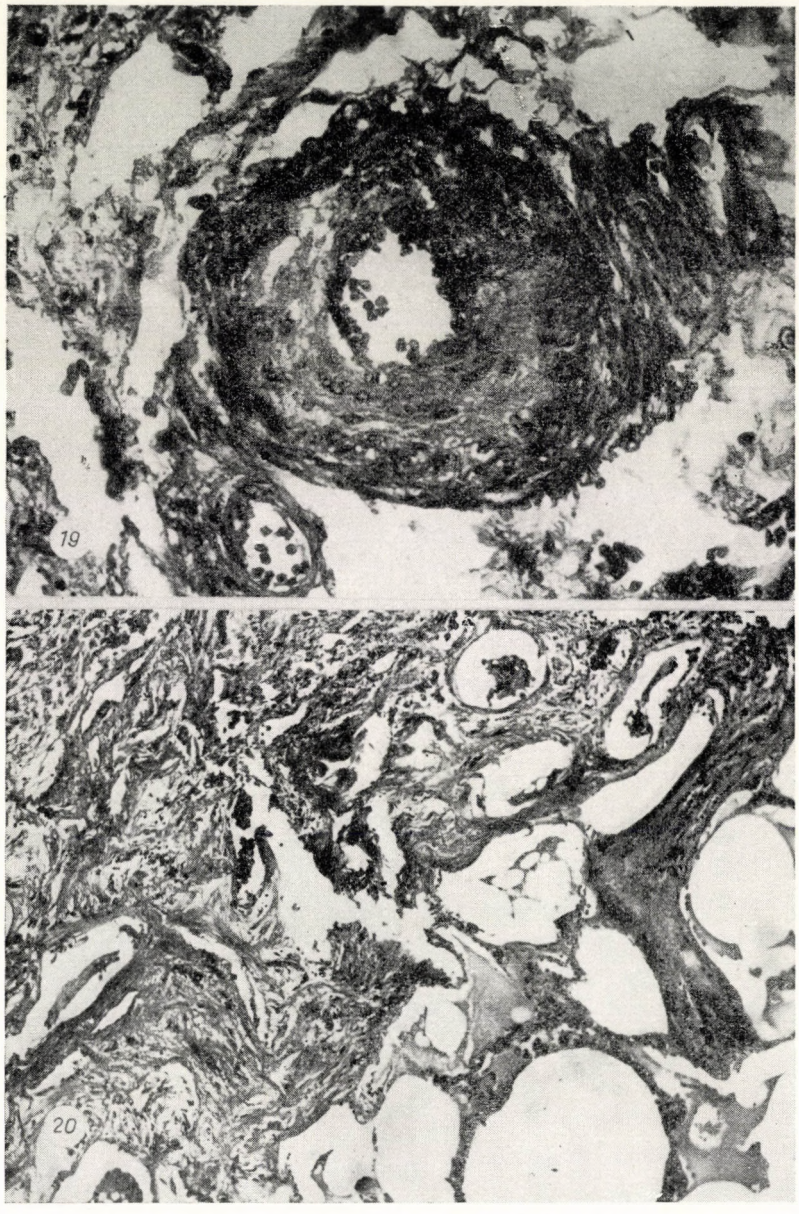

Fig. 19. Rheumatoid arthritis. Pulmonary arteriole with thick wall and narrow lumen. H. E. — ×340

Fig. 20. Rheumatoid arthritis. Scar tissue with minute cysts and Masson bodies (sclerocystic lung). H. E. — ×80

cough and discharge of sputum, while in the cases with massive fibrosis there had been sometimes grave respiratory distress. X-rays had revealed no specific features, only atelectasis of various size, pleural callus, less frequently bronchiectasis and in one instance, a cystic change. The clinical course had not been dominated by the pulmonary changes.

At autopsy, in the lungs usually bilateral fibrosis and even sclerosis of various extent was found, accompanied by bronchiectasis associated with pleural thickening and adhesions (Fig. 18). In one case there was a moderate, in another a marked sclerocystic change with honeycomb structure in the marginal portions. The histological picture was less dominated by these acute phenomena than by scarring. Signs of necrotizing arteritis — similar to that demonstrated by one of the present authors in other organs in connection with rheumatoid arthritis [72] — were fairly frequent, but pneumonitis in the parts of the lung not affected by scarring manifested itself only with slight serous-mucinous oedema and moderate histiocytic-lymphocytic infiltration. Much graver were the chronic changes; the arterial walls were thickened, scarred, sclerotic, with their lumen constricted (Fig. 19). The parenchyma consisted likewise of thick bundles of scar tissue surrounding cavities, which were considerably larger than the alveoli. They had arisen in the course of the destruction and rupture of non-fibrotic alveolar walls (Fig. 20), and were mostly devoid of epithelium, while in the cavities a pseudoadenomatous proliferation of bronchiolar epithelium sometimes occurred. The pattern was further complicated by premortal bronchopneumonia and pulmonary oedema. In one instance there was beside slight bronchial adenomatosis a small epithelioma within the sclerosed parenchyma embracing several lobes. Another case had not presented the usual clinical picture because of the absence of articular changes. We regarded this case nevertheless as one of rheumatoid arthritis on the anatomical and histological evidence of the pulmonary lesions. Acute vascular changes associated with the chronic fibrotic pulmonary process pointed to acute exacerbation, as in CHRISTIE's [13] case. In view of the absence of articular changes we feel justified in considering this case as one of rheumatoid disease, as proposed by ELLMANN and BALL [20] and RUBIN [89]. The pulmonary changes accompanying rheumatoid arthritis and rheumatoid disease have become known in the last decade [20, 38, 6, 39, 3, 16]. CAPLAN [10] pointed to the frequency of pulmonary fibrosis among coal-miners suffering from rheumatic arthritis. PRICE and SKELTON [70] have introduced the concept "rheumatoid lung". HEPPLESTON [41, 53] ascribed a great importance to rheumatic arthritis among the collagenoses giving rise to pulmonary changes and it is now generally accepted that the condition induces in the lungs a mild necrotizing inflammation of the small vessels and the parenchyma, with grave and widespread fibrosis and sclerosis of the vessels and the interstitium.

Scleroderma

Six of the patients with scleroderma showed pulmonary involvement. All were females between 37 and 66 years of age. Clinically, the respiratory symptoms had been less serious than the cutaneous phenomena in four cases, while the symptoms of pulmonary disease had dominated the picture in the other two. These symptoms had been essentially those of a protracted pneumonia, with fever, cough and an abundant discharge of sputum. The X-rays

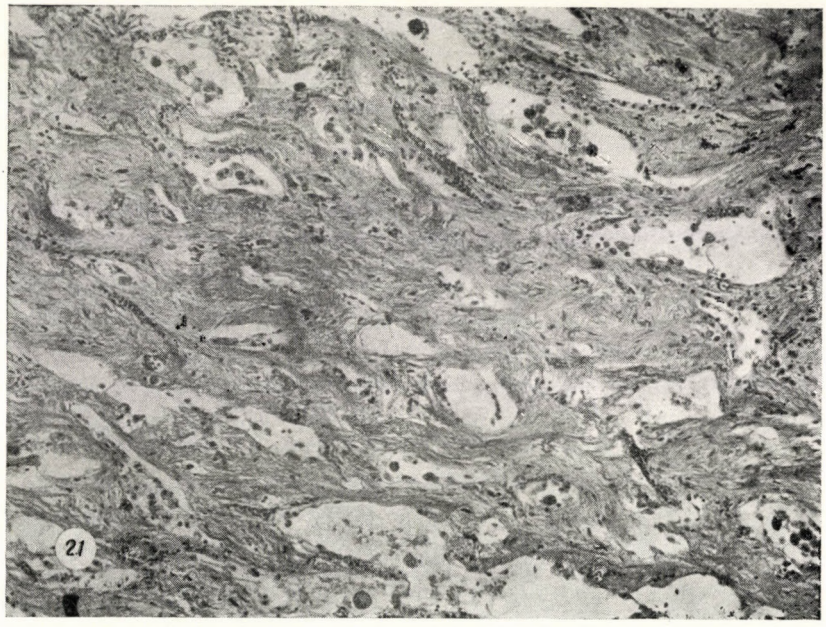

Fig. 21. Scleroderma. Diffuse sclerosis of lung. H. E. — ×120

had revealed pronounced bilateral density especially at the periphery of the basic parts, further bronchiectasis and, in some areas, a cystic pattern within inhomogeneous shadows.

At autopsy the picture was not characteristic. Beside pleural adhesions there were compact, scarry, fibrotic areas extending in some cases over several segments, with bronchiectases and sometimes sclerocystic changes. Histologically there was chronic scarring in the vessel-walls and the parenchyma. The fibrosis was either cystic, as that observed in rheumatic arthritis, or compact (Fig. 21). Scarring was followed by extensive bronchial adenomatosis and its cancerous transformation in one case, as described in detail earlier [46]. Acute changes such as an oedematous loosening and fibrinoid necrosis of the vessel-walls, accompanied by moderate inflammatory reaction, were rare. Secondary

bronchopneumonia, obstructive pneumonitis and congestive bronchitis diversified in some instances the otherwise monotonous pattern.

The correlation of the dermal and pulmonary changes in scleroderma had been almost forgotten since FINDLAY's observation in 1891 [27] and was revived half a century later when systematic investigations into the collagen diseases had been started. GETZOWA [31] distinguished two types of pulmonary fibrosis associated with scleroderma, a compact and a fibrocystic type, and offered also information regarding the genesis. The clinical, anatomical [62, 91, 86, 21, 57, 65] and radiographic [85, 61] aspects of the question have formed the subject of numerous papers. ISRAEL and HARLEY [48] observed pneumothorax consequent upon the rupture of a fibrocystic lung and several authors the cancerous transformation of fibrosed areas [101, 11, 49, 8, 80, 46]. Our own observations agree with literature in that the most characteristic feature of the pulmonary changes associated with scleroderma consists in a gradually developing fibrosis and sclerosis which are rarely accompanied by more than moderate acute inflammatory phenomena. Sclerosis of the parenchyma progresses hand in hand with that of the vessels.

Discussion

Relying on our own findings and data in the literature, we have attempted to give a comprehensive survey of the morphologic aspects of pulmonary changes observed in connection with some collagen diseases. We also endeavoured to point out those features which seem to characterize any particular disease. Since vascular lesions — in one form or the other — are encountered in all collagen diseases, it was the pulmonary parenchyma which promised to present a characteristic point. Various pulmonary changes have been found to occur in all types of collagenosis. For example, the features described by MASSON as characteristic of pneumonitis were observed in all of our cases. This applies to different degrees of fibrosis and sclerosis as well. As a rule, necrosis of the lung tissue is perceptible under the microscope only, but could be well observed with the naked eye in some cases. Granulomatous changes were perhaps the only phenomena which may be regarded as characteristic of certain diseases. We have, thus, failed to find such changes as are, in themselves, characteristic of this or that disease and have to state that there is no qualitative difference between the various collagen diseases in respect of the associated pulmonary involvement; differences exist, at most, in respect of quantity or degree.

Many observations substantiate the notion that, beyond a morphological similarity between the various pathological patterns, there exist cases which show the histological features of more than one collagen disease so that they cannot be classed under any of the sharply distinguishable separate categories.

Such transitory forms between DLE and rheumatoid arthritis [56], between polyarteritis nodosa and necrotizing polyangiitis [81], DLE and polyarteritis nodosa [93] or between necrotizing polyangiitis and rheumatoid arthritis [12] have been described in literature. They prove that the morphological picture does not suffice to make sharp distinctions between the various diseases.

The pulmonary changes observed in collagen diseases are morphologically related to those occurring in some other conditions. HEPPLESTON [41], for instance, demonstrated certain histological similarities between the collagen diseases and the HAMMAN—RICH [37] syndrome, as also between the group of honeycomb-lungs and the changes associated with sarcoidosis, eosinophilic granuloma and tuberous sclerosis. BOHROD [7] pointed to a histological similarity between the diseases described in this paper on the one hand and Löffler's eosinophilic infiltration on the other, as also to those observed in pancreatic fibrosis and pulmonary amyloidosis. AULD [1], further ENGELFELDT and ZETTERSTRÖM [22] established relationships between lung involvements in collagen diseases and eosinophilic granuloma. Other authors [98, 96, 29, 78] suggested the existence of a similarity between the pulmonary changes of collagen diseases on the one hand and antigenic pneumonitis (in the wider sense of the term) on the other hand.

Our above findings have convinced us of the futility of trying to distinguish between the pulmonary changes belonging to different collagen diseases on the evidence of specific patterns, and have led to the conclusion that if we want to distinguish the pulmonary changes of one collagen disease from those of another such disease, if we further want to separate the pulmonary changes of collagen diseases from most of those of an allergic-hyperergic nature, and — finally — if we want, in general, to arrive at a more precise definition and classification of pulmonary lesions, we have to rely on the comparative frequency in the occurrence of certain histological phenomena. It seemed therefore necessary to group these phenomena, independently of the diseases in which they occur, exclusively on the evidence of the morphological picture, according to structural types.

We found that the pulmonary changes associated with all the conditions in question belong to one of three fairly well distinguishable structural types, *viz.* the pneumonitic, the necrotic-granulomatous or the sclerotic.

Pulmonary changes of the *pneumonitic* type seemed to occur most frequently and to be most manifest in connection with DLE and rheumatic fever, while — in a milder form — they may occur in all collagen diseases. The changes observed by GOLDFISCHER et al. [35] in dermatomyositis appeared in the form of extensive pneumonitis or proliferative arteritis. We observed no such cases. We usually found pneumonitis in the acute phase of the pulmonary process, although its milder form is an almost permanent concomitant of protracted processes as well. For all the acuity of the histological phenomena, the clinical

course of pneumonitis need not necessarily be malignant (this depends, of course, also on the extent of the process) and, once the acute phenomena have subsided, it may change into fibrosis and sclerosis.

Pulmonary changes accompanying polyarteritis nodosa and necrotizing polyangiitis usually belong to the necrotic-granulomatous type, although in a mild form they frequently occurred in connection with DLE. Pulmonary manifestations of this type seem to indicate a malignancy of the process and show even in comparatively benign cases its progress or exacerbation. (This might have been the cause why in one of our cases where pneumonitis was associated with DLE, steroid treatment was followed by the appearance of a necrotizing-granulomatous process). The process is not always restricted to the lung parenchyma; it may also manifest itself in the form of vascular changes even with extrapulmonary ones, and this generalization may be one of the factors responsible for the comparative malignancy.

The most pronounced forms of sclerosing pulmonary changes usually appear in connection with rheumatoid arthritis and scleroderma, although — in a milder form — they may occur with rheumatic fever or DLE and even with certain cases of gradually progressing polyarteritis nodosa. Cancers developing on the ground of widespread sclerosis have repeatedly been observed, so that the process might be considered a precancerous manifestation.

The above classification has been based chiefly on morphological grounds. Still, each morphological type is characterized by a more or less specific clinical course. The pneumonitic type usually runs an acute course with healing, the necrotic-granulomatous type a subacute and malignant, the sclerotic type a chronic, course.

The morphological pattern may therefore allow some prognostic conclusions, a possibility which may become of value with a wider adoption of lung biopsy.

Practical importance attaches to our results also in other respects. Some of the above-described pulmonary changes (fibrosis, pleural adhesions) were usually considered secondary affections not connected with the collagen disease or else were looked upon as its usual concomitants (pneumonia, pulmonary infarct). It is beyond doubt that they are actually manifestations of collagen diseases.

It must be borne in mind that pulmonary processes — even if extremely grave and dominating the clinical picture — are but local manifestations of a systemic disease. The morphological picture of the lung may reveal in such cases the nature of the general process, a consideration which induced Heppleston [43] to regard the pulmonary changes to be the index of collagenosis.

Summary

The lungs have been examined in 30 cases of collagen disease (rheumatic fever, disseminated lupus erythematosus, polyarteritis nodosa, necrotizing polyangiitis and granulomatosis, rheumatoid arthritis, scleroderma). The pulmonary lesions were not specific; although with varying severity, all the observed changes were found to occur in every case of collagenosis. The differences were quantitative rather than qualitative.

It is recommended to classify the pulmonary changes according to morphological types and not according to the collagen diseases with which they are associated. The three structural forms are the pneumonitic type, the necrotic-granulomatous and the sclerotic type. One of these three types is encountered in every collagen disease: since their degree varies from disease to disease they allow conclusions regarding the activity of the process.

REFERENCES

1. AULD, D.: 1957. Pathology of Eosinophilic Granuloma of the Lung. Arch. Path. (Chicago) **63,** 113. — 2. AITCHISON, J. D. and WYNN WILLIAMS, A.: 1956. Pulmonary Changes in DLE. Ann. rheum. Dis. **15,** 26. — 3. ARONOFF, A., BYWATERS, E. G. and FEARNLEY, G. R.: 1955. Lung Lesions in Rheumatoid Arthritis. Brit. med. J. **1** — 4. BAGGENSTOSS, A. H.: 1952. Visceral Lesions in Disseminated Lupus Erythematosus. Proc. Mayo Clin. **27,** 412. — 5. BERGSTRAND, H. J.: 1946. Morphological Equivalents in Polyarthritis Rheumatica, Periarteritis Nodosa, Transient Eosinophilic Infiltration of the Lung and other Allergic Syndromes. J. Path. Bact. **58,** 398. — 6. BEVANS, M., NADELL, J., DEMARTINI, F. and RAGAN, CH.: 1954. The Systemic Lesions of Malignant Rheumatoid Arthritis. Amer. J. Med. **16,** 197. — 7. BOHROD, M. G.: 1958. Pathologic Manifestations of Allergic and Related Mechanisms in Diseases of the Lungs. Int. Arch. Allergy, **13,** 39. — 8. BONARD, E. C.: 1958. Le poumon dans la sclerodermie. Schweiz. med. Wschr. **88,** 373. — 9. CAMBIER, J.: 1955. Le syndrome de Wegener et les formes "respiratoires" de la périarterite noueuse. Presse méd. **63,** 821. — 10. CAPLAN, A.: 1953. Certain Unusual Radiological Appearance in Chest of Coalminers Suffering from Rheumatoid Arthritis. Thorax, **8,** 29.— 11. COLLINS, D. H., DARKE, C. S. and DODGE, O. S.: 1958. Scleroderma with Honeycomb Lungs and Bronchiolar Carcinoma. J. Path. Bact. **76,** 531. — 12. CHRISTIE, G. S.: 1954. Pulmonary Lesions in Rheumatoid Arthritis Australas. Ann. Med. **3,** 49. — 13. CORDASCO, E. M., HASERICK, J. R., SKIRPAN, P. J. and VAN ORDSTRAND, A. S.: 1957. Pulmonary Manifestations of Systemic Lupus Erythematosus. J. Chron. Dis. **5,** 290. — 14. CHURG, J. and STRAUSS, LOTTE: 1951. Allergic Granulomatosis, Angiitis and Periarteritis Nodosa. Amer. J. Path. **27,** 277. — 15. DICKSON, W. E. C.: cit. Rose and Spencer. — 16. DIXON, A. ST. J. and BALL, J.: 1957. Honeycomb Lung and Chronic Rheumatoid Arthritis. Rheum. Dis. **16,** 241. — 17. DUBOIS, E. L. et al.: Harvey et al. — 18. EDWARDS, J. E., PARKIN, TH. W. and BURCHELL, H. H.: 1954. Recurrent Hemoptysis and Glomerulonephritis and Periarteritis Nodosa. Proc. Mayo Clin. **29,** 193. — 19. EHRLICH, J. C. and ROMANOFF, A.: 1951. Allergic Granuloma of the Lung. Arch. intern. Med. **87,** 259. — 20. ELLMANN, P. and BALL, R. S.: 1948. "Rheumatoid Disease" with Joint and Pulmonary Manifestations. Brit. med. J. **2,** 816. — 21. ELLMANN, P. and CZUDKOVICH, L.: 1954. Pulmonary Manifestations in Diffuse Collagen Diseases. Thorax, **9,** 46. — 22. ENGELFELDT, B. and ZETTERSTRÖM, R.: 1956. Disseminated Eosinophil "Collagen Disease". Acta med. scand. **153,** 338. — 23. EVANS, M. and PARKER, R. A.: 1954. Honeycomb Lung and Mitral Stenosis in Scleroderma. Thorax, **9,** 154. — 24. FAHEY, J. L., LEONARD, E. and CHURG, J.: 1954. Wegener's Granulomatosis Amer. J. Med. **17,** 168. — 25. FERRARI, E.: cit.: Rose and Spencer. — 26. FIENBERG, R.: 1953. Necrotising Granulomatosis and Angiitis of the Lung. Amer. J. clin. Path. **1,** 413. — 27. FINDLAY, cit: Opie. — 28. FOLDES, J.: 1946. Acute Systemic Lupus Erythematosus. Amer. J. clin. Path. **16,** 160. — 29. FRENCH, W. O. and CIVIN, W. H.: 1956. Cholesterol Pneumonitis and Wegener's Granulomatosis. Arch. Path. (Chicago) **97,** 798. — 30. FRICSAY-TELBISZ, MARTHA: 1956. Die pulmonale Form des Lupus erythematodes disseminatus acutus. Schweiz. Med. Wschr. **86,** 269. — 31. GETZOWA, SOPHIA: 1945. Cystic and Compact Pulmonary Sclerosis in Progressive Scleroderma. Arch. Path. (Chicago) **40,** 99. — 32. GINZLER, A. M. and FOX, T. T.: 1940. Disseminated Lupus Erythematosus: a Cutaneous Manifestation of a Systemic Disease. Arch. intern. Med. **65,** 26. — 33. GRIFFITH, N.: cit: Lustok and Kuzma. — 34. GODMAN, G. C. and CHURG, J.: 1954. Wegener's Granulomatosis. Arch. Path. (Chicago) **58,** 533.—35. GOLDFISNER, J. and RUBIN, E. H.: 1959. Dermatomyositis with Pulmonary Lesions. Ann. intern. Med. **50,** 194. — 36. GOLDGRABER, M. B. and KIRSNER, J. B.: 1958. Granulomatous Lesions an Expression of a Hypersensitive State. Arch. Path. (Chicago) **66,** 618. — 37. HAMMAN, L. and RICH, A. R.: 1944. Acute Diffuse Interstitial Fibrosis of Lungs. Bull. John Hopk. Hosp. **74,** 177. —

38. HARRIS, L. H.: 1954. Pulmonary Manifestations of "Rheumatoid Disease". Lancet. **2,** 119. — 39. HART, F. D. and MACKENZIE, D. H.: 1955. Pulmonary Rheumatoid Disease. Brit. med. J. **2,** 890. — 40. HARVEY, A. M., SCHULMAN, L. E., TUMULTY, P. H. A., CONLEY, C. L. and SCHOENRICH, EDITHU: 1954. Systemic Lupus Erythematodes: Rewiew of the Literature and Clinical Analysis of 138 cases. Medicine. (Baltimore) **33,** 291. — 41. HEPPLESTON, A. G.: 1951. Coal WORKER's Pneumoconiosis: Pathological and Etiological Considerations. Arch. industr. Hyg. **4,** 270. — 42. HEPPLESTON, A. G.: 1956. The Pathology of Honeycomb Lung. Thorax, **11,** 77. — 43. HEPPLESTON, A. G.: 1958. The Lungs as an Index of Systemic Disease. Proc. roy. Soc. Med. **51,** 661. — 44. HOLLÓSI, KATALIN; FÁBRY, L.: 1958. Tüdőelváltozások disseminált lupus erythematodesben. Orv. Hetil. (Budapest) **99,** 668. — 45. HOLLÓSI, KATALIN; RADNAI, B., GERŐ, A., REMENÁR, L.: 1958. Necrotisáló polyangiitis és granulomatosis. Orv. Hetil. **99,** 729. — 46. HOLLÓSI, KATALIN; SZÁM, I., GERŐ, A.: Sklerodermás tüdőfibrosis alapján fellépő tüdőrák. In Press. — 47. ISRAEL, M. S.: cit Harvey et al. — 48. ISRAEL, M. S. and HARLEY, B. J. S.: 1956. Spontaneous Pneumothorax in Scleroderma. Thorax, **11,** 113. — 49. JONSSON, S. M. and HOUSER, J. M.: 1956. Scleroderma (Progressive Systemic Sclerosis) Associated with Cancer of Lung; Brief Review and Report of Case. New Engl. J. Med. **255,** 413. — 50. KAULBERSZ-MARINOVSZKA, A. and STOLARCIK, J.: 1954. Inflammatory Reactions of the Lungs in Rheumatic Fever. Pediat. pol. **29,** 1179. — 51. KLEMPERER, P.: 1954. General Considerations on Collagen Diseases in Asboe-Hansen, G.: Connective Tissue in Health and Disease. Munksgaard, Copenhagen. — 52. KORNBLUM, D. and FIENBERG, R. A.: 1955. Roentgen Manifestations of Necrotising Granulomatosis and Angiitis of the Lungs. Amer. J. Roentgenol. **74,** 587. — 53. KNOWLES, H. C., ZEEK, P. M. and BALNKENHORN, M. A.: 1953. Studies on Necrotising Angiitis (IV. Periarteritis Nodosa and Hypersensitivity Angiitis). Arch. intern. Med. **92,** 789. — 54. KUZMA, J.: 1957. Pulmonary Changes in Collagen Diseases. Dis. Chest **32,** 265. — 55. LUSTOK, M. J. and KUZMA, J.: 1956. Rheumatic Fever Pneumonitis: a Clinical and Pathological Study of 35 cases. Ann. intern. Med. **44,** 337. — 56. MCKOY, F. W., PATTERSON, MARJORIE and FREYSBERG, R. H.: 1955. A study of DLE Diagnosed in Patients Formerly Considered to have Rheumatoid Arthritis. Ann. rheum. Dis. **14,** 415. — 57. MAHRER, P. R., EVANS, J. A. and STEINBERG, I.: 1954. Scleroderma: Relation of Pulmonary Changes to Esophageal Disease. Ann. intern. Med. **40,** 92. — 58. MARSDEN, H. B. and MORGAN, J. K.: 1957. Allergic Granuloma. Arch. Path. (Chicago) **63,** 411. — 59. MÁRK, I. und FEHÉR, J.: Allergische Granulomatose. Zbl. allg. Path. path. Anat. **99,** 369. — 60. MASSON, P., RIOPELLET, J. L. et MARTIN, P.: 1937. Poumon rhumatismal. Ann. Anat. path. méd.-chir. **14,** 359. — 61. MEDA, A. et EINAUDI, G.: 1956. Rilievi sulla pneumopatia sclerodermica. G. ital. Tuberc. **10,** 3. — 62. MURPHY, J. R., KRAININ, P. and GERSON, M. J.: 1941. Scleroderma with Pulmonary Fibrosis. J. Amer. med. Ass. **116,** 499. — 63. NEGUS, V.: 1957. Collagen Disorders of the Respiratory Tract. Ann. Otol. (St. Louis) **66,** 699. — 64. NEUBUERGER, cit: Lustok and Kuzma. — 65. OPIE, L. H.: The Pulmonary Manifestations of Generalised Scleroderma (Progressive Systemic Sclerosis). Dis. Chest **28,** 665. — 66. OPHÜLS, W. cit Rose and Spencer. — 67. DEUTSCH, B. és ORMOS, P.: 1956. Scleroderma tüdőbeli manifestatioja. A hódmezővásárhelyi kórház Prosecturájának közleményei. p. 63. — 68. OSLER, cit Harvey et al. — 69. PAUL, cit Lustok and Kuzma. — 70. PRICE, T. M. and SKELTON, M. O.: 1956. Rheumatoid Arthritis with Lung Lesions Thorax. **11,** 234. — 71. PURNELL, D. C., BAGGENSTOSS, M. O. and OLSEN, A. M.: 1955. Pulmonary Lesions in Disseminated Lupus Erythematosus. Ann. intern. Med. **42,** 619. — 72. RADNAI, B.: 1953. Vascular Changes in Peripheral Nerves and Skeletal Muscles in Rheumatoid Arthritis. Acta morph. hung. **3,** 87. — 73. RADNAI, B. és HOLLÓSI, KATALIN: 1959. Pathomorphology of Pulmonary Changes in Collagen Diseases. Acta morph. hung. Suppl. **8,** 35. — 74. RAKOV, H. L. and TAYLOR, J. S.: 1942. Acute Disseminated Lupus Erythematodes. Arch. intern. Med. **70,** 88. — 75. RASPONI, L.: 1954. Contributo alla conoscenza dell'eritematodes sistemico acuto e subacuto. Arch. ital. Derm. **26,** 333. — 76. REIFENSTEIN, E. C., REIFENSTEIN, E. C. JR. and REIFENSTEIN, G. H.: 1939. A Variable Symptom Complex of Undeterminated Etiology with Fatal Termination. Arch. intern. Med. **63,** 533. — 77. RICH, A. R. and GREGORY, J. E.: 1947. Experimental Anaphylactic Lesions of the Coronary Arteries of the "Sclerotic" Type, Commonly Associated with Rheumatic Fever and Disseminated Lupus Erythematosus. Bull. Johns Hopk. Hosp. **81,** 312. — 78. RICH, A. R. and GREGORY, J. E.: 1958. Experimental Evidence that Lesions with the Basic Characteristics of Rheumatic Carditis Can Result from Anaphylactic Hypersensitivity. Bull. Johns Hopk. Hosp. **73,** 238. — 79. RICH, A. R.: 1958. Studies on Hypersensitivity. Canad. med. Ass. J. **78,** 163. — 80. RICHARDS, R. L. and MILNE, J. A.: 1948. Cancer of the Lung in Progressive Systemic Sclerosis. Thorax, **13,** 238. — 81. ROSE, G. A. and SPENCER, H.: 1957. Polyarteritis Nodosa. Quart. J. Med. **26,** 43. — 82. ROSS, G. A. and WELLS, B. B.: 1953. Systemic Lupus Erythematosus. Amer. J. clin. Path. **23,** 139. — 83. RUBIN, E. H.: 1955. Pulmonary Lesions in Rheumatoid Disease with Remarks on Diffuse Interstitial Pulmonary Fibrosis. Amer. J. Med., **19,** 569. — 84. SANTE, L. R. and WYATT, J. P.: 1951. Roent-

genological and Pathological Observations in Antigenic Pneumonitis to Relationship to the Collagen Diseases. Amer. J. Roentgenol. **66,** 527. — 85. SCHINZ, H. R.: 1950. Lehrbuch der Röntgendiagnostik. Thieme, Stuttgart. — 86. SNUFORD, W. H., SEAMAN, W. B. and GOLDMAN, A.: 1953. Pulmonary Manifestations of Scleroderma. Arch. intern. Med. **92,** 85. — 87. SIMÁRSZKY, J.: 1956. Besondere tuberkulotoxische Form von granulomatöser Periglomerulitis. Zbl. allg. Path. path. Anat. **95,** 177. — 88. SOKOLOFF, L. and BUNIM, J. J.: 1957. Vascular Lesions in Rheumatoid Arthritis. J. Chron. Dis. **5,** 668. — 89. SMITH, J. F. J.: 1948. Disseminated Focal Necrosis with Eosinophilia and Arteritis in a Case of Asthma (Löffler's syndrom). J. Path. Bact. **60,** 489. — 90. SÖVÉNYI, E. und BENCZE, GY.: 1957. Lungenveränderungen bei systematischem Lupus Erythematodes. Fortschr. Röntgenstr. **86,** 17. — 91. SPAIN, D. and THOMAS, A. G.: 1950. Pulmonary Manifestations of Scleroderma: Anatomic-physiological Correlation. Ann. intern. Med. **32,** 152. — 92. SWEENEY, A. and BAGGENSTOSS, A. H.: 1949. Pulmonary Lesions of Periarteritis Nodosa. Proc. Mayo Clin. **24,** 35. — 93. SYMMERS, W. ST. C. and GILETT, B.: 1951. Polyarteritis Nodosa. Arch. Path. (Chicago) **52,** 489. — 94. TEILUM, G.: 1945. Miliary Epitheloid-cell Granulomas in Lupus Erythematosus Disseminatus. Acta path. microbiol. scand. **22,** 73. — 95. TEILUM, G. and POULSEN, H. E.: 1957. Disseminated Lupus Erythematosus. Arch. Path. (Chicago) **64,** 414. — 96. TUMULTY, PH. A., BERTHRONG, A. and HARVEY, A. M.: 1951. A Peculiar Pneumonia Associated with Retinal Cytoid Bodies. Bull. Johns Hopk. Hosp. **88,**209. — 97. VARRÓ, V. és SÖVÉNYI, E.: 1955. Polyarteritis nodosa esete tüdő és emésztőszervi elváltozásokkal. Orv. Hetil. (Budapest) **96,** 1192. — 98. WADDEL, W. R., SNIFFEN, R. C. and SWEET, R. H.: 1949. Chronic Pneumonitis; its Clinical and Pathological Importance. Report of 10 Cases Showing Interstitial Pneumonitis and Unusual Cholesterol Deposits. J. Thorac. Surg. **18,** 707. — 99. WALTON, E. W.: 1958. Giant-cell Granuloma of the Respiratory Tract (Wegener's Granulomatosis). Brit. med. J. **2,** 265. — 100. WEGENER, F.: 1936. Über generalisierte, septische Gefässerkrankungen. Verh. dtsch. path. Ges. **29,** 202. — 101. ZATUCHNI, J., CAMPBELL, W. N. and ZARAFONETIS, CH. J.: 1953. Pulmonary Fibrosis and Terminal Bronchiolar („alveolar cell") Carcinoma in Scleroderma. Cancer, **6,** 1147. — 102. ZEEK, P., SMITH, C. C. and WEELER, J. C.: 1948. Studies on Periarteritis Nodosa; Differentiation between Vascular Lesions of Periarteritis Nodosa and of Hypersensitivity. Amer. J. Path. **24,** 889. — 103. ZEEK, P. M.: 1952. Periarteritis Nodosa: a Critical Review. Amer. J. clin. Path. **22,** 772.

ДАННЫЕ К ЕДИНОМУ ПАТОМОРФОЛОГИЧЕСКОМУ ВОЗЗРЕНИЮ НА ЛЕГОЧНЫЕ ИЗМЕНЕНИЯ ПРИ КОЛЛАГЕНОВЫХ БОЛЕЗНЯХ

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Авторы провели в 30 случаях патоморфологическое исследование при различных коллагеновых болезнях (ревматическая лихорадка, рассеянная красная волчанка, узловатый полиартерит, некротизирующий полиангит и грануломатоз, ревматоидный артрит). На основании своих исследований авторы установили, что не наблюдаются при этом специфические легочные изменения, характерные для той или иной коллагеновой болезни. Они наблюдали, что все морфологические явления, хотя в различной степени, встречаются при всех коллагеновых болезнях. Изменения при различных болезнях скорее количественные, чем качественные.

На основании своих исследований авторы считают, что легочные изменения могут быть классифицированы не по болезням, а по морфологическим типам. Такими морфологическими типами являются пневмонитические, некротически-грануломатозные и склеротизирующие легочные изменения. Каждый из этих трех типов, хотя в различной степени, но обнаруживается у всех коллагеновых болезнях и на основании этого можно делать выводы относительно динамизма процесса.

Наблюдения авторов дают возможность рассматривания легочных изменений с единой патоморфологической точки зрения, что имеет значение как в отношении патологии, так и клиники.

BEITTRÄGE ZUR EINHEITLICHEN PATHOMORPHOLOGISCHEN ANSCHAUUNG DER LUNGENVERÄNDERUNGEN BEI KOLLAGENERKRANKUNGEN

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In 30 Fällen verschiedener Kollagenerkrankungen (rheumatisches Fieber, Lupus erythematodes disseminatus, Polyarteritis nodosa, nekrotisierende Polyangiitis und Granulomatosis, Arthritis rheumatoides, Sklerodermie) wurden die Lungen untersucht. Es wurde keine solche Lungenveränderung gefunden die für die eine oder andere Kollagenerkrankung charakteristisch wäre. Alle Veränderungen kamen bei sämtlichen Kollagenerkrankungen vor, doch wiesen sie bei den verschiedenen Krankheitsbildern Unterschiede auf, die eher quantitativ als qualitativ waren.

Auf Grund der Untersuchungsergebnisse wird die Ansicht vertreten, daß die Lungenveränderungen nicht den Krankheiten, sondern dem morphologischen Typ gemäß gruppiert werden sollen und zwar als pneumonitische, nekrotisch-granulomatöse und sklerotische Typen. Ein jeder dieser drei Typen ist — obwohl in verschiedenem Grade — bei sämtlichen Kollagenerkrankungen zu finden, und aus ihnen kann man auf den Dynamismus des Prozesses entsprechende Schlüsse ziehen. Diese Feststellungen ermöglichen eine einheitliche pathomorphologische Anschauung der Lungenveränderungen, was sowohl vom Gesichtspunkt der Pathologie, als auch in der Klinik von Bedeutung ist.

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