BRITISH MEDICAL JOURNAL

LONDON SATURDAY JULY 17 1943

A FATAL CASE OF ATYPICAL PNEUMONIA WITH ENCEPHALITIS

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[WITH PHOTOGRAVURE PLATE]

Recent investigation (Kneeland and Smetana, 1940; Longcope, 1940; Blake *et al.*, 1942; Reimann *et al.*, 1942) indicates that the term "atypical primary pneumonia" embraces a clinical group of closely related infectious diseases, in certain cases of which viruses have been definitely established as the aetiological agents. In other instances where no virus has yet been isolated the pathological and clinical evidence suggests a virus infection. Such viruses hitherto isolated appear to be antigenically related to, although not identical with, the viruses of psittacosis, lymphocytic choriomeningitis, and lymphogranuloma venereum, all of which can produce meningitis as well as pneumonia in man or animal. Moreover, Smadel and his co-workers (1942) report two cases of lymphocytic choriomeningitis, in both of which extensive pneumonitis was found at necropsy. The lungs closely resembled those described in the few available pathological descriptions of atypical pneumonia.

Scadding (1937) reported a case of encephalitis and "disseminated focal pneumonia" (atypical pneumonia) in a patient previously treated in hospital for atypical pneumonia. The presenting syndrome was that of laryngeal paralysis. At necropsy the medulla, pons, and midbrain contained small areas of softening and haemorrhage; microscopically, perivascular "cuffing" and focal degeneration of nerve cells were prominent. In two other adult cases in which the brain was examined (Longcope, 1940) no evidence of encephalitis was found. In nine necropsies on infants with "primary virus pneumonitis" (Adams, 1941) no clinical or pathological evidence of encephalitis was discovered.

Reimann (1938) reported a case of atypical pneumonia in which positive Kernig and Babinski reflexes and ankle clonus could be elicited. The patient was comatose at intervals, the pupils sluggish and dilated; strabismus was noted and the neck was slightly rigid. Spinal fluid pressure was 220 mm.; the cell count varied between 220 and 350, with 78 to 91% polymorphonuclear cells; total protein was 74 mg. per 100 c.cm. Attempts to isolate a virus from the spinal fluid were unsuccessful. Complete recovery took place.

Hein (1943) reported two cases of atypical pneumonia showing clinical and laboratory evidence of meningo-encephalitis. One was that of a 23-year-old soldier who developed photophobia, stiff neck, and a positive Kernig sign on the fifth day of his illness. Cerebrospinal fluid contained 380 cells (77% polymorphs, 23% lymphocytes); Pandey's reaction was positive, sugar content raised, chlorides low; cultures were sterile. Temperature eventually fell to normal and the chest became clear, but the cerebrospinal fluid continued to have a high lymphocyte count for some time. Eventual recovery was

complete. The second case was that of a 34-year-old soldier with a maculo-papular rash who on the fourth day in hospital complained of headache, became confused, and developed a stiff neck. Cerebrospinal fluid contained 26 cells, all lymphocytes; Pandey's reaction was positive, sugar and chlorides normal. In this case, also, clinical improvement preceded clearing of the cerebrospinal fluid.

Case Report

Corporal A., aged 20, was admitted to an American Army hospital in England on Feb. 1, 1943. His illness had begun the previous day with cough, soreness in the throat on coughing, fever, nasal obstruction, moderate headache, and some aching pains in the chest and arms. Except for frequent attacks of tonsillitis during the previous year his past history was negative. The family history was also non-contributory.

On admission his temperature was 101.2°, pulse 95, and respirations 20. He appeared moderately prostrated; face and neck were flushed; eyes watery and injected. The right naris was partially obstructed, and a scant nasal discharge was present. The pharynx and posterior half of the palate were diffusely reddened; tonsils were moderately enlarged. The neck was not stiff. Lungs were clear and the rest of the examination was essentially negative.

Laboratory findings were as follows: Urine: Negative except for trace of albumin in terminal specimen. Blood count: Feb. 2, Hb 90%, R.B.C. 4,250,000, W.B.C. 5,700—79% polymorphs; Feb. 6, W.B.C. 8,700—97% polymorphs; Feb. 7, Hb 90%, R.B.C. 4,450,000, W.B.C. 6,550—90% polymorphs; Feb. 10, Hb 103%, R.B.C. 4,040,000, W.B.C. 6,900—85% polymorphs. Sedimentation rate: Feb. 3, 10 mm., Feb. 5, 22 mm. per hour. Blood cultures on Feb. 4, 7, and 10 were negative. Throat cultures on Feb. 2 gave *Staph. albus*, and sputum cultures on Feb. 5 and 6 showed *Staph. albus* and pneumococcus. On Feb. 11 the spinal fluid contained 8 polymorphs and 68 lymphocytes per c.mm.; culture was sterile.

Radiographs of the chest on Feb. 8 revealed a large area of consolidation in the right lower lung field; both lung fields were filled with numerous small soft shadows.

Clinical Course (see Chart)

On admission the patient was placed on sulphadiazine, 1 g. every four hours by mouth. Despite this the temperature rose to 104° each afternoon, and he was moderately toxic. At times slight cyanosis was observed. On his fifth day in hospital rales were heard in the left chest. Because of increasing dyspnoea and cyanosis, oxygen was administered, with immediate disappearance of cyanosis. Moderate amounts of bloody sputum were expectorated. Sticky, bubbling, and crepitant rales and wheezes became audible throughout both lungs; inspiratory dilatation of the alae nasi and expiratory grunting were observed. On the sixth day in hospital sulphadiazine was stopped and the patient was transfused from another patient three weeks convalescent from severe atypical pneumonia. After 125 c.cm. of blood had been given the procedure was halted because of restlessness and increased dyspnoea. Five hours later the temperature had dropped sharply to normal, and the patient seemed greatly improved. The next day he complained considerably of generalized headache; fever recurred in the evening associated with considerable abdominal distension, which was relieved by rectal tube, turpentine stupes, and

posterior pituitary extract. Chemotherapy was resumed, with two 4-g. intravenous doses of sodium sulphathiazole; a blood level of 2.6 mg. per 100 c.cm. was obtained. The oral dose of sulphadiazine was doubled to 2 g. every four hours, and the blood level rose to 12.5 mg. without clinical improvement. Dullness and bronchial breathing appeared in the right axilla. Although dyspnoea was diminished somewhat, the pulse rose from 120 to 140-150 and became thready at intervals. The patient became progressively less

membrane-like layer of fibrinoid material and occasionally enmeshed in typical fibrin strands. The mononuclear cells predominated in most fields, but were about equalled by the polymorphonuclears in a few areas. Much of the alveolar epithelium had been stripped from the lining surfaces, and formed part, at least, of the mononuclear-type cells. The remainder occurred as a desquamated layer of cuboidal, columnar, or somewhat spheroidal cells. Occasional larger mononuclear cells with hyperchromatic nuclei and

responsive; moderate neck rigidity was noted, and motion of the head evidently caused pain. Fluids, sodium chloride, and glucose were given orally, by infusion, hypodermoclysis, and per rectum. The loss of panniculus and muscular atrophy were marked and progressive. Digitalization with 18 cat units of digitalis intramuscularly appeared to slow and strengthen the pulse. A second transfusion of 300 c.cm., using the blood of a two-weeks-convalescent who had had a moderately severe atypical pneumonia, was given on the tenth day without noticeable effect. On the eleventh day the patient could no longer swallow sulphadiazine tablets; and chemotherapy, having failed to produce any improvement, was discontinued. The pupils became widely dilated, the skin clammy, cyanotic, and mottled, and the eyes glazed. A third transfusion of 250 c.cm. of blood from a two-weeks-convalescent moderately severe case improved the patient's general condition somewhat, but during the night the pulse became irregular and thready, and respiration stopped. After intramuscular caffeine respiration was restored, and a large mucous plug was extracted from the pharynx. Three hours later respiration again stopped and further stimulation was unsuccessful; the heart ceased shortly thereafter. The patient died on the thirteenth day in hospital.

Necropsy Findings

Post-mortem examination was performed three hours after death. The body was well developed and moderately well nourished. There was slight rigidity, and livor of transient type was present in the dependent parts. Pupils were equal, 7 mm. in diameter. There was no discharge from ears, nose, or mouth. The thorax was symmetrical and the abdomen flat. Extremities revealed marked cyanosis. Superficial vessels and lymph nodes were normal.

Lungs.—The right lung weighed 1,260 g., and its size and position were as usual. It appeared uniformly bright red. The entire lung was firmer than normal, the most notable increase in consistency being present in the middle and lower lobes. The pleural surfaces were smooth and glistening, with the exception of a small area on the antero-lateral surface of the lung 3 cm. from the apex. Here there were several fine adhesive bands with minimal roughening. Sectioned surfaces of lung revealed intense bright-red colour of the parenchyma with moderate increase in moisture. Consolidation was of lobular and confluent lobular type. Several small areas of emphysema were present throughout the upper lobe. In the parenchyma of the upper lobe beneath the pleural adhesions several small areas of necrosis, measuring 1.5 mm. in diameter and appearing much like miliary seedlings, were observed. Yellow muco-purulent exudate pouted from the small bronchi, and the larger air passages were plugged with this secretion to within 3 cm. of the tracheal bifurcation. The bronchial walls were swollen and congested. Hilar nodes were slightly enlarged and firm. The left lung weighed 1,010 g. The left upper lobe was red, moist, and similar in appearance to the right lung. The lower lobe was nodular in appearance, and revealed marked increase in consistency. The cut surface of both lobes was intensely red, and the muco-purulent exudate was present throughout the bronchial tree. The hilar nodes were enlarged and firm.

Microscopical Examination of Lungs.—The alveoli contained varying quantities of exudate consisting of large numbers of mononuclear cells (macrophage type) and polymorphonuclears lying within a

abundant cytoplasm were seen contiguous with the layer of alveolar epithelial cells. No inclusion bodies were seen in these cells. Some zones of interalveolar haemorrhage were present. Bronchi and bronchioles presented varying degrees of ulceration and deposition of abundant fibrinoid material. The remaining epithelium was of a stratified variety. The bronchial walls showed extensive lymphocytic infiltration, plasma cells, polymorphs, and some eosinophils. The pleura revealed some engorged vessels but no exudate. One section showed a nodular zone of fibrosis with a central area of caseous and coagulation necrosis. Rare foreign-body giant cells were present. No acid-fast bacilli were demonstrated with Verhoeff's acid-fast stain.

The heart, aorta, and vessels revealed no pathological changes. The spleen weighed 252 g. and measured 13.5 by 6 by 3 cm. It was red-grey in colour. The capsule stripped with slightly increased difficulty. The cut surface was deep-red and moist. Markings were vague, and pulp scraped slightly. Microscopical examination revealed areas of haemorrhage into the pulp with moderate increase in polymorphs. The liver, pancreas, and adrenals were normal. Gastro-intestinal and genito-urinary tracts were normal.

The Brain.—The dura did not appear swollen. Vessels were of average size. The leptomeninges showed no gross pathology. Spinal fluid was clear and there was no exudate. Convulsions and sulci appeared normal. The consistency of the brain was slightly softer than usual. On sectioning the cerebrum numerous pinhead-sized areas of dark-brown pigmentation were noted in grey and white matter. It could not be determined, by gross examination, whether these were small areas of haemorrhage or inflammation. The cerebellum, pons, and medulla were normal.

Microscopical Examination of the Brain.—This revealed frequent foci of increased cellularity in white matter of sections from parietal, temporal, and occipital lobes, from the region of the basal ganglia, paraventricular (III, IV) tissue, and cerebellum. These were located in juxtaposition to or surrounding small vessels, and were usually associated with a ring of peripheral haemorrhage. Cells forming these foci were astrocytes and microglia, with predominance of the former, and occurred in a density approximately ten times that of the regional white-matter. There was slight phagocytosis of erythrocytes in a few areas. The grey matter presented occasional large swollen, diffusely staining cells. The ependyma of all ventricles was negative. Leptomeninges presented areas of lymphocytic perivascular infiltration in sections from parietal and temporal zones. Vessels both of leptomeninges and of brain parenchyma were considerably engorged, and scattered "ring" haemorrhages without focal cell proliferation were present in grey and white matter.

Diagnosis

Lungs.—(1) Pneumonia—primary, atypical, of lobular and confluent lobular type—with ulcerative bronchitis and membranous and interstitial pneumonitis. (2) Tuberculosis—minimal, old, focal, inactive.

Brain.—Encephalitis—acute. (Encephalitis is used in the general sense and not necessarily as the designation of direct reaction to the specific infectious agent. The severity of the reaction and doubt as

to the purely degenerative character of the lesions make this term seem preferable to encephalopathy or encephalosis.)

Bacteriology.—Cultures from brain, heart, and right and left lung were all sterile at the end of 72 hours.

Virus Studies.—The following virus studies were negative: (1) Lung tissues were inoculated into twelve mice, one rabbit, and one guinea-pig intranasally by Major T. F. McNair Scott, M.C., U.S.A. (2) Glycerinated lung tissues were inoculated into cotton-rats and were reported as non-effective by Dr. C. H. Andrewes, National Research Institute, Hampstead. (3) Brain tissues were inoculated by Major McNair Scott intracerebrally into six mice, one rabbit, one guinea-pig, and one hamster. The rabbit died with encephalitozoon infection on the fifth day after inoculation.

Discussion

Clinical descriptions of cases of atypical pneumonia often stress the frequency and severity of headaches. Thus out of 87 cases we have observed at one hospital, 41 (47%) complained of headache—14 mild, 6 moderately severe, and 21 severe. The headache is usually frontal or ocular, though it may be generalized in severe cases. It occurs as a rule at the onset of the disease, and is rarely absent in severe cases of atypical pneumonia. Coughing increases the headache considerably.

Excluding the case reported above—the sole fatality in our series—lumbar puncture was performed in only one other case. This was one with severe frontal headache but no signs of meningitis or encephalitis; spinal fluid was normal. We have had under observation another patient who, during a previous attack of atypical pneumonia, had severe headache and positive Babinski, Chaddock, and Oppenheim reflexes. Unfortunately lumbar puncture was not performed. Recovery was complete.

Apparently our patient died of encephalitis rather than of pneumonia, since dyspnoea and rales became less in the last few days and abdominal distension disappeared. Indications of central nervous system involvement appeared abruptly on the sixth day in hospital, when the patient began to complain of severe headache. At the same time the temperature rose and slight neck rigidity was noticed. This encephalitis must be distinguished from a post-infectious encephalitis, which is characterized histologically by patchy areas of demyelination. These were not a prominent feature in this case, in which the brain lesions resembled more closely those of epidemic encephalitis.

If our case of atypical pneumonia was due to a virus it might be conjectured that, as with analogous virus infections, antibodies would develop in the blood of convalescents, and that transfusions of convalescent blood might favourably affect the course of the disease. Flexner and Garon (1943) report three cases in which small transfusions from convalescents were administered. Two of these patients, very ill at the time of transfusion, eventually died; the third, who had had a sustained temperature of about 103°, became afebrile within 24 hours and remained well. Kneeland (personal communication) has informed us of two unpublished cases in which convalescent blood was employed. In one case a husband, three weeks convalescent, gave 500 c.cm. of blood to his wife, who had apparently contracted the infection from him. The patient, who was pregnant and desperately ill, showed marked and rapid improvement. In the other case, receiving only 50 c.cm. of convalescent blood, no apparent benefit was obtained.

Our patient seemed to show a remarkable, though transient, response to the first transfusion; this was manifested by a rapid drop in temperature to normal, and by definite clinical improvement. The second transfusion appeared to have no effect. The third seemed to benefit him somewhat without affecting the temperature. The amounts of blood given on each occasion were small, as circulatory failure was feared from a larger transfusion. Yet the smallest transfusion, the first, appeared to have the greatest effect. The first donor had been the most severely ill of the three and had been longer convalescent than the others. Thus it might be supposed that his serum would have a higher antibody titre than the others'.

Summary and Conclusions

A case of fatal atypical pneumonia with encephalitis is presented, with necropsy findings.

The incidence of encephalitis in atypical pneumonia is discussed.

Convalescent blood transfusion in atypical pneumonia is considered.

Special thanks are due to Lieut.-Col. Yale Kneeland, jun., M.C., U.S.A., for the unpublished data recorded above. We are deeply indebted to Lieut.-Col. John B. Hazard, M.C., U.S.A., for the histopathological descriptions and review of findings in the reported case.

REFERENCES

- Adams, J. M. (1941). *J. Amer. med. Ass.*, **116**, 925.
 Blake, F. G., Howard, M. E., and Tatlock, H. (1942). *Yale J. biol. Med.*, **15**, 139.
 Flexner, M., and Garon, M. (1943). *Kentucky med. J.*, **41**, 5.
 Hein, G. E. (1943). *Lancet*, **1**, 431.
 Kneeland, Y., and Smetana, H. F. (1940). *Johns Hopk. Hosp. Bull.*, **67**, 229.
 Longcope, W. T. (1940). *Ibid.*, **67**, 268.
 Reimann, H. A. (1938). *J. Amer. med. Ass.*, **111**, 2377.
 ———, Havens, W. P., and Price, A. H. (1942). *Arch. intern. Med.*, **70**, 513.
 Scadding, J. G. (1937). *British Medical Journal*, **2**, 956.
 Smadel, J. E., Green, R. H., Paltauf, R. M., and Gonzales, T. A. (1942). *Proc. Soc. exp. Biol.*, N.Y., **49**, 683.

THE FAILURE OF H 11 TO INHIBIT GROWTH OF TUMOURS IN MICE

BY

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The preparation known as H 11, which is being used in the treatment of cancer, is an extract of urine. It is claimed that the extract contains "anti-growth substances" which have "an inhibitory effect upon cancerous growth." The method of preparation of H 11 and the standardization of the "growth-inhibitory power" of the product by its effect in checking the growth of oat seedlings are described by Thompson and his collaborators (1941). Thompson, Holt, and Forbes Jones (1943) claim that certain fractions of urine have been obtained which stimulate the growth of transplanted tumours. The urine is fractionated by precipitation with copper salts; the precipitate is extracted with dilute hydrochloric acid, which yields a tarry substance partially soluble in sodium hydroxide. The part soluble in alkali is said to accelerate growth, and therefore it would appear that by removal of the "growth-promoting fraction" the "growth-inhibiting properties" of the residue are increased. The improved extract is called 80 K.

It is not our purpose to examine or discuss the general questions of "growth promotion" and "growth inhibition" in relation to the problems of the pathology and treatment of cancer. We wish simply to put on record the results of experiments designed to test whether H 11 or the new improved preparation obtained after precipitation with copper salts does in fact inhibit or affect in any way the growth of cancer cells. Mr. J. H. Thompson of Hosa Research Laboratories has provided generous supplies of H 11 and of his new preparation 80 K; for his kindness we wish to express our indebtedness.

General Remarks on the Testing of "Cancer Cures"

In these laboratories we have gradually worked out routine methods of examining substances supposed to have valuable therapeutic properties for cancer. Our first step is usually a test of the direct action of the substance on cancer cells. For this purpose we use the technique of tissue culture. The substance to be tested is applied in various dilutions to cultures consisting of growths of normal and malignant tissues. The growth of the tissues is measured before and after varying periods of treatment. Control cultures are measured at the same time. From the two sets of measurements the extent to which normal and malignant growth are influenced by the substance can be calculated. Confirmatory tests are made by adding the substance under investigation, in the weakest concentration previously found to arrest malignant growth, to the

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FIG. 1.—Photomicrograph, by Wellcome Research Institute, of brain tissue; cerebral vessel showing engorgement, oedema, and perivascular infiltration. ($\times 175$.)

FIG. 2.—Photomicrograph, by Wellcome Research Institute, of brain tissue; showing focal area of increased cellularity. ($\times 100$.)

FIG. 3.—Photomicrograph, by Wellcome Research Institute, of bronchiole; showing scanty exudate. Note infiltration of bronchiolar walls. ($\times 100$.)

FIG. 4.—Photomicrograph, by Wellcome Research Institute, of lung; showing area of heavy exudate, fibrin, mononuclear cells of macrophage type, and stripping of alveolar epithelium. ($\times 100$.)

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FIG. 5.—Photomicrograph, by Wellcome Research Institute, of exudate from lung; showing predominance of mononuclear cells, with red blood corpuscles, occasional polynuclears, and fibrin. ($\times 1000$.)

FIG. 6.—Radiograph of chest taken on February 8, 1943; showing a large area of consolidation in right lower lung field; both lung fields filled with numerous soft shadows.