

standing position. It is interesting that the hypotension in the sitting position is not greater, and, in fact, that the blood pressure rises promptly on sitting down.

A great deal of attention has been paid in these experiments to recording blood pressure in the erect posture, using a fixed time limit as described. Standing systolic readings have proved to be a convenient measure of the total effect of the drug on the blood pressure, since the changes in these readings are bigger in proportion to the errors of technique than in the sitting or recumbent positions, and, moreover, they provide an important measure of the maximum effect of the drug.

The distribution of hexamethonium in the body and its excretion at a rate comparable to that of inulin correspond to its quaternary nature. Bases in general penetrate the cell membrane only in the un-ionized form (Höber, 1945). Salts of quaternary nitrogen when in solution are completely ionized, and hence can only traverse the cell membranes very slowly. Accordingly they must lead an extracellular existence in the body, and should be unable to be either secreted or reabsorbed by the kidney tubules.

The indication from clinical data (Fig. 4) that normal subjects vary considerably in their response to hexamethonium was borne out and further elucidated by the plasma-concentration curves. Part of this variation is obviously due to the differences in absorption, distribution, and excretion already described; but the main variation, and one that cannot be eliminated by changing the route of administration, lies in the actual response of different subjects to the same concentration of the drug in the plasma (Fig. 6). The immediate practical application is that it is not safe to give initial doses of more than about 30-40 mg. subcutaneously to ambulant patients, even though this dose may produce little response in many individuals.

The somewhat unexpected finding of a linear rather than a logarithmic relationship between the plasma concentration and the effect on the blood pressure has some practical importance in addition to its theoretical interest; when treating patients for hypertension the dose should not be increased too rapidly. Increments of not more than 25-50 mg. should be used according to the individual patient's sensitivity.

The manner in which these findings in normal subjects may be applied to hypertensive patients under treatment is being studied and will be reported later.

Summary

A detailed study of the clinical effects of a subcutaneous test dose of hexamethonium in 16 normal individuals is reported, and plasma-concentration curves are described in eight of these.

No effects have been observed which could not be attributed to ganglionic block, with the possible exception of drowsiness.

Calculations from the concentration-time curves of hexamethonium in the plasma indicate that the drug is evenly distributed through the extracellular fluid, and they are compatible with its excretion by glomerular filtration.

Considerable variation in the response of different individuals to hexamethonium has been shown to occur, in relation both to the dose given per kilogram of body weight and to plasma levels. The thresholds for reduction of blood pressure, for elevation of pulse rate, and for interference with three separate pupillary functions varied from subject to subject, independently of each other.

For a given individual there was a close linear relationship between the plasma concentration and the degree of blood-pressure reduction.

We should like to thank Professor J. McMichael for his advice and helpful criticism in the carrying out of this work.

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FARMER'S LUNG

BY

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A condition conveniently named "farmer's lung," readily recognized clinically and radiologically, has been reported in the medical literature in the past, but some confusion has existed about the causal mechanism and the natural history of the disease. The purpose of this paper is to review the literature, to present a small series of cases, and to advance a theory to explain its aetiology.

Review of the Literature

Campbell (1932) presented case histories of a small number of agricultural workers from North Westmorland who were referred to his clinic as possible cases of tuberculosis. All gave a history of sudden onset of intense breathlessness, cough, slight fever, and, in some, loss of weight following exposure to dust from mouldy hay.

The clinical picture in each case was of a distressed, blue, dyspnoeic patient, and clinical examination revealed widespread crepitations throughout the lungs. Radiologically the picture was of increased lung markings with superimposed soft shadows. Spontaneous recovery in one to two months occurred, but some residual fibrosis and emphysema were noted in a few cases. One patient subsequently died, but necropsy showed coincidental cystic disease of the lungs (Campbell, 1950—personal communication). Through the kindness of Dr. Campbell it has been possible to study the x-ray films of one of his original cases followed up for 18 years. Some fibrosis and emphysema were the only findings.

Fawcitt (1936, 1938, 1940) studied the condition in West Cumberland and concluded from culture of similar moulds in the sputum and the hay dust that this was a fungous infection of the bronchi and lungs. He used the term "bronchomycosis feniseiorum" and advocated treatment with iodides. It should be stated that the condition described by Campbell (1932) and that of many of Fawcitt's (1938) cases were clearly not true aspergillosis, which is a distinct and well described clinical entity (Sayers and Meriwether, 1932; Smith, 1947). "Thresher's lungs," if aspergillosis is excluded, is an analogous condition in workers exposed to mouldy corn dust, and presents a picture identical to farmer's lung.

Duncan (1945), in a review of fungous diseases, stated that he had received specimens of sputum relating to this disorder from physicians in rural areas stretching from Cumberland to Devon. He cultured many varieties of

fungus from the specimens, but came to the conclusion that this only indicated exposure of the patient to dust containing the relevant spores, and was no criterion of actual infection. He put forward a theory that the symptoms could be explained by an irritation of the lungs from a fine vegetable dust resulting from breakdown of hay fibres by the fungus, and that the disease was comparable to byssinosis.

The *Lancet* (1948) made a plea for further investigation of this and allied conditions, but the *British Medical Journal* (1950) still quoted the fungus theory and recommended iodide treatment.

Distribution and Frequency

The distribution of reported cases is of interest, as the condition appears to be most common in the North-West of England. Possible reasons for this are the high rainfall at hay-time, and primitive methods of harvesting and storage in closed barns. The old threshing barns with fixed installation are still in use, and many farmers remember cases of sudden death following acute chest symptoms in men working all day in some of the old ill-ventilated barns. Threshing engineers and farmers are familiar with the clinical picture of farmer's lung, and refer to being "moulded." The white irritant dust set up when mouldy hay is disturbed is locally referred to as "stour" and treated with respect. "Broken-windedness" in horses is attributed to the feeding of mouldy hay, and is largely prevented by dampening the hay before feeding.

The rarity of the disease in hospital practice was in contrast with the evidence of the farmers, and so it was decided to circularize the practitioners of the area asking for information. The response was excellent, and a clearer picture of its true distribution emerged. Family practitioners in the smaller market towns were quite conversant with both the clinical picture and the natural history of the disease, and could advise the farmer suffering from these symptoms of his probable progress and time off work. As there was no problem in their minds, these doctors did not, as a rule, refer their patients to hospital unless radiological confirmation was sought. It was from conversation with Dr. A. G. Abraham, of Cockermonth, Dr. E. Braithwaite, of Egremont, and Dr. H. P. Nelson, of Brampton, that many valuable facts about the disease were learned.

The present series consists of six cases—confirmed radiologically, and six probable cases—radiologically inconclusive.

Proved Cases

Case 1.—A farm labourer aged 22 had no history of chest trouble until January–March, 1950, when he had bouts of mild bronchitis, often following exposure to hay dust. On August 4 he worked all day stacking poor-quality hay from which there was a lot of white irritant dust. By evening he was distressed, coughing, and breathless. After a rigor he started to sweat, felt very feverish, and vomited. After six days of persistent breathlessness and distress, despite sulphamide therapy, he was admitted to hospital. The clinical picture was that of a cyanosed, breathless, and ill man. Clubbing of the fingers was not noted, and chest examination revealed generalized fine crepitations, without any localized dullness or signs of consolidation. There was no evidence of cardiac enlargement or failure. An x-ray film of the chest taken on August 10 showed: "An overall opacity of both lung fields, excluding the apices and costophrenic angles, with the greatest density in the lower mid-fields, and extending to the extreme periphery of the lung. In the areas of least involvement the opacity fades to a

fine granular mottling. . . . The detail of the lung roots is almost completely obliterated. There is no pleural fluid, and no cardiac enlargement" (Figs. 1 and 2). The sputum was cultured and yielded a good growth of *Bacillus subtilis*, but no fungi. A differential white blood cell count showed

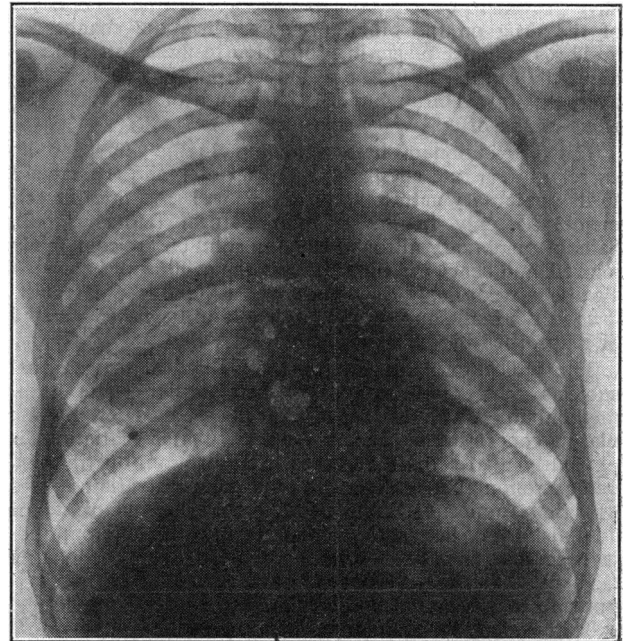


FIG. 1.—Case 1. X-ray film taken on August 10, 1950.

no eosinophilia. Dust from the barn grew *B. subtilis* and various aspergilli. Skin tests showed no specific reaction to dust extracts or mould cultures. Treatment with mepyr-amine maleate, 0.1 g. thrice daily, was instituted without obvious effect, but the patient gradually improved, and a follow-up x-ray film taken four months later showed normal lung fields.

Case 2.—A married woman aged 47 was admitted to hospital on December 17, 1947. She had been quite healthy until two weeks before admission, when she and her son (Case 3) swept out a closed barn in preparation for the storage of some newly threshed corn. She became very breathless that night, and symptoms persisted until she was admitted. She complained of slight fever, a dry cough, and intense breathlessness out of proportion to her other symptoms. On admission her temperature was 100.4° F.

(38° C.), pulse 100, and respirations 56. There were widespread fine crepitations, maximal at the left apex, and an x-ray film showed: "An opacity mainly of the left upper zone, but, in lesser degree, of both lower zones. As in Case 1, the opacity extends to the periphery of the lung fields, and fades to fine mottling. The root shadows also show loss of detail, particularly the left." The white blood count was 7,200 per c.mm., with 4% eosinophilia, the sputum was

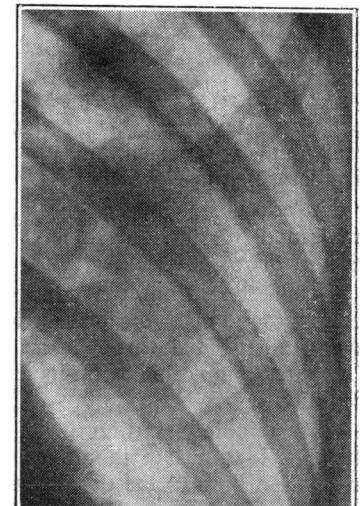


FIG. 2.—Enlarged view of part of Fig. 1.

mucopurulent, but yielded no significant organisms or fungi. She was treated with diphenhydramine hydrochloride, and improvement was gradual. On January 1, 1948, she was discharged home and continued to do well.

Case 3.—The son of Case 2, aged 24, was seen on December 17, 1947, as an out-patient, complaining of cough with mucopurulent sputum, nausea, night sweats, weight loss, and intense breathlessness. On examination he was cyanosed, with rapid respirations and generalized crepitations. An x-ray film of the chest showed: "A complete ground-glass opacity of all zones, extending to the periphery and showing the typical granular mottling in areas of least density. The detail of the root shadows in this case is not obliterated." He was not admitted to hospital, as the condition was recognized and progress at home was uneventful. Follow-up x-ray examination in 10 weeks showed almost complete clearing and he was clinically well.

Probable Cases

Case 4.—On October 13, 1950, a man aged 48 swept out his barn containing old corn and oats prior to threshing day. The dust was very irritant and white, and that evening he became breathless and ill. He had never had chest trouble before, but he described himself as being "broken-winded" and ill for the next month, with a dry cough and night sweats. He was referred as a possible case of tuberculosis on December 13, but by then he felt better and clinical and radiological examination revealed only non-specific changes.

Other cases in this group gave a clear history of exposure, but could not be classed as definite without clear radiological confirmation. If practitioners become aware of the condition and refer such cases for early chest x-ray examination it is thought that many more cases will come to light.

Clinical Picture

The clinical picture emerges of a non-specific lung irritation which may follow exposure to mouldy vegetable dusts of any type, but mainly contact with poor-quality hay and corn. It may occur during stacking, baling, threshing, forking of hay for animal feeding, or sweeping out a barn in preparation for new grain or hay. Before the severe reaction there may be minor bronchitic episodes following short contact, but this is not invariable, and a clear distinction must be drawn between true farmer's lung and an asthmatic attack following exposure to mouldy dust (see Case 5).

The main feature of the disease is the intense breathlessness and cyanosis which develop within 12 hours of exposure. If symptoms are delayed for more than 24 hours an alternative diagnosis must be considered (see Case 6). The onset is sudden, and may be associated with a rigor, vomiting, a dry cough, and a feeling of suffocation. Irritation of the eyes and nose commonly occurs after contact with the dust, but is not a feature of the disease. The picture at this stage resembles that of a case of acute oedema of the lungs, but there is no evidence of cardiac embarrassment. Widespread fine crepitations are found on examination of the chest, but no localized area of consolidation is detected. Pleurisy is not a feature, and the finding of clinical or radiological evidence of this makes the diagnosis suspect. No case presented with haemoptysis.

The clinical course is fairly constant, and clearing of the radiological picture and physical signs is usual in six to eight weeks. After the first two to three weeks the breathlessness becomes less distressing, but during this period loss of weight and night sweats occur.

After three months the patient appears to be well, but there is a tendency for the condition to recur on re-exposure, and some evidence to suggest that there is a predisposition to the development of some degree of emphysema and fibrosis. No diminution in vital capacity has been noted in the follow-up of the present series over one to five years, but Dr. Campbell's case followed for 18 years showed some fibrosis and emphysema. Dr. W. G. Scott-Harden describes

the radiological picture in the acute phase as a ground-glass opacity extending to the periphery of the lung fields, and fading to a granular mottling in the areas of least involvement. Although the distribution is most commonly in the mid- and lower-lung fields, with the exclusion of the apices and costophrenic angles, this cannot be taken as invariable. Case 2 illustrates this point, and it is of interest that this patient is the only female in the series and to postulate the relationship between this and the greater frequency of thoracic, as opposed to abdominal, respiration in women. The detail of the root shadows is usually obliterated by the opacity, and return to normal lags behind peripheral clearing. There is no case in the series in which there were dense localized opacities in the lung or evidence of pleurisy, and there was no cardiac enlargement. Clearing is gradual, starting at the periphery, and is usually complete in three months.

Pathological Investigations.—The red blood cells and haemoglobin remain unchanged. The total and differential white-cell counts show no specific change, the maximum eosinophilia being 4% of 7,200 white cells per c.mm. in Case 2. The E.S.R. is normal or slightly raised.

Sputum examination in proved and probable cases yielded a mixed growth of aspergilli in five, penicillium in four, *B. subtilis* in four, and monilia in five cases, in addition to the usual commensals.

Examination of the incriminated dust showed a comparable growth of mixed fungi, but this similarity of cultural characteristics in dust and sputum was only taken as evidence that the patient had recently inhaled the dust, but not in any way as proof of active disease in the bronchi or lungs (see Cases 5 and 6). Assessment of average particle size of the dusts was found to present some difficulty, and is the subject of further investigation, but the impression gained from two samples was that the average diameter of particles was greater than 10 μ .

Animal experiments were carried out by Fawcitt (1938) on a limited scale in an attempt to demonstrate the pathogenicity of spore-laden dust to animals' lungs, without conclusive results.

Skin tests with extracts of the offending dusts and stock solutions of aspergillus, penicillium, and mucor were carried out without obtaining specific reactions in any case.

Differential Diagnosis

1. **Asthma and bronchitis** brought on by contact with mouldy hay or grain is not uncommon in farmers, and seven such cases were seen.

Case 5.—A farm worker aged 62 was seen on September 16, 1950. There was one year's history of dyspnoea and wheezing, made worse by working in a closed barn with poor-quality hay, but no single explosive episode of breathlessness. Examination of the chest revealed signs of chronic bronchitis, with dry rhonchi throughout the lungs, and x-ray films confirmed an emphysematous picture without specific changes. Culture of the sputum yielded a good growth of aspergillus and monilia. Dust from the barn showed aspergillus, monilia, and *B. subtilis*. Skin tests with dust extracts showed marked reaction.

The finding of mixed spores in the sputum of this group of cases was invariable and of no significance beyond demonstration of contact with a potential allergen.

2. **Coincidental Pneumonia.**—Most cases were initially treated as pneumonia by the general practitioner, and if any doubt exists this is a wise precaution. It would be a disservice to the farming community if the diagnosis of farmer's lung was made too lightly. The points to be stressed are the dramatic onset within a few hours of exposure, and the absence of signs of consolidation, pleurisy, or haemoptysis in farmer's lung; but confusion may arise in the case of virus pneumonia.

Case 6.—A farmer aged 42, whose previous health had been good, was working a baler and putting through poor-quality hay on February 6, 1952. He had no untoward symp-

toms until 48 hours later, when he felt feverish and breathless, and complained of left-sided chest pain. He was referred after two days as a possible case of farmer's lung. Clinically and radiologically there was evidence of a patchy virus pneumonia, and treatment with chloramphenicol produced a dramatic response. It was the time interval of two days, combined with the patchy radiological appearance, including a basal pleurisy, which made a diagnosis of farmer's lung untenable, despite the finding of aspergillus in the sputum. The risk of converting such a case into true aspergilliosis by intensive treatment with chloramphenicol is appreciated.

3. *Miliary tuberculosis* is often clinically suspected, but the mistake can be made only if the history of exposure to dust has not been elicited: also the radiological features are quite different.

4. *Miliary diffuse granulomatous pneumonitis* of unknown aetiology has been reported in men cleaning out a water-tower in Cincinnati which was heavily contaminated with pigeon excreta (Felson *et al.*, 1950). Similar radiological appearances occurred in soldiers clearing out dusty barns in Missouri (Idstrom and Rosenberg, 1944); in soldiers spending some time in a deserted storm cellar in Oklahoma (Cain *et al.*, 1947); and in 21 men who visited a deserted chalk pit in Arkansas (Washburn *et al.*, 1948). All of these cases have been reported as specific entities, but it would appear that, with farmer's lung, they constitute a non-specific lung reaction to a variety of irritants. In each case clinical and radiological clearing occurred in one to twelve months.

5. *Aspergilliosis* is an infection of the lungs with pathogenic strains of aspergillus, particularly *A. niger* and *A. fumigatus* Fisher, which may occur in grain handlers. It is a true fungous infection, with active branching hyphae in the sputum, severe illness, and dense infiltration or cavitation of the lungs. There is no spontaneous improvement when the case is removed from the source of infection. It is possible that it may present as a miliary lung picture without serious systemic upset, and proceed to scattered calcification, mainly at the lung bases (Sayers and Meriwether, 1932). Skin tests are variable. Confusion with farmer's lung is unlikely, provided that the finding of the spores of aspergillus in the sputum is taken at its true value.

Treatment

Treatment is largely symptomatic. Fawcitt (1936, 1938, 1940) advocated iodides, but his results differed little from the spontaneous clearing noted in untreated cases. Anti-histamine drugs have been used in this series without obvious effect, and antibiotics seem to have a limited value in preventing secondary infection.

As the initial condition has much in common with acute pulmonary oedema, mercurial diuretics may be tried, but in the absence of cardiac enlargement their value is doubtful.

Discussion

The currently quoted view that farmer's lung is an actual fungous infection of the lungs does not bear close examination. The explosive onset, spontaneous clearing, and radiological picture are totally unlike any true fungous disease, and no real evidence has been produced to support this theory. The silica content of vegetable dusts has been analysed with reference to hay dust (Fawcitt, 1936) and dust in cotton mills (Prausnitz, 1936) and found to be negligible, so this may be excluded as a possible factor. That the condition is not simply a severe asthmatic reaction is shown by the distinct clinical and radiological pattern, although it is possible that personal allergy may play a part.

The two remaining theories which explain most aspects of the disease are: (1) irritation of the lungs by fungus spores or some noxious breakdown product; and (2) a mechanical irritation of the lungs by a fine vegetable dust of sufficiently small average particle size to allow deep penetration: this dust may be formed from the action of the fungus on hay fibres, which subsequently disintegrate.

In examining these theories it was considered reasonable to compare the clinical picture of farmer's lung with diseases thought to fall within these two groups, and note points of similarity. Group 1: (a) coniosporiosis (Towey *et al.*, 1932); (b) weaver's cough (Collis, 1915); and (c) possibly the miliary granulomatous lung lesions already mentioned. Group 2: (a) byssinosis ("monday fever"); (b) bagassosis.

Group 1 (a) Coniosporiosis.—Towey *et al.* described this as a pneumonitis in lumbermen involving 10% of the men working on one camp as maple-bark strippers. The cork layer of the bark was heavily contaminated with the black spores of *Coniosporium corticale*, which rose in a cloud when the bark was stripped. The men became suddenly ill with severe dyspnoea, cough, cyanosis, and variable fever. Widespread crepitations were noted on examination of the chest, and x-ray films showed areas of soft infiltration, tending to spare the apices, with generalized increase of lung markings and reticulation. Spontaneous cure occurred in six to eight weeks, but recurrence of symptoms followed re-exposure. Sputum contained spores of *C. corticale* and mixed monilia, but the latter were non-pathogenic. Animal experiments with the black residue of the spores were not entirely convincing, but the extract caused toxic effects on guinea-pigs' lungs. The authors postulated an irritative lung lesion with local reaction and giant-cell formation, and regarded the two months needed for clinical clearing as a reflection of the time necessary for phagocytosis of the spores to be complete.

Group 1 (b) Weaver's Cough.—This is a comparable condition occurring in workers handling mildewed cotton, which gives off a white dust of aspergillus, penicillium, and mucor spores.

Group 2 (a) Byssinosis.—On beginning to work in the cardroom of a cotton-mill a transient irritative cough known as "mill fever" used to be very common, but this cleared with continued exposure. After a variable time a certain number of workers developed a tendency to an irritant cough and attacks of breathlessness when returning to the mill after the weekend—hence the name of monday fever. At first the condition wore off on re-exposure, but gradually, symptoms spread over the whole week, with severe disability. After a rest of weeks or months they felt quite fit, but return to the mill resulted in an overwhelming recrudescence of symptoms, and eventual disablement from byssinosis (Prausnitz, 1936). X-ray films showed non-specific fibrosis and emphysema. The cardroom dust was mainly less than 10μ in average diameter, and this is regarded as the critical level for deep penetration of particles into the lung (National Silicosis Conference, 1937). In certain conditions the dust contained mixed fungus spores and minute amounts of histamine and a cotton-seed lipid called gossypol. The view generally held (Caminita *et al.*, 1947) is that monday fever and subsequent byssinosis may be due to sensitization of the lung tissues to irritation by proteins in the dust. Haworth and Macdonald (1937) postulated inhalation of histamine+allergen as the cause.

The clinical similarity of coniosporiosis, monday fever, and farmer's lung is striking, but the radiological analogy with byssinosis is less complete. Weaver's cough, however, again appears to be identical with farmer's lung, and I have reached the conclusion that all of these conditions represent a lung reaction to a non-specific irritant, probably some foreign protein. There is obviously some degree of personal sensitivity, as there may be only one case of farmer's lung in a group of farm workers handling the same batch of mouldy hay, or one case of coniosporiosis in a group of ten lumbermen. It is felt that no useful purpose is served in attempting to give specific names to the conditions, and that "hay-dust irritation of the lungs" would be an accurate description of some cases, and "corn dust," "cotton dust," or "coniosporium-spore dust" irritation of others.

Comparison of x-ray films of farmer's lung with other conditions is instructive, and there is a close resemblance to many diverse diseases, notably the "bats-wing" appearance of uraemic pneumonia. It seems probable that some similar interstitial lung reaction may play a part in the production of the radiological appearance of these conditions, however dissimilar their aetiological basis.

Further work on the nature of this reaction is necessary before any definite hypothesis can be advanced, and animal experiments on lung reactions to a variety of contaminated dusts may provide the answer. Lung puncture in the acute phase would also be enlightening, but could hardly be justified in a disease without any appreciable mortality. It is felt that, on clinical and radiological grounds alone, there

is enough evidence to support the theory that farmer's lung is not a specific entity, but only a single facet of a similar lung reaction to a variety of irritants.

Summary

A small series of cases of farmer's lung is described, stressing the acute onset and tendency to spontaneous recovery in six to eight weeks.

The close similarity to coniosporiosis, byssinosis, and diffuse granulomatous pneumonitis is stressed.

The theory is put forward that the condition is a non-specific interstitial lung reaction to some material in the fungus-laden dust, rather than a true fungous infection of the lungs.

My thanks are due to Dr. W. G. Scott-Harden for his advice on the radiological aspects of the paper, to Dr. J. M. Campbell for access to x-ray films of one of his original cases, to Dr. T. McL. Galloway for permission to include reports of Cases 2 and 3, to Dr. J. S. Faulds and his staff for pathological details, and to the general practitioners of Cumberland and Westmorland.

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INTRACTABLE GASTRIC CRISES RELIEVED BY CHORDOTOMY

BY

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Stokes (1944) states that the figures of the American Co-operative Clinical Group show that 45% of patients with tabetic gastric crises are completely relieved by treatment and that an additional 22% are benefited. He adds that standard chemotherapy—that is, neoparsphenamine plus bismuth—is more effective than fever plus tryparsamide or intraspinal methods, and that “the whole surgical field for relief in gastric crises is at best a matter of last and desperate resort.” Moore (1941) believes that routine treatment will produce relief of symptoms in 25% of cases, that tryparsamide is of little value, and that the use of fever in addition will relieve a further 25%. Of the 50% of cases thus benefited, however, only 10% may be regarded as cured, and he quotes Keidel's opinion that “if, as rarely occurs, severe attacks are almost continuous, operation may be the only alternative to starvation, morphinism, or suicide.” He also states that later experience with penicillin suggests that it is inferior to fever therapy in the treatment of this distressing condition (Moore, 1947).

The following history demonstrates the extent of the problem presented by those cases which do not respond to antisyphilitic treatment and emphasizes the additional fact that neurosyphilitic patients may suffer from unrelated organic intra-abdominal disease.

Case History

A seaman aged 37 was first seen in September, 1947, having had intermittent “stomach pains” and vomiting during the previous nine months. The pains occurred approximately every three weeks, were not related to meals, but were alleviated by alkaline powders. During these periodic episodes the pain was not constantly present, but came in sudden bouts, each lasting about 15 minutes and recurring at frequent though irregular intervals. The pain consisted of a sickening steady ache in the epigastrium, and was accompanied by retching and vomiting. In the previous nine months he had lost 2 st. (12.7 kg.) in weight, and at the time of examination he weighed 8 st. 2 lb. (51.7 kg.). He also complained of shooting pains in both legs of about one year's duration.

On full clinical examination no abnormalities were found except for Argyll Robertson pupils. Serological examination of the blood showed: Wassermann reaction, weak to moderately strong positive (+ to ++); quantitative, five doses of complement fixed; Kahn, strong positive (+++). The cerebrospinal fluid showed: cells, 200 per c.mm.; Wassermann reaction, very weak positive (±); gold sol, 0111000000.

Antisyphilitic treatment was begun with penicillin, but as the condition was strongly suggestive of either peptic ulceration or neoplasm an exploratory laparotomy was performed on October 3 (Professor W. Mercer). No abnormality was found, but the opportunity was taken to remove a small fibrosed appendix.

Treatment with penicillin (100,000 units three-hourly) was continued to a total of 12,000,000 units, and on October 17 he was discharged from hospital. Thereafter he continued to attend for treatment as an out-patient while following his usual occupation of trawlerman, although symptoms recurred at intervals despite continuous treatment with oxophenarsine hydrochloride, tryparsamide, and bismuth. The attacks were the same as those previously described, and lasted sometimes for several days.

Serological examination on June 12, 1948, showed much improvement—blood: Wassermann reaction, weak positive (+); quantitative, four doses of complement fixed; cerebrospinal fluid: cells, 5 per c.mm.; protein, 20 mg. per 100 ml.; globulin, no increase; Wassermann reaction, very weak positive (±); gold sol, 0000000000.

In September, 1948, the patient ceased to attend after having received a total of 12,000,000 units of penicillin, 0.88 g. of oxophenarsine hydrochloride, 39 g. of tryparsamide, and 4.1 g. of bismuth. Later it was learned that in October a recurrence of crises had necessitated his admission to a distant hospital, where he was treated with 16,100,000 units of penicillin, 34 ml. of bismuth tryparsamide, and one session of inductopyrexia—five and a half hours at 104–105° F. (40–40.6° C.).

Between January and June, 1949, he received no treatment, but on June 28 he was again in hospital in a state of extreme misery after further crises. Serological investigation of the blood on June 27 showed quantitative Wassermann reaction ++ (six doses). On July 21 the cerebrospinal fluid showed: cells, 4 per c.mm.; protein, 40 mg. per 100 ml.; globulin, no increase; Wassermann reaction, 0.2 ml. ±; 0.5 ml. +; 1 ml. ++; gold sol, 0000000000. On this occasion treatment consisted of penicillin (100,000 units three-hourly) to a total of 12,000,000 units, malaria (seven rigors), intravenous glucose-saline, pethidine (2 ml. intramuscularly as required). He returned home on September 2, but was readmitted on two further occasions for short periods (October 19 and