increases. Conversely, continuous drug therapy prevents relapse in bronchitis, and the longer the duration of therapy the more effective the preventive measure against relapse appears to be. It would seem that relapse in chronic bronchitis during the summer and autumn months is considerably reduced, if not entirely prevented, by continuous antibiotic therapy. Without such continued treatment about half of the bronchitics during a six-monthly review period may be expected to relapse, and this seems to occur irrespective of whether antibiotics were used continuously in the previous season or not. Once a severe exacerbation occurs, many bronchitics are often appreciably disabled for a long period unless the relapse is intensively treated with antibiotics. These appear to be adequately suppressive in controlling the effects of bronchial infection.

The suppressive action of oxytetracycline is apparently effective only during the period of its administration, and does not seem to prevent or even delay the appearance of relapse following its withdrawal. The relapse rates during six winter months from November to April in patients treated without antibiotics are but little different from those occurring in the months from April to November. However, 80% of all relapses observed in the four treatment groups appeared between September and February. This may well be related to the climatic and atmospheric changes associated with the onset of autumn, particularly in highly industrialized communities.

It would thus seem reasonable to initiate a six-months course of continuous broad-spectrum antibiotic therapy when the first significant relapse occurs. Since most of these relapses occur in the autumn and winter, such a course of treatment may well overcome the relapse itself and also prevent further deterioration during the winter months, when most bronchitics are mainly at risk. Also it may be anticipated that no further continuous antibiotic therapy may be required for about six months after completing this course of treatment. It would therefore seem that only one period of continuous prolonged treatment with oxytetracycline in a dosage of 0.5–1 g. daily for about six months—the actual duration depending on the time of starting the treatment—may be required to prevent incapacitating exacerbations and maintain many bronchitics in effective and useful employment throughout the whole year.

Comment has already been made concerning the expense of prolonged therapy with the tetracycline group of drugs for a period of six months. If a course of antibiotic treatment is started at the time of the first major relapse and continued for six to seven months, as may be required, the total cost to the National Health Service would be about £45–£55, and would be occasioned but once in each year. The arguments already adduced for suggesting that such a course of treatment with a seemingly expensive drug may in fact be an economy when other aspects of national expenditure—such as National Insurance benefit, the cost of a hospital bed, etc.—are considered, now have added significance.

No untoward difficulties or complications occurred in those patients on prolonged antibiotics; toxicity was minimal, significant drug resistance was not observed, and the development of bronchial or intestinal oxytetracycline-resistant coagulase-positive staphylococci and of monilia did not materially differ in any of the treated or control groups.

Summary

The results of an 18-months follow-up of 42 patients with chronic bronchitis, when treated with or without oxytetracycline for periods of varying duration, are presented.

Continuous and prolonged antibiotic therapy for one year or more not only prevents relapse in chronic bronchitis but increases the rate of improvement the longer the therapy is maintained.

Acute exacerbations of chronic bronchitis assume major proportions during the autumn and winter, particularly between September and February, when 80% of relapses tend to occur.

It is suggested that continuous therapy with oxytetracycline for one period of about six months in each year, to include the period of maximum relapse, may prevent exacerbations and maintain most bronchitics in effective and useful employment.

We acknowledge with thanks the considerable clinical assistance in the management and review of these patients we have received from Dr. A. R. Buckley, late senior registrar to the Leeds Chest Clinic. We are also grateful to Dr. G. B. Ludlam, of the Public Health Laboratory Service, and to Dr. H. T. Levi, of St. James's Hospital, Leeds, for the routine laboratory investigations they carried out. We are indebted to Messrs. May and Baker, Ltd., and Messrs. Pfizer, Ltd., for the generous supplies of "sulphatriad" and "terramycin SF" respectively, and the appropriate dummy controls. Part of the expenses involved in this work were defrayed by a grant from a Joint Research Fund administered by the British Tuberculosis Association in conjunction with the Association of Industrial Medical Officers.

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CARBON DIOXIDE POISONING

REPORT OF EIGHT CASES, WITH TWO DEATHS

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Although rarely reported, carbon dioxide poisoning is probably not so infrequent an occurrence. McNally (1937) states that it is one of the most commonly occurring of all gases, and is often the cause of death of persons entering caves, wells, and other low-lying or confined spaces. Smith and Cook (1948), on the other hand, state that death from carbon dioxide poisoning is very rare, and that cases so reported are nearly always due to other gases, such as carbon disulphide.

Deaths due to carbon dioxide poisoning are included in the rubric E894 of the *International Classification of Diseases, Injuries, and Causes of Death*, "Accidental Poisoning by Other Specified Gases and Vapours," and in 1955 17 males and one female died from this cause in England and Wales. These figures include deaths due to gases other than carbon dioxide, and it is not known how many of them were caused by carbon dioxide poisoning.

The following cases are reported to illustrate the occurrence of carbon dioxide poisoning as a hazard in the handling of ships' cargoes.

Early in March, 1956, a liner arrived at Penang with a cargo of onions. The particular hold had been loaded six days previously, and contained 5,000 bags of onions and a quantity of "jaggery" (a crude brown sugar obtained from the sap of palm trees). It was full to within 9 ft. (2.7 m.) of the deck. At about 1 p.m. the ship was boarded by labourers, who removed the hatch covers and opened the hatch. One entered the hold and collapsed as he was standing on the onions. Another went in to help him and also collapsed. Then the ship's doctor was sent for; he went

into the hold, followed by one of the ship's officers, and assisted him to lift the unconscious man who had first entered the hold. As he was doing so the doctor collapsed, and the ship's officer carried the man out. One of the ship's crew then went into the hold to assist, but he collapsed. Another ship's officer then entered with breathing apparatus, and brought out the doctor and the other unconscious men. The four men who had collapsed were then taken to hospital, where it was found that two of them were dead.

Four other labourers who had also entered the hold for short periods developed minor symptoms and were taken to hospital.

Estimates of the length of time that the men were lying in the hold varied considerably, but it seems that the doctor was lying there unconscious for about five minutes, and the others for variable periods up to about 15 minutes.

The first patient was admitted to hospital about an hour and a quarter after he had gone into the hold. On admission he was deeply comatose and having continuous convulsions. Breathing was stertorous, the pupils were non-reactive, the conjunctivae were injected, but there was no cyanosis. The pulse rate was 156 a minute, and the blood pressure 160/100 mm. Hg. He was immediately given continuous oxygen, and an injection of nikethamide was administered and, after about an hour, paraldehyde by injection to control the convulsions.

Spasms passed off after two hours, and the patient recovered consciousness about seven hours after admission. He was able to get up two days later, but complained of giddiness, which passed off after three days. He was discharged eight days after admission. Spectroscopic examination of his blood the day after admission showed no abnormal pigment.

The doctor was admitted about one and a half hours after he entered the hold. He was conscious on admission, but gave a history of loss of consciousness for about half an hour. He complained of headache and aching in the joints. The pulse rate was 100 and the blood pressure 114/80 mm. Hg. The conjunctivae were injected, but there was no cyanosis. He recovered rapidly and was discharged four days later.

The remaining four patients were admitted later in the day. They all stated that when they entered the hold they became giddy, and three of them complained also of pains in the legs and of pain and dryness of the throat. Only one showed any injection of the conjunctivae, and none showed cyanosis. They were all discharged after one or two days.

Post-mortem Examinations.—The bodies of the two men who died were brought to the mortuary and kept in the cold overnight. At the urgent request of the relatives, only an external examination was performed. Neither body had any sign of injury, but both showed marked injection of the conjunctivae, and cyanosis of the finger- and toe-nail beds and of the buccal mucosa. Death was certified as being due to carbon dioxide poisoning.

Analysis

An analysis of the gases present in the hold was carried out by the senior chemist about an hour and a half after the hold had been opened. He obtained an appreciable reaction for carbon dioxide in the hold, particularly beneath the deck; and on examining other holds in the ship, as yet unopened, he obtained a strong reaction. No other poisonous gases were detected. For three months following this accident, the department of chemistry carried out inspection on all ships carrying onions for unloading at Penang. Nineteen ships were inspected, and carbon dioxide was found in significant amounts in one instance, in which it appeared that the onions had come from the same source as those held responsible for the incident.

Later, experiments were carried out, using onions from the ship, and it was found that the atmosphere in a sealed flask containing $\frac{1}{3}$ v/v of onions contained over 30% carbon dioxide after five days. It was not possible to give an accurate estimate of the quantity of carbon dioxide present in the hold, as a good deal had been dispersed by the time tests were made.

Discussion

The toxic action of carbon dioxide is twofold. By dilution of the air it reduces the oxygen tension, thus acting as a simple asphyxiant, and it also has a chemical action as a respiratory stimulant and narcotic. There is, however, a great deal of difference of opinion over what concentration of carbon dioxide will be fatal. Jacobs (1941) states that 25% of carbon dioxide is required for several hours to produce death, and cites an incident in Brooklyn in 1936 when several workers were asphyxiated in the hold of a ship in which solid carbon dioxide was used as a refrigerant. Owen (1935) gives a concentration of 10% as sufficient, or even 5% if the oxygen tension is lowered, but makes no mention of the time of exposure before death occurs. He describes an incident in which 13 men were poisoned in the hold of a ship which contained bags of grain of various sorts. Elkins (1950) mentions 10% as an intolerable concentration, and states that at higher levels coma and death result. He suggests that carbon dioxide acts primarily as a narcotic at very high concentrations. Peterson *et al.* (1923) give figures similar to those of Elkins.

Anselmo *et al.* (1951) describe an incident in which five persons were overcome with carbon dioxide in a well 4.75 metres deep. Two died, but in these cases carbon dioxide was not the immediate or the only cause of death. Analysis of the air in the well later showed a concentration of 12.5% carbon dioxide and 10.5% oxygen at a level of 1 metre above the surface of the water. In this case it is clear that the decreased oxygen tension would have some effect.

Although it was not possible to give any figure of the concentration of the carbon dioxide present in the hold in the incident described, it seems likely, from the rapidity of onset of unconsciousness and the speed with which death followed in the two cases, that the concentration of carbon dioxide must have been in the region of 25–30%, and this figure is supported by the subsequent experiments. Indeed, it is possible that at the lower levels, only a foot or so above the cargo, the concentration may have been somewhat higher, owing to the density of carbon dioxide in relation to the atmosphere. Elkins (1950) states that in order to reduce the oxygen tension to a fatal degree the vapour content must be about 50%. It is possible that the concentration of carbon dioxide at lower levels may have been of this order.

The symptoms displayed by these men accord well with descriptions given elsewhere. Owens describes symptoms of headache, giddiness, tinnitus, and loss of muscular power. He suggests that carbon dioxide has primarily a narcotic action, and mentions convulsions as being sometimes present. The symptoms described by Smith and Cook (1948) are similar; and the cases described by Anselmo *et al.* (1951) also gave symptoms of mental excitement and later giddiness, weakness, and headache.

The doctor subsequently described his experiences, and said that when he entered the hold he was aware that the atmosphere seemed to make breathing difficult, and that there was a fairly pungent smell. He had no pain or any warning signs, but became unconscious very rapidly.

Summary

An incident is described in which eight persons were poisoned by carbon dioxide. The mode of action of carbon dioxide as a poison, its rate of action, and the symptoms are discussed.

My thanks are due to Dr. R. A. Pallister, senior physician, General Hospital, Penang, for clinical details of the patients; to Mr. S. A. Baron, senior chemist, Penang, for details of the

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TRIAL OF DEQUALINIUM FOR SKIN INFECTIONS

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Despite the many preparations now available for the treatment of infective skin conditions, none are universally acceptable. The older agents, particularly the heavy metals, will occasionally irritate or cause sensitization, and the dyes—though effective and still widely used—are cosmetically unattractive. Sulphonamides and penicillin, used locally on the skin, are particularly apt to sensitize, and on this account are avoided by dermatologists.

Although the modern polyvalent or " wide-spectrum " antibiotics are very efficient and rarely irritant, their dangerous influence on the adaptable staphylococcus raises new problems. The skin infections may be improved at the price of increasing the cadre of existing staphylococci and of subjecting the patient to a subsequent, and more serious, attack by the resistant strain thus created.

Antibiotics that are not generally used parenterally—such as neomycin, framycetin, tyrothricin—have been preferred for local applications. Even so, resistant strains are already developing to some of these and may well become more prevalent. This potential danger of outrunning the future supply of antibiotics suitable for skin treatment, and to which the staphylococcus remains sensitive, justifies the search for suitable alternatives. There are sufficient grounds, therefore, for assessing any new synthetic bacteriostatic agent which seems likely to fulfil the necessary criteria. Many such synthetic chemicals are widely used by surgeons for the sterilization of wounds, burns, grafts, and other abraded surfaces, but in these instances the problem of epidermal sensitivity is not of great importance and they are not all suitable for use on the skin itself.

The qualities required of such a preparation are: (1) freedom from irritant action, (2) a low rate of sensitization, (3) a wide range of bactericidal or bacteriostatic activity, (4) ease of application and cosmetic acceptability, and (5) cheapness. Monilicidal or fungicidal activity would be an additional advantage.

We have recently carried out a preliminary clinical investigation of a new preparation claimed to have a wide spectrum of activity against pyococcal organisms, *Candida albicans*, and some fungi. This substance, dequalinium (decamethylene bis-(4-aminoquinaldinium) chloride), is marketed by Allen and Hanburys Ltd. as " dequadin."

The wide antibacterial activity of dequalinium *in vitro* was reported by Babbs *et al.* (1956), who found that it inhibited the growth of all of 21 species of pathogenic bacteria tested, including Gram-positive, Gram-negative, penicillin-resistant, and acid-fast bacteria; and some fungi. In a concentration of 100 μg. per ml. at 20° C. it destroyed within one hour 99.99% of organisms in a suspension of *Staphylococcus aureus*. Its activity was not inhibited by serum.

The local antiseptic action was demonstrated by injecting dequalinium solutions intraperitoneally into mice half an hour after lethal doses of bacterial suspensions had been injected into the same site. When streptococci were used, a dose of 0.9 mg. of dequalinium per kg. of body weight protected all mice from death, and when staphylococci were used 4 mg. per kg. was fully effective.

Clinical reports of the use of dequalinium for its local antibacterial action have been published by Trotter (1956) and by Fowler and Jones (1957). The former used dequalinium chloride in gelatin sponge as a bacteriostatic and haemostatic dressing after dental extractions in over 900 patients, and found it effective in counteracting and preventing sepsis and promoting healing. Fowler and Jones used a powder containing dequalinium chloride 0.1% as a wound dressing in veterinary practice. The powder was applied topically to accidental and surgical wounds in over 100 animals and was effective in controlling infections due to the common bacterial contaminants occurring in infected wounds in animals.

Clinical Investigations

We have used dequalinium on 241 patients suffering from various skin conditions. Of these, seven defaulted, and 254 clinical trials were completed on the remaining 234, 20 of whom suffered from two separate conditions or took part in two separate trials. The preparations used were dequalinium cream, containing 0.4% dequalinium chloride, and dequalinium paint (propylene glycol base) containing 0.5% dequalinium chloride. Dequalinium lozenges were used in a few cases.

In order to satisfy ourselves of the absence of toxic or irritant effects on the human skin, we first used these preparations on 12 patients with acute or extensive epidermal damage—eczematous, bullous, and ecthymatous. No adverse effects were encountered after a minimum of two weeks' treatment, and it was therefore considered justifiable to continue with a full trial. The trial was conducted in three parts.

Range of Activity

First, we applied dequalinium to a wide variety of skin diseases in order to determine its range of activity. The results are shown in Table I.

124 trials were carried out, the preparation being used for a period of two weeks in most cases and from four to six weeks in paronychiae and *Trichophyton rubrum* infections. Cure, or considerable improvement, resulted in 43