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Antibiotic Therapy of Staphylococcal Infections

GORDON H. HAWKS, M.D.,* *Toronto*

ABSTRACT

The antibiotic treatment of staphylococcal infections remains a problem. Isolation of the organism and sensitivity testing are necessary in the choice of antibiotic. Penicillin G is the most effective penicillin against non-penicillinase-producing staphylococci; for the penicillinase producers there is very little to choose between the semisynthetic penicillins, methicillin, cloxacillin, nafcillin and oxacillin. For patients who are hypersensitive to penicillin, the bacteriostatic drugs (erythromycin, novobiocin, tetracycline, chloramphenicol, oleandomycin) are useful for mild infections, while for more severe illness the bactericidal drugs (vancomycin, ristocetin, kanamycin, bacitracin, neomycin) have been used successfully. Acute staphylococcal enterocolitis is probably best treated by a semisynthetic penicillin. Other antibiotics which have been found useful, with clinical trials, for staphylococcal infections are cephalosporin, fucidin, cephaloridine and lincomycin. The latter drug has been reported of value in the treatment of osteomyelitis. There is little justification for the prophylactic use of antibiotics to prevent staphylococcal infection. Surgical drainage is still an important adjunct in the treatment of many staphylococcal infections.

SOMMAIRE

L'antibiothérapie des infections staphylococciques demeure un problème. L'isolement du microbe et l'épreuve de sensibilité sont indispensables au choix de l'antibiotique. La pénicilline G est la pénicilline la plus efficace contre les staphylocoques qui ne sont pas générateurs de pénicillinase; quant aux souches génératrices de pénicillinase, le choix est limité aux pénicillines semi-synthétiques, méthicilline, cloxacilline, nafcilline et oxacilline. Pour traiter les malades qui sont hypersensibles à la pénicilline, les antibiotiques bactériostatiques (érythromycine, novobiocine, tétracycline, chloramphénicol, oléandomycine) sont des médicaments utiles pour les infections bénignes. Dans les infections plus graves, les bactéricides (vancomycine, ristocétine, kanamycine, bacitracine, néomycine) ont été employées avec succès. L'entérocolite staphylococcique aiguë peut probablement être le mieux traitée par une pénicilline semi-synthétique. D'autres antibiotiques, dont des essais cliniques ont démontré l'utilité dans des infections staphylococciques, sont la céphalosporine, la fucidine, la céphaloridine et la lincomycine. Ce dernier antibiotique a été signalé comme traitement efficace de l'ostéomyélite. Il n'existe guère de justification à l'emploi prophylactique des antibiotiques dans les infections staphylococciques. Le drainage chirurgical demeure un moyen adjuvant capital du traitement de nombre d'infections staphylococciques.

THE majority of staphylococcal infections are caused by coagulase-positive, pigment-producing, mannitol-fermenting strains of *Staphylococcus aureus*. Certain of these coagulase-positive strains can be typed by means of bacteriophage. The factors responsible for virulence of a staphylococcus are not well understood. It may be that some strains have an enhanced virulence, and it is common knowledge that certain phage types, for example 80/81, have given rise to serious hospital epidemics. Such epidemics have had a world-wide distribution which simulates a pandemic. Temple and Blackburn[1] have recently described an increase in the number of infections in Scotland due to a new phage type of *Staphylococcus aureus*, and there is some evidence that this same strain is turning up as a common cause of infections in other countries.

The phage type of a staphylococcus and its pattern of response to various antibiotics do not correlate exactly, the latter tending to depend more on the particular hospital environment of the organism and the amounts of the various antimicrobial agents used there.

It can be safely stated that the majority of staphylococcal infections treated intelligently with the most suitable antibiotic or combination thereof will show a favourable response. Those cases in which treatment failures occur may generally be placed in one of the following three categories: (1) Infections for which the mortality continues to remain high because of the severity of the illness. The list is not long but includes meningitis, septicemia, endocarditis and pneumonia in infants. (2) Infections occurring in patients who are rendered more susceptible by some other complicating disease, for example, influenza, diabetes,

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*Chief Bacteriologist, St. Michael's Hospital, Toronto; Assistant Professor, Department of Bacteriology, University of Toronto, Toronto, Ontario.

chronic lung disease and neoplastic diseases. (3) Infections inadequately treated owing to inexperience of the physician or delay in treatment.

Cockcroft,[2] in a recent issue of this Journal, reviewed the subject of antibiotic therapy of staphylococcal infections, listed the drugs of value for this purpose, and discussed appropriate dosage schedules for the treatment of infections of varying severity. It is not the purpose of this communication to reiterate this material or to discuss specific staphylococcal infections, but rather to arrange the antibiotics that have somewhat similar activity against the staphylococcus into a few suitable groups, to examine their effectiveness in the treatment of staphylococcal infections, and to consider the small number of newer antistaphylococcal drugs such as cephalosporin, fucidin, lincomycin and cephaloridine.

ANTIBIOTICS OF THE PENICILLIN GROUP

With a few exceptions penicillin G is still the most effective drug for the treatment of staphylococcal infections in which the organism is found to be sensitive, and should therefore be the antibiotic of first choice. At ordinary dosages it has a bactericidal effect and it is not inactivated by pus. Fifty-four per cent of staphylococci isolated from patients in St. Michael's Hospital, Toronto, in 1964 were found to be resistant to penicillin by the antibiotic disc method. Since many of the strains were isolated from patients attending the outpatient clinic and the emergency department, this figure represents a mixed population rather than that from an enclosed hospital environment. This percentage has remained between 50 and 60 over the past five years, so that the distribution of sensitive and resistant strains seems to have become stabilized. However, one Canadian hospital[3] has reported that as many as 82% of staphylococci isolated from hospital patients were resistant to penicillin. Penicillin G, although sensitizing to some patients, is relatively non-toxic and can be used in very high doses if necessary—as much as 100 million units a day.

Pathogenic staphylococci fall into three groups in regard to their response to penicillin: those that are non-penicillinase-producers and are fully sensitive to penicillin G, those that are weak penicillinase-producers and are slightly resistant, and those that are strong penicillinase-producers and are completely resistant to penicillin G. It is well known that staphylococci rarely, if ever, develop resistance to penicillin *in vivo* during the course of an infection. They are resistant by virtue of the fact that they produce penicillinase and this appears to be characteristic of only certain strains of staphylococci. To handle these resistant strains we now have the semisynthetic penicillins—methicillin, oxacillin, nafcillin and cloxacillin—which are not destroyed by staphylococcal penicillinase. When the organism is resistant to penicillin G, the antibiotic to use should be one of these newer penicillins and the choice will depend on the route of administration selected. In the majority of staphylococcal infections the sensitivity of the organism will not be known, and in fact it may be impossible to obtain suitable material from the patient for culture. In such circumstances treatment should be begun with a semisynthetic penicillin. If the subsequent sensitivity tests prove that the organism is sensitive to penicillin G, it is advisable to change to this drug because it is more active against sensitive strains of staphylococci than are the semisynthetic penicillins. In fact, because penicillin G is so much more effective against staphylococci that do not produce penicillinase and are therefore sensitive, it is acceptable and not unsound treatment to administer a combination of both penicillin G and methicillin, for example, to begin with in the case of a serious infection when the sensitivity of the staphylococcus is not known. Then, depending on the sensitivity of the organism, one penicillin is discontinued and treatment is continued with the appropriate one. Fortunately, however, doses of methicillin recommended for the control of infections due to penicillin G-resistant staphylococci are sufficiently large to control most strains of non-penicillinase-producing staphylococci, but the dose may have to be increased for other strains.

Methicillin, oxacillin, nafcillin and cloxacillin have been tested clinically in the treatment of a variety of staphylococcal infections, and to date many reports of their effectiveness have been recorded in the literature. There is very little to choose among the four except for ease of administration, as there is no oral preparation of methicillin available. On an oral dosage basis cloxacillin may be preferable to nafcillin[4] or oxacillin, owing to the fact that it gives higher blood levels and is slightly more effective *in vitro* than is oxacillin against penicillinase-producing staphylococci.[5]

Development of drug resistance to these four semisynthetic penicillins during treatment has not been reported. It is possible to induce resistance to all of these drugs in the laboratory by passage of staphylococcal strains in the particular penicillin. Furthermore, resistant strains have been isolated on rare occasions from patients in clinical practice, but these appear to be naturally resistant strains rather than strains with drug-induced resistance. Such strains do not inactivate the drug by the production of penicillinase or any other enzyme such as a methicillinase.[6] Since there is cross-resistance between these four penicillin analogues, it is well to observe some practical precautions in their use. They should be reserved for the treatment of infections caused by penicillin G-resistant staphylococci.

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BACTERIOSTATIC DRUGS

In many cases patients are unable to receive penicillin because they have become hypersensitive to the drug. For less severe staphylococcal infections in such patients it may be necessary to choose an antimicrobial agent from the group listed in Table I, to which the organism may be sensitive but which has a predominantly bacteriostatic action.

TABLE I.—DRUGS WITH A BACTERIOSTATIC ACTION

Erythromycin
Novobiocin
Tetracycline
Chloramphenicol
Oleandomycin

Whether or not the infecting staphylococcus will be sensitive to any of the agents in this group depends usually on the extent to which these drugs are used in the area where the infection was acquired. Table II lists the number of staphylococcal strains tested in 1964 in St. Michael's Hospital, Toronto, and the percentage of these strains found to be resistant to the various drugs. Again, these staphylococci were isolated from in-hospital patients predominantly, but isolates from outpatients and from the emergency department are also included.

TABLE II.—STAPHYLOCOCCI ISOLATED IN ST. MICHAEL'S HOSPITAL, TORONTO, 1964

Antibiotic	*No. of strains tested*	*No. of strains resistant*	*Per cent resistant*
Penicillin G	948	511	54
Oxacillin	948	0	0
Erythromycin	955	254	27
Novobiocin	949	35	4
Tetracycline	885	324	37
Chloramphenicol	941	103	11

Penicillin G and oxacillin are included in this table in the interest of completeness. They are, in fact, bactericidal agents. It will be noted that few strains of staphylococci were resistant to novobiocin and few more were resistant to erythromycin. The number of erythromycin-resistant strains probably reflects the extent to which this drug was used for other infections in the hospital. Both of these drugs are effective in the treatment of staphylococcal infections in which the organism is found to be sensitive by laboratory tests. However, staphylococci rapidly develop resistance to these drugs *in vivo* and *in vitro* when each is used alone. Barber, Csillag and Medway[7] have reported a series of 108 cases of staphylococcal infection treated with the combination of erythromycin and novobiocin in which no resistance to erythromycin developed but in which novobiocin-resistant strains emerged in two of their cases. This and other evidence indicates that these two drugs should be used in combination with each other or with some other agent to which the staphylococcus is sensitive, to prevent the emergence of drug-resistant strains. Both antibiotics should be used in full dosage in such cases.

Staphylococci are prone to develop resistance to tetracycline. Thirty-seven per cent of strains isolated at St. Michael's Hospital in 1964 were found to be resistant as indicated in Table II. Today there is little reason to use this drug in the treatment of staphylococcal infections unless it is given in combination with other agents to which the organism is sensitive, when penicillin cannot be used. Because of the profound effect the tetracyclines have on the normal bacterial flora and the possibility of consequent superinfection with tetracycline-resistant staphylococci, it is advisable to avoid administration of this drug as much as possible in hospitalized patients.

Few strains of staphylococci develop resistance to chloramphenicol, and this antibiotic is often effective in the treatment of staphylococcal infections. However, in view of the large number of antistaphylococcal agents now available and because of its toxicity to the bone marrow, it is advisable not to use chloramphenicol in the treatment of staphylococcal disease.

Oleandomycin is closely related to erythromycin. It is slightly less effective against staphylococci than is erythromycin and it enjoys no special advantages that render it more useful in the treatment of staphylococcal infections.

BACTERICIDAL DRUGS

A number of antibiotics which have a bactericidal effect in ordinary therapeutic dosage have largely been replaced by the newer penicillins in the treatment of staphylococcal infections. These include the products listed in Table III.

TABLE III.—DRUGS WITH BACTERICIDAL ACTION

Vancomycin (Vancocin)
Ristocetin (Spontin)
Kanamycin (Kantrex)
Bacitracin
Neomycin
Framycetin (Soframycin)

It may still be necessary to resort to these drugs when a patient who is hypersensitive to penicillin has a severe staphylococcal infection due to a penicillin-resistant organism which is also resistant to erythromycin and novobiocin, and where a bactericidal drug is necessary, as in the treatment of endocarditis. Naturally resistant strains of staphylococci to vancomycin and ristocetin are extremely rare and resistance to these two drugs is not readily acquired. Both drugs are effective in the treatment of staphylococcal infections and are administered intravenously so that one is as-

sured of good bactericidal levels in the blood stream. Welch and Finland[8] ranked vancomycin, ristocetin and kanamycin in that order of preference when such drugs are indicated. Strains of staphylococci develop resistance fairly rapidly to kanamycin when exposed to the drug.

The staphylococcus is usually sensitive to both bacitracin and neomycin, and resistance, although it has been recorded more frequently for neomycin, is only moderate and slow to develop. Neither drug is absorbed after oral administration, and although bacitracin has been used successfully by intramuscular injection for severe staphylococcal infections, because of the extreme toxicity when these products are given parenterally they are now used mainly as topical antimicrobial agents or for preoperative bowel antisepsis. Bacitracin has been employed by Meleney and Johnson[9] in the treatment of furuncles, carbuncles and superficial abscesses by direct injection of an aqueous preparation into the centre of the lesion. This procedure resulted in prompt elimination of the organism and shortened healing time or permitted less extensive surgery than would be expected in a high percentage of cases.

Framycetin is identical with neomycin B and has been used effectively in the treatment of superficial staphylococcal infections and in a cream, or preferably a spray for nasal instillation, in the control of staphylococcal nasal carriers and recurrent styes or boils.

Since bacitracin, kanamycin and particularly neomycin have been used in the therapeutic suppression of bowel flora, this is a logical place to mention briefly the complication of staphylococcal enterocolitis which may arise in conjunction with such therapy. Hummel and Altemeier[10] reviewed 155 cases of this disease which occurred between 1958 and 1962. In 44 of these patients the only antimicrobial agents received prior to development of the enterocolitis were neomycin, administered alone or with sulfasuxidine or sulfathalidine. More often this condition is caused by the preoperative administration of a broad-spectrum antibiotic such as tetracycline, or the combination of penicillin and streptomycin. Barber and Garrod[11] listed the following three factors that predispose to the development of acute staphylococcal enterocolitis: (1) antibiotic treatment suppressing the normal bowel flora; (2) an empty small intestine in which antibiotics can attain an abnormally high concentration, and (3) the presence in the environment of a virulent antibiotic-resistant staphylococcus. As well as discontinuing the antibiotics to which the staphylococcus is resistant, the patient should receive an antimicrobial agent to which his organism is sensitive. Cloxacillin, oxacillin, or, if necessary, methicillin would be appropriate drugs to use under these circumstances.

RECENTLY INTRODUCED ANTISTAPHYLOCOCCAL AGENTS

A small number of antibiotics that have recently been introduced are effective in the treatment of staphylococcal infections, *viz.* cephalosporin, fucidin, lincomycin and cephaloridine.

Cephalosporins

The cephalosporins may present an alternative to methicillin and cloxacillin for the treatment of penicillin G-resistant staphylococcal infections in patients who are allergic to the latter drug. They are closely related to penicillin but show no cross-hypersensitivity with it. A number of cephalosporins have been produced by adding side-chains to the cephalosporanic acid nucleus in the same manner as the semisynthetic penicillins are prepared. Cephalothin, one of the most effective of these, is reported to compare favourably with penicillin G on a clinical basis against penicillin-sensitive micro-organisms.[12] It is resistant to the action of penicillinase and is as active against penicillinase-producing staphylococci as methicillin. Cross-resistance occurs between cephalothin and methicillin against these penicillin-resistant strains. Cephalothin must be given parenterally, and to date clinical trials show that it is effective in the treatment of staphylococcal infections caused by penicillinase-producing staphylococci.

Fucidin

Fucidin is an antibiotic that is mainly used in the treatment of staphylococcal infections, although it is also active against other Gram-positive bacteria and Gram-negative cocci. It is the sodium salt of fusidic acid, an antibiotic chemically related to cephalosporin P_1. Almost all strains of staphylococci, regardless of whether they produce penicillinase or not, are highly sensitive to fucidin. An interesting feature of the drug is that staphylococci are prone to develop resistance to it very easily when passaged through increasing amounts of fucidin in the laboratory, but the development of resistance rarely occurs in patients receiving the drug in the treatment of clinical infection. The reasons for this phenomenon are not clearly understood, but it makes one wonder about the future of this antibiotic after it has had wider clinical use. Fucidin is bactericidal in its effect upon staphylococci and can be used alone. But a synergistic effect has been described between fucidin and penicillin G, and its main use is in combination with this drug against penicillin G-resistant organisms. This synergistic effect is evident, however, only against those staphylococcal strains that are weak producers of penicillinase and that inactivate penicillin relatively slowly. According to Taylor and Bloor,[13] the fucidin reduces the bacterial population to a sufficient degree that penicillinase production is negligible,

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so that the penicillin G, given in addition to the fucidin, will be available to attack the staphylococci. Such staphylococcal infections as boils, carbuncles, paronychia, wound infections, osteomyelitis and septicemia have been treated successfully with fucidin. Taylor and Bloor attribute special healing properties to the drug in addition to its antibacterial activity, on the strength of the observation that in several of their cases more rapid healing of the lesion took place than would have been expected. Fucidin is given by mouth, the usual dosage being 500 mg. two or three times a day. The drug is not yet available in Canada.

Lincomycin

Lincomycin is another antibiotic effective against the Gram-positive cocci, including *Staphylococcus aureus*. Against the latter organism it has the same level of activity as erythromycin. Strains of staphylococci naturally resistant to lincomycin occur but they are rare. Resistant strains emerge on exposure of the organism to increasing concentrations of the drug *in vitro*, and Holloway, Kahlbaugh and Scott[14] reported a case of acute staphylococcal pyelonephritis which failed to respond to lincomycin therapy owing to the development of resistance, *in vivo*, of the originally sensitive strain. A type of cross-resistance between lincomycin and erythromycin in certain staphylococcal strains has been described by Barber and Waterworth.[15] This observation, together with the fact that naturally resistant varieties do occur, suggests that lincomycin should be reserved for special cases of staphylococcal infections in which other antibiotics are not effective or cannot be used owing to the patient's hypersensitivity to them.

Clinical studies have shown that treatment with lincomycin was successful in a variety of staphylococcal infections including septicemia, pyelonephritis, parotitis, wound infection and osteomyelitis. It is of interest that relatively high concentrations of lincomycin occur in the bone, and the effects of this have been borne out clinically in the remarkable responses exhibited by patients with acute and chronic osteomyelitis who were treated with this drug.[3, 16] Undoubtedly this observation requires further investigation, but it might well be that lincomycin will be the antibiotic of choice for patients allergic to penicillin who have an acute osteomyelitis caused by penicillin-resistant staphylococcus, or an old, chronic osteomyelitis refractory to treatment with other antimicrobial agents.

Cephaloridine

Cephaloridine is a synthetic derivative of cephalosporanic acid which has the advantage of being twice as active against penicillinase-producing staphylococci as cephalothin. As it is not cross-allergenic with penicillin, it too may be a useful drug for the treatment of patients unable to take methicillin. Results of therapeutic tests in mice showed that the curative dose of cephaloridine was much lower than that of methicillin in the treatment of infections caused by each of seven strains of staphylococci.[17] To date, however, there are too few clinical reports of the effect of this drug in the treatment of staphylococcal infections in humans to assess its real value. The antibiotic is useful also in the treatment of a variety of Gram-negative bacillary infections and appears to rival ampicillin in its effectiveness in this respect. As yet cephaloridine is not available in Canada and it is included in this consideration of antistaphylococcal agents for the sake of completeness only.

PROPHYLACTIC ANTIBIOTICS IN STAPHYLOCOCCAL INFECTIONS

The prevention of postoperative wound infections caused by *Staphylococcus aureus* by the administration of preoperative antibiotics is a questionable procedure. Most successful results with prophylactic antibiotic therapy have occurred in the case of *Streptococcus hemolyticus*, where one is dealing with a highly sensitive organism with virtually no resistant strains—an organism so sensitive that, as Barber and Garrod[18] put it, a mere whiff of penicillin is enough to keep it away. On the other hand, there are many penicillin-resistant strains of staphylococci, and resistance develops readily to most of the other antibiotics. Pre-treatment with antibiotics often eliminates the highly sensitive organisms and prepares the way for colonization of wounds or other potential sites of infection by more resistant organisms. Dowling, Lepper and Jackson[19] have shown that many patients treated in hospital with penicillin or tetracycline rapidly become nasal carriers of antibiotic-resistant staphylococci. Moreover, there are unknown factors in the patient which play a large part in the development of a postoperative infection. Dineen[20] was able to render mice more susceptible to intravenous injection of staphylococci by alteration of the normal intestinal flora of these animals with antibiotics. There are many clinical reports in the literature of surgical patients treated with prophylactic antibiotics, and most of these have failed to demonstrate any advantage in the procedure, no matter what antibiotics or combination thereof was used. One of the most extensive of these trials, which took into account the type of operation, the condition of the patient, and many other variables, was published in the *Annals of Surgery*[21] in a Supplement on Postoperative Wound Infections. No evidence of the prophylactic value of antibiotics in the prevention of wound infections was apparent in this study.

Certainly the use of antibiotics preoperatively should be restricted to a small number of selected cases. Since most postoperative wound infections

are caused by *Staphylococcus aureus* and the organism will most likely be a penicillin-resistant one, methicillin or one of the newer oral penicillins would probably be the drug of choice in such cases.

The staphylococcal lesion is characterized by an accumulation of pus surrounded by a wall of inflammatory tissue. It is well known that penicillin is highly diffusible and is not inactivated by pus. But the fact remains that it is often unable to sterilize large collections of pus or tissue slough. The reason for this is not clear. If the disease is diagnosed early before tissue destruction has occurred and before pus has formed, the inflammation can often be made to regress by the administration of a suitable antibiotic alone. If an abscess has formed, however, the pus must be evacuated, foreign bodies must be removed if present, and debridement of necrotic tissue must be performed. With appropriate surgical management it is often not necessary to use any antibiotic therapy if the abscess is small and well localized. Where the infection is extensive, large and spreading, multiple, associated with blood stream invasion or in a critical location, antibiotics will be an important adjunct to therapy whether or not surgical treatment is indicated.

SUMMARY

The antibiotic treatment of a staphylococcal infection should be governed by (1) the severity of the infection and (2) the probable source of the infection. If the infection is not severe and is contracted outside of hospital where resistant strains of staphylococci are less common, treatment with penicillin G will most likely be adequate: if the patient is allergic to penicillin, the bacteriostatic drugs may be used in such circumstances. In the case of a severe infection or one due to an organism which is likely to be penicillin-resistant, it is advisable to begin treatment with methicillin or cloxacillin or a combination of either with penicillin G, discontinuing the first two if sensitivity tests show the organism to be penicillin-sensitive. In the event that the patient is unable to take one of the penicillins, it may be necessary to resort to a newer antibiotic, such as lincomycin or cephalothin, which is resistant to the destructive action of penicillinase.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

LATE EFFECTS OF GAS POISONING

There were ninety-six cases before us. We saw no recent cases. With, I think, no exception, they were men who had been poisoned at Ypres on April 23 or 25, i.e., three months after having been subjected to the fumes. As far as our observation goes it would seem that while the Germans inflicted serious damage on our troops during those few days in the latter part of April, they never succeeded again in their diabolical effort to gain ground by this contemptible method of poisoning men. Prompt measures were taken to protect our men against the influence of gas and these efforts seem to have been wholly successful so that it seems certain that no further injury will be caused by such means. Regarding the more serious effects of gas we learn that not a few cases proved fatal soon after exposure or within the first few days. In our board work we had to deal with many cases of serious poisoning who had passed the initial danger but were still suffering from symptoms more or less distressing. Shortness of breath was complained of on exertion, or, at times, coming on apart from exertion, the man occasionally waking at night with dyspnœa. These men usually complained also of excessive secretion with expectoration particularly in the morning. The physical signs on examining the chest were practically negative and it was remarkable that one was never able to detect by this means any serious lesion in the lung. Next in order came marked gastric irritability, evidenced by the fact that the man was unable to retain any solid food. Many of these cases were able to take milk and soups but the moment they took solid food of any description they vomited. Occasionally we were told that the man would vomit in the morning only, this occurring immediately upon his first meal for the day, no matter what type of food was taken, but that he had no trouble with dinner or supper provided he took fluids. Over a period of weeks in many cases there had been no improvement. We also got a history in several instances of hæmorrhage from the bowel with diarrhœa and hæmaturia in the early stages.

The problem which thus far we are unable to solve is whether or not the damage done to the gastro-intestinal tract or to the respiratory organs is permanent. These men continue to have symptoms three months after the exposure to the gas, and occasionally with little or no tendency to improve. We have no previous experience of such cases to go upon and we are therefore quite unable to determine whether the damage done is permanent or not.—A. Primrose, *Canad. Med. Ass. J.*, 5: 859, 1915.