TETANUS AND THE ANAESTHETIST
A Review of the Symptomatology and the Recent Advances in Treatment

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INTRODUCTION

Treatment of this preventable disease is purely symptomatic and is a carefully integrated attack aimed at supporting life until the disease process has worn itself out. With advancing knowledge of physiological and pathological processes, this has become a most complex problem requiring much diversion of human effort. While this may be possible in the larger centres where experienced staff and full auxiliary services are available, it so happens that in the more highly civilized communities tetanus now is rare and experience of the disease itself hard to gain. On the other hand, in those countries where the disease is common, adequate facilities, both staff and equipment, are so often lacking. A form of treatment possible in one centre may be quite inapplicable in another, and even in the most fully equipped hospital, the best therapeutic regime has yet to be devised.

These facts must be remembered when assessing newer methods of treatment and comparing mortality rates, a rate which in this country remains disconcertingly high.

The anaesthetist, because of his specialized knowledge of respiratory physiology and its application to the paralyzed or unconscious patient, is now frequently an active member of the therapeutic team. The purpose of this paper is to present a brief review of the disease, and to discuss some of the problems of symptomatology and treatment in severely ill patients.

INCIDENCE AND MORTALITY

Tetanus is not notifiable in England and Wales. Its general incidence, estimated at approximately 150 to 200 cases a year, can only be inferred from the mortality statistics of the Registrar-General, and from the average case mortality of published series. Two recent reports quote a mortality of 42 per cent at Aberdeen (Galloway and Wilson, 1955), and of 30 per cent at Oxford (Honey et al., 1954). Figures may well be higher at smaller hospitals, where an admission might be a rare event.

The average yearly number of deaths have been: for the decade 1934–43, 102 (variation from 126 to 85); for the decade 1944–53, 73 (variation from 88 to 61); in the year 1954, 37; a significant fall.

The mortality (and by inference, the incidence) is highest in childhood, lowest in the middle years of life, and rises again after the age of 50. Active immunization of Service personnel is probably directly responsible for the lower incidence in the middle years (Coneybeare and Logan, 1951).

PATHOGENESIS

Clostridium tetani produces spores which occur naturally in soil and in the intestines and excreta of animals. They are highly resistant and can remain dormant for years.

Germination is anaerobic and in wounds depends on the oxidation-reduction potential of the tissues (Wright, 1954). If this is reduced, the spores can develop; if not they remain in the tissues, some to be destroyed by phagocytes; but some may continue latent and capable of germination later, for instance after a re-exploration of the wound. During development they produce a neurotoxin which is absorbed into the blood stream (the "circulating" toxin), and which eventually reaches the nervous system (the "fixed" toxin), where it probably affects the anterior horn cells in the spinal cord, and the cranial nerve nuclei and basal ganglia in the brain.
Two forms of tetanus appear to exist, both experimentally and clinically: "local" tetanus and the classical "general" form, the type usually seen in man. This has led to much controversy regarding the route taken by the toxin, but the bulk of evidence suggests a centripetal spread up the regional motor nerves from the motor nerve endings to the spinal cord and brain stem (Wright, 1954, 1955), though some maintain that it is blood borne direct to the affected cells (Abel et al., 1935).

The mode of action and the nature of injury inflicted on the cells are not known (Wright, 1955), though Brooks et al. (1955) have reaffirmed its similarity of action to strychnine.

The effect, unlike that of strychnine, is a progressive tonic spasticity of all voluntary muscles, protagonists and antagonists alike, and superimposed on this, reflex convulsions may occur. Aberrant forms are known in which paralysis, not rigidity, is the predominant feature, as occasionally seen in "cephalic" tetanus (Bagratuni, 1952).

Baker (1942, 1943), when studying the histopathological appearances, found that the cranial nerve nuclei were more extensively poisoned than the anterior horn cells; there was often a selective involvement of these nuclei, notably of the 5th and 10th. Occasionally, there appeared to be a direct involvement of the medulla, accounting possibly for the sudden cardio-respiratory collapse and death occurring sometimes in a patient who appeared to be improving.

These deductions, if correct, are of considerable clinical importance, for most of the changes described by Baker (1942) were reversible. The balance may well be tipped unfavourably if, to this toxæmia, the effects of anoxia and depressant drug therapy are added.

SYMPTOMS AND SIGNS

1. **Tonic rigidity.**

The commonest early symptom is trismus, associated frequently with a difficulty in eating and swallowing, and a stiffness and aching in the neck and back. Gradually, as the muscles tighten up so the body becomes stiff and extended. The face shows the typical risus sardonicus, furrowed forehead and clenched jaws. The neck is stiff, with resisted flexion, the erector spinae muscles in tonic contraction, and later there is marked opisthotonus. The abdomen is board-like, but not opisthotonus. The thoracic cage rigid and deep inspiration is restricted. The limbs are the last, and the least, to be affected, while the reflexes are normal, or increased.

The state of generalized tonic rigidity persists throughout the illness until recovery or death. In mild cases it may progress no further, but usually it gradually increases in intensity, and it may be many days before it reaches a peak. Concurrently, there is an increase in reflex excitability, the slightest stimulation or manipulation evoking an exaggerated response, with painful cramp-like muscle contraction. This state waxes and wanes unpredictably and is itself a prelude to the reflex spasms or convulsions to follow.

2. **The reflex spasms (convulsions).**

These are by far the most frightening and dangerous feature of the disease. They are characterized by a violent rigidity, usually sudden in onset, but sometimes working up to a crescendo, with every single voluntary muscle in the body thrown into intense, painful tonic contraction. The eyes stare, the jaw clenches, the tongue is bitten, the neck is retracted, the back arched, and opisthotonus is extreme. Often there is a muffled inspiratory cry, as the diaphragm contracts and draws air through the apposed vocal cords. Finally, laryngeal spasm becomes complete, the chest fixed and respiration ceases from muscle spasm. At the same time there is a gross outpouring of secretion, with profuse perspiration and foaming at the mouth.

Such an attack varies from a fleeting stiffening of a few seconds, with a slight increase in pulse rate and little effect on respiration, to the severe convolution with a rapid bounding pulse and cessation of respiration, perhaps with cyanosis. The attack may last several minutes, and as it passes off, the patient lies exhausted, but he can never relax. Such spasms are quite unpredictable, both as regards their violence and their frequency, but the more severe the disease, the more frequent and severe are the convulsions.

They may be provoked by (a) external stimuli, such as noise, movement, and light; (b) internal stimuli, such as attempts to swallow, to talk, or
to cough; by abdominal colic or the desire to micturate; or (c) "spontaneously".

Death may be rapid from direct asphyxia; or, later, from exhaustion and cardiac failure; from central medullary failure, either from the direct action of the toxin, or from anoxia; from respiratory infection; or from the treatment itself, when so often the immediate cause is in doubt (Saint, 1953).

CLINICAL TYPES

Six clinical types are recognised (Knott and Cole, 1952) which, however, merge into each other.

Type 1. Local, usually mild and confined to the region of the wound, though it may take one of three forms (Millard, 1954).
(a) Purely local.
(b) Local, later becoming general.
(c) General, becoming secondarily local.

Type 2. Generalized tonic rigidity, which gradually increases and then slowly passes off without spasm, the whole process lasting 1 to 4 weeks.

Type 3. Generalized tonic rigidity, passing into reflex spasms and gradually becoming more severe. They may then subside, with recovery, or get worse until death.

Type 4. In which the muscles of deglutition and respiration are mainly affected, with less emphasis on generalized spasm; said to be usually fatal.

Type 5. Cephalic tetanus, a form of local tetanus in which actual paralysis of a cranial nerve is the usual feature; this carries a good prognosis.

Type 6. Tetanus neonatorum, from infection of the umbilical cord; this carries a high mortality.

PROGNOSTIC CRITERIA

The severity of the disease is proportional to the rapidity of its onset. Two factors help to determine the likely severity.

(1) The incubation period is the time between injury (when known) and the first symptom. Under 7 days, the prognosis is bad; between 7 and 14 days, it is equivocal; over 14 days, the chances are good. In many patients, there is no wound (Cooke, 1948, found none in 20 out of 57 tetanic children).

(2) The period of onset is a more accurate indication of the severity and is the time between the first symptom and the first generalized reflex spasm. Under 48 hours, the prognosis is bad; over 7 days, reflex spasms are unlikely to develop. The chances increase with every day that convulsions are delayed.

Other factors to be considered are:

Of unfavourable significance.
(1) A severe or septic wound.
(2) The extremes of age—infancy or over 60 years.
(3) Pre-existing disease (especially pulmonary.)

Of favourable significance.
(1) Previous active or passive immunization.
(2) The presence of local tetanus.
(3) A healthy patient.

By a careful consideration of all these factors patients can be divided into three prognostic groups (Cole, 1951; Saint et al., 1953).

Group 1. Incubation period long, over 14 days; no spasms—a good prognosis.

Group 2. Incubation period 7 to 14 days; period of onset over 2 days. Reflex spasms of moderate severity, but may be severe. Prognosis equivocal.

Group 3. Incubation period under seven days. Period of onset under 48 hours. A rapid development of severe and frequent spasms. The prognosis is very poor.

These criteria serve only as a guide, as this is a variable disease (Cole, 1935; Godman and Adriani, 1949). In some patients, it is said, no treatment will avail (McIntyre, 1953), since death or survival depends almost entirely on the dose of toxin absorbed before antitoxin is given (Cole, 1953), though some doubt has recently been cast in this fatalistic view (Shackleton, 1954). Reports of patients treated, therefore (and failures are as important as successes), should contain all the details of the treatment and the full prognostic criteria, so that these may be used to assess the newer forms of treatment based on the conventional methods (Cole, 1953; Bodman, 1954).

IMMUNIZATION

Man has no natural immunity to tetanus. Indeed, an attack does not necessarily confer
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protection, for a recurrence of the disease has been reported in at least 55 instances (Martin and McDowell, 1954). These authors report the interesting occurrence of a Negro heroin addict who was readmitted to a New York hospital with the same complaint only 9 months after his discharge, his wife having died a short time before, 3 days after the onset of similar symptoms.

Passive Immunization.
This is by injection of antitoxin. The prophylactic dose is 1,500 to 3,000 international units (1950) of antitetanic serum as soon after the injury as possible. Allergic reactions are frequent and the protection is temporary.

Active Immunization.
Toxoid is used. Two injections, each of 1 ml, the second given after an interval of 6 weeks, with a “booster” dose 1 year later. Its effect will last many years and its value is beyond doubt. In the last World War there were 35 patients with tetanus in 300,000 British and Commonwealth wounded (Cole et al, 1952), and only 12 in two and three-quarter million admissions to hospital for injuries in the American forces (Stafford et al., 1954).

Active immunization is now advocated: (a) for all those exposed to occupational risks of infection; (b) in infancy (as in the present field trials with “triple” vaccine); (c) in the convalescent stage of clinical tetanus; (d) in an injured person, previously actively immunized, when a booster dose of toxoid should be given—not prophylactic antitetanic serum.

RESPIRATORY PROBLEMS OF THE SYMPTOMATOLOGY

Many recent authors (Herzon et al., 1951; Van Bergen and Buckley, 1952; Woolmer, 1953; and others) have stressed the importance of the airway. Some aspects of this problem will be discussed.

1. Neuromuscular Dysfunction of Peripheral Origin (Spinal Cord).
In normal muscle movement voluntary or reflex contraction of a muscle (excitation of the protagonist) is accompanied by simultaneous relaxation (reflex inhibition) of its antagonist (Best and Taylor, 1955).

In tetanus there is generalized tonic spasticity which affects all the muscles of respiration, frequently with simultaneous activity in both protagonists and antagonists. This in time causes:

(a) A shallow respiration, with, in severe cases, tachypnoea and progressively smaller tidal volume, as the total minute volume rises from exertion and metabolic needs.

(b) A reduction in vital capacity due to restriction of forced inspiration and expiration.

(c) Loss of effective cough reflex.

(d) In reflex convulsions there may be complete respiratory standstill with all muscles in violent spasm.

2. Dysfunction of Central Origin (Brain Stem).
All cranial motor nerves are involved, with often a selective and exaggerated effect on certain nuclei, notably the 5th and 10th (Baker, 1942, 1943); to a lesser extent the 7th, 9th, 11th, and 12th. The resultant dysfunction of the pharyngeal and laryngeal reflexes in particular is of fundamental importance.

Swallowing becomes difficult or impossible. Secretions collect, and, since the patient cannot expectorate, they either pass out through the nose or mouth or overflow on to the larynx.

The normal laryngeal mechanism is disturbed. The voice changes, often to a mere squeak. The adductors being stronger than the abductors, the laryngeal aperture becomes a slit, with resultant stridor and reduced airway. Frank laryngeal spasm occurs on the slightest provocation; locally from above, from the overspill of pharyngeal contents; locally from below, from tracheobronchial secretions and the desire to cough; remotely, from manipulations and movement; generally, as part of a reflex convulsion.

The cough mechanism is disorganized; peripherally, by the spasticity of the respiratory muscles preventing adequate inspiration, and also by the laryngeal dysfunction; centrally, by the direct action of the toxin, and by hypoxia and depressant drugs acting on the medullary centres.

The larynx, therefore, is no longer the protective watchdog of the lungs, and the inhalation of pharyngeal secretions and the stagnation of bronchial secretions become common complications.
Further, as the disease progresses, there may be evidence of central medullary failure, either from the toxin itself, or from the effects of the disturbed airway, intercurrent infection or treatment itself.

3. **Mechanical Obstruction of the Airway.**

Several factors combine to restrict the airway:

(a) Trismus, which may be so severe as to prevent any separation of the jaws.
(b) Trauma to the tongue, which may become swollen.
(c) Salivation and pooling of secretions in the mouth and pharynx.
(d) The presence of a nasal tube, blocking one nostril.
(e) Laryngeal spasm or oedema.
(f) Rigidity of the respiratory muscles.
(g) Stagnant secretions in the trachea and bronchi.
(h) Pulmonary collapse, infection or oedema.

4. **Alterations in Chemical Physiology.**

As the disease progresses, the tonic spasm of the muscles, the low volume rapid tidal respiration, the restricted airway and the sudden convulsions, combine to produce hypoventilation. The hypoxia with acute anoxic episodes causes increasing restlessness and dyspnoea, which are, in turn, a further stimulus to the tetanus, and a vicious circle starts. At the same time there is retention of carbon dioxide, increased by the excessive metabolism and the violent exertion, and this causes further restlessness and dyspnoea. Respiratory decompensation sets in and acidosis ensues. Eventually the anoxia and hypercapnoea together or separately may cause central medullary depression and failure.

**TREATMENT**

As soon as the diagnosis is established arrangements must be made to provide constant supervision of the patient. Vigilance at this early stage is as important as later, for a sudden crisis may arise at any time, especially if the incubation period has been short. If possible, special nurses should be allocated, a quiet darkened room obtained, and suction and resuscitation apparatus provided, with a selection of suitable endotracheal cuffed tubes, laryngoscope, and ampoules of a muscle relaxant.

Treatment and the later arrangements will depend on the initial severity and subsequent progress of the disease, but in ill patients the full resources of the smaller hospital may be considerably strained in order to give the best possible chance of survival.

The anaesthetist, if it is likely that he may be asked to take part, either for emergency resuscitation or in planned treatment, should be notified early so that he may assess the particular problems that concern him, in full consultation with his colleagues.

The general principles of treatment are more conveniently considered under five main headings:

1. **The prevention of further absorption of the toxin.**
2. **The protection of the lungs and the prevention of intercurrent infection.**
3. **The control of reflex spasms and tonic rigidity.**
4. **The maintenance of strength and fluid balance.**
5. **General management, including nursing and organization.**

**1. PREVENTION OF FURTHER ABSORPTION OF THE TOXIN**

**1. Neutralization of “circulating” toxin.**

Antitoxin must be given as soon as possible. Usually, 100,000 to 200,000 international units (1950) of antitetanic serum are given to neutralize the free "circulating" toxin in the bloodstream. It has no action on the "fixed" toxin in the nervous tissue and has no effect on the subsequent development of the disease. Opinion is divided as to whether further doses of antitoxin should be given later. The intravenous route can be dangerous because of the serious, even fatal, anaphylactic collapse that sometimes occurs; intramuscular injection is considered preferable.

**2. Toilet of the wound (if present).**

This is usually of secondary importance. Anaesthesia for such an operation, however minor, should be undertaken with great care because of the ever present danger of laryngeal spasm or reflex convolution. If further surgical operations are contemplated, for example tracheotomy, it may be
(2) PROTECTION OF THE LUNGS

Most of the respiratory troubles occurring in tetanus are preventable. The most common cause of death—up to 95 per cent—is some respiratory complication, whether from direct asphyxia in severe spasm or other mechanical obstruction; or from the indirect effects of anoxia; or later from the results of secondary infection. At one centre, for instance, 16 out of 17 deaths were directly attributable to pulmonary complications (Honey et al., 1954).

Undue reliance is too often placed on the antibiotics. Valuable as they are in preventing infection, they cannot overcome mechanical obstruction or hypoxia. More active measures are necessary.

Active protection of the lungs involves three main principles:
(1) Maintenance of a clear airway, if necessary by tracheotomy.
(2) The prevention of obstructive pulmonary complications.
(3) The prevention of secondary lung infection.


In all but the mildest cases the maintenance of a clear airway becomes increasingly more difficult as the disease progresses.

(1) Oropharyngeal airway. To overcome trismus and to separate the jaws, to prevent trauma to the tongue, to allow aspiration of retained saliva, and to permit the maintenance of oral hygiene, a modified dental prop or an oropharyngeal airway is sometimes tried. But the presence of one of these, except in deep coma, can provoke further spasms, increase salivation, prevent swallowing, or may initiate laryngeal stridor or, much worse, retching and vomiting.

Frank laryngeal spasm is obvious. Less obvious, yet more dangerous because of its insidiousness, is the slow progressive hypoxia arising from trismus, with retained naso-pharyngeal secretion. These difficulties, and many others, can be avoided by the safety bypass of a tracheostome.

(2) Tracheotomy. Early, tracheotomy, as a prophylactic measure, is strongly advocated, particularly by those who have had experience of many patients (Godman and Adriani, 1949; Creech et al., 1950; Herzon et al., 1951; Saint et al., 1953). It should not be applied as a routine, but there should be no hesitancy in using it when indicated; in severe attacks it must be done early (Woolmer, 1953).

There is unfortunately a conservative attitude on the part of many to this operation, even in the presence of specific indications. In tetanus, this conservatism is no longer justifiable (Saint, 1953). Undue delay will jeopardize the patient's life from sudden spasm, complete exhaustion, or dangerous hypoxia. An unnecessary strain is thrown both on the patient and on those fighting for his life.

In the following list of indications, each relevant factor must be considered in association with the general condition of the patient, the success or otherwise of the treatment, and the severity and stage of the disease.

(a) Indications for tracheotomy in tetanus.
(1) Prophylactically, when the disease is likely to be severe, with the early and rapid onset of severe spasms.
(2) Reflex spasms which cannot be adequately controlled by treatment with sedatives.
(3) Unrelieved trismus or gross oedema or trauma of the tongue.
(4) Disorganized swallowing, with pooling of saliva, or danger from retching and vomiting.
(5) Laryngeal disorganization, with stridor, obstruction or oedema, and absent cough reflexes.
(6) Pulmonary stagnation, atelectasis or pneumonia.
(7) Prolonged unrelieved spasm of the respiratory muscles, interfering with efficient pulmonary ventilation.
(8) Paralysis from muscle relaxants.
(9) Deep coma from over-sedation.

(b) The operation.

Tracheotomy, through the second or third tracheal ring, can be more easily performed as an elective operation under endotracheal anaesthesia. Galloway and Wilson (1955), advise a rapid induction with an intravenous barbiturate; relaxation with a neuromuscular blocking agent, e.g., suxamethonium; oral intubation with a cuffed tube; and maintenance with nitrous oxide-oxygen anaesthesia.
For the emergency relief of obstruction, oral intubation under relaxant cover is to be preferred to a hurried tracheotomy. An elective operation can be done later, but oral tubes should not be left in place for longer than 12 hours because of the danger of ulceration of the vocal cords, or of the trachea in the subglottic region (Gusterton, 1955).

In patients for transfer, tracheotomy is more conveniently done at the receiving hospital. When any danger from asphyxia might arise during transfer, a preliminary oral intubation should be done.

(c) The choice of tracheotomy tube.

The type of tube will depend on the reason for the tracheotomy. (1) The standard silver tube with fixation flange is adequate for those patients in whom a free or alternative airway is all that is required, and in whom there may be no danger from pharyngeal aspiration. Sometimes, a smaller tube can be used, with the central blocker kept in place, this being removed only for suction purposes or as an emergency airway. In such cases breathing occurs round the tube and humidification problems do not arise. (2) The cuffed rubber tube will be required in patients with laryngeal disorganization to prevent aspiration; or when intermittent positive pressure respiration (I.P.P.R.) is contemplated.

The rubber tube commonly used is a standard endotracheal cuffed tube, shortened in length to approximately 3½ inches, cut and chamfered just distal to the cuff, and fitted with a Cobb's suction union.

This standard tube has certain disadvantages. Fixation of the external end without a suitable flange can be difficult, especially when connected to respiration apparatus. Kinking may occur with complete or partial obstruction of the lumen. Insufficient curvature of the tube may exert undue pressure on the posterior wall of the trachea, while over-inflation of the cuff will cause mucosal ischaemia leading to ulceration. A long tube may pass into a bronchus, especially if the tracheostome is too low.

There is no satisfactory tube to meet all these objections. Rubber angular tubes have been tried, of which the Swedish Sjoberg tube is an example. Hodges et al. (1956) used the outer shell of a standard silver tube and slid this inside a cut down rubber cuffed tube, with the angle of the silver tube above the cuff. Careful selection is important, but this modification, made from apparatus in common use, overcomes many of the troubles that may arise.

(d) Management.

Two serious complications, infection and drying up of secretions, can follow tracheotomy.

(1) Prophylaxis of infection. Careless technique is responsible for much of the tracheobronchitis that occurs, so often associated with an antibiotic-resistant pathogen. The importance of strict asepsis must be impressed on nurses, and tracheal catheters must be kept separately from nasal and pharyngeal suckers.

Too vigorous and too powerful aspiration can cause extensive damage to the delicate tracheal mucosa. Tracheobronchial toilet must be done as gently as possible, and a side hole, or Y-tube, incorporated in the suction holder to prevent too high a build-up of negative pressure. Plum and Dunning (1956), reporting on 8 postmortem specimens removed from patients who had died within one and a half to four days after tracheotomy, found extensive haemorrhage and ulceration of the trachea and right bronchus due to careless and vigorous suction.

(2) Humidification. The drying up and crusting of the tracheobronchial tree that can follow tracheotomy may become so serious as to jeopardize the purpose of the operation, and the patient’s life. Secretions, initially increased, become so thick and tenacious that ciliary action ceases, suction is ineffective, and a viscid mucus cast may form, restricting the lumen and blocking the bronchi. Such a complication is prevalent in patients with absent cough reflexes.

Humidification of some sort is essential. The problem is to ensure that the air or gases inspired through the tracheotomy are already at body temperature and fully saturated. The time-honoured technique of bubbling gases through hot water in a Woulfe’s bottle is not very effective, while the conventional steam kettle, tent or humidified room, to be at all efficient, makes conditions unbearable for both patient and staff.
The "Radcliffe" humidifier, developed by Marshall and Spalding (1953), is an excellent apparatus. Designed primarily for positive pressure respiration techniques, it can be adapted for spontaneous breathing by placing a special plastic bag over the free end of the tracheotomy tube and blowing the warmed humidified air from the apparatus into it (Crampton Smith et al., 1954). Alternatively, a modified Ayre's T-piece can be attached to the tracheotomy tube, with one arm connected to the humidifier and to the other a short piece of wide bore tubing open at the distal end. In either case the patient can breathe a mixture, which can be varied, of warmed humidified air and ordinary room air. The disadvantage is that more apparatus—a respiration pump or cylinders—is required to deliver the air or gases to the humidifier.

e) The advantages of Tracheotomy in Tetanus.

1. It provides a reliable airway, bypassing the sites of obstruction.

2. It provides ease of aspiration of the tracheobronchial secretions.

3. It allows efficient pulmonary ventilation, natural or applied, and is essential in I.P.P.R. techniques.

4. It can prevent aspiration of saliva or vomit if a cuffed or closely fitting tube is used.

5. It reduces the frequency and violence of the spasms (Galloway and Wilson, 1955), as increased respiratory effort, especially in the presence of obstruction, is itself a stimulus to reflex spasms.

6. Less sedation is required (Saint, et al., 1953, and others).

7. Oxygen consumption is lowered, because the accessory muscles of respiration need no longer be used to overcome the restricted airway (Pitman and Wilson, 1955).

8. Both the patient and the nursing staff are to some extent, relieved of anxiety and strain.

2. The Prevention of Obstructive Pulmonary Complications.

The most common complication is atelectasis, that is, collapse of the lung distal to a block in a bronchus. It may be segmental or lobar and usually it is preventable.

The active co-operation of the patient with severe tetanus is generally not possible and breathing exercises are difficult to apply; other more active measures are necessary to loosen and drain the pulmonary secretions. The greater the severity of the disease, the more important these measures become. These are:

(a) Postural drainage. By this is meant the frequent change of position of the patient so that each part of the lung fields can be drained in rotation. The cycle is repeated every 2 to 4 hours, depending on the profuseness of secretions or on the tendency to atelectasis.

(b) Chest physiotherapy. The importance of the physiotherapist cannot be overemphasized. Her treatment supplies an artificial cough for her patient. Prophylactic therapy is essential from the onset. The principles of this treatment are firstly, clapping and percussion of the chest to loosen the secretions in the bronchioles, and secondly, expiratory vibration and shaking to squeeze loosened secretions into the larger bronchi and trachea, where they are more easily removed by ciliary action or by aspiration. Combined with postural drainage each lung is dealt with in turn and the treatment repeated as least twice daily, or more frequently if required.

(c) Aspiration. Where there is a tracheotomy, aspiration is done as often as necessary. Strict attention must be paid to gentleness and to asepsis.

(d) Other measures include frequent auscultation and daily radiological examinations of the chest.

Comment. These energetic measures, diligently applied, will keep the patient's lungs remarkably free. If they cannot be applied, either because of unrelieved tetanic tone in the respiratory muscles or for fear of evoking reflex convulsions, it would appear that the form of treatment being given for the tetanus might be basically unsound, especially if pulmonary complications develop.

Treatment of Atelectasis.

(a) An intensification of the general prophylactic regime with particular emphasis on the collapsed lung is the most important therapeutic measure. The turning routine is modified to allow free drainage of the affected part.
Chest physiotherapy must be really vigorous, and as this may stimulate reflex spasms in a patient not fully controlled, increased analgesia, or better still anaesthesia plus relaxation, may be necessary. Abolition of the tetanic tone in the respiratory muscles is an essential aid to success. These vigorous methods are repeated frequently, even hourly, until the offending mucus plug has been dislodged, and the lung expands.

(b) Bronchoscopy. If physiotherapeutic methods fail, bronchoscopy should not be unduly delayed. Its use should be considered a reflection on the preventive regime. It is best done under general anaesthesia, with additional relaxation, and through the mouth rather than through the tracheostome (Crampton Smith, 1955).

(c) Other measures. Where secretions are thick and tenacious, humidification (even without a tracheotomy) may be of considerable help; the instillation of sodium bicarbonate or, more recently, the use of "Alevaire" and enzymes, such as trypsin, by aerosol may be of value.


The prophylactic and therapeutic use of the antibiotics has reduced the incidence, morbidity, and indeed the mortality of lung infection.

3) CONTROL OF REFLEX SPASMS AND TONIC RIGIDITY

Introduction.

Until recent years sedation had been the only form of treatment. Formerly, as the disease progressed, so more sedation was required, and the induced coma, or its complications, often proved fatal.

Although curare had been tried, notably in 1935 (Cole, 1935; West, 1936) the "relaxant era" did not start until the middle 1940s, and for the next few years the various drugs in this group, combined with the sedatives, were tried in many patients. Some reports were enthusiastic, but in many of these the prognostic histories were already favourable. Other reports cast much doubt on their benefit. Many emphasized the difficulty of achieving sufficient release of the excess muscle tone without producing respiratory depression, while occasionally their use seemed to hasten the end.

In 1952 there were two important developments. Firstly, intentionally induced total paralysis was combined with artificial respiration, an anaesthetic technique already common practice in the operating theatre. Van Bergen and Buckley (1952) in America are credited with being the first to apply this principle. They saved a 5-year-old child with severe tetanus, moribund from heavy sedation, by inducing complete curarization, combined with artificial respiration; they maintained this for 6 days, no further sedatives being required. This report received little attention at the time, and it was not until the spectacular success was published of I.P.P.R. methods, applied to the many paralysed poliomyelitis patients in Copenhagen in 1952, that the importance of this new principle was realized.

The second development was the rapid increase in knowledge and experience in the long-term management of the paralysed patients gained in that epidemic and to which Lassen (1953) and Ibsen (1954) have contributed so much.

This technique of induced total paralysis, so simple in concept yet fraught with many technical difficulties, should reduce the mortality in tetanus to almost nil (Russell et al., 1955). Hitherto, in the severe forms, death might have occurred within a few days. The application of this new principle together with conventional methods of treatment should prevent many deaths from the more common complications of this disease. With life prolonged it may reveal that a proportion of patients may develop new complications or die from other possible effects of the toxin (Bodman, 1954). Such untoward effects already have occurred, notably from depression of the bone marrow. (Fatal agranulocytosis—Lassen et al., 1954; Gormsen, 1955; and the author and his colleagues.)

More recently Kelly and Laurence (1956) have stressed the impracticability of the total paralysis regime in countries where tetanus is common and skilled anaesthetists few. They and others (Bodman et al., 1955; Cole and Robertson, 1955; and others) have found chlorpromazine a drug of some promise.

Meanwhile Forbes and Auld (1955) have published an impressive series of 15 consecutive cases of tetanus with no deaths, all being treated with sedatives alone.

It would appear that treatment has turned a
complete circle. In so doing, the concept of “totality of endeavour” (Forbes and Auld, 1955) has become foremost, with particular attention paid to the problems of the airway and the maintenance of adequate respiration.

Tetanus is such a variable disease that an accurate assessment of any form of treatment can be hard to make. Undoubtedly some patients will survive with sedation alone; in others a combination of drugs might be more suitable, while in a few the logical and diligent application of induced paralysis would seem to offer the best chance of recovery.

There are, therefore, two principal methods of controlling reflex spasms; the use primarily of sedatives, with or without additional relaxation, and the use primarily of the muscular relaxants with light anaesthesia or mild sedation.

1. Sedation: (a) The Sedatives.

Sedation—“the keystone of treatment” (Forbes and Auld, 1955)—is essential to relieve anxiety, to induce sleep, to lessen exhaustion, and to reduce the incidence of reflex spasms. Large doses may be required even when spasms are absent or only mild and infrequent. As the disease progresses, heavier sedation may become necessary, with the risks of deep coma. Van Bergen and Buckley’s (1952) patient, previously quoted, is an example of the overdose that may result from efforts to control the severe convulsions, with sedation alone, and an example, too, of how such a moribund patient can be saved.

The sedatives in common use, for example the barbiturates, paraldehyde, and chloral, have little effect on the gross muscle rigidity, except in excessive doses. In such doses they are all central depressants. They act on the basal ganglia and medullary centres; so does hypoxia from deficient pulmonary ventilation or a restricted airway; so does the tetanus toxin (Baker, 1942, 1943; Woolmer, 1954).

The severity of the spasms and the degree of hypertonia vary unpredictably, and in maintaining a patient free from dangerous spasms and relieved of some of the excess tone by sedatives alone the level of sedation may be barely sufficient at one moment, yet excessive the next. To avoid this risk of overdose a combination with drugs such as mephenesin or chlorpromazine, separately or together, might be more effective. If adequate control still cannot be safely achieved, the regime of induced paralysis (see later) should be implemented if facilities allow.

Cumulative and toxic drugs are better avoided. Routine set-interval administration (every three hours, for instance) can also lead to accumulation; each dose can be carefully assessed. Phenobarbitone, to provide a basal sedation, has the advantage of infrequency of administration, but paraldehyde or the medium-acting barbiturates (sodium amylobarbitone, pentobarbitone) are more satisfactory. A short-acting drug such as thiopentone in continuous infusion can provide a more immediate and flexible control, especially when combined with a basal sedative.

Grant and McNeill (1953) successfully used continuous thiopentone 0.4 per cent in a patient aged 20, without tracheotomy. They found that 1.0 g thiopentone was required every 7 hours, and this, combined with pethidine 100 mg 6 hourly, was continued for 16 days. On the second and fourth nights of this treatment there were major crises in which severe spasms were followed by inhalation of regurgitated stomach contents. On each occasion the youth was intubated and large quantities of mucus and gastric contents were aspirated.

A boy aged 7 (Batten, 1956) was successfully treated with thiopentone 1.5 per cent at a daily average of 2.25 g per day for 15 days without tracheotomy. Trismus persisted throughout, and tonicity varied from full opisthotonus to mild tightness while “several attacks of laryngeal spasm caused cyanosis.”

These examples illustrate the precarious state of the patient if undue, some would say unnecessary, risks are taken. Over-emphasis of one aspect (sedation), neglect of another (the airway), of the therapeutic or prophylactic measures, may well compromise the patient (Forbes and Auld, 1955). For instance, a boy aged 9 with a period of onset of only 21 hours (Bodman et al., 1955) was being treated with chlorpromazine and nitrous oxide anaesthesia when, after 12 days of hard battle, a sudden severe convulsion asphyxiated him, and he died. Tracheotomy had been considered but not done, partly for fear of the known complications of this operation.

(b) Chlorpromazine.

Experimentally, Hougs and Anderson (1954) found that either chlorpromazine (1 mg/kg of
body weight) or promethazine (1 mg/kg) injected intravenously could abolish local tetanus in rabbits. Kelly and Laurence (1956) have confirmed these findings (though promethazine—4 mg/kg—had a weaker action), while Dasgupta and Werner (1955) suggested that chlorpromazine has an action on the spinal cord similar to mephenesin.

Clinically, using chlorpromazine alone, Kelly and Laurence (1956) successfully treated a child of 2½ years with severe tetanic spasms. The dose varied from 15 mg (1 mg/kg) to 40 mg as single intravenous injections every 2 to 5 hours, while the total reached 330 mg in one 24-hour period. A total of 3,145 mg was given in 16 days, the aim of the treatment being to subdue the spasms, rather than to achieve complete relaxation. There was no tracheotomy, and several cyanotic episodes from convulsions occurred.

Cole and Robertson (1955), in Tanganyika, found chlorpromazine in 50 mg doses, by injection, combined with sedation (phenobarbitone 3 grains) useful in inhibiting seizures, the effect lasting 8 to 12 hours. Both they and Kelly and Laurence offer no opinion as to its effect on mortality or its place in treatment.

Bodman et al. (1955) combined chlorpromazine, pethidine, and promethazine, given separately in 25 mg doses every 4 hours, with nitrous oxide oxygen anaesthesia. This controlled the convulsions without impairing adequate spontaneous respiration. Withdrawal either of the nitrous oxide or of the chlorpromazine resulted in the reappearance of the convulsions.

Anderson et al. (1955) used chlorpromazine 25 mg, 6 hourly for 36 hours, and then combined it with induced total paralysis using curare, I.P.P.R., and nitrous oxide anaesthesia through a tracheotomy. This regime was maintained satisfactorily for 12½ days, when all treatment was withdrawn except the nitrous oxide. Four and a half days later there was a sudden resurgence of "cyanotic spasms" due, it was thought, to secondary tetanus. Total paralysis was re-instituted, but death occurred 3 days later from agranulocytosis (Gormsen, 1955).

Adriani and Kerr (1955) combined chlorpromazine with mephenesin and barbiturates in 11 patients, with 5 deaths. Finally, the use of "arti-

2. The Muscular Relaxants.

(a) Drugs with a central action – Mephenesin. Mephenesin, introduced by Berger and Bradley (1946), has a central action depressing reflex excitability. The sites of action are on the inter-nuncial cells and neurones in the spinal cord and the reticular bulbar formation in the brain stem (Henneman et al., 1949; Kaada, 1950). The polysynaptic reflexes are depressed with small doses, the monosynaptic reflexes only with larger doses (Taverner, 1952). The drowsiness and nystagmus that occurs with heavy doses suggest an action higher still in the brain stem (Kelly and Laurence, 1955). There is also a definite but important (from the swallowing viewpoint) local analgesic action when applied directly to the pharynx and larynx (Newhouse et al., 1950). All actions are of short duration.

Clinically, it produces a muscular relaxation without respiratory depression, except in excessive doses. Its use in tetanus was first suggested by Belfrage (1947).
The advantages of mephenesin in tetanus.

1. It overcomes hypertonia, and relieves the pain from muscle spasm.
2. It increases the vital capacity and allows the conscious patient to do active breathing exercises, even to cough.
3. Trismus is relieved and normal swallowing becomes possible.
4. It reduces the violence of the spasms but it does not prevent them. It may reduce their frequency when combined with sedation.
5. It has a wide margin of safety, the first signs of overdose being diplopia, nystagmus, and drowsiness.
6. By intravenous infusion, a continuously controlled relaxation is possible.
7. It can be given intravenously, intramuscularly, orally and rectally.
8. It is non-cumulative.

Disadvantages.

1. Intravenously, its action is transient, the effect lasting some 30 to 45 minutes following a single injection. Intramuscular injection may last a little longer.
2. Concentrations above 4 per cent may produce venous thrombosis, or intravascular haemolysis leading to haemoglobinuria (Pugh and Enderby, 1947). (The commercial ampoule contains 1 g in 10 ml of a solution containing alcohol.)
3. Temporary hypotension sometimes occurs, possibly from overdose (Gammon and Churchill, 1949; Smith, H., 1953; Taverner, 1952).
4. The oral preparations should not be given by mouth when dysphagia is present; administration by indwelling intragastric tube is preferable. Undue delay in swallowing mephenesin, whether as elixir, powder, tablets or suspension, may result in pharyngeal or laryngeal analgesia, with possible inhalation of saliva and food.
5. Nausea and gastritis are common when high doses are given; the elixir, which contains alcohol, can produce a drunken stupor, particularly in children.

Dosage.

In the normal conscious subject an intravenous injection of 30 mg/kg of body weight (200 mg/stone) produces a generalized muscular relaxation with sometimes a little respiratory depression.

In the tetanic subject higher doses may be necessary. The aim in mephenesin therapy is to relieve some or all of the excess muscle tone. For a continuous effect an intravenous infusion of a 1 to 1.5 per cent solution is the most satisfactory method, the concentration and drip rate being adjusted to maintain the desired effect and to suit fluid requirements.

Examples.

Recent reports have shown a much heavier dose used than formerly, and in the following examples a continuous infusion was used: Davison (1951) in a boy of 13 years used 91 g. in 6 days; Laurence (1952) quotes a child of only 1½ years in whom 37 g. were given in 3 days (i.e., approximately 40 mg/kg/hour); Docherty (1955) in a youth aged 16 used 198 g. in 14 days.

In a boy aged 13, with a period of onset of 7 days and an approximate weight of 35 kg (5½ stone), 386 g. were successfully infused in 13 days by the author and his colleagues, an overall average of 1.25 g./hour (35 mg/kg/hour) with a maximum 24-hour total of 40 g. (46 mg/kg/hour). At this dosage there was a mild sedative effect with no depression of respiration, and reflex spasms were mild and infrequent. Without mephenesin there was gross tetanic rigidity, pain, sweating, and fairly frequent spasms of variable severity. The oral preparations were tried during the acute phase but to achieve comparable conditions they caused nausea or, with the elixir, a drunken stupor. They were used successfully at a smaller dosage in the convalescent stage.

Comment. The overriding disadvantage of mephenesin is its brief action. The high dosage frequently required usually necessitates a continuous infusion to avoid the gastric disturbances caused by the oral preparations. The oral route is suitable only for the mild case or the convalescent stage of the more severe, by indwelling gastric tube if there is any dysphagia.

(b) Peripheral Neuromuscular Block.

The relaxants such as curare and gallamine often caused depression of respiration and their use frequently proved disappointing. Subsequently, the method of induced relaxation with assisted respiration was advocated, with suxa-
methonium as the drug of choice, since a continuous infusion (0.1 to 0.3 per cent) could be adjusted to follow the minute-to-minute variations in the hypertonia (Woolmer, 1953, 1954).

As an example, a woman aged 58 required a dose of 2.5 mg/min in the acute phase to produce some relaxation without affecting breathing, yet later only 0.2 mg/min caused respiratory depression with cyanosis, requiring pulmonary inflation with oxygen (Woolmer and Cates, 1952). Brinton and Burk (1955), in a man aged 54, found 5 mg/min necessary during periods of hyperexcitability, yet paralysis was not complete. Their patient was unsedated, and although on artificial respiration in a Drinker apparatus, he was able to indicate the rate of drip which varied from 200 to 300 mg/hr of scoline, later falling to 160 mg/hr. They gave 28 g. in 6 days. Both examples illustrate the higher dosage required during the acute stages of the illness.

Though physiologically more correct, this method might be difficult in prolonged treatment. More recently, induced total paralysis with artificial respiration has become an established method, and this highly specialized technique is indicated when other methods fail to control severe spasms, though it can make considerable demands on the expert staff and the ancillary services of the hospital.

The "Total Paralysis" Regime.

The essentials of the induced total paralysis regime are: (1) tracheotomy, with a cuffed tube (previously discussed); (2) induced paralysis; (3) I.P.P.R.; and (4) minimum sedation.

Induced Total Paralysis.

The Longer-acting Group—Curariform Drugs.

Curare has several advocates (Lassen et al., 1954; Honey et al., 1954; Anderson et al., 1955; and others). The advantages claimed are that the return of muscle tone is slow (a rapid return is unnecessary); intramuscular injection is effective and "depot" forms in a wax base ("Tubadil") may be advantageous. Intravenous infusion for injection purposes, though preferable, is not essential. Overdose, provided I.P.P.R. is adequate, carries no material risk.

The disadvantages are that repeated injections are required and a waxing and waning in the degree of paralysis can occur, which can affect the efficiency of a mechanical respirator. The cumulative effect of curare can cause considerable delay in the return of sufficient spontaneous respiration. One patient aged 42, who received 1,005 mg tubocurarine chloride and 350 mg Tubadil in 6 days, took 24 hours to regain adequate respiration following cessation of the curare to assess progress during treatment (Honey et al., 1954).

The Short-acting Group—Suxamethonium.

22.5 g. of suxamethonium, in a continuous infusion, was used by Forrester (1954) in 5½ days (3 mg/min) of total paralysis, with manual inflation of the rebreathing bag, supplemented with nitrous oxide-oxygen anaesthesia.

Employing mechanical inflation, the author and his colleagues found that a profound paralysis was necessary. In a youth aged 15 years, with a period of onset of 30 hours, they successfully used 77 g. of suxamethonium in 11 days of total paralysis, 7 to 8 mg/min being required in the acute stages; it was supplemented throughout with nitrous oxide anaesthesia, with to-and-fro carbon dioxide absorption, and intermittent pethidine.

The disadvantages of continuous suxamethonium are that failure of the infusion may result in a rapid and undesirable return of muscle tone; succinyl monocholine may be produced (Collier and Macauley, 1953); salivary and bronchial secretions may be increased; and the blood pressure may be unduly sensitive to variations in pulmonary ventilation.

Intermittent Positive Pressure Respiration (I.P.P.R.).

Manual inflation, for emergency use, is essential. For long-term treatment, it can be difficult to maintain constant respiratory rates and volumes; it is laborious and dependent on the availability of relays of human volunteers whose "inflating" efficiency can be most variable. "Assisted" respiration would be even more technically difficult to apply over long periods.

Mechanical means of inflation, recently reviewed in this Journal (Mushin and Rendell-Baker, 1954), provide a more controllable and uniform pulmonary ventilation. There are two main groups of apparatus; those primarily for use
with anaesthetic circuits (Aintree, Fazakerley); and those which can inflate the patient with air and are independent of anaesthetic apparatus (Beaver, Radcliffe Respiration Pump).

With mechanical inflation, a complete paralysis is desirable, for any increase in the resistance to inflation may not be compensated by a pulmoflator set at constant inspiratory pressure. A fall in the respiratory minute volume would result, causing carbon dioxide retention. Such a condition can be due either to returning muscle tone, in which case more relaxant would reverse these effects; or to the development of obstruction (atelectasis) within the pulmonary tree, when further relaxant would have no effect, since a greater pressure is required to inflate the diseased chest in a patient totally paralysed (Spalding, 1955; Spalding and Young, 1955).

Constant and physiologically correct ventilation is not easy to maintain in paralysis from disease; it can be even more difficult under the artificial conditions of induced paralysis. As a guide to efficient pulmonary exchange, the following should be observed, where applicable:

(a) Colour changes in the skin.
(b) Incidence of sweating.
(c) Changes in the size of the pupil.
(d) Frequent pulse and blood pressure recordings (½ hourly).
(e) Frequent measurements of minute volumes, and of CO\(_2\) in the expired air.
(f) Inflationary pressure readings.
(g) Oximetry measurements.
(h) Daily urinary pH.
(i) Daily blood biochemistry.

Sedation, with Total Paralysis.

With convulsions fully controlled, only the minimum of sedation is necessary; light anaesthesia can be used or the sedatives, or a combination of both, depending on the method of I.P.P.R.

Nitrous oxide is noncumulative and rapidly eliminated, but additional hazards are introduced, anaesthetic apparatus is necessary, and because the gas is expensive, carbon dioxide absorption is desirable. In semiclosed circuits there may be a frequent incidence of atelectasis due to the rapid absorption of the gases from the alveoli should a bronchial block occur. The author and his colleagues have found that the addition of nitrogen, which is slowly absorbed, to the mixture reduces the incidence of atelectasis.

The sedatives are usually required when the air respiration pumps are used. For instance, Honey et al. (1954) employing the Radcliffe pump, used sodium amylobarbitone 200 mg every 4 hours supplemented by thiopentone.

It may be difficult to assess the level of consciousness or of coma in the patient completely paralysed. E.E.G. recordings may be of some help. These authors mention that “large amounts of barbiturates may be required and the immediate danger of barbiturate poisoning—namely respiratory arrest—is eliminated, since respiration is controlled”.

Additional central depression of the medulla in the severely ill patient would appear undesirable. Some anaesthetists prefer a method such as nitrous oxide anaesthesia which, despite its admitted disadvantages, is flexible. Combined with mild basal sedation and with pethidine as an analgesic, the risk of overdose with any one drug might be reduced.

(4) THE MAINTENANCE OF STRENGTH AND FLUID BALANCE

Tetanus is an exhausting disease, with a raised metabolic rate (Holmdahl and Thorén, 1954), and with excessive loss of fluid from sweat and saliva. Nutrition as well as fluid and electrolyte balance should be carefully maintained since treatment may be prolonged and the convalescent stage of “residual tetanus” difficult (Wilson and Care, 1955).

Feeding by mouth should be avoided as it can be dangerous in the presence of dysphagia. Some rely on parenteral feeding alone (Forbes and Auld, 1955) because of the ever present danger of gastric regurgitation, though this complication can be minimized with a cuffed tracheotomy tube; with such a tube nutritional and fluid needs can be better supplied, either by an indwelling nasal intragastric plastic tube or by a Kader Senn gastrostomy. High daily calorie intake (2,000 to 3,000 calories) is required by frequent small volume feeds or by continuous drip. A constant watch should be kept on fluid and electrolyte
balance with biochemical analyses of blood, daily if necessary, and changes in the haemoglobin content or red cell count of the peripheral blood should be corrected.

(5) ORGANIZATION

Recovery is complete in those who survive. Much will depend on good nursing, attention to detail, and adequate facilities. The application over long periods even of the regime of sedation, parenteral feeding and tracheotomy advocated by Forbes and Auld (1955) can make considerable demands on hospital staff. Even greater effort and vigilance is required when induced paralysis methods are used and for which specially trained teams are desirable.

These newer forms of treatment requiring the constant presence of the expert, especially the anaesthetist, may be impracticable in some hospitals; they should not be undertaken lightly. Special centres, examples of which are the Tetanus Unit at Leeds and the Respiration Unit at Oxford, are better equipped to deal with the complex problems that may arise.

SUMMARY

1. A review is given of the symptomatology and treatment of tetanus.
2. The respiratory problems peculiar to the disease have been discussed and the methods of preventing the more common complications and causes of death are mentioned.
3. Emphasis has been laid on the importance of maintaining a clear airway and effective pulmonary ventilation.
4. Tracheotomy as a prophylactic measure is advocated in all severe cases and its specific indications and management are discussed.
5. The different forms of treatment with sedatives, chlorpromazine, mephenesin, and induced paralysis are reviewed.
6. Treatment in all but the mildest cases consists of a carefully integrated therapeutic regime demanding constant vigilance, adequate staff, and full hospital facilities.

ADDENDUM

Since this review was written, Lassen et al. (1956) have published some important observations on the possible toxic effects on the bone marrow from continuous nitrous oxide anaesthesia. Quoting two cases of fatal agranulocytosis following its use (Lassen et al., 1954; Gormsen, 1955), they published a third fatal case, and also report two further patients in whom, after 5 days of continuous nitrous oxide, severe leucopenia and thrombocytopenia developed. In both patients, haematological remission occurred 3 days after the gas was discontinued. Bone marrow biopsies showed disturbance of granulocytopenia and "severe depression of erythropoiesis of the megaloblastic type", changes which they consider typical.

In reviewing the treatment of 13 cases of tetanus, they found that in 6 who received continuous nitrous oxide, there were changes in the peripheral blood.

In this country, continuous nitrous oxide was used by Forrester (1954) and Bodman (1955), but no changes in the blood were reported. In cases as yet unpublished, the author and his colleagues used this agent with success (August, 1954) continuously for 11 days in one patient (previously mentioned) without ill-effects; but in another (September, 1955), treated initially with mephenesin and subsequently by total paralysis, marrow aplasia of the type described by Lassen (1956) occurred after 6 days of anaesthesia; this patient died on the twelfth day of treatment. A third patient aged 74 (April 1956), treated with mephenesin and chlorpromazine and intermittent nitrous oxide anaesthesia (for turning and chest physiotherapy), also developed a similar aplasia on the eleventh day of treatment; this patient also died.

Hitherto, nitrous oxide has been considered non-toxic. In view of these new complications, caution should be exercised in its prolonged use.

Whatever form of treatment is adopted, careful haematological control is necessary, since in severe tetanus, boldness may be required in pressing drug therapy to the limits of safety (Kelly and Laurence, 1956). Further experimental work is required to determine what these limits are.

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