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ORGANIZING INTERSTITIAL PNEUMONIA. DEFINITION OF THE LESION AND ATTEMPTS TO DEVISE AN EXPERIMENTAL MODEL**

For several years Professor Liebow and I have been studying a group of diffuse chronic pulmonary diseases known as interstitial pneumonias.[1] Because of the primitive state of our knowledge, this study has until recently been concerned primarily with the classic approach of recognizing, sorting, naming, and fitting together the clinical, roentgenological, and morphological observations in order to obtain more nearly homogeneous categories. This has been pursued in the hope that such classification would aid clinical recognition and facilitate efforts to define pathogenesis, to determine etiologies, and to evaluate by empirical means the diverse approaches to therapy.

As is so often the case, the use of spontaneous human lesions imposes distinct limitations on the endeavor to understand pathogenesis and anatomical-physiological relationships because of the complete independence of the lesions from the observers. Experimental models of such lesions would obviously be of considerable aid to these studies. My discussion will be concerned with a brief description of one of these interstitial pneumonias and of our efforts to reproduce it in the laboratory.

ORGANIZING INTERSTITIAL PNEUMONIA—THE SPONTANEOUS LESION

Although none of the chronic interstitial pneumonias is common, one type is seen much more frequently than any other and can thus be referred to as the "common" or usual interstitial pneumonia, hereafter abbreviated U.I.P. Several good descriptions of the lesion are available[2-10] with early reports going back at least six decades.[11-14] It is unnecessary to discuss the merits of the many names that are used for this lesion. For clarity of definition, I merely point out that the following are synonyms for the lesion under discussion:

Usual interstitial pneumonia (U.I.P.)
Interstitial pneumonia
Organizing interstitial pneumonia
Diffuse interstitial pneumonitis
Chronic interstitial pneumonitis
Interstitial pulmonary fibrosis

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Idiopathic pulmonary fibrosis
Idiopathic interstitial pulmonary fibrosis
Chronic interstitial fibrosis of lungs
Diffuse interstitial pulmonary fibrosis
Chronic diffuse interstitial fibrosis of lungs
Acute diffuse interstitial fibrosis of lungs
Hamman-Rich syndrome
Bronchiolar emphysema
Muscular cirrhosis
Chronic diffuse fibrosing alveolitis

Present concepts of the pathogenesis of U.I.P. are based on observations of static points in its progress as seen in histological preparations from biopsies and autopsies of many dozens of patients. It must be emphasized that progression from early to late stages can be described as it applies to any single focus in the lung but that in the lung as a whole, early, intermediate, and late stages are usually observed simultaneously in different foci. Therefore clinical progression, except in the few instances when a sudden massive injury to the lung can be identified, is best considered the result of gradual accumulation of affected foci in contrast to the progression observed anatomically in a given focus.

The anatomical changes, as best they can be assembled from current data, begin with damage to the alveoli resulting in interstitial edema and proteinaceous exudates. This is often but not invariably accompanied by hyaline membranes and an exudate in the air spaces. In some instances edema in the alveoli is very severe for a brief period, but even then it is less conspicuous than that in the interstitium after the first few days. There is some experimental evidence[15] that the hyaline membranes are composed of a mixture of acellular exudate with necrotic debris from the epithelial lining of the alveoli, but this has not been studied adequately in human material. This initial reaction is rapidly supplemented and gradually replaced by an infiltration of cells, primarily lymphocytes and macrophages, into the interstitium and, again to a much less conspicuous degree, into the small air spaces. The cellular and acellular exudates produce a marked thickening of the alveolar septa; and in some foci these thickened septa coalesce and obliterate the air spaces, a process in part enhanced by simultaneous organization of exudates in the airways as described below. Proliferating fibroblasts are soon identifiable among the infiltrated cells. Gradually reticulin and collagen are deposited and the process of organization continues to hyalinized scar but with persistence of some round cell infiltrates. This cellular infiltration, fibroblastic proliferation, and collagen deposition is analogous to repair and healing by granulation tissue, but in U.I.P. the process of healing is relatively avascular as compared to ordinary granulation tissue. It is likely that necrosis of entire septa and possibly of the pro-

liferating fibroblasts and cellular infiltrates contribute to destruction of the normal architecture, but if present this is of such subtlety that frank necrosis is infrequently observed by light microscopy.

Whereas the interstitial components are the most prominent part of the lesion, the small air spaces also are involved, as indicated above. Organization of exudate within the air spaces occurs simultaneously with organization in the interstitium; by overgrowth of the regenerating epithelium, this airway exudate becomes incorporated into the interstitial tissue as described below.

Epithelial proliferation is invariably a prominent component of U.I.P. From observations on cases of acute interstitial pneumonia with rapid death, epithelial proliferation of epithelium is known to be well underway within a few days of the initial alveolar damage. This rapid regeneration of epithelium has been noted in various experimental lesions as well. The regenerating epithelial cells provide a lining much thicker than the delicately thin cytoplasmic lining of normal alveoli, and they are readily seen with the light microscope. Evidence of active cell division is provided by the frequency with which mitoses can be identified histologically. The rapid proliferation of epithelium is interpreted as further evidence that epithelial necrosis is an important feature of the initial tissue injury. An additional stimulus for epithelial proliferation and particularly for the persistent metaplasia observed is the thickened and stiff condition of the scarred alveolar walls. This alteration in the septa is usually accompanied by epithelial metaplasia long after any form of injury to the lung has healed and the injurious agent or process vanished. In U.I.P. the epithelial proliferation is remarkable in that it covers over the small masses of organizing exudate lying in the air spaces. Such material thereby becomes incorporated into the interstitium along with that which was interstitial from the beginning. The result is that scar tissue seen between air spaces in the late stage is in fact the end product of interstitial *and* airway exudates.

Finally it must be noted that various secondary changes are seen in the late stages of U.I.P. Thus in addition to abundant fibrous tissue, abnormally large amounts of smooth muscle are often seen in the lungs of such patients. Although this is sometimes so abundant as to have led some observers to suggest special names for the lesion in such cases, the differences from case to case are better described as quantitative rather than qualitative.[16] The late stage of U.I.P. is certainly not unique in this regard, as hypertrophied and hyperplastic smooth muscle is often noted in lung tissue subjected to abnormal tension and stretch, e.g. as in some bullae. Because of the focal traction produced by the scar tissue in the lung with U.I.P., "traction emphysema" contributes in some part to the abnormal size and

shape of the residual air spaces. Obstruction of some of the small airways also can result from their being surrounded by the organizing reaction which, as with any ordinary granulation tissue, shrinks as it reaches the final stage of scarring. Obstruction is not of a degree as to be apparent as such in pulmonary function tests, however. Secondary bacterial infection often complicates the clinical course of patients with U.I.P. Despite the fact that many such infections are controlled by antibiotic therapy, they are often important in the terminal illness. Both the infections that are overcome and those that result in widespread pulmonary sepsis and death contribute significantly to the abnormal structure of the lung as seen at necropsy. There is no evidence at present, however, that bacterial infection plays an important role in the pathogenesis of the primary process of U.I.P., and cultures and antibiotic therapy are both unrewarding during the chronic course of the illness.

The end result of U.I.P. is honeycombing, the lung being composed of air spaces of less than normal alveolar size to more than a centimeter in diameter. These air spaces, which are randomly interconnected in labyrinthine fashion without regard for the normal manner of airway branching, are separated by thick walls richly supplied with fibrous tissue and varied amounts of smooth muscle. The abnormal air spaces are lined by metaplastic epithelium of several types. Even at necropsy, such a lung has normal regions interspersed with the honeycombed portions, the distribution having no constant relationship to pre-existing structures such as blood vessels or bronchioles. In addition, such a lung frequently has foci in which the process seems to be in the very earliest stage with edema and hyaline membranes but little other change. Intermediate stages are found in still other foci. It should be noted that honeycombing itself is the final stage of a number of other pulmonary lesions in addition to U.I.P.

In a few instances, as in the accidental inhalation of certain toxic substances or when ionizing radiation is administered for treatment of another disease, the onset of U.I.P. can be determined precisely and symptoms related accordingly. More often the clinical course is one of insidious onset, the patient becoming gradually aware of dyspnea or even cyanosis and clubbing without being able to date the beginning more accurately than within a few months. Characteristically there is evidence of arterial hypoxemia at rest or at least with exercise; but carbon dioxide retention, if ever noted at all, is not appreciable until the terminal phase of the illness. The hypoxemia can often be improved by having the patient breathe 100 per cent oxygen, but a complete return to normal values may not be produced by this maneuver. The residual volume of the lung is either normal or slightly reduced. Pulmonary compliance is markedly reduced, but evi-

dence of airways obstruction is absent. "Diffusion capacity" is frequently lower than normal when measured by standard techniques. The chest roentgenogram typically reveals reticular and finely granular opacities throughout the upper and lower lung fields, and these become increasingly numerous as the course progresses. Rarefactions are apparent when coarse honeycombing develops. Although U.I.P. may result in death within a few weeks or progress slowly for more than a decade, two to four years is the ordinary duration. Death usually results from respiratory insufficiency, bacterial infection, cor pulmonale, or a combination of these.

The etiology of U.I.P. in many patients eludes detection despite the most intensive search for clues. A number of interesting observations have been made in other case studies, however. U.I.P. has thus been noted after inhalation of fumes or dusts of metals such as mercury,[1,17,18] cadmium, and beryllium.[19] Additional cases have been associated with administration of certain drugs such as hexamethonium,[20-22] bulsulfan,[23,24] and hydantoin.[25] Nearly one quarter of the cases published before 1961 were encountered in patients simultaneously suffering from a "collagen disease" such as rheumatoid arthritis or progressive systemic sclerosis.[26] Both the sporadic occurrence of U.I.P. in patients treated with drugs usually harmless to pulmonary tissue irrespective of dosage and the association with collagen diseases have led to hypotheses that abnormal immune mechanisms (hypersensitivity, autoimmunity) are etiologically important. To date there is little additional evidence to substantiate or refute these hypotheses. A remarkable incidence of U.I.P. has been noted in a few carefully studied families. By examining many near and not-so-near relatives some investigators have found the number of cases with a familial history to account for nearly one quarter of their patients. Because of these studies, a genetic factor has been suggested to be important to the development of U.I.P. The pulmonary lesion induced by ionizing radiation also falls into the category of U.I.P. Although such examples can sometimes be identified specifically by subtle changes in fibroblast nuclei, blood vessels, and bronchial glands, all other morphological features of radiation pneumonia are typical of those described above. The majority of these cases cannot be differentiated from other examples of U.I.P. except by history.

The problem of the relationship between viral infections and U.I.P. deserves special mention. The acute pulmonary reaction in several viral infections is typical of the early changes in U.I.P. Clinically, most viral pneumonias resolve with little or no residual pulmonary damage. Whether or not such pneumonias occasionally progress to organization and hence become typical organizing interstitial pneumonias is an intriguing but still unsolved problem. Much as is the case with many patients with diffuse

myocardial fibrosis, the patients with U.I.P. are recognized at a stage when viral particles are unlikely to be found even if they had initiated the lesion. The situation is further complicated by the many differences in growth requirements of different viruses. It is difficult as well as expensive to attempt viral isolation in a given instance unless one has a reasonably good idea of what virus he expects to find. Doubtless our knowledge of the spectrum of pathogenic viruses is still far from complete, and negative cultures are therefore insufficient proof of absence of such infectious agents even when the cultures are performed at the onset of the disease. To a large degree the same problems encountered in trying to relate viruses to U.I.P. also apply to efforts to similarly relate mycoplasma organisms.

In reviewing the various factors associated with some cases of U.I.P., it would appear necessary that we consider this lesion to be a rather nonspecific type of pulmonary reaction which can follow pulmonary injury initiated by several different agents or processes. In the sense of having a single specific etiology it is not a sharply defined disease. Seen in this light, U.I.P. is somewhat analogous to aplastic anemia or lymph node hyperplasia.

The above described progression in U.I.P. from edema and hyaline membranes through organization to honeycombing is not always seen after diffuse alveolar damage. Already mentioned is the fact that acute viral pneumonias that have lesions morphologically similar to early U.I.P. usually resolve. The same is true of exposure to mercury fumes. In the accidental exposure of several workers described by Teng and Brennan[17] and by Tennant, *et al.*[18] only a small number of those who developed an acute reaction went on to develop a chronic progressive lesion. Some patients treated with busulfan also have had resolution, or at least arrest of progression, after cessation of the drug therapy.[23,24] Thus we are faced with the fact that seemingly identical pulmonary injuries sometimes organize and sometimes resolve. Is this due to differences in severity or extent of injury inapparent in the relatively late stage that we examine or inapparent to light microscopy at any stage? Is it due to a persistent abnormality such as tissue-fixed metals, an abnormal immune mechanism, or permanent nuclear damage induced by ionizing radiation or incorporation of viral genetic information? Is it related to subtle differences in reaction controlled by inherent genetic factors? Of great clinical importance is the question of how to interfere with the process so as to induce resolution rather than organization and to prevent progression in that majority of patients in whom some organization and honeycombing are already present when first identified clinically. In addition, clinically observed physiological defects are as yet imperfectly correlated with the anatomical observations. All of these prob-

lems are difficult to study with spontaneous human material. The investigation of some, at least, might be aided by an experimental model.

AN ATTEMPT TO DEVELOP A LABORATORY MODEL

In order to evaluate the attempts to experimentally reproduce U.I.P. in laboratory animals, I have abstracted from our observations a few criteria that I believe important. These have been combined with certain experimental considerations in Table 1, to represent, in the context of our present knowledge, the features of an ideal model. While these provide useful guidelines, it is probably too much to expect that all of these features will be immediately realized.

In our experimental model there must be a mixed cellular exudate in the interstices. This should be mostly mononuclear cells and lymphocytes.

TABLE 1. FEATURES OF AN IDEAL MODEL OF U.I.P.

ESSENTIAL
Mixed cellular exudate in interstitium
Protein exudates in air spaces, ± leukocytes
Proliferation of lining epithelium
Gradual progression to fibrosis and honeycombing—slow enough for serial physiological studies
Continuing "activity" even when partly fibrotic
Diffuse distribution, but may have "skip zones"
FAVORABLE
Hyaline membranes
Interstitial muscle proliferation
Multiple species for the same agent
Multiple agents for the same species—especially useful if some organize and some do not
MUST NOT HAVE
Abundant polys, at least after first few days
Prolonged state of extensive edema
Localization by bronchioles
Respiratory failure too soon for serial function studies or definite organization
Contamination by ordinary bacterial disease (? L forms, mycoplasma, virus)
PHYSIOLOGICAL FEATURES
Decreased or normal total lung volume
Significant hypoxemia before CO_2 retention, partly or wholly corrected by 100% O_2
Minimal airways obstruction

There should be some proteinaceous exudate in the airways, usually with a negligible number of leukocytes. If there are any cells in the exudate in this location, they should be primarily macrophages and especially proliferated epithelium since the latter is so prominent in the human cases. There should be gradual progression to fibrosis and honeycombing, preferably progressing sufficiently slowly for serial physiological studies to be performed. Whether progression is slow or fast is not important as far as the lesion is concerned, but for laboratory study a slowly progressive lesion would be much better.

To reproduce the human lesion accurately there must be continuing "activity" even when the lung is partly fibrotic. In other words, this must not be a pulmonary reaction that goes through a rapid organization with scarring and then stops. The lesion must be distributed diffusely through the lung—diffuse in that it is not constantly related to any particular structure; but there may be "skip" regions where some alveoli are destroyed, some nearby spared. It would be nice if such a model also produced hyaline membranes and significant interstitial muscle proliferation, but neither of these is universal in human cases. For manipulating the model and trying to study various factors, it would be convenient if several agents could be used for any given species and if several species would react similarly with any given agent. Multiple agents in one species would be particularly useful if some resulted in organization while others resulted in an acute lesion followed by resolution.

Doctors Liebow, Cottrell, Glusman, and I have performed a number of preliminary experiments in an attempt to achieve a lesion that fulfills at least some of these criteria. From practical considerations it seems best at present to concentrate on exposure to a toxic material for inciting a U.I.P. reaction while ignoring for the present possible genetic and immunologic predispositions. Lacking any clear guides, we have also chosen to eliminate infectious agents from these preliminary experiments. Mercury and cadmium were selected as toxic agents because they have been associated with some human cases. Ozone was also chosen because of data reported by Gross[27] and others which suggested that it might be suitable for our purposes. It should be emphasized that in this model we are attempting to reproduce in controlled fashion the *pulmonary reaction* as it is observed in humans without necessarily providing a definite etiological link with the many human cases that are still idiopathic.

In instances where man has inadvertently inhaled significant amounts of cadmium or mercury salts or fumes, pulmonary edema in the acute phase has sometimes been so severe as to result in rapid death simply from asphyxiation. In order to prevent such a premature end to an experiment,

it was decided to use a unilateral exposure. Another advantage of unilateral pulmonary damage is that the other lung can be used as a control (of sorts), not only for morphological studies but for physiological studies in which the two lungs can be simultaneously observed under identical conditions of cardiac function.

We chose the dog as our experimental animal because its size facilitates physiological observations and because of our own familiarity with this species' pulmonary structure and function. A differential bronchoscope proved to be a reasonably convenient instrument for administering the toxic agent unilaterally. Inasmuch as the animal must be anesthetized for insertion of the bronchoscope, short exposures are a necessity in this system.

Our first efforts employed mercury fumes. Acute pulmonary edema was noted within two to four hours after exposure was started, and the tidal volume and oxygen uptake of the exposed lung were greatly decreased by the end of the five-hour exposure used. Three days after the exposure there was a little interstitial infiltrate, although it was not very impressive. There was abundant proliferation of epithelium in the small bronchioles. By this time the edema had largely cleared, although a few macrophages and small amounts of proteinaceous material were sometimes present in a few foci. After seven days the structure of the lung was again normal. Indeed, after as many as three exposures at weekly intervals, and despite the fact that each time pulmonary edema (and presumably epithelial damage and regeneration) developed, the lung was always normal morphologically and in terms of oxygen uptake by seven days after the last exposure. Thus in this situation mercury fumes caused a mild form of the acute lesion that we presume to be the first stage of U.I.P., but resolution rather than organization always followed.

We next tried an aqueous solution of cadmium sulfate administered as a coarse aerosol. Many of the problems related to this part of our experiment were the result of our primitive methods of producing an aerosol, which could be described more appropriately as a mist. The material was not very evenly distributed in the lung but tended to be concentrated and indeed to pool in several foci because of condensation within the bronchoscope and bronchi. Within these focal regions, however, the reaction was promising. At three days after exposure the lung was similar to that of the animals exposed to mercury but the interstitial infiltrate was more abundant. Unlike the mercury lesion, this reaction was still active after 14 days, at which time an extensive interstitial infiltrate of lymphocytes and macrophages was noted along with some bronchiolar infiltrate and abundant proliferating epithelium in the respiratory bronchioles and in many alveoli. After four months epithelial proliferation still appeared active and the

round cell infiltrates were still prominent. By nine months, however, only scar and honeycombing were observed, the leukocytic infiltrate and epithelial proliferation having subsided. The tissue from one animal sacrificed approximately one year after exposure was analyzed chemically by Dr. David Groth, and at this time there was still a remarkably large amount of cadmium in the exposed lung. The reaction to cadmium sulfate was therefore much closer to that described as "ideal"; but because of the type of aerosol used the lesion was inadequately diffuse to permit meaningful physiological studies.

Next we turned to ozone, and this study has just begun. We have examined tissue only from the first two animals, so obviously the results are quite tentative. Ozone has the advantages of being a gas, thus easy to administer through the bronchoscope, and of decomposing into oxygen, thus eliminating problems of carry-over to the other lung via the blood stream. The first animal was exposed to 500 ppm for 15 minutes. At the end of this short interval tidal volume and oxygen uptake were unmeasureable on the exposed side. This is a little fast even for the development of pulmonary edema, and I suspect that bronchospasm accounted for these functional changes. After three days there was some oxygen uptake from the damaged lung, but it was not yet normal. Morphologically the lesion in this animal was most severe in the terminal and respiratory bronchioles. There was still some pulmonary edema and interstitial mononuclear cell infiltrates were noted in alveolar septa. Once again regenerating bronchiolar epithelium was prominent. Regenerating epithelium in more distal air spaces was confined to para-bronchiolar alveoli, however.

In the second animal a 60-minute exposure to 25-50 ppm ozone was used. In this animal, decrease in tidal volume and oxygen uptake was not so complete or so rapid. The lungs were examined three days after the exposure. The lesion in this instance is much more promising. Although there is still some bronchiolar reaction, there is also extensive thickening of alveolar septa by interstitial proteinaceous exudate in which rare fibroblasts can be recognized. In addition, the epithelial regeneration is extensive in alveoli as well as in respiratory bronchioles. Obviously many additional studies are needed before we can adequately evaluate the potential of ozone in our system.

SUMMARY

In summary, our efforts to produce an experimental model of U.I.P. have thus far yielded results that are far from satisfactory. Nevertheless they show enough promise to justify further endeavor along the same general line. If, indeed, ozone in the concentration of 50 to 100 ppm proves

effective in inducing an organizing lesion, then with it and mercury fumes we will have the means of investigating factors relevant to organization and resolution after diffuse pulmonary damage. In addition, we will then have a model that can be further manipulated with the addition of infectious agents, that can be used for serial physiological studies, and that might provide material for investigating immunological changes concurrent with or secondary to this type of pulmonary lesion.

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