formation of blood thromboplastin, and it is possible that neodymium displaces calcium from combination with one or more of the proteins involved in this reaction. In their chemical properties calcium and neodymium are similar enough to support such a possibility and dissimilar enough to be biochemically non-interchangeable. Neodymium may in fact be an antimetabolite of calcium in the blood coagulation process, although we have found that excess of calcium does not prevent the action of neodymium *in vitro*. A more probable explanation of the actions described is selective combination with plasma proteins, as described by the German workers.

Summary

In intravenous doses of the order of 5 mg. per kg. in man and rabbits, neodymium 3-sulpho-isonicotinate leads to impairment of intrinsic blood thromboplastin generation by inhibiting two factors normally present in serum—Christmas factor and factor X—and also to variable reduction in factor VII (stable factor, S.P.C.A.) activity. There is no detectable effect on prothrombin. The effect is demonstrable in four hours and lasts for 24 hours. With much larger doses in animals, in addition to the above effects the clotting-time of whole blood is prolonged and the activity of antihæmophilic globulin is reduced.

[Clinical trials since this paper was written in April, 1956, have revealed the presence of hæmoglobinaemia in some patients receiving the drug. Further studies of the toxicity of neodymium in animals and man are in progress.]

We are indebted to Dr. R. G. Macfarlane and Dr. Rosemary Biggs for suggesting some of the experiments elucidating the mode of action of the compound.

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FARMER'S LUNG IN RADNOR AND NORTH BRECONSHIRE A REPORT OF TEN CASES

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An acute or subacute respiratory illness of farm workers developing after exposure to mouldy hay and known as farmer's lung was first reported by Campbell in Cumberland in 1932. Fawcitt in 1936 and 1938 described further cases occurring in Westmorland and Cumberland. Törnell (1946) reported eight similar cases from Sweden under the term "thresher's lung," and Sweeney (1952) four cases occurring in North-West Ireland. In 1953 Fuller had collected 32 cases in Devon since the end of the last war and published a review of the subject. Although the condition has been fully described, a report of a further ten cases is considered to be of sufficient interest to justify publication, it being

felt that not enough attention has been drawn to this occupational hazard of farm workers, and the condition may be more prevalent than it was previously thought to be.

Incidence

All but the first case in the present series were seen within a period of four months, some of them within the same week and two actually on the same day (see Table I). The epidemic occurred mainly in the early part of the year when stored hay is old and dusty and liable to have developed moulds if incompletely dried before harvesting. All the patients developed the disease after exposure to dust-laden air in cow-houses and hay-barns during hand-feeding of cattle. The complaint that the hay was particularly "mouldy" on account of the poor harvest weather in 1954 was unanimous, and most of the victims considered this to be the cause of their symptoms. All the patients lived in the hilly district of mid-Wales, where rainfall and humidity are high, and it is worth recalling that cases previously described in the British Isles also occurred in hill areas. In the present epidemic no other victims were discovered where contact to mouldy hay was known to exist. The fact that out of a total of 17 workers exposed at six farms only six were affected suggests that other factors than mere inhalation of hay dust must be involved. Age did not seem to play a part, as this ranged from 29 to 73 years. No females were included in the series, but the case of a female farm worker seen in a previous year is described later.

Clinical Features

Marked dyspnoea on exertion developing soon after contact with mouldy hay was the prominent feature in all cases. This was usually present for several weeks and was the main reason for referring the patients to the chest clinic. Slight cough with or without expectoration was usual. Occasionally there was loss of appetite with some loss of weight. Physical signs were often absent, but when present consisted of fine basal crepitations. The chest radiograph in all but one case showed fine mottling confined mainly to the middle and lower zones, corresponding with the appearances seen in the cases classified by Fuller as Phase 2. The exception was Case 8, in which no pulmonary changes were present (Phase 1), but the diagnosis was based on the similarity of the history to that of other cases in the area and the patient's response to treatment.

The main features of each case are summarized in Table I.

Progress and Treatment

Response to treatment had been poor in every case until the real nature of the condition was recognized and potassium iodide administered in large doses, when improvement followed. In fact this response to potassium iodide tended to confirm the diagnosis. Avoidance of further contact with hay dust was also insisted upon, and in most cases symptoms ceased within a month. X-ray changes, however, took at least three months to clear up. All patients were back at work within one to three months of their first attendance at the clinic. One patient (Case 4) appeared to go downhill so rapidly with dyspnoea, cyanosis, and loss of weight that his removal to hospital became necessary before improvement in his condition occurred. Antibiotics were not given except in one case (No. 6), which was complicated by a secondary bacillary infection of the respiratory tract. The patient was given a course of penicillin, which cleared a localized area of pneumonitis as shown by the radiograph.

Differential Diagnosis

In an outbreak such as that described here the typical history of severe dyspnoea following contact with mouldy hay or corn coupled with characteristic radiological appearances makes the diagnosis comparatively easy. Diagnosis may be much more difficult, however, in sporadic cases, as is illustrated by the following three cases seen in previous years.

(a) A farm worker aged 21 complained of retrosternal pain on walking which had been present for six weeks when he was seen

in March, 1952. He had been off work for two weeks on account of dyspnoea on exertion, and he had a cough at night. His general condition was poor, but there were no abnormal physical signs in the chest. Radiography showed fine miliary mottling in both lung fields. A diagnosis of miliary tuberculosis of the lungs was made and he was admitted to a sanatorium. Here he made a remarkable response to an intensive course of streptomycin, and he was discharged 14 months later with a clear radiograph. At no time were tubercle bacilli recovered from his sputum. Review of the original radiograph three years later shows that the mottling was confined mainly to the middle and lower zones, conforming to the picture seen in farmer's lung. It is concluded that the diagnosis of miliary tuberculosis was not proved and the condition was probably farmer's lung.

(b) A farmer's wife aged 51 was first seen in June, 1954, complaining of dyspnoea since an attack of influenza the previous Christmas. She had a productive cough. In the course of her work in the barns she came into contact with mouldy hay-dust. A radiograph showed fine mottling in the lung fields. A fungal infection was suspected, but a specimen of sputum was reported as showing acid-fast bacilli on microscopy, though a further specimen two days later was negative. She was given a total of 32 g. of streptomycin combined with P.A.S., but chemotherapy was discontinued when it became known that the positivity of the sputum had not been confirmed by culture. Her symptoms gradually subsided and the radiological appearances improved. The Mantoux reaction was negative. This case was also regarded as one of farmer's lung.

(c) A farmer aged 40 was first seen in March, 1951, complaining of a cough with expectoration and shortness of breath since threshing the previous autumn. A radiograph showed light shading in the mid-zone of both lungs. Sputum at that time was negative, but a further specimen obtained four months later was positive for acid-fast bacilli after concentration. This result was not, however, confirmed by culture, and radiography now showed

complete clearing of the lung fields. From the history and clinical course it was concluded that this too was a case of farmer's lung.

In the last two cases a tentative diagnosis of farmer's lung was made originally, but doubt arose when at the initial sputum examination the presence of acid-fast bacilli was reported. It is known that a number of saprophytic bacilli giving the same staining reaction as, and corresponding closely to, tubercle bacilli have a comparatively wide distribution in nature, being found in various species of grass, in butter, milk, manure, on animal surfaces, and in water. Examples are the timothy-grass bacillus (*Mycobacterium phlei*), butter bacilli (*M. butyricum* and *berolinensis*), and the "mist" (dung) bacillus (*M. stercoreis*).

It would appear that acid-fast rods or bacilli do occur and may be more common in the respiratory flora of farm workers than of others. Unless these facts are remembered and the results of sputum culture for tubercle bacilli awaited, an incorrect diagnosis may be made. In the meantime confirmation of the presence of saprophytes could be obtained by culture on artificial media, as growth is usually visible within 48 hours (Browning and Mackie, 1949).

Discussion

Fawcitt contended that the presence of fungi in the sputum indicated a true bronchomycosis, and this opinion was also held by Törnell, who grew monilia from the sputum of seven of his patients. Törnell did not, however, appear to realize the frequency with which this organism appears in the sputum as a saprophyte. The finding of fungi and yeasts in the sputum of some of our patients did not necessarily

TABLE I.—Main Features in Ten Cases of Farmer's Lung in Males

Case No.	Age (Years)	Date First Seen	Main Symptoms and Signs	Radiographic Appearances of Lungs	Progress	Mantoux Reaction	Sputum	Comments
1	33	3.1.55	Dyspnoea on exertion. Haemoptysis small. Slight cough. Retrosternal tightness for 6 weeks. No signs	Fine mottling of both lung fields more marked in mid and lower zones. Slight cardiac enlargement	4.4.55: No dyspnoea. No staining. Slight cough. Working—radiograph clear	Negative	Not examined	Phase 2. Recovered
2	43	21.3.55	Dyspnoea on exertion. Slight cough for 3 weeks. Bilateral basal crepitations	Fine mottling throughout lung fields—heavier towards lower zones	5.12.55: Breathing improved. Little cough. Appetite better. Radiograph clear	Negative	Culture T.B. negative. No fungi—a few yeasts only	Phase 2. Convalescence slow—symptoms now abating after radiological improvement
3	31	28.3.55	Dyspnoea on exertion. Productive cough for 3 weeks. Some weight loss. No signs	Fine mottling throughout lower two-thirds of both lungs	18.4.55: Little dyspnoea or cough. Considerable clearing of lung shadows in radiograph	Not tested	Not examined	Phase 2. Failed to return after second visit—probably recovered
4	40	4.4.55	Dyspnoea on exertion. Slight productive cough for 5 weeks. Bilateral moist sounds	Fine mottling throughout both lungs with exception of apices	20.6.55: Improved but dyspnoeic with exertion. Radiograph—incomplete clearing. N.A.D. Working	Negative	" "	Phase 2. Increasing dyspnoea requiring removal to hospital. Recovered. 12.12.55: radiograph clear
5	43	5.4.55	Dyspnoea on exertion, productive cough, loss of weight and appetite of 4 weeks' duration. Scattered rales and crepitations both bases	Fine mottling throughout middle and lower zones both lungs—heavier on right side	28.6.55: No dyspnoea. Radiograph clear. Working	Positive	Mixed growth of pneumococci and some fungi. T.B. negative—direct. Cultures contaminated	Phase 2. Recovered
6	69	18.4.55	Dyspnoea on exertion and dry cough for 3 months. Bilateral moist sounds	Mottling lower two-thirds both lungs, with denser shading in right mid-zone	5.9.55: Breathing improved. Some cough with sputum. Radiograph—considerable clearing	Negative	A few yeasts only. Negative Ziehl film	Phase 2. Recovered. 5.12.55: radiograph shows complete clearing
7	29	18.4.55	Dyspnoea on exertion. Productive cough for a few weeks. No signs	Fine mottling throughout both lung fields	16.5.55: No dyspnoea. Cough less. Radiograph—slight clearing	Not tested	Not examined	Phase 2. Improved. Failed to return
8	66	16.5.55	Dyspnoea on exertion. Slight productive cough for 3 months. No abnormal physical signs	Flattening of left dome of diaphragm. No definite lesion in lung fields	13.6.55: No dyspnoea, no cough. Radiograph—no change. Working	Negative	Light growth of fungi and yeasts. T.B. cultures contaminated	Phase 1. Recovered. Diagnosed on clinical grounds only. 12.12.55: remains well
9	73	6.5.55	Dyspnoea on exertion with cough for 3 months. Bilateral basal crepitations	Fine mottling in mid and lower zones. Localized area of emphysema left lower zone	13.9.55: Improved. Slight tightness of chest only. Radiograph clear. Working	Not tested	No fungi. Culture for T.B. negative	Phase 2. Improved. Residual dyspnoea probably due to long-standing emphysema
10	51	17.6.55	Dyspnoea on exertion and dry cough for 4–6 weeks. Similar attack two years previously	Fine mottling throughout mid and lower zones of both lungs	9.12.55: Radiograph—no change. Relapse after initial improvement. Not working	Positive	Moderate growth of fungi	Phase 2. Recurrent

TABLE II.—Results of Examination of Sputum and of Hay Samples for Fungi

Case No.	Sputum	Hay Samples
2	No fungi—a few yeasts only	Mixed assortment— <i>Aspergillus</i> , <i>Penicillium</i> , <i>Mucor</i> , <i>Absidia</i> , <i>Cladosporium</i> . Fewer fungi and more bacteria
6	A few yeasts only	Mixed assortment— <i>Aspergillus</i> , <i>Penicillium</i> , <i>Mucor</i> , <i>Absidia</i> , <i>Cladosporium</i>
8	Light growth of fungi and yeasts	Mixed assortment— <i>Aspergillus</i> , <i>Penicillium</i> , <i>Mucor</i> , <i>Absidia</i> , <i>Cladosporium</i>
9	No fungi	Mixed assortment— <i>Aspergillus</i> , <i>Penicillium</i> , <i>Mucor</i> , <i>Absidia</i> , <i>Cladosporium</i> . Relatively large number of <i>Aspergillus fumigatus</i> colonies

confirm the presence of an infecting agent (Table II). In other cases no fungi and only a few yeasts were found. Specimens of the offending hay were examined for fungi in four cases, but no fungus predominated and all samples showed the usual wide assortment of moulds. The specimen of hay in Case 9 differed from the others in that relatively large numbers of colonies of *Aspergillus fumigatus* were present, only one colony of this species being recognized in the other three specimens. The patient in Case 9 did not show any deviation from the usual clinical picture and x-ray appearances, neither were any fungi found in his sputum. The hay specimen in Case 2, however, differed in that many more bacteria developed on the culture plates and fewer fungi were present. The patient in this case had a slower convalescence, and it may be that the course of his disease was modified by secondary or concomitant bacterial infection. In this case no fungi were found in the sputum.

There appeared to be no relationship between the fungi found in the sputum and those grown from the corresponding specimen of hay in the cases examined. Although the cases fulfilled Fawcitt's criteria for the diagnosis of bronchomycosis, and although they had the same occupational history, the same mode of infection and of onset, the same clinical findings, with dyspnoea out of all proportion to other symptoms, similar radiological appearances, and a tendency to recover after administration of large doses of potassium iodide, there was no evidence that the same infecting agent was responsible in each case or that there was any growth of the organism within the bronchial tree. Therefore, in our opinion, the condition was not a true bronchomycosis.

Intradermal tests for allergic reactions were not performed owing to the difficulties in making arrangements in a widely scattered hilly area. In any case, Fuller's experience of the intradermal injection of extracts of both good and mouldy hay did not prove that sensitization was due to anything more than the presence of a histamine-like substance in hay.

It is our impression that in the development of farmer's lung there is such a high concentration of hay dust, consisting largely of mould spores, in the lower respiratory tract that the terminal bronchioles become literally choked. In addition to this purely mechanical interference with normal respiratory function it is probable that there is also a mild inflammatory response by the bronchial epithelium. Mere mechanical action and multiple minute traumata to the bronchial epithelium cannot, however, be the only factors involved, as several patients declared they had never had anything wrong with their chests before and were well accustomed to working in normal dust from good hay. Furthermore, relatives and others working under the same conditions were unaffected by the mouldy hay. The presence of fungi in the dust is undoubtedly the chief factor, but in the absence of histological proof their mode of action is uncertain. There is no evidence to explain why only certain persons are susceptible and others are not. Any tissue changes which may occur are usually of a temporary nature and clear up quickly once the invader is removed. The effect of potassium iodide may be twofold: (1) by a specific action as in actinomycosis; and (2) by increasing the flow of bronchial secretion due to stimulation of the epithelial cells it enables the dust particles and spores to be washed out of the bronchioles.

It is concluded that exposure to the dust arising from mouldy hay or corn is responsible for the development in susceptible persons of a distressing respiratory condition known as farmer's lung. In our experience hill farmers as a class are usually very reluctant to seek medical advice, either because of the inaccessibility of their farms or owing to pressure of work; therefore it is reasonable to suppose that many cases, especially when of mild degree, are not recorded at all. Failure to see and recognize the condition and to take the necessary precautions to avoid repeated attacks may lead to irreversible changes in the lungs and permanent incapacity.

Summary

Brief reference is made to the literature of the condition known as farmer's lung. A further ten cases are reported which occurred in epidemic form in 1955 in a hilly district of mid-Wales. Three sporadic cases seen earlier in which the diagnosis of farmer's lung was not readily apparent are also described. Evidence is presented in support of the view that the condition is not a true bronchomycosis.

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EXPERIENCE WITH ABO AND Rh BLOOD-GROUPING CARDS (ELDON CARDS)

BY

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After some years' experimental and practical work with cards for simultaneous ABO and rhesus determinations (Eldon, 1955; Jordal, 1955), these cards were put into large-scale industrial production by Nordisk Insulinlaboratorium. The technical process ensured uniformity of all the cards of each series, each card being packed in a moisture-proof envelope.

In February, 1955, the cards were released for use in hospitals and by practitioners, and in the ensuing year 64,000 cards were distributed in Denmark, of which at least 60,000 are estimated to have been employed up to the present.

The Card and Method of Use

The card has four panels covered with regenerated cellulose ("cellophane"). In each panel 0.06 ml. (1 minim) of reagent is allowed to dry (100 ml. of reagent is composed of 10 ml. of serum, 90 ml. of 6% dextran, and two drops of 5% heparin solution). Anti-A and anti-B for ABO grouping and anti-D (anti-Rh₀) for Rh grouping are found in that order in the panels (see Fig.). The serum in the control panel does not contain antibodies.

Moulded plastic sticks fashioned with a flat terminal surface for measuring capillary blood are delivered with the cards, together with a controlled dropper pipette.