LYMPHOCYTIC MENINGITIS WITH LUNG INVOLVEMENT OCCURRING IN CHILDHOOD

BY

JOHN APLEY, M.D., M.R.C.P.

(From the Children's Hospital, Bristol)

Little more than twenty years ago Wallgren (1925) separated from the confused group of the meningitides those with pronounced lymphocytosis in the cerebrospinal fluid yet not due to tuberculosis or to syphilis. Since that time his 'acute aseptic meningitis' has become variously known as lymphocytic meningitis, choriomeningitis, and so on. It is considered that in approximately one-third of the cases a virus is undoubtedly implicated (Baird and Rivers, 1938), and at least three different types of virus have so far been identified.

In the past two decades the term 'atypical pneumonia' has come into common use, to cover a clinical group of infectious diseases which are similar in many respects. In a considerable proportion of cases in this group viruses are also considered to be the causative agents, and have in some instances been isolated.

Relating these two groups of diseases, both at one time euphemistically labelled 'benign,' some interesting facts have recently come to light. A virus isolated from a case of atypical pneumonia in man gave rise either to pneumonia or to meningitis in mice, according to the site of inoculation (Francis and Magill, 1938). As a corollary, the antigen developed in animals by this so-called 'meningopneumonitis' was fixed by human serum from many cases of atypical pneumonia (Rake et al., 1941). Moreover, rare cases have now been recorded in which both the nervous system and the lungs were affected by virus disease in the same patient (Scadding, 1937; Reimann, 1938; Smadel et al., 1942; Hein, 1943; Perrone and Wright, 1943). In one case the virus of lymphocytic meningitis was shown to have changed its site of election; at autopsy it was demonstrated that the lungs were affected, while the nervous system remained uninvolved (Smadel et al., 1942). There is, therefore, some relationship, albeit a rare one, between these two disease groups. The apparent rarity of involvement of both systems in a single patient may, however, be

fallacious. In part it can be explained by the commonly benign course of the infections, so that revealing autopsies are exceptional; and it may be also, to some extent, an index of incompleteness of investigation. On the one hand, in atypical pneumonia symptoms suggesting the possibility of nervous involvement are notably common. Severe headache, for example, is a prominent symptom; lumbar puncture, however, is rarely performed. It is particularly in childhood that mild nervous manifestations occurring with chest disease tend to be labelled 'meningism,' and may, with improvement, be dismissed without investigation. On the other hand, in lymphocytic meningitis minor abnormal physical signs in the lungs tend to be regarded as of no significance. Atypical pneumonia is notoriously difficult to detect clinically, yet in how many instances of lymphocytic meningitis is the chest radiographed? In this connexion, perusal of eleven consecutive case reports of infants and older children who had suffered from lymphocytic meningitis revealed that abnormal physical signs in the chest had been recorded in four.

Lymphocytic meningitis is predominantly a disease of childhood. Atypical pneumonia, on the contrary, commonly affects adults. The remarkably few recorded cases in which both the nervous and respiratory symptoms have been demonstrably involved in the same patient are confined to adults; the following cases suggest a similar combination in children.

Case Reports

Case 1. D. P., ten months old, was admitted to hospital on March 7, 1946, with a history of four days' anorexia, constipation, and repeated vomiting. On the second day of the illness she had become feverish and drowsy, and a macular rash appeared all over the body, passing off by the next day. On the fourth day she developed a stiff neck; the parents became alarmed, and she was brought to hospital.

FIG. 1.—Case 1: opaque shadow at right lung base.

FIG. 2.—Case 1 (after thirteen days): basal shadow resolved, new area of opacity in right upper lobe.

EXAMINATION ON ADMISSION. The temperature was 103° F.

CENTRAL NERVOUS SYSTEM. Neck rigidity was marked. The spinal fluid contained 17 cells (85 per cent. lymphocytes) per c.mm., 100 mg. protein, and 680 mg. chlorides per 100 c.cm., but no organisms were seen on direct examination and culture was sterile. Nine days later the cells had increased to 50 per c.mm., almost all lymphocytes. The neck rigidity passed off in about two weeks.

RESPIRATORY SYSTEM. On admission the respiration rate was 40–45 per minute, and harsh breath sounds were audible throughout the lungs. Next day a radiograph showed a shadow at the right lung base (fig. 1). At no time was coughing a feature of the illness, and no localizing signs were elicited in the lungs, but thirteen days later a radiograph showed that the original shadow had cleared and a new one had appeared in the right upper zone

(fig. 2). Three weeks later the lungs were clinically and radiologically clear. A Mantoux test (1/10,000) was negative.

The general condition remained poor for two weeks, then quickly improved. Irregular fever persisted for five weeks, after which the patient was sent home. When seen two months later she had remained well, there were no abnormal physical signs on examination, and a radiograph showed that the chest was clear.

Sulphadiazine had no appreciable effect on the disease process. The effect of penicillin was extremely doubtful; 360,000 units given during three days at the commencement of the period in hospital produced no evident change, but 960,000 units during eight days about the middle of this period coincided with a fall in temperature almost to the normal level.

Case 2. N. B., five years and ten months old, was admitted to hospital on March 11, 1946. There was a history of two weeks' cough and cold, with vomiting and fever after the first few days. A few days before admission the fever became more pronounced and was accompanied by thirst and constipation, and photophobia developed.

CENTRAL NERVOUS SYSTEM. When first seen at hospital he was drowsy and extremely irritable. Photophobia was marked, neck rigidity pronounced, and Kernig's sign positive. The spinal fluid

FIG. 3.—Case 2: consolidation of right upper lung and left base.

FIG. 4.—Case 2 (after five days): complete resolution at left base, consolidation and segmental collapse of right upper lung.

FIG. 5.—Case 3: enlarged left hilar shadow.

contained 26 cells per c.mm., predominantly lymphocytes, and 70 mg. protein per 100 c.cm., but no organisms were visible on direct examination, and culture was sterile. A few days later the cells had increased to 51 per c.mm., protein was 45 mg. per cent., and chlorides 720 per cent., and direct examination and culture were again non-productive. After a further eleven days the fluid contained 6 lymphocytes per c.mm., protein and chlorides were respectively 15 and 720 mg. per cent., direct examination and culture were again negative, Lange test showed 0000000000, and Wassermann reaction was negative.

RESPIRATORY SYSTEM. On admission to hospital the respiration rate was 40 per minute, and there was clinical evidence of consolidation of the right upper lung, and possibly of the extreme left base. Chest radiograph showed shadows in these regions (fig. 3). After five days the smaller of these shadows, that at the left base, had completely cleared (fig. 4), but in the right upper lung a minor degree of segmental collapse was superimposed. The shadow in the right lung gradually cleared, though even after three months a small thickened area the size of a pea was still visible in the radiograph. One month later the radiograph was completely clear. Mantoux tests to a dilution of 1/100 were negative, and sputum examination revealed no tubercle bacilli.

At the height of the illness the blood contained 14,000 cells per c.mm., of which 68 per cent. were polymorphonuclear leucocytes.

For two weeks after admission the temperature was raised four or five degrees; for a further three weeks irregular fluctuation round the 99° F. level was maintained. The respiration rate quickly fell to normal, but a mild cough persisted for several weeks. Photophobia was noted for about a month after admission, and during this period the patient vomited occasionally.

There was no evident response to sulphadiazine administered over two separate periods of several days.

Case 3. K. F., one year and eight months old, was admitted on March 13, 1946, with a history of irritability and vomiting for one week.

CENTRAL NERVOUS SYSTEM. On admission he was markedly irritable, the anterior fontanelle was patent and bulging, neck rigidity was noted, Kernig's sign was positive, and the left pupil was larger than the right, though both reacted to light and accommodation. The spinal fluid contained 350 cells per c.mm., predominantly lymphocytes, the protein content was considerably higher than 200 mg. per cent., and direct examination and culture were negative for organisms. Two weeks later the number of cells had fallen to 31 lymphocytes per c.mm., protein and chlorides were respectively 80 mg. and 700 mg. per cent., and again direct examination and culture were non-productive. Signs of meningism persisted for two weeks; bulging of the fontanelle was the last abnormal sign to disappear.

RESPIRATORY SYSTEM. The respiration rate on admission was 25 per minute. The patient had no cough, but moist sounds were audible at the left lung mid-zone. These adventitia persisted locally for a week, but repeated chest radiographs showed only enlargement of the left hilum (fig. 5). Mantoux tests were negative to a dilution of 1/1,000.

After five days in hospital the child's general condition improved, though signs of meningism persisted longer, and the temperature was slightly and irregularly raised for three weeks from the date of admission.

There was no evidence of response to sulphadiazine given over two separate periods of several days' duration.

Comment

It is a striking fact that all three cases were admitted to hospital within the space of one week, two to one hospital and the third to another. The patients were admitted from one large city, but their homes are separated from each other by a mile or more. No epidemic was prevalent at the time, and no connexion between the cases has been suggested.

General symptomatology. Persistent vomiting was an unexpected symptom common to all three patients. A macular rash, as in case 1, has been reported in similar cases (Reimann et al., 1942, and Hein, 1943), and occurs in apparently uncomplicated cases of lymphocytic meningitis.

Central nervous system. In all cases meningeal involvement was marked. The photophobia in case 2 and the pupillary changes in case 3 suggest in addition some degree of encephalitis. This is consistent with previous findings; in the few cases of lymphocytic meningitis which have come to autopsy there has been no limitation of the infection to the meninges as distinct from the brain tissue (Viets and Warren, 1937). The five weeks duration of the photophobia in case 2 is striking; the symptom itself was noted in five of eight cases reported by Reimann (1938). As compared with the majority of cases of lymphocytic meningitis, the duration of signs of meningeal involvement was unusually protracted in the three cases reported in this paper.

Respiratory system. In only one instance (case 2) was coughing a symptom. Admittedly, the remaining two patients were infants, in whom the presence or absence of cough is notoriously unreliable as a guide to respiratory infection; nevertheless the observation lends force to the suggestion that lung involvement may occur more commonly than is suspected in cases of apparently uncomplicated lymphocytic meningitis.

The time relationship between the onset of nervous and respiratory involvement is of interest, but is

difficult of assessment since both systems were manifestly implicated when the patients were first examined. In case 1 both systems were involved by the fourth day of apparent illness, with no clue as to the sequence. In case 2, according to the history, infection of the lungs evidently preceded that of the nervous system. In case 3 the degree of hilar enlargement suggested pulmonary infection of some considerable duration, probably antedating that of the nervous lesion. From this incomplete evidence the possibility of simultaneous involvement of the two systems concerned cannot be excluded. In case 2 almost certainly, and in case 3 probably, it seems more reasonable to postulate primary infection of the lungs with subsequent involvement of the nervous system.

Diagnosis. The diagnosis of a lymphocytic type of meningitis seems clear. It was based on the clinical evidence of meningeal involvement, on the characteristic findings in the cerebrospinal fluid, on the lack of response to chemotherapy, and on the course of the illness.

The diagnosis of atypical pneumonia was made on the clinical and radiological findings, on the lack of response to treatment, and on the course of the disease. The coincident occurrence of lesions in two systems suggested a common pathogenesis, and tuberculosis was excluded by the repeatedly negative Mantoux responses and by the benign course of the disease. In case 1, as is common in atypical pneumonia, the radiological appearances were out of proportion to the scanty physical signs, and an additional shadow appeared as the first regressed. Characteristically, the shadows were indefinitely outlined, were comparatively lacking in density, and did not extend to the lung periphery. In case 2 the larger of the two areas of consolidation was easily demonstrable clinically in the early stages, but persisted radiologically for many weeks. In atypical pneumonia the persistence of radiographic shadows long after the patient has recovered clinically is not uncommon (Turner, 1945). In case 3 the consistent localization of the physical signs in the lung, over a period of a week of repeated examinations, indicated an inflammatory lesion of the lung parenchyma, and militated against a diagnosis of simple bronchitis. Not infrequently, the earliest radiological evidence of atypical pneumonia is an increase in the hilar shadow (Weber, 1944), and the usual sequence of extension from the hilus into the lung substance may possibly fail to develop. Nevertheless, in this single case doubt remains; but the tentative diagnosis of atypical pneumonia is advanced to emphasize the possibility of the occurrence of incomplete examples of the syndrome.

Summary

1. An account is given of virus disease producing lymphocytic meningitis and pneumonia simultaneously.

2. It is suggested that the rarity of this coincident involvement of two systems is more apparent than real.

3. The diagnosis of lymphocytic meningitis with atypical pneumonia, presumably due to virus infection, was made in three cases occurring in children.

My thanks are due to Dr. L. M. Brierley and to Dr. T. Stratton for their unstinting co-operation in the investigation of these cases. For permission to publish and for his stimulating advice and continued interest I am greatly indebted to Prof. C. Bruce Perry.

REFERENCES

- Baird, R. D., and Rivers, T. M. (1938). *Amer. J. Publ. Hlth.*, **28**, 47.
 Francis, T., Jr., and Magill, T. P. (1938). *J. exp. Med.*, **68**, 147.
 Hein, G. E. (1943). *Proc. roy. Soc. Med.*, **36**, 387.
 Perrone, H., and Wright, M. (1943). *Brit. med. J.*, **2**, 63.
 Rake, G. et al. (1941). *Proc. Soc. exp. Biol. Med. N.Y.*, **48**, 528.
 Reimann, H. A. (1938). *J. Amer. med. Ass.*, **111**, 2377.
 —, et al. (1942). *Arch. intern. Med.*, **70**, 513.
 Scadding, J. G. (1937). *Brit. med. J.*, **2**, 956.
 Smadel, J. E., et al. (1942). *Proc. Soc. exp. Biol. Med. N.Y.*, **49**, 683.
 Turner, R. W. D. (1945). *Lancet*, **1**, 493.
 Viets, H. R., and Warren, S. (1937). *J. Amer. med. Ass.*, **108**, 357.
 Wallgren, A. (1925). *Acta paediatr. Stockh.*, **4**, 158.
 Weber, H. M. (1944). *Amer. J. med. Sci.*, **208**, 680.