Walker, as a medical officer in an L.C.C. hospital, made two important contributions to the knowledge and treatment of myasthenia gravis. In 1934 she discovered the beneficial effects of Prostigmin on the symptoms of myasthenia and so established the first effective treatment of the disease (and the one which is still in use.) Four years later[2] she showed that the paralysis in myasthenia gravis was not due, as had been thought, to deficiency of a chemical transmitter at the neuromuscular junction but must be due to a positive toxic substance produced in the course of muscular activity, and it is this discovery that she describes here. As an appendix she adds the description of an experiment, the outcome of which was that the injection of the serum from 10 ml of "myasthenie" blood into a rabbit did not cause any apparent symptoms.

The design of the main experiment should be noticed, because the effect which Dr. Walker wished to observe required that the patient's condition should be capable either of aggravation or of improvement, and so would not have been seen if the patient had already been at her worst or at her best.

Dr. Walker twice uses the term "curarizing substance." At the time of which she is writing curare was a topical subject because Dr. Ranyard West had applied this dangerous alkaloid to the treatment of severe cases of tetanus and many people had seen its clinical effects, but it was Mary Walker who had the intelligence to look up the antidote to curare and try its effect on the similar symptoms occurring in disease.

For her first observation (1934) Dr. Walker gained her M.D. at Edinburgh and was awarded a gold medal. More recently (1963) she was the first recipient of the Jean Hunter prize awarded by the Royal College of Physicians for work on nervous exhaustion.

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Appendix: The Experiment

The experiment was performed on one of the two patients to show the effect of myasthenia serum on a rabbit on 12 May 1938 at the request of E. C. Hoff, who was present.

10.15 a.m. Patient lying "flat" (last Prostigmin given at 1 p.m. on 11 May). Ptosis, unable to sit up, and unable to move arms more than a little. Mask-like facies. Right arm occluded with blood-pressure cuff inflated to 140 mm Hg (systolic pressure about 140 mm Hg).
10.21 a.m. Blood-pressure cuff 190 mm Hg. Patient making weak movements of fingers and hands.
10.22 a.m. Blood sample (10 ml) taken from right basilic vein (cuff at 190 mm Hg).
10.23 a.m. Cuff deflated (pulse 90/min).
10.24 a.m. Ptosis, left arm feels heavier than before the experiment.
10.31 a.m. Prostigmin 7·5 mg + 1/100 grain (0·65 mg) atropine subcutaneously.
10.35 a.m. Still lying as before (pulse 66/min).
10.37 a.m. Made some small movements.
10.38 a.m. Slight movements of head, slight elevation, slight twitching in neck.
10.40 a.m. Moves mouth, fingers clench and unclench, moves hands, supinates arm, speaks, voice stronger.
10.41 a.m. Eyelids open. Patient sits up, talks, feels fairly strong.
10.42 a.m. Patient gets out of bed, walks up and down the ward quite steadily.

The rabbit was unaffected by the myasthenic serum. The timing of the effects on the patient is interesting. She recovered her strength 11 minutes after the injection of 7 mg of Prostigmin.

A New Look at Infectious Diseases

Q Fever

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Q. fever is an infectious disease caused by an organism which, because of its size and cultural characteristics, is intermediate between the bacteria and viruses. Though it resembles the rickettsia organisms—which are responsible for diseases such as epidemic typhus fever, tick typhus, and Rocky Mountain spotted fever—because it is resistant to both drying and many chemical agents which destroy most rickettsiae it has been put into the special classification of *Coxiella*.

The disease was first described in 1937,[1] when it was observed in abattoir workers in Queensland, in Australia. It appeared to be a new disease of yet unexplained origin and so it derived the name "Q"—standing for "query fever." In 1939 Burnet and Freeman[2] showed that the infection was due to a rickettsia-like organism and for this reason it was first named *Rickettsia burneti*, changed subsequently to *Coxiella burneti*.

During the second world war Q fever caused widespread sickness among members of the allied Forces in Italy and the Balkans. Since then the disease has been shown to be world wide in its distribution. In Great Britain it is associated mainly with rural rather than urban communities and in particular it is prevalent where sheep farming and dairy farming are carried on. The organism infects both sheep and cattle but does not appear to cause any clinical disease in these animals, though they do act as carriers of the disease. The organism is excreted in the milk as well as in the urine and faeces of infected animals and is also present in the placenta and uterine discharges at parturition. Characteristically it is very resistant to drying so that the dust in sheep pens and cattle sheds becomes heavily contaminated. Inhalation of infected dust is thought to be the main method of spread of the infection within the flocks and herds, and, of

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course, movement of infected animals from one part of the country to the other is responsible for the widespread distribution of infection on our farms. In Australia the infection was shown to be spread among cattle by ticks, and in Britain probably some infection may spread by this means.

Epidemiology in Man

Infection in man is seen mainly in farming communities, but not exclusively so. Infection spreads from cattle and sheep to man mainly by inhalation of infected dust. Among sheep farmers the incidence is higher in the spring, in association with the lambing season; but among dairy farm workers there is not the same seasonal incidence, as calving takes place all the year round. In one outbreak among Royal Air Force personnel[3] the men affected had helped to clean out sheds into which sheep had strayed and where lambing had probably taken place. The infection was presumed to have been acquired from the inhalation of the infected dust.

Another example of spread by inhalation of dust in a cow shed was seen in Staffordshire, where a self-employed builder was engaged in reconstructing an old byre. He had had no contact with the animals but had inhaled a lot of dust as he ripped out the old woodwork, and about two weeks later developed a typical attack of Q fever. Infection may also occur in an urban setting, as is illustrated by a group of students at Canterbury Art School[4] who became infected from the dust from straw in a packing case.

In infected cows *C. burneti* is present in high concentration in the udder and may be excreted in the milk over a prolonged period. Evans[5] recorded that about 5% of milk samples from individual herds in South Wales were infected with the organism and Hooper[6] found 18% of herds affected in Staffordshire.

Numerous instances have been reported from various parts of Britain of isolated cases of Q fever where the infection had been acquired from drinking unpasteurized milk. One striking example of a group of people being infected in this way was reported from North Staffordshire in 1968.[6] The outbreak occurred in one of H.M. detention centres, where there were 100 detainees and 20 members of staff at risk. The centre had its own dairy farm, from which the milk was sent for pasteurization before being marketed by a local retailer. The milk required for the centre itself, however, was sent to the kitchen direct from the farm. Nineteen detainees and five prison officers were affected. Twenty cows were kept on the farm and all were apparently healthy but on investigation two of these cows were actively excreting *C. burneti* in their milk. Workers in abattoirs are also at risk by handling infected pelts or infected carcases. Ticks on infected animals may themselves become infected and their faeces contain the organism. Spread may therefore occur to slaughtermen from this source.

UNUSUAL SPREAD

Spread of infection from man to man has occasionally been reported, usually associated with hospitals. Holland[3] recorded an outbreak which occurred in a Royal Air Force sick bay. The original patient acquired his infection on a farm in Cornwall. On return to his unit he was admitted to the sick bay with a febrile illness, which was subsequently shown to be Q fever. He infected four attendants and one other airman who visited him in the sick bay. Spread of infection was presumably by droplet spray.

In a hospital in London a patient died of Q fever. One of the nurses who attended him acquired the infection and at necropsy both the pathologist and the mortuary attendant who had been present subsequently became victims of the disease. Infections may also occur among laboratory staff because of the high degree of resistance of the organism. The handling of egg cultures and laboratory animals inoculated with *C. burneti* is dangerous and therefore for routine diagnosis evidence of a rising antibody titre is recommended rather than any attempt to culture the organism.

INCIDENCE

The true incidence of this disease remains unknown, but some idea may be gathered from the results of an investigation carried out by the Public Health Laboratory Service in North-West England and North Wales.[7] Of veterinarians tested 17 (28%) had antibodies in the blood; 29 (33%) abattoir workers and 24 (13%) members of farm families were likewise positive. Among members of an urban population the incidence is, however, much lower: 161 sera from patients attending antenatal clinics in Liverpool were examined and only three (1·9%) were positive for antibodies. No doubt many of these resulted from subclinical infection, but many cases of Q fever remain undetected and are diagnosed on clinical grounds as "influenza."

Clinical Manifestations

The onset of illness is sudden, with a temperature ranging from 101-105°F (38·3-40·6°C) together with shivering, sweating, and backache. In addition, the patients frequently complain of general muscular pains, headaches, and sore throat. On examination the throat is red and inflamed but tonsillar exudate is not a feature. Headache and neck stiffness are sometimes sufficiently obvious to call for a lumbar puncture to be carried out but the cerebrospinal fluid is invariably normal. Pain in the back and loins suggest some renal disease but apart from a little protein, associated with the considerable pyrexia, the urine is otherwise normal. Profuse sweating is a fairly constant feature and injection of the conjunctivae is also common.

Most patients develop a troublesome unproductive cough in the early pyrexial phase of the disease but on clinical examination of the chest it is unusual to detect any dullness or crepitations. If routine *x*-ray examination of the chest is carried out, however, several of these patients will show soft shadows in the lung fields. Sometimes this shadow is single but more often it is multiple and located mainly in the lower lobes. Slight mucoid sputum, which is occasionally blood-stained, may be produced.

Fine crepitations may be detected in the lungs later in the illness and follow-up chest *x*-ray films show that the areas of consolidation sometimes take several weeks to resolve. Nevertheless, the patient is usually afebrile by the end of the first week, and by the end of the second or third week has apparently recovered completely.

It is generally believed that one of the features which distinguishes *C. burneti* infections from the rickettsial diseases is the absence of a rash but cases of Q fever have been reported in which mild erythema has been present in the early stages.

In view of what is known about spread of infection from person to person by droplet spray these cases should be isolated from the rest of the community, and attendants should use face masks when the patient has a troublesome cough with sputum.

Treatment

Symptomatic treatment with aspirin or paracetamol is usually indicated. Because of the heavy sweating in the early stages frequent changes of night clothes may be necessary. Tetra-

cycline has been shown to be effective against the coxiella in vitro but there appears to be little difference in the rate of recovery of the average patient whether or not he is treated with tetracycline. In recent years it has been recognized that the disease may persist in a chronic form and for this reason I would advocate treating all acute cases with an antibiotic. Any relapse or persistance of fever should likewise be treated. If a chronic infection fails to respond to treatment it may be found that the infection has settled on the heart valves and given rise to endocarditis. The latter nearly always occurs on valves that have been previously damaged and the infection is very persistant despite antibiotic therapy. Excision of the damaged valve and replacement by an artificial valve is sometimes the only way of halting progressive deterioration in the patient's condition. The aortic valve is the one most commonly affected and the signs of endocarditis are frequently not manifest until months or even years after the original acute infection.

Clearly there are no distinctive clinical feature in the acute phase of the disease that differentiates it from such infections as influenza and brucellosis. The knowledge that the patient comes from a farming community may be helpful; consumption of unpasteurized milk may suggest Q fever or brucellosis as a likely cause of the illness, but a firm diagnosis can be made only by the help of the laboratory. A four-fold, or greater, rise in titre of complement-fixing antibody is convincing evidence on which to base a diagnosis. Attempts to culture the organism on the yolk sac of developing eggs or by guinea pig innoculation are hazardous for laboratory personnel and are seldom justified except in specially equipped research departments.

The sporadic case is always difficult to diagnose unless there is some background history which points to a likely source of infection. In an urban community where practically all the milk supply is either pasteurized or sterilized the practitioner may not consider Q fever as a likely cause of an acute febrile illness. But it should be remembered that in the summer many families spend their holidays at a farm or park their caravans in the farmer's field and one of the so-called pleasures of such a holiday is getting the milk supply "straight from the cow."

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Any Questions?

Endometrial Tuberculosis

In what circumstances should specimens of endometrium be examined for tuberculosis?

This was recently discussed at a meeting of microbiologists experienced in these matters where opinion was that examination for tuberculosis is now likely to be rewarding only in selected cases. The indications are: a history of tuberculosis or strong evidence of past or present infection; a history of pneumonia complicated by pleural effusion or delayed resolution; a moderate or strong tuberculin reaction (Heaf grade 3 or more, 8 mm induration after a 1 TU Mantoux test or 12 mm after 10 TU). Biopsy specimens are likely to be inadequate and curettings or aspirates should be provided. In the absence of any of the indications above the examination of specimens from patients who have received B.C.G. would appear to be hardly justified.

The opinion has been expressed[1] that improvement in cultural methods now permits these to be used in place of animal inoculation.

[1] Marks, J., *Tubercle*, 1972, **53**, 31.

Mixing Mandrax and Alcohol

In an incident recently in a coastal resort several young people were involved in an affray, and were described as being "berserk." It was alleged that some of them had been taking Mandrax tablets and alcohol. Does this combination commonly result in uncontrollable behaviour?

Each tablet of Mandrax contains 250 mg methaqualone hydrochloride and 25 mg diphenhydramine hydrochloride. When Mandrax and alcohol are taken together, the pharmacological event is complex but the leading effect will be that the action of alcohol is potentiated. The individual will get drunk quickly and cheaply. Whether that person then behaves as a sleepy drunk or alternatively creates mayhem will depend on his personality and the expectations given him by his friends and the occasion. A belief that Mandrax and alcohol lead to wild acting-out could be at least as important as the pharmacology in shaping the consequences of intoxication. When the interreacting elements are Mandrax and alcohol, a sub-cultural belief that Mandrax leads to high spirited aggression, the frustrated exuberance of an adolescent gang who want something (almost anything) to happen, the ring of spectators waiting for that something to happen—when these are the elements the recipe is all there for "a bit of aggro" and Mandrax is really only a small part of the total mix.

How those tablets come to be in the hands of adolescents is of course a rather disturbing question. The source may partly be a black market fed by pilfering from warehouses or chemists' shops, but that careless prescribing also makes its contribution is not to be doubted. Any belief that methaqualone is a "safe" substance which can be prescribed with lesser care than a barbiturate is misguided. Mandrax has been abused by young people in this country for at least the last six years;[1] it is frequently used as an adjunct to heroin taking;[2] overdosage can set serious problems;[3] its ability to induce dependence is not to be doubted, and a withdrawal state has been reported which is akin to delirium tremens.[4]

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