THE PATHOLOGY OF UNCOMPLICATED INFLUENZA

R. G. F. PARKER, M.D.(Camb.), D.P.H.
Consultant Pathologist, East Birmingham Hospital, Birmingham

Secondary bacterial infection was so overwhelmingly important in the great 1918 influenza pandemic that the existence of non-bacterial lesions was not established with certainty at that time. It was only slowly that specifically viral changes came to be recognized, and even as late as 1953 Professor Stuart-Harris, in his book on influenza, could not find certain evidence that such viral changes occurred in man. Long before this, however (following the identification of the influenza virus in 1933), he and other workers had described the lesions produced by uncomplicated viral infection in the ferret and other animals.

Briefly these are as follows:

The normal nasal mucosa of the ferret consists of a superficial layer of columnar, ciliated cells and a layer of small basal cells. Forty-eight hours after inoculation of the influenza virus the mucosa is stripped to one or two basal cells with many pycnotic nuclei. By the 6th day regeneration has occurred producing a stratified but not a squamous epithelium. By the 14th day the epithelium becomes columnar again and a more or less normal mucosa is reached by about the 20th day. In the ferret's lung more or less similar epithelial changes are seen in the bronchi and there is also a little surrounding alveolar exudate.

Lesions more or less similar to these were described in the 1918 pandemic and occasionally thereafter, but it was the Dutch worker Hers (1954) and his colleagues who first went a long way towards establishing that these human lesions were viral and not bacterial in origin. He studied fatal cases from all over Holland, dividing them into those with secondary streptococcal infection and those with secondary infection by Haemophilus influenza or Streptococcus pyogenes. Since infection by these two latter bacteria alone did not produce mucosal lesions in the main air passages he considered that such lesions in the non-streptococcal cases were due to the influenza virus. The change he described was a superficial necrosis of the tracheal and bronchial epithelium which spared the basal layer. The necrosis was often preceded by a vacuolated type of degeneration (Fig. 1) but sometimes it was coagulative in type. Similar abnormalities could be recognized in exfoliated cells in the sputum.

By about the 4th to 5th day or even earlier regeneration commenced, and by the 9th day outstripped degenerative changes. Undifferentiated stratified epithelium developed (Fig. 2), reaching its maximum thickness at about 16 days. This regeneration might occasionally become quite exuberant and produce tumour-like nodules in the alveolar ducts and alveoli. That these lesions are in fact viral in origin has been confirmed in bacteriologically sterile material from the Asian 'flu epidemic of 1957, where however the necrosis sometimes involved the entire thickness of the mucosa. Walsh and his colleagues in a biopsy study reported in 1961 found similar changes in non-fatal cases.

Are these changes specific? Hers maintains that they are not produced by bacterial infections although very similar regenerative changes may occur whenever the mucosa is destroyed—for instance following gassing or experimental trauma. But they are undoubtedly produced by other virus diseases, for instance measles and vaccinia.

It is reasonable to suppose that this mucosal damage is important in allowing the subsequent establishment of a bacterial infection, and in the bronchioles a measure of obstruction may result. But it is pneumonia rather than this bronchitis
or bronchiolitis which is likely to kill in influenza, and despite experimental evidence that it could occur, the existence of a true influenza virus pneumonia in man was not established with any degree of certainty until the Asian 'flu epidemic of 1957 (Rock, Braude and Moran, 1958; Louria, Blumenfeld, Ellis, Kilbourne and Rogers, 1959; Hers and Mulder, 1961). Almost certainly the reason why it was recognized with near certainty in the 1957 epidemic whereas it remained only a possibility in 1918 was the suppression of bacterial infection by antibiotics in the later epidemic.

If it is to kill the patient, a pure virus pneumonia does so very rapidly and few of the reported cases have survived more than 48 hours. To the naked eye the lungs are voluminous and rather heavy. There may be a pleural effusion but no fibrinous exudate. On section the picture is that of congestion, oedema and often haemorrhage producing a more or less airless, rubbery, plum-coloured lung. In the American cases the lesions have been very diffuse but some of the Dutch cases were apparently more focal, often confined to the lower lobes. Microscopically the alveoli are filled with oedema fluid, usually rich in protein, but with little fibrin. There are often many red blood cells but leucocytes are relatively scanty. Hyaline membranes are common. The alveolar walls are thickened either by congestion or by swelling of the alveolar lining cells with an inflammatory infiltrate and oedema. There are often focal necroses of the alveolar walls with thrombi in the capillaries. Hers feels that the primary lesion is in the alveolar lining cells and he considers that he can recognize specific changes in them.

Fatal cases of influenza in which secondary bacterial infection can be excluded are seldom encountered. But most pathologists will have seen changes identical to the above in cases complicated by staphylococcal pneumonia (Figs. 3 and 4). Hers and Mulder found mixed viral and bacterial lesions in 76% of their cases. The contention that the type of pneumonia described above is caused by the influenza virus alone has been criticized on two counts. First, it has been suggested that growth of bacteria has merely been suppressed by antibiotics in the recorded cases that have been bacteriologically sterile. It may be noted that in some cases which have been described as fulminant staphylococcal or streptococcal pneumonias imposed upon influenza the entire picture apart from the presence of the bacteria has been identical to that described in pure
virus pneumonia. Second, a high proportion of allegedly pure viral pneumonias have been in patients with heart disease, especially mitral stenosis, and although these patients have not usually been in frank heart failure it is possible that circulatory factors have played some part in their deaths. On the other hand, it has been suggested that changes in the lining cells of the alveoli in heart failure may predispose them to infection by the influenza virus.

REFERENCES

HERS, J. F. Ph. (1954): 'The Histopathology of the Respiratory Tract in Human Influenza'. Leyden:

Discussion

DR. LESLIE enquired whether there was evidence of difference in virus toxicity or virulence between the 1919 pandemic and the present virus; how different was the histological picture?

DR. PARKER: The pathological picture in fatal cases was not very different; the difference was in the effects of the secondary infection.

PROFESSOR STUART-HARRIS referred to Hers' work in Holland; Dr. Parker's slides were in line with what had been found there. It was clear that various, supposedly upper respiratory viruses could attack the bronchi.