THE TREATMENT OF TETANUS

A thesis presented by R. WRIGHT for the degree of Doctor of Medicine in the University of Cape Town.

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INTRODUCTION

"If I am wrong, contemporaneous observers will prove it.
If I am right, future generations will feel it."

With these words written in 1846, Dr. J. Marion Sims, the famous gynaecologist, concluded an article on tetanus neonatorum or trismus nascentium, as it was then known, in which he stated that it was "a disease of centric origin depending upon a mechanical pressure exerted on the medulla oblongata" (Hartigan, 1884). Sims and later Hartigan claimed to be able to cure the disease by posturing the infant, or elevating the occipital bones surgically.

Strange as their treatment and theories of etiology may seem in the light of modern knowledge, the current mortality rate of over 80% in most large series of neonatal tetanus shows little therapeutic advance in this, the most severe form of the disease.

On the other hand, in non-neonatal tetanus (tetanus after the age of one month) there has been a progressive decline in mortality rate during the last 50 years largely due to the better management of cases of lesser severity (Creech et al., 1957; Christensen and Thurber, 1957). In some series mortality has been reduced to very low levels (Cole, 1959, Forbes and Auld, 1955), but a group of patients remains, in which severity is comparable to that usually seen in the newborn,

where conventional methods of treatment are ineffective (Christensen and Thurber, 1957; Cole, 1959). Furthermore recent figures based on national statistics in the United States of America (Amick and Alexander, 1957) and Germany (Hübner and Freudenberg, 1954) show a relatively high mortality rate and this is likely to be even higher in areas where tetanus is common but nursing and medical facilities poor. It is in such areas that a simple method of treatment is most needed and assessment of the place of the more complicated regimes recently advocated of great importance.

In an historical review of the treatment of tetanus, Drew (1954) considered that the period of rational treatment of the disease began with the isolation of the organism and the development of an antitoxin. He stated that it had previously been largely empirical and cites numerous "cures" for the disease in the "pre-scientific era". An abstract of a communication on tetanus by O'Beirne (1836) illustrates the treatment used at that time. He treated 20 patients with "tobacco, the gum-elastic tube, and croton oil", and his claims of success in 11 of the 20 patients using this rather unorthodox method of treatment, emphasises the need for care in evaluating new therapeutic regimes based on isolated case reports or on small series.

There are probably only two principles of treatment which are universally accepted:-

1) The need for good nursing and supportive care of the patient, and

2) the need for adequate control of reflex spasms.

Of the numerous therapeutic agents or regimes which have been advocated in the treatment of tetanus the following have been the subject of most debate:

Tetanus Antitoxin. The introduction of tetanus antitoxin into therapeutics led to innumerable claims and counter claims as to its effectiveness, dosage and route of administration. Until recently this controversy dominated the literature on the treatment of the disease. While the value of its prophylactic use was soon established, its efficacy as a therapeutic agent was questioned from the outset (Brew, 1924). Despite these doubts most clinicians considered it to be of value and few were prepared to withhold its use, although some such as Bryant and Fairman (1940) claimed good results without administering tetanus antitoxin.

Johnstone (1958) and Tompkins (1958, 1959) after treating some patients with tetanus antitoxin and withholding it from others found higher mortality rates in the untreated groups, but the differences were not statistically significant. In a randomised trial on 79 patients using a method of sequential analysis however, Laurence (1960) showed a significantly lower mortality rate in a group given 200,000 international

units (i.u.) of tetanus antitoxin compared with another group in which no antitoxin was used (49% compared with 76%).

Following the experimental work of Sherrington (1917) and others, it was claimed that the intrathecal route of administration of antitoxin was superior to other routes (Amhurst, 1926; Voth, 1932; Vener and Bower, 1941). Several workers have found no evidence of its value and stressed practical difficulties (Cole and Spooner, 1935; Huntington, et al., 1937). Wainwright (1926) considered the argument for the intrathecal use of antitoxin to be "that of a geographer based on propinquity, not that of a physician based on physiology", and led the almost universal recent condemnation of its use (Dietrich, 1940; Spaeth, 1940; Silverthorne, 1947). Dietrich (1940) and Silverthorne (1947) favoured the use of the intramuscular rather than the intravenous route for the administration of antitoxin and advocated repetition of the dose. While reactions are probably more frequent when the latter route is used, they can be reduced to a minimum by careful preliminary testing for sensitivity and if necessary by the administration of adrenalin.(Turner et al., 1958). Cole and Spooner and Turner and his colleagues after measuring serum antitoxin levels in their patients considered that a single dose should be given intravenously as soon as the diagnosis is made, and that it need not be repeated unless the wound is extensive and healing delayed. Recently most authors have compromised by giving half the dose intramuscularly and the other half intravenously,

doses of 100,000 i.u. or more generally being recommended (Vimmard, 1945; Forbes and Auld, 1955; Creech et al., 1957; Garcia-Palmieri and Ramirez, 1957).

The care of the wound: Wound excision, sometimes extensive, and debridement have been favoured by many workers who have achieved some of the lowest mortality rates recorded for large series (Venor and Bower, 1941; Vimmard, 1945; Veronesi, 1956; Creech et al., 1957). There is, however, no evidence that these results were related to the treatment of the wound. In the absence of any controlled comparative study, it seems reasonable to adopt a more conservative approach, such as that recommended by Spaeth (1940), Pratt (1945) and Cole (1953), who suggested limited interference if indicated by the state of the wound on its own merits, with particular attention to the removal of necrotic tissue and foreign bodies, and to irrigation with oxidising solutions.

Penicillin: Although it seems likely that penicillin produces little alteration in the course of the established disease (Altemeier, 1946), it has been shown that the organism usually disappears rapidly from the wound after the systemic injection of the antibiotic (Dias-Riviera et al., 1948). Apart from a possible action on Clostridium tetani the use of penicillin has been recommended for its effect on associated wound infections, and the prevention of pulmonary complications.

Methods of control of reflex spasm: The need for isolation of patients

in a quiet darkened room and the reduction of external stimuli to a minimum is generally accepted. Innumerable sedatives, hypnotics and muscle relaxants have been tried in an attempt to reduce the frequency and severity of reflex spasms.

a) Sedatives and hypnotics: Those still commonly used include barbiturates (Vinnard, 1945; Garcia-Palmieri and Ramires, 1957), paraldehyde (Johnstone, 1958), tribromoethanol (Cooke, 1948; Cole, 1953; Forbes and Auld, 1955) and chloral hydrate (Sloss, 1953). All these drugs cause central depression to a varying degree and are therefore often only used in combination, or with a muscle relaxant (Godman and Adriani, 1949; Veroneai, 1956). Numerous methods of sedation have also been used in the treatment of neonatal tetanus. Controlled comparative trials of these sedatives have not been performed, but it would seem that there is little to choose between them.

b) Phenothiazine derivatives: Laurence (1958) considered that "a drug with ideal antitetanus properties .....should abolish tetanus convulsions without interfering with respiration in any way", and that chlorpromazine and related drugs fulfilled these criteria in part. Chlorpromazine was first synthesised in 1950 by a group of French workers who found it to have a wide variety of pharmacological actions which led to its extensive use therapeutically (Dundee, 1954; Robson and Keele, 1956). Several of these actions suggested the use of chlorpromazine in tetanus. It has been shown to have a muscle relaxant

effect on skeletal muscle (Burn, 1954; Katkin et al., 1956). In addition it acts as a sedative and hypnotic and potentiates the action of d-tubocurarine, nephenesin and barbiturates (Courvoisier et al., 1953; Burn, 1954; Brodie et al., 1955). Experimentally chlorpromazine has been shown to abolish local tetanus in rabbits (Hougs and Anderson, 1954; Kelly and Lawrence, 1956) and Barr (1958) has demonstrated its relaxant effect on trismus in human tetanus.

Although chlorpromazine was tried clinically in the treatment of tetanus soon after its introduction into anaesthetic practice (Hellaret et al., 1952), it was used empirically in combination with other drugs and in inadequate dosage so that its antitetanus effect was not evident (Lawrence, 1958). Cole and Robertson (1955) treated six patients with chlorpromazine in 50 mg. doses given intravenously or intramuscularly with added barbiturate or chloral hydrate. They did not claim a reduction in mortality but were impressed with its ability to inhibit spasms and relax rigid muscles and state that "a lazy sleepiness replaced the conscious tension of the disease." Gelfand (1955) was impressed with its use in neonatal tetanus. However, Anderson and his colleagues (1955) could not control spasms in a ten-year-old patient suffering from severe tetanus, with chlorpromazine 25 mg. given six-hourly intramuscularly. Adriani and Kerr (1955) while disappointed with its lack of effectiveness when used alone thought it a valuable adjunct if combined with nephenesin and barbiturates. Bodman

and his colleagues (1955) combined chlorpromazine, promethazine and pethidine with nitrous oxide anaesthesia in a patient with tetanus and although he died, they were impressed with the relaxant and sedative effect of the phenothiazine derivatives as well as their ability to reduce secretions.

Kelly and Laurence (1956) tried to determine the usefulness of chlorpromazine when given alone. They produced local tetanus in one hindleg of a rabbit, and tested the effect of various drugs on tetanic spasms produced by a standard afferent stimulus. Chlorpromazine was found to be the most promising of the drugs tested. It was therefore used clinically, in doses of up to 350 mg. daily, in a child aged 2½ years suffering from severe tetanus. The child recovered and their conclusions as to the ability of chlorpromazine to control reflex spasms and reduce rigidity were similar to those of Cole and Robertson.

Subsequently favourable reports have appeared of the use of chlorpromazine alone or in combination with sedatives such as barbiturates or paraldehyde, in small numbers of cases (Martin, 1957; Packard et al., 1958; Hamilton, 1959) as well as in larger series (Golfand, 1955, 1957; Laurence et al., 1958; Earle and Mellon, 1958; Adams et al., 1959; Shamber and Mehrotra, 1959; Vahil, 1960) in both neonatal and non-neonatal tetanus. Phenothiazine derivatives have also been used together with barbiturates and pethidine in the so-called "lytic cocktail" (Rossi, et al., 1954; Jansson, 1957; Lorens, 1957; Roten and Chigier, 1957; Mollaret, 1959) or with muscle relaxants (Adriani and Kerr, 1955; Sarroux et al., 1956;

Veronesi, 1956; Pinheiro, 1957; Crouch et al., 1957; Giese, 1959).

While most of these reports have been favourable, the extent to which the phenothiazine derivatives can reduce mortality in tetanus is uncertain and requires further assessment.

e) Muscle relaxants: Although not the first to employ curare, Velle (1859) focused attention on its use. Its unreliability and the danger of death from respiratory paralysis was soon recognised (Lamont, 1859) and it was seldom used until revived by Cole (1934), Mitchell (1935) and West (1936). Favourable reports have come from Wood and his colleagues (1949), Benger and Devnich (1950) and Segar and his colleagues (1952), in which various preparations of curare, including a depot form were used. However, Codman and Adriani (1949) felt that the degree of paralysis even with a depot form was unpredictable and Knott and Cole (1952) considered that there was no preparation of curare which was reliable and safe.

Succinylcholine (Woolmer and Gates, 1952; Littlewood et al., 1954) and gallamine triethiodide (Smith and Therme, 1952; McIntyre, 1953; Parkes, 1954) are other muscle relaxants which have been tried with variable results, overdosage with consequent respiratory paralysis being a constant danger.

Mephenesin has largely replaced curare and the other muscle relaxants when used without total paralysis and assisted respiration.

It is said to produce muscular relaxation with little intercostal or diaphragmatic impairment (Berger and Bradley, 1946, 1947; Hallinson, 1947; Stephen and Chandy, 1947). Belfrage (1947) was the first to use mephenesin in the treatment of tetanus and favourable reports on small numbers of cases followed (Terrone et al., 1948; Davison et al., 1949). These served to stimulate further trial and also to confirm the danger of thrombophlebitis and haemoglobinuria when the drug was given parenterally in high concentration (Pugh and Enderby, 1947). When an oral preparation has been used, reports have been variable (Godman and Adriani, 1949; Newhouse et al., 1950; Boles and Smith, 1951; Diez-Rivera et al., 1954).

Veronesi (1956) has tried the intravenous route extensively and has recorded the remarkably low mortality rate of 18.2% in 236 consecutive cases. Adriani and Kerr (1955) and Creech and his colleagues (1957) were favourably impressed with the combination of oral mephenesin and parenteral chlorpromazine and barbiturate.

From these reports it would seem that mephenesin alone or in combination with drugs such as chlorpromazine and barbiturate is of value in the control of rigidity and reflex spasms. Its toxicity, the difficulty of continuous intravenous infusion and the uncertainty of its action when given orally are factors limiting its usefulness.

Cortisone: On the grounds that it might prevent death from exhaustion, Christensen and his colleagues (1952) successfully used cortisone in a

child with severe tetanus. Sloss (1953) treated twelve patients suffering from tetanus of varying severity with cortisone or adrenocorticotrophic hormone (ACTH), and considered it to be life-saving in one. Lewis and his colleagues (1954) reported a clinical trial in a group of 40 selected patients suffering from severe tetanus, and claimed that if given orally cortisone produced a significantly lower mortality. In neonatal tetanus, Klemerman and Scragg (1955) used ACTH with favourable results.

Although further trials to assess the place of these drugs in the treatment of tetanus seem indicated, the experimental work of Chang and Weinstein (1957) suggests the need for caution in their use. They concluded that cortisone may be contraindicated in human tetanus after showing that in mice it reduced the effectiveness of tetanus antitoxin. On the other hand Sloss found that the level of circulating antitoxin in three of his patients was uninfluenced by its use.

Tracheotomy: According to Herson and his colleagues (1951), the use of tracheotomy in tetanus was first suggested by Thomas Curling in 1837, and first performed by Humphrey in 1856. However it is only as a result of recent reports that it has been frequently used (Harris et al., 1948; Turner and Galloway, 1949; Creech et al., 1950; Herson et al., 1951). These workers as well as Saint and his colleagues (1953), Woolmer (1953), Ablett (1956) and Wilson (1956) have stressed the importance of tetanus as a respiratory problem and put forward sound theoretical reasons

for tracheotomy. Segar and his colleagues (1952), Forbes and Auld (1955) and others have obtained excellent results with its use and tracheotomy appears to be one of the factors responsible for the low mortality at the Charity Hospital (Creech et al., 1957). The place of tracheotomy in the treatment of tetanus and the problems and complications associated with its use will be discussed later.

Total paralysis and assisted respiration: Prior to 1952 some reports such as that of Turner and Galloway (1949) mentioned the use of mechanical means of assisting respiration in the treatment of tetanus with muscle relaxants. However, Van Bergen and Buckley (1952) are usually credited with being the first to treat a patient suffering from tetanus by deliberately inducing total paralysis and then maintaining artificial respiration over a prolonged period. This principle did not receive wider application in the treatment of tetanus until the development of the technique of manual positive-pressure ventilation by Lassen and his colleagues during the Danish poliomyelitis epidemic (Lassen, 1953; Ibsen, 1954). Ibsen and his colleagues (1953) treated the first case of tetanus along these lines using tubocurarine to produce total paralysis for 17 days. Shackleton (1954) and Forrester (1954) also used manual inflation but chose intravenous succinylcholine as the relaxant in the treatment of an adult suffering from severe tetanus. Henry and his colleagues (1954) produced total paralysis with curare in their patient for 6 days and maintained respiration by means of a mechanical respirator (Russell and Schuster, 1953). All patients in these early reports of

total curarisation and intermittent positive-pressure respiration (I.P.P.R.) recovered, and it seemed as though tetanus even in its most severe form could be treated successfully. However, it was soon apparent that problems associated with this method of treatment were numerous, and it was suggested that because of the increase in survival time as a result of its use, complications of tetanus previously unrecognised could become manifest (Lassen et al., 1954).

Large numbers of single cases reports as well as small series have been recorded during the past 6 years, and although it would appear that patients who would otherwise have died have been saved by this technique it has often proved unsuccessful. Gleenup and Low (1957) and Alhady and his colleagues (1960), working in areas where facilities were limited, were able to save only 1 out of 7, and 2 out of 10 patients respectively when treated with I.P.P.R., thus emphasizing the warning of Cole (1959) that these new methods are still under trial.

The Present Study:

Five hundred and fifty patients suffering from generalised tetanus, admitted without selection to a separate unit at King Edward VIII Hospital, Durban, between May 1956 and June 1960, form the material for this study. A special case sheet was designed to record the clinical features and a typewritten summary of each is filed in the Department of Medicine, University of Natal. Two examples of these summaries are included in an appendix to this thesis together with brief details, chiefly in tabular form, of all patients.

Some of these patients were investigated in a series of therapeutic trials to assess the value of chlorpromazine, acetylpromazine and tracheotomy, and later I.P.P.R. in the treatment of tetanus.

In this thesis the design of the trials will be described, and the results and their significance discussed.

In order to develop criteria of severity and prognosis for the comparison of the different treatment groups and for the selection of patients for I.P.P.R., the clinical features and cause and mechanism of death in patients treated before the start of the trial of I.P.P.R. will be analysed.

The frequency of vertebral fractures as a complication of the disease will be indicated as a point of interest.

The local incidence of the disease will be compared with that elsewhere and problems of treatment and prevention in areas where tetanus is common will be discussed.

The author has been responsible for the day to day management and the keeping of case records and summaries of approximately 450 patients who were admitted to the unit after January 1957. The design and conduct of these trials have been the work of a team and some of the material included here has already been published (Lawrence, Berman, Scragg and Adams, 1958; Adams, Wright, Berman and Lawrence, 1959; Wright 1960 a and b).

DIAGNOSIS

The diagnosis was seldom difficult and was usually made by an out-patient officer before the patient was admitted to the tetanus unit.

Non-neonatal patients: The typical clinical picture of trismus, risus sardonicus, tonic stiffness of abdominal, spinal and limb muscles with or without generalized reflex spasms occurring in a conscious patient who had often had a recent injury provided no problem in diagnosis. However, the occasional case showed an association of marked opisthotonus, trismus, high fever and stupor, initially mistaken for meningitis or encephalitis. Subsequent experience and mention of similar cases in the literature (Cooke, 1948; Veronesi, 1956), led to this clinical picture being accepted as tetanus. It is of some interest to note the conditions most frequently misdiagnosed as tetanus by admitting officers. They were schizophrenia, hysteria, meningitis and encephalitis.

Neonatal patients: Jelliffe (1958) has said that there is no really valid differential diagnosis of tetanus neonatorum. While in general, experience in the present series confirms this statement, atypical forms have occurred. Although 90% of infants were having generalised reflex spasms at the time of admission, and the diagnosis was obvious, in a small minority reflex spasms were never observed, but facies, trismus and generalized rigidity were characteristic, and appeared to correspond to mild tetanus in non-

neonatal patients. Occasionally a very severe case having cyanotic attacks showed muscular flaccidity between bouts of reflex spasms. Infants suffering from meningitis, scleroma, tetany and cerebral haemorrhage have been admitted to the unit in error, but because of the local prevalence and severity of tetanus neonatorum, out-patient officers have seldom made an incorrect diagnosis.

Necropsies were performed on all patients who died and in only one, an adult seen early in the series who died of uraemia, was the clinical diagnosis of tetanus disproved. Bacteriological confirmation of the diagnosis was attempted in some early cases, but soon abandoned because of lack of success due to technical difficulty in a busy routine laboratory. Recently, however, as a result of improved technique, toxigenic strains of Clostridium tetani have been cultured from the umbilical pus of 6 infants treated on the I.P.P.R. trial.

INCIDENCE

Of the 550 patients suffering from tetanus who were admitted to the unit during the period May 1956 to June 1960, 329 were under the age of one month and the remainder were aged from 10 months to 61 years. An additional 32 cases of neonatal tetanus were admitted to the paediatric wards of the hospital during the period under review.

In an attempt to determine the incidence of the disease in Natal, figures of hospital admissions and deaths from tetanus were obtained for the years 1957, 1958 and 1959 either by personal contact or by circularising medical officers at all provincial and mission hospitals in the Province (table 1). Only two deaths from tetanus were reported among Europeans or Coloureds during this period so that these racial groups are not included in the analysis. Based on these figures, combined death rates from tetanus among the African and Indian races in Natal are 55.0, 74.5 and 69.8 per million living for the years 1957, 1958 and 1959 respectively. It is likely that this does not represent the true incidence of the disease, since in many outlying areas hospital facilities are not available, and in infants in whom the course is fulminating death may occur before medical aid is sought.

African and Indian birth rates are unknown so that accurate specific neonatal mortality rates cannot be calculated. Some indication of the local incidence of tetanus neonatorum can, however, be obtained from an analysis of the neonatal mortality rate in this hospital (table 2).

TABLE 1

INCIDENCE OF TETANUS IN NATAL AMONG AFRICANS AND INDIANS FOR THE YEARS 1957, 1958, 1959

NEONATAL PATIENTS

	1957		1958		1959	
	Cases	Deaths	Cases	Deaths	Cases	Deaths
Durban Area	62	54	111	92	106	83
Provincial Hospitals	28	22	53	38	43	34
Mission Hospitals	4	3	8	4	11	9
Total	94	79	172	134	160	126

NON-NEONATAL PATIENTS

	1957		1958		1959	
	Cases	Deaths	Cases	Deaths	Cases	Deaths
Durban Area	62	26	53	22	48	20
Provincial Hospitals	38	18	46	21	41	28
Mission Hospitals	5	3	5	2	7	2
Total	105	47	104	45	96	50

TABLE 2

NEONATAL DEATHS AT KING EDWARD VIII HOSPITAL FOR THE YEAR ENDED 30 JUNE 1959

		% of Total
Prematurity	167	26.2
Tetanus	90	14.2
Asphyxia neonatorum and atelectasis	87	13.2
Bronchopneumonia	79	12.4
Gastro-enteritis	72	11.3
Miscellaneous	61	9.6
Haemorrhagic disorders	49	7.7
Cerebral haemorrhage	18	2.8
Meningitis and septicaemia	12	1.9
Total	635	

It will be seen that tetanus is second only to prematurity as a cause of neonatal death.

Age, race and sex incidence: Table 3 shows the age incidence and table 4 the race and sex incidence in both neonatal and non-neonatal patients.

Seasonal incidence: There was a slight increase in the number of patients suffering from tetanus who were admitted to the hospital during the early summer months, with a fall during mid-winter.

Geographical incidence: It is difficult to determine with any accuracy the local geographical incidence of the disease. Patients often travelled long distances for treatment, or were transferred from outlying mission hospitals to larger centres. Table 1, however, suggests that the incidence in the Durban area is greater than in the rest of Natal. The number of patients transferred to the unit from outside the Durban area was small, although a larger number travelled long distances from rural areas for treatment at the hospital.

It is even more difficult to compare the local incidence of tetanus with that elsewhere. Sloss (1953, 1954) has shown that the disease is common throughout South Africa, but figures are not available for comparison on a provincial basis. Tetanus is not a notifiable disease and records of deaths from tetanus occurring among African patients are not kept by the Registrar of Births and Deaths, Pretoria.

Reports in the literature indicate that tetanus neonatorum is

TABLE 3

AGE INCIDENCE OF 550 NEONATAL AND NON-NEONATAL PATIENTS

NEONATAL PATIENTS

Age (Days)	3	4	5	6	7	8	9	10	11	12	13	14	>14
No. of Patients	3	18	67	74	64	38	21	15	6	9	3	5	6

NON-NEONATAL PATIENTS

Age (Years)	1	1-5	6-10	11-15	16-20	21-30	31-40	41-50	>50
No. of Patients	1	22	51	39	20	38	23	17	10

TABLE 4

RACE AND SEX INCIDENCE OF 549 NEONATAL AND NON-NEONATAL PATIENTS

(1 Coloured patient excluded)

	NEONATAL PATIENTS			NON-NEONATAL PATIENTS		
	African	Indian	Ratio	African	Indian	Ratio
Race	301	28	10.75 to 1	137	83	1.65 to 1
	Male	Female	Ratio	Male	Female	Ratio
Sex	183	146	1.25 to 1	147	74	1.99 to 1

a common cause of neonatal death in some countries although no accurate figures of its incidence are available. While it would appear that tetanus neonatorum has almost disappeared in Great Britain (Conybeare and Logan, 1951; Ferguson, 1958), it still occurs not infrequently in parts of the United States of America (Annick and Alexander, 1957). Reports from Nigeria (Jelliffe, 1950; Tompkins, 1958), India (Prasad, 1956; Verma, 1956), Brazil (Pinheiro, 1957), Malaya (Loh Siew Gek, 1951), Iraq (Critchley, 1958), the Belgian Congo (Rahayt, 1950; Lambotte-Legrand, 1950), Haiti (Earle and Mellen, 1958) and Thailand (Stahlie, 1960) indicate the high incidence of tetanus neonatorum in these areas and the problems of treatment and prevention which are posed.

Most of these authors emphasise lack of hygiene during confinement and primitive customs associated with the care of the cord as aetiological factors. In the present series about one-third of the mothers gave a history of the application to the umbilicus of a 'black powder' obtained from a witch-doctor, and Clostridium tetani has been cultured from this substance. Other substances which have been used include soil and animal excreta. The disease has affected all of two sets of twins, and two families have lost successive babies from the disease. Confinement on a mat in a hut or shack with an earthen floor, and the use of an unsterilised razor blade, pair of scissors or sharp reed for cutting the cord, has not surprisingly resulted in umbilical sepsis. However, quite frequently the delivery took place in a domestic servant's quarters, and some of the mothers, occasionally with teaching

or nursing experience, had obviously made some attempt at an hygienic confinement.

Of 100 recent consecutive cases of tetanus neonatorum admitted to the unit 12 were born in this hospital. Their average age on admission was greater than that for the series as a whole (9.2 days compared with 7.1 days), but the mortality no lower. Many confessed to having applied one of the substances mentioned above to the umbilicus after discharge from hospital. Furthermore a recent increase in the number of hospital-born infants contracting the disease appears to be associated with the necessity, due to overcrowding, for the earlier discharge after confinement of infants born in this hospital during the past year. These facts suggest that, in infants discharged prematurely, infection can occur at home despite confinement in hospital.

Problems of prevention of the disease will be referred to when the treatment used in the present series is discussed.

CRITERIA OF SEVERITY AND THE ASSESSMENT OF PROGNOSIS

Mortality has been related to race, sex, age, site and nature of wound, incubation period, and period of onset (Cole, 1940). The time between the first symptom of tetanus and the admission of the patient to hospital (Huntington et al., 1937; Spaeth, 1940; Johnstone, 1958; Kelphy, 1958) or the administration of antitoxin (Cole, 1940; Sloss, 1953), the height of fever (Spaeth, 1940; Johnstone, 1958; Tompkins, 1958, 1959) and the severity of reflex spasms (Pratt, 1945; Christensen, 1957), have also been used as prognostic criteria. Some of these criteria will be analysed in the present series, to determine their relative value as a guide to prognosis for the selection of patients for total paralysis and I.P.P.R. and for comparing the severity of randomized groups. Only patients seen before the introduction of I.P.P.R. in the unit will be analysed. These comprise 165 non-neonatal and 217 neonatal patients.

AGE, RACE & SEX: The increasing mortality rate in the older age groups (table 5) with a low mortality rate during adolescence is in keeping with that usually found elsewhere (Cole, 1940; Sloss, 1953).

In infants there is a marked reduction in mortality rate with increasing age (table 5). This is shown clearly if the mortality in infants below the age of eight days (92.7%) is compared with that in infants aged eight days or more (59.1%), and at the age of ten days the difference is even more striking (90.4% compared with 31%).

The higher mortality rate among non-neonatal Indian patients cannot be explained (table 6). Postabortal tetanus, known for its severity, was commoner in this group but the numbers were relatively small. However, postabortal tetanus accounts for the slightly higher mortality rate among non-neonatal female patients (table 7).

Type and severity of the wound: A careful history was taken from all patients, and an examination made to determine the site of entry of the organism.

Neonatal patients: In all infants the umbilicus was presumed to be the site of infection. It was almost always septic but even in those in whom it appeared normal superficially, deep-seated pus was frequently found.

Non-neonatal patients: In table 8 the mortality rate according to the site of wound is shown.

The higher mortality in the group in which the uterus was the portal of entry is well recognised (Weinstein and Rosenau, 1941; Sloan, 1953; Hübner and Freudenberg, 1954; Adams and Morton, 1955). Nine were postabortal cases and one resulted from a septic pedunculated fibroid, which had protruded through the cervix into the vagina (case 160). Comparison of the remaining sites shows little significant difference in mortality. Of interest is the lower mortality rate in patients with wounds of the head when compared with those of the legs, a finding contrary to that in most series (Cole, 1940; Moore and Singleton, 1939; Virnard,

TABLE 5

MORTALITY RATE IN RELATION TO AGE IN 217 NEONATAL AND 165 NON-NEONATAL PATIENTS

NEONATAL PATIENTS

Age (Days)	3	4	5	6	7	8	9	10	11	12	13	14	>14
Cases	1	12	44	50	44	21	16	10	4	6	3	3	3
Deaths	1	11	42	46	40	18	12	3	1	2	2	1	0
Mort.%	100	83	95	92	91	86	75	30	25	33	67	33	0

NON-NEONATAL PATIENTS

Age (Years)	1-5	6-10	11-15	16-20	21-30	31-40	41-50	>50
Cases	20	37	31	18	26	14	11	8
Deaths	9	24	8	5	8	7	5	4
Mort.%	45	65	25	28	32	50	45	50

TABLE 6

MORTALITY RATE IN RELATION TO RACE IN 217 NEONATAL AND 165 NON-NEONATAL PATIENTS

	NEONATAL PATIENTS			NON-NEONATAL PATIENTS		
	Cases	Deaths	Mort.%	Cases	Deaths	Mort.%
Indian	19	16	84.2	63	31	49
African	198	163	82.5	102	40	39

TABLE 7

MORTALITY RATE IN RELATION TO SEX IN 217 NEONATAL AND 165 NON-NEONATAL PATIENTS

	NEONATAL PATIENTS			NON-NEONATAL PATIENTS		
	Cases	Deaths	Mort.%	Cases	Deaths	Mort.%
Males	128	109	85.1	110	44	40
Females	89	70	78.6	55	27	49

TABLE 8

MORTALITY RATE IN RELATION TO SITE OF WOUND IN 165 NON-NEONATAL PATIENTS

Site of Wound	Cases	Deaths	% Mort.	% of Total
Leg	66	30	45.5	42.3
Multiple	19	4	21.0	5.6
Head	18	7	38.8	9.9
Uterus	10	9	90.0	12.7
Arm	9	3	33.3	4.2
Trunk	3	1	33.3	1.4
No Wound	40	17	42.5	23.9

1945; Sloss, 1953). The proportion in whom no portal of entry could be found was higher than that usually reported (Cole, 1940; Vinnard, 1945; Veronesi, 1956; Garcia-Palmieri and Ramirez, 1957; Christensen and Thurber, 1957), but confirms the findings of Johnstone (1958), who suggested that infection in these patients resulted from trivial injuries to the feet which occur more frequently in a primitive community. Contrary to the findings of Cole(1940), the mortality rate in this group was similar to the overall mortality rate (43%).

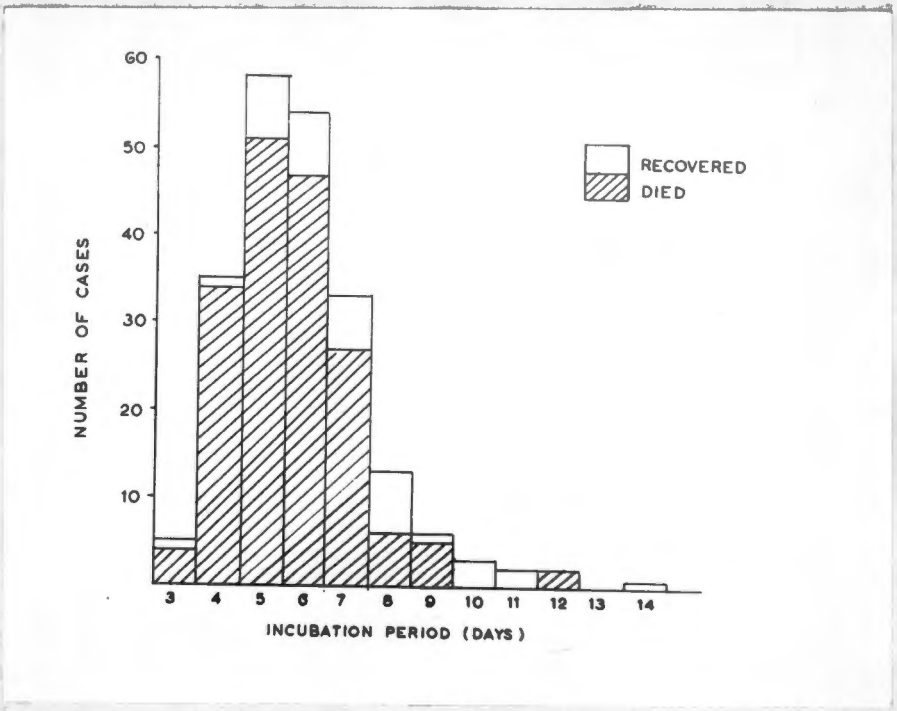
The majority of injuries were of a minor nature and included punctured wounds of the feet, minor lacerations and abrasions, superficial stab wounds and burns. Otitis media, septic vaccination marks and chronic ulcers of the legs were occasionally implicated as the portal of entry. Seldom was the injury thought to have contributed to death. One patient (case 138) developed septicaemia following traumatic amputation of a toe, 2 with a uterine focus (cases 94 and 160) were complicated by blood loss and sepsis and 1 (case 107) died following nephrectomy for a carcinoma of the kidney. Contrary to the findings of Sloss (1953) mortality rates were no higher in postoperative cases or in those with burns and, in fact, 2 patients suffering from severe tetanus recovered despite extensive burns. Passive immunisation at the time of injury did not appear to modify severity, since 4 of the 9 patients who were immunised died.

Incubation period, period of onset and admission time:

Incubation period: We have defined the incubation period as the interval between the receipt of the wound and the first symptom of tetanus. In neonatal patients it has been assumed that infection takes place soon after birth. In non-neonatal patients only wounds occurring within 21 days of the onset of symptoms have been analysed.

Figure I shows a decline in mortality with increasing length of incubation period in neonatal patients. Spivey and his colleagues (1953) considered that a 7 day incubation period is a critical one for assessing prognosis. Only 1 of their patients died among those in whom the incubation period was more than 7 days, and only 1 recovered in whom it was 7 days or less. In this series, if similarly grouped, mortality rates were 48% and 89% respectively, figures almost identical with those in 347 cases reported by Critchley (1958). It will be noted that there were only 2 deaths among patients in whom the incubation period was greater than 10 days, and that 9 patients with an incubation period of 5 days or less recovered.

There is a similar decline in mortality with increasing length of incubation period in non-neonatal patients (figure 2). The most significant difference in mortality rate occurred when patients with an incubation period of 8 days or less were compared with those in whom it exceeded 8 days (70% compared with 28.6%), a difference slightly more marked than that found by Johnstone (1958). Although, in general, Cole's finding that a short incubation period usually meant a severe and fatal



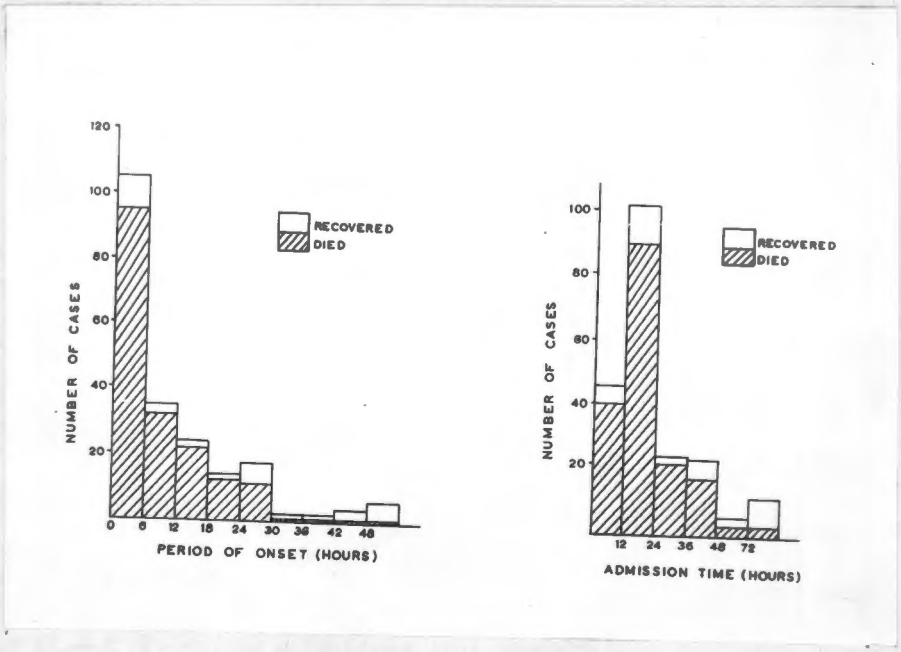
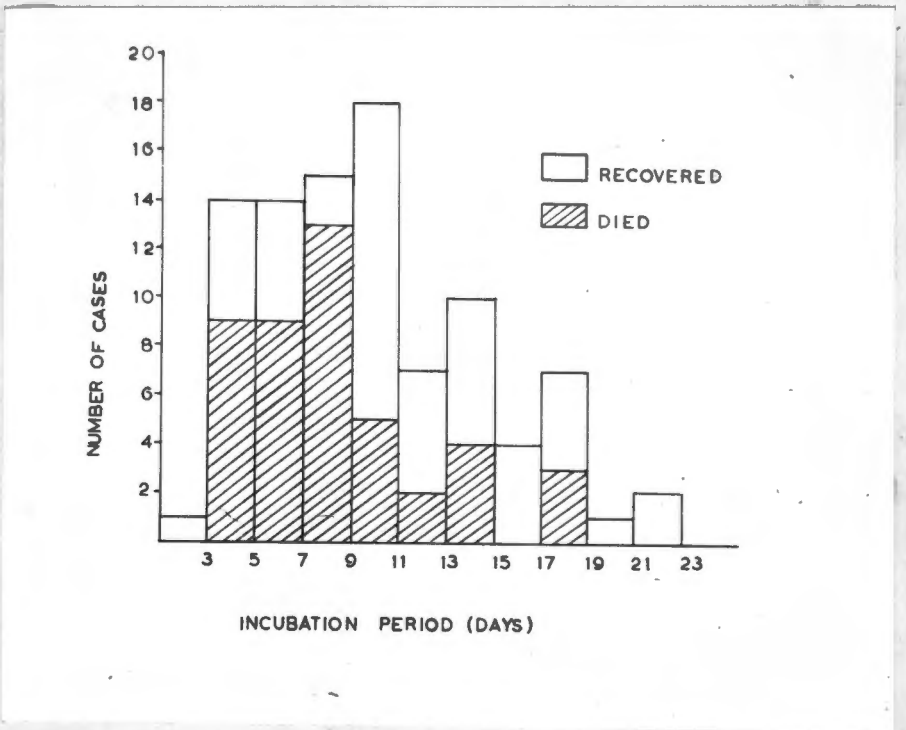


Figure I - Mortality in relation to incubation period, period of onset and admission time (Neonatal patients).



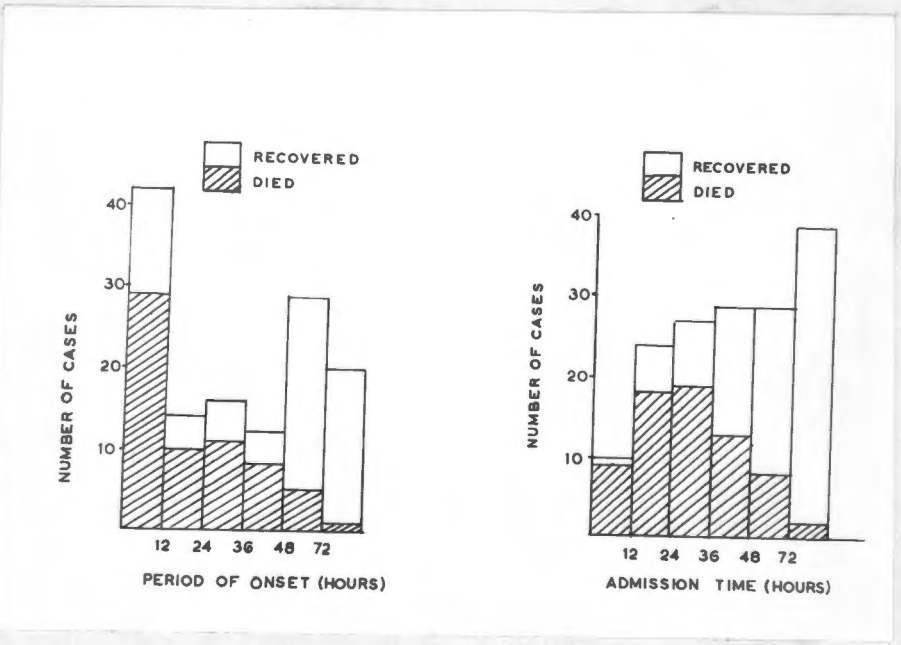


Figure II - Mortality in relation to incubation period, period of onset and admission time (Non-neonatal patients).

attack was confirmed (Cole (1940)), 6 patients recovered despite an incubation period less than 5 days. Recovery with a short incubation period has been even more common in some series (Moore and Singleton, 1939). The mortality rate was 20% in patients whose injury had occurred more than 21 days before the onset of symptoms. Wounds in these patients were usually chronic ulcers and the incubation period therefore uncertain.

Period of onset: We have defined the period of onset after Cole (1940), as "the time between the first symptom of the disease and that of the first reflex spasms." In both neonatal and non-neonatal patients in this series trismus or inability to feed has almost always been the presenting symptom.

The finding that the period of onset was less than 6 hours in almost half of those neonatal patients in whom it was known is in keeping with the severity of the disease in this group. The mortality rate was 90% if the period of onset was 24 hours or less and 50% if over 24 hours (figure 1), findings similar to those of Tompkins (1958). Of 6 patients in whom it was over 48 hours only 1 died.

Six of 49 non-neonatal patients with a period of onset exceeding 48 hours died, a mortality rate of 12½%. Although a period of onset less than 48 hours usually indicated a poor prognosis, the recovery rate of 31% was higher than is usually reported (Cole, 1940).

Admission time: We have taken the admission time to denote the interval between the first symptom of the disease and the time of admission of the patient to hospital.

Figures 1 and 2 show that mortality rates according to admission time run roughly parallel to those according to period of onset in both neonatal and non-neonatal patients. However, a short admission time gives the better guide to prognosis, particularly in non-neonatal patients.

Severity of reflex spasms: Tetanus was classified as "mild" if generalised reflex spasms were never observed; "moderate" if they were either mild or infrequent; and as "severe" if they were both frequent and severe.

Patients were allotted to these groups in retrospect as a result of personal observation by at least two members of the team, and no reliance was placed on nursing records when assessing severity. Reid and his colleagues (1958) found difficulty in defining a generalised reflex spasm. For the purpose of this classification spasms were considered to be generalised if the muscles of the trunk were involved in a sudden clonic contraction with arching of the back. When in doubt it was found that the simultaneous contraction of the abdominal and spinal muscles which occurred during a reflex spasm, could best be detected by placing one hand on the anterior abdominal wall and the other under the arched back. If laryngeal or pharyngeal spasms occurred in the absence of severe generalised spasms, even though fatal, the case was classified as mild or moderate. It is impossible to define exactly the number and severity of reflex spasms which class a given case as severe rather than moderate. In general, patients were classified as

severe if they had more than two or three spasms during a ten-minute period of observation. With experience, considerable uniformity was achieved between observers in the assessment of severity in relation to reflex spasms.

Table 9 shows that it was not unusual for non-neonatal patients who appeared mild at first to become severe after admission to hospital. The severity of reflex spasms is related to mortality in non-neonatal patients in figure 3. In all but 5 of the non-neonatal deaths, frequent severe reflex spasms were observed at some time. In 3 of these generalised reflex spasms were never observed. One (case 140) was atypical and showed the picture of high fever, increasing opisthotonus and death from respiratory failure referred to earlier. The other two were elderly (cases 129 and 142), and died of complications rather than the disease itself. Of the 2 patients having only moderately severe spasms, 1 (case 59) was found dead in bed, the cause of death unknown, the other (case 100) died following severe laryngeal spasms.

If incubation period, period of onset and admission time are related to mortality in patients having severe reflex spasms the general trend noted when all cases were analysed is emphasised (figure 4). This shows that patients with severe reflex spasms who have a short incubation period have a grave prognosis. Although much lower if the incubation period was long the mortality rate was still substantial. While patients with severe reflex spasms who had a short admission time and period of

TABLE 9

MORTALITY RATES IN RELATION TO SEVERITY ON ADMISSION AND DURING SUBSEQUENT COURSE

(165 Non-neonatal patients)

Severity on Admission	No. of Cases	No. of Deaths	Mortality %	No. that became severe	No. of Deaths	Mortality %
Mild	55	14	25.5	20	11	55
Moderate	37	14	37.8	19	12	63.2
Severe	73	43	59.0	-	-	59

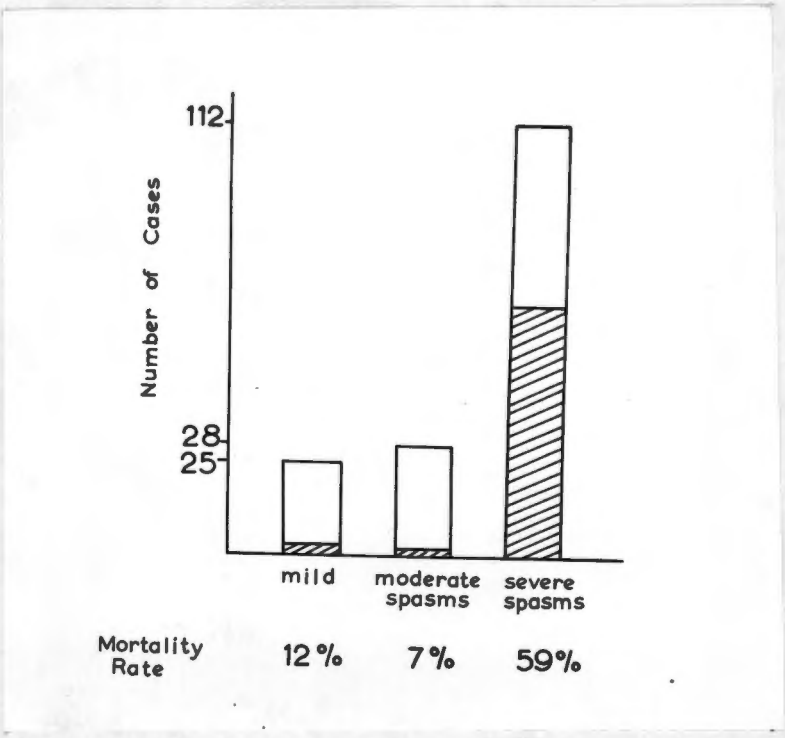
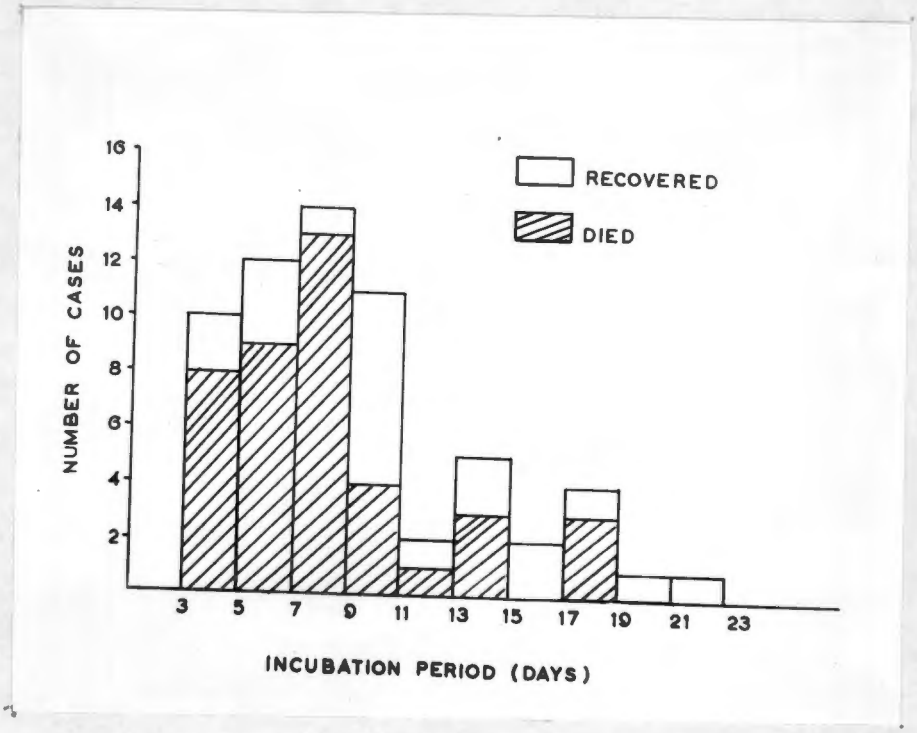


Figure III - Mortality in relation to occurrence and severity of reflex spasms (Non-neonatal patients).



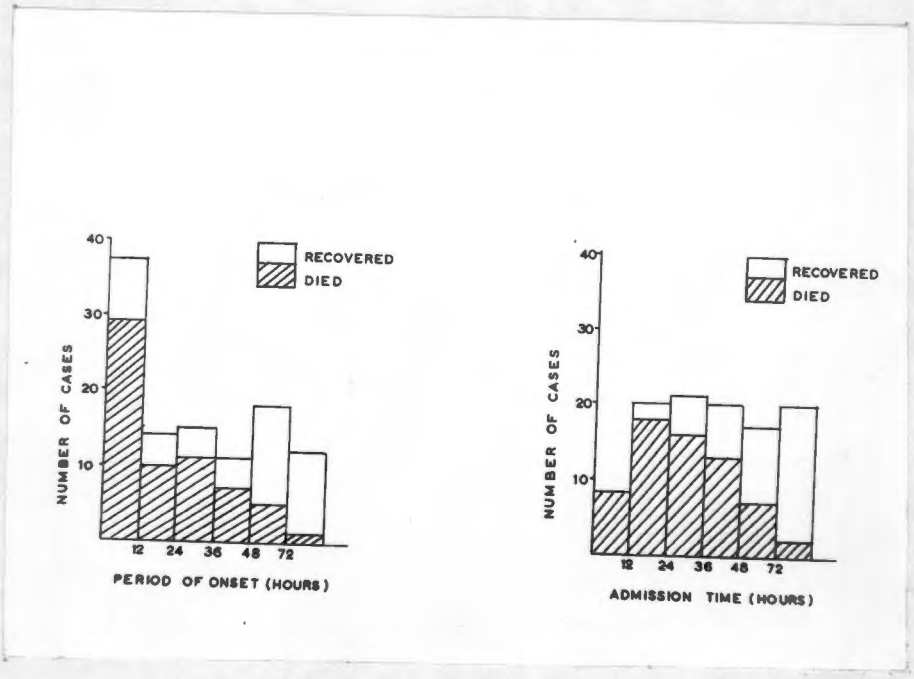


Figure IV - Mortality in relation to incubation period, period of onset and admission time in severe cases only (Non-neonatal patients).

onset had a grave prognosis, the mortality was low if either of these criteria were favourable. It is surprising that 12 patients recovered despite a period of onset of less than 24 hours. Many of these, however, had a long admission time and it is likely that the period of onset was inaccurate, since it may be difficult to take an accurate history through an interpreter from a seriously ill patient, of events which happened several days previously. In this respect a short admission time would appear to be superior to a short period of onset as an indication of a grave prognosis, since only 2 patients with an admission time below 24 hours recovered.

Spasms were so severe in the majority of infants that an attempt was made to sub-divide these according to whether spasms occurred spontaneously or only as a result of disturbance. This assessment was made immediately on arrival in the ward before any sedation was given, the infants being placed in a quiet, darkened room and observed for a few minutes, the presence and severity of reflex spasms unrelated to obvious external stimuli being noted. In figure 5 the severity of reflex spasms as seen in infants at the time of admission is related to mortality rate. Only 1 patient recovered of the 65 in whom spasms were occurring spontaneously, but the prognosis among those in whom spasms were not severe was relatively good. Of 193 patients in whom frequent severe reflex spasms were observed at any time during their stay in hospital 178 died (92.2%), whereas only 2 died (8.3%) of 24 patients in whom spasms were either never observed (8), or were only moderately severe (16). Since

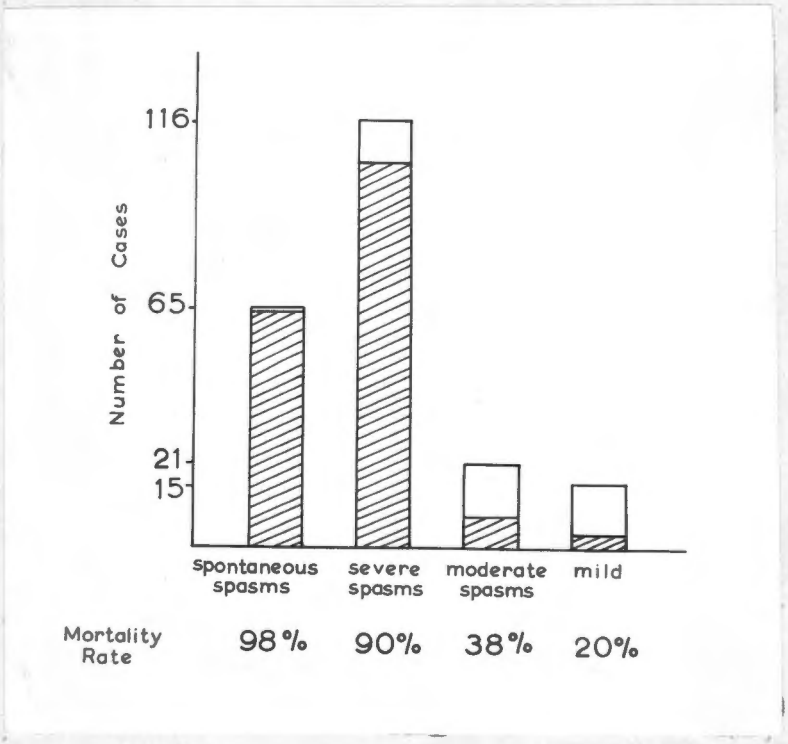


Figure V - Mortality in relation to occurrence and severity of reflex spasms on admission (neonatal patients).

almost all neonatal patients were severe at the time of admission; incubation period, period of onset and admission time have not been analysed separately.

An occasional recovery despite a short incubation period and period of onset occured even in infants having severe reflex spasms, as had been found in non-neonatal patients. Similarly, if the admission time is long and the period of onset short, the latter is likely to be inaccurate.

Conclusions

The presence of frequent severe generalised reflex spasms is the most important criterion indicating a poor prognosis in the patients analysed. Incubation period, period of onset and admission time are additional criteria which may be of value. If short they usually indicate a poor prognosis but where possible all three must be assessed together. A long admission time and period of onset usually indicate a good prognosis despite the occurrence of severe reflex spasms, but a long incubation period is of less value in this respect. If generalised reflex spasms are not severe the prognosis is good, provided laryngeal and pharyngeal spasms or an atypical, but characteristic, form of the disease is not present. Prognosis varies little with the presence of a wound or its site, unless the uterus is the portal of entry when the prognosis is grave. In non-neonatal patients the severity of reflex spasms at the time of admission is not a good guide to prognosis and additional criteria,

particularly the admission time must be used in any attempt at an early assessment of prognosis.

In infants the disease is so severe and the onset so rapid that the severity of reflex spasms at the time of admission gives a good indication of prognosis in most cases. Age, incubation period, period of onset and admission time, if long, are of some value in indicating a favourable outcome.

It must be emphasized that none of these criteria are absolute and in particular single criteria which depend on an accurate history may be misleading in any given case. Careful observation of progress during adequate treatment is ultimately the most important factor in assessing prognosis.

CAUSE AND MECHANISM OF DEATH

The extensive and often conflicting literature on the pathogenesis and mode of action of tetanus toxin has been well reviewed by Sloane (1953) and Wright (1954, 1955 and 1956). It would seem that the theory of a peripheral action of tetanus toxin on the motor end plate as postulated by Harvey (1939) is no longer tenable; however the relative importance of the motor nerves and the circulation in the transmission of the toxin from the site of entry of the organism to its site of action in the central nervous system in human tetanus is unknown. Brookes and his colleagues (1957) have shown that while monosynaptic reflexes are little affected, polysynaptic reflexes are increased by the tetanus toxin selectively suppressing synaptic inhibition. They considered that further knowledge of the actual mechanism whereby tetanus toxin disturbs function in the central nervous system will depend on the isolation of the inhibitory transmitter substances, and recently van Heyningen (1959 a & b) has made some progress in this direction by developing a method for the assay of a receptor substance in the grey matter of nervous tissue which has a highly specific affinity for tetanus toxin.

Whatever the pathogenesis and mode of action of tetanus toxin, it is apparent that the functional disturbance which it produces within the central nervous system gives rise to the characteristic muscular rigidity and reflex spasms. As shown in the previous section death is

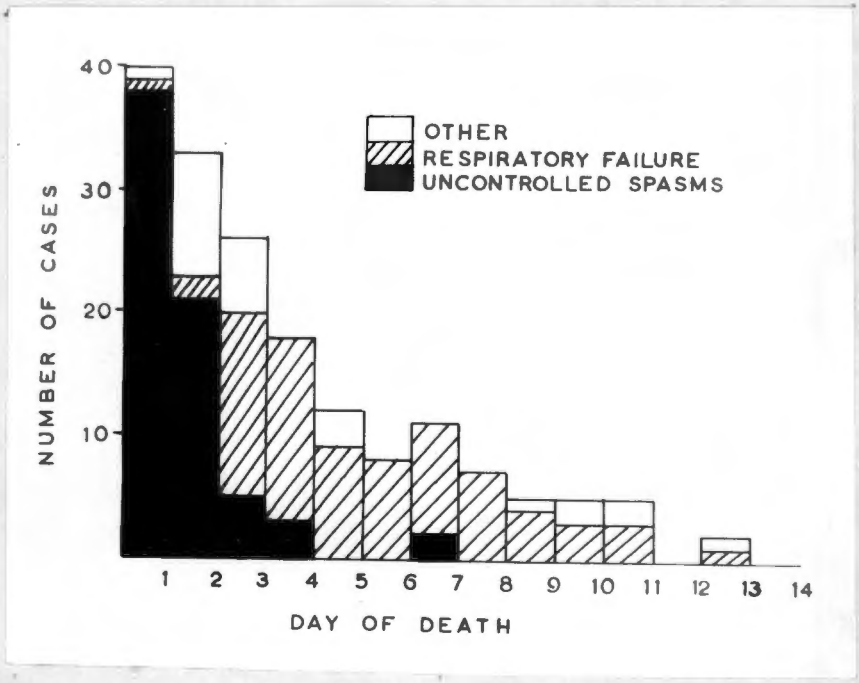


Figure VI - Relationship of respiratory failure and uncontrolled spasms to death in neonatal patients.

closely related to the severity of reflex spasms, but the exact cause of death in our patients has been difficult to determine.

Necropsies have been performed in all but 18 deaths in this series, since a postmortem examination of patients dying from tetanus is compulsory by law in this area. The majority have been attended personally by the author or by another member of the clinical team. Although a routine macroscopic examination was made to exclude gross pathology, histological examination was omitted in a few cases. In general, more detailed necropsies were performed on non-neonatal patients and those infants treated on one of the therapeutic trials. One hundred and seventy-nine neonatal and 71 non-neonatal deaths which occurred before the start of the I.P.P.R. trial will be analysed and an attempt made to determine the cause of death based on clinical and necropsy findings.

Neonatal deaths: There were 69 deaths associated with poor control of spasms, 38.5% of the total. As seen from figure 6 the majority of these occurred within the first 48 hours and only 22% of deaths during this period occurred in infants whose spasms were well controlled. The clinical picture in this group was one of prolonged bouts of spasms with apnoea and cyanosis. Necropsy revealed intense congestion of all organs particularly lung, liver and brain, sometimes with intra-alveolar haemorrhages and dilatation of the right side of the heart. Histologically there was evidence of mild pulmonary oedema or atelectasis in

approximately a third of deaths examined.

The majority of infants who died after 48 hours presented a strikingly different clinical picture. After a variable period, during which control of spasms was achieved, the infant became cold, flaccid and often oedematous with irregular gasping respiration, bradycardia and peripheral cyanosis. In some, spasms could not be provoked even after marked stimulation, but in others opisthotonus was prominent and reflex spasms of variable frequency and severity still occurred. At necropsy pulmonary oedema and atelectasis were again a common finding, but congestion was not as severe as in earlier deaths. Aspiration of milk with atelectasis was found in 6 cases but whether it was terminal or the actual cause of death is uncertain. Histological evidence of bronchopneumonia increased with the length of survival (figure 7) but the extent varied and it was considered to be the actual, or a contributory, cause of death in less than half.

There were 7 deaths between the sixteenth and forty-second days. Spasms were mild or infrequent in all, although rigidity persisted, and death was due to complications such as bronchopneumonia, marasmus and a trachoe-oesophageal fistula from prolonged tube feeding.

Non-neonatal deaths: There were 26 patients in whom death was associated with poor control of spasms, 36.6% of the total. One of these died of laryngeal spasm and in 5 others this was the immediate cause of death, although generalised spasms were well controlled. As in infants the

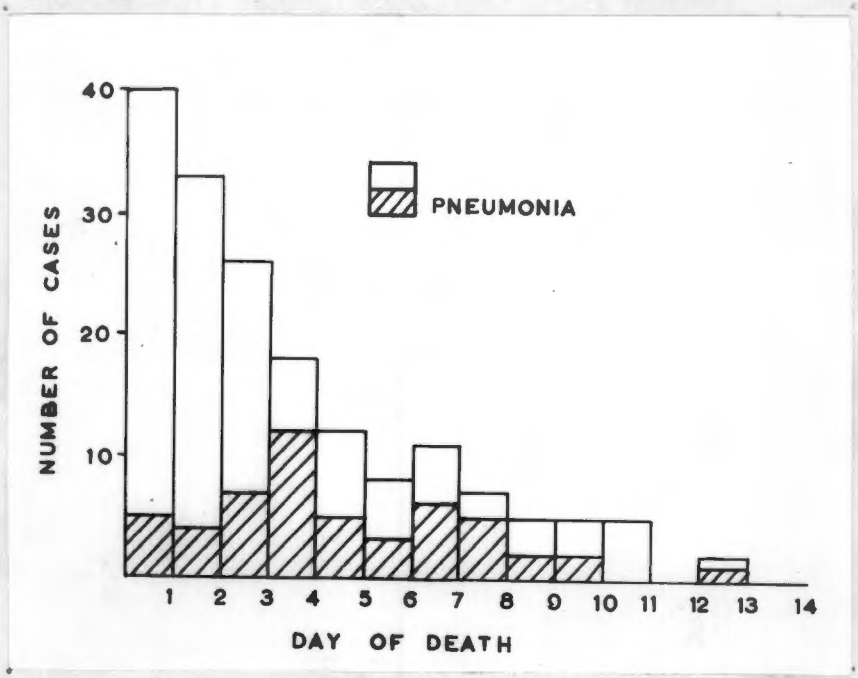


Figure VII - Histological evidence of bronchopneumonia in neonatal deaths.

majority of deaths associated with poor control of spasms occurred on the second or third days. The clinical picture was one of acute distress, sweating, a moderate to high pyrexia and death during or immediately after a severe bout of spasms. In some the course was fulminating, but in others partial control of spasms was achieved exceptionally for as long as 7 days (case 53) before the terminal episode. The only abnormal findings at necropsy were intense congestion, patchy atelectasis and occasionally dilatation of the right side of the heart. Those patients dying of laryngospasm usually showed oedema of the glottis and extensive atelectasis.

Histological evidence of bronchopneumonia was present in 25 patients, but was insignificant in nearly half of these. Its incidence increased with the length of survival, although this was not as striking as in infants. In 4 patients pneumonia was considered to be the major cause of death and in 10 others a contributory cause. Some died of what appeared to be primary respiratory failure, none within the first 24 hours. These patients were observed to develop a rising temperature and pulse rate, marked tachypnoea and increasing depth of respiration which often became irregular and suddenly ceased. This respiratory arrest occurred in the absence of a severe bout of spasms, respiratory obstruction or oversedation. In some such cases spasms were frequent and severe but well controlled at the time of death as illustrated by case 128:

> E.N., an African male, aged 9 years, whose incubation period was unknown and period of onset less than 24 hours. On admission frequent severe generalised spasms were present but adequate control

was achieved with a total of 225 mg. chlorpromazine and 7½ gr. phenobarbitone intramuscularly. On the second day his temperature rose to 103 degrees with tachycardia and increasing depth and rate of respiration. Sudden apnoea followed and attempts at resuscitation failed. Pulmonary congestion and diffuse fatty infiltration of the liver were the only abnormalities found at necropsy.

In others, although severe spasms had been seen at some stage, they were usually moderate, infrequent or absent, such as in case 132:

T.S., an Indian female, aged 21 years, was admitted during the period of onset which was 72 hours. Trismus was noticed 15½ hours before admission; 7 days after an abortion. Spasms were severe on the third day but were well controlled on a maximum daily dose of 300 mg. chlorpromazine and 6 gr. phenobarbitone sodium. Later that day she developed a marked tachycardia, increasing opisthotonus and irregular respiration which suddenly failed. Pulmonary congestion with some atelectasis and oedema were the only abnormalities found at necropsy.

One patient (case 140), appeared to die of respiratory failure without ever having reflex spasms.

W.N., an African boy, aged 5 years, was admitted to hospital 36 hours after the onset of trismus. The incubation period was unknown. Trismus, generalised rigidity and opisthotonus were severe and his

temperature fluctuated between 103 and 104 degrees. The cerebrospinal fluid was normal. Respiration increased in depth and rate and suddenly ceased on the third day without reflex spasms ever having been observed. A total of 275 mg. chlorpromazine and 4½ gr. phenobarbitone sodium was given intramuscularly during this period. At necropsy fatty infiltration of the liver, mild cerebral and pulmonary oedema and an active tuberculous focus in the left lung were the only abnormal findings.

Only 3 non-neonatal deaths occurred after the first week. One patient (case 160) died on the tenth day, bronchopneumonia, pelvic sepsis, anaemia and prolonged intravenous feeding contributing to death. Two patients (cases 51 and 142) died on the eleventh day. The first developed severe spasms on the fourth day, became progressively worse and appeared to die of respiratory failure. The second was elderly and appeared to die of debility and hypostatic bronchopneumonia, pharyngeal spasm being severe and necessitating prolonged intravenous feeding although generalized spasms were never observed.

Discussion

Although related to the severity of reflex spasms, it is apparent that deaths in this series cannot be classified into well defined groups according to the cause. However, 3 broad groups emerge depending on the predominance, at the time of death, of reflex spasms, of a clinical picture of respiratory failure, or of complications such as debility and bronchopneumonia

Death during a laryngeal spasm was undoubtedly due to acute anoxia, but whether anoxia was the cause when death occurred while generalised spasms were poorly controlled, is less certain. However, the enormous increase in oxygen consumption as a result of violent muscular activity together with prolonged periods of apnoea during bouts of spasms are likely to produce a severe oxygen debt, particularly in infants. It is possible that such attacks, repeated over a period of hours, may produce death from anoxia in the absence of acute asphyxia from laryngeal spasms. The acute congestion, pulmonary and cerebral oedema, and dilatation of the right side of the heart found at necropsy while essentially non-specific, are compatible with death from this cause (Potter, 1952). Petechial haemorrhages were occasionally found in the pleura and myocardium, but never in the brain.

It has often been said that patients having uncontrollable tetanic spasms die of exhaustion. This appeared to be so in several infants in this series who ran a fulminating course with continuous spasms completely unaffected by sedation. Nevertheless the exact mechanism of death in such cases is uncertain.

The clinical picture of death from respiratory failure in neonatal and non-neonatal patients differed considerably. In the latter it was more acute and was preceded by tachypnoea and often a rising temperature, whereas in infants slow, irregular gasping respiration was usually associated with marked hypothermia which sometimes continued for days so that medical and nursing attendants often had difficulty in deciding when death had

occurred. It is recognised that respiratory failure can result from overdosage with sedatives or muscle relaxants, but recently the possibility that it may be due to the disease itself has been considered. Baker (1942) found histological evidence of definite changes within the central nervous system in 12 fatal cases of tetanus. Subsequently, in a detailed pathological study in another case of tetanus where death had appeared to be due to respiratory failure with cardiac irregularity, he found extensive involvement of the motor nucleus of the fifth cranial nerve and the dorsal nucleus of the vagus (Baker, 1943). He concluded that certain cases of tetanus must terminate fatally due to severe damage to the medullary centres with resultant cardiac and respiratory failure. More recently several authors have suggested on clinical grounds that death in tetanus may be due to medullary failure (Knott and Cole, 1952; Garcia-Palmieri and Ramirez, 1957). Hyperpyrexia, excessive sweating, tachycardia, profuse pharyngeal secretions and hyperglycaemia have all been attributed to brain stem involvement (Herman, et al., 1951; Gleeson and Low, 1957; Lawrence and Sando, 1959). Supportive evidence for such an action of tetanus toxin has come from experiments on animals which have demonstrated the highly lethal effects of tetanus toxin when injected directly into the brain stem even in small quantities (Piner, et al., 1940; Wright, 1953, 1954).

Clinically, oversedation could be excluded as the cause of the respiratory failure seen in non-neonatal patients in this series, and it is likely that it was due to a central action of tetanus toxin. In infants

the problem was more complex. Hypothermia sometimes as low as 84 degrees F. was a constant terminal feature and heavy sedation often necessary, so that tetanus intoxication of the brain stem could not be implicated with certainty as the cause of death. Convincing evidence of cardiac failure was not found either clinically or at necropsy. Studies of electrocardiographic changes in patients suffering from tetanus treated along conventional lines have usually shown abnormal but non-specific alterations (Veronesi, 1956; Garcia-Palmieri and Ramirez, 1957b). Recently an action of tetanus toxin on the myocardium, with electrocardiographic and histological evidence of myocarditis has been reported in some cases of tetanus treated with I.P.P.R. (Lassen et al., 1954; Allsady et al., 1960). These findings together with records on patients in the present series will be discussed later.

Conclusions

An analysis of the causes of death in this series based on clinical and necropsy findings in conservatively treated patients seen before I.P.P.R. was introduced into the unit, shows that, in a few, death was due to pneumonia or asphyxiation.

In the majority it was associated either with inadequate control of reflex spasms or with respiratory failure, which probably resulted from a direct action of tetanus toxin on the medullary centres.

THERAPEUTIC TRIALS IN THE PRESENT SERIES

More than half of the 550 patients in the present series have been studied in a number of randomised therapeutic trials to assess the place of chlorpromazine, tracheotomy and total paralysis with I.P.P.R. The remainder were treated as "off series" cases. Some of these were used for preliminary studies of various drug combinations or of tracheotomy or I.P.P.R. Others were patients excluded from series by reason of having had treatment before admission; or because the diagnosis at the time of admission was in doubt. Many patients were not admitted to the tracheotomy and I.P.P.R. trials because they were not sufficiently severe, or had refused tracheotomy, or because a respirator was not available at the time.

The relative numbers in these different groups are shown in table XX.

In each of the trials all treatment other than the sedative or procedure under investigation was standardised and the patients allocated at random to one or other of the two regimes being compared. In the first two trials all patients irrespective of severity were admitted to the trial provided they had not received treatment before admission which might prejudice the assessment of the drugs being compared. The tracheotomy and I.P.P.R. trials were confined to patients suffering from severe tetanus.

TABLE 10

DISTRIBUTION OF PATIENTS IN CLINICAL TRIALS

NON-NEONATAL PATIENTS

Trial	Treatment Groups				Total
Trial I	Chlorpromazine	23	Barbiturate	21	44
Trial II	Chlorpromazine	29	Barbiturate -Chlorpromazine	27	56
Trial III	Tracheotomy	8	Conservative	7	15
Trial IV	I.P.P.R.	8	Conservative	8	16
"Off Series"	Miscellaneous				90
					221

NEONATAL PATIENTS

Trial	Treatment Groups				Total
Trial I	Chlorpromazine	14	Barbiturate	17	31
Trial II	Chlorpromazine	20	Barbiturate -chloral hydr.	20	40
Trial III	Tracheotomy	13	Conservative	17	30
Trial IV	I.P.P.R.	25	Conservative	25	50
"Off Series"	Miscellaneous				178
					329

Standardised Treatment

As far as possible the dosage of tetanus antitoxin, chemotherapy, feeding, nursing care and care of the wound were standardised throughout. Certain minor variations occurred from time to time particularly in the frequency with which intravenous feeding was used, the type of artificial feed given to neonatal patients, and the chemotherapy used for complications such as pneumonia, but there was no conscious bias for one or other of the treatment groups being compared.

Neonatal patients:

Procedure on admission: The infant was undressed, placed in a bassinet in a quiet darkened room and the frequency and severity of reflex spasms noted. It was then sedated with the appropriate sedative, and left alone for a period of 30 minutes before a more complete examination or any further nursing procedures were performed. Oxygen was administered by funnel if spasms were severe.

Tetanus antitoxin: Fifty thousand i.u. of tetanus antitoxin was given, using the intramuscular route only, and without any preliminary test dose.

Chemotherapy: Benethamine penicillin 300,000 units was injected intramuscularly every third day. The treatment in the event of the development of clinical pneumonia was not constant. During the first trial 500,000 units of soluble penicillin was given six-hourly but subsequently the tendency was to substitute streptomycin 0.5 g. daily in combination with half the above dose of soluble penicillin. Tetracycline, erythromycin

or chloramphenicol were used when the above antibiotics proved ineffective.

Feeding: Here too there was some variation. The initial practice was to pass a tube by the nasal or oral route as soon as possible after the first dose of sedative, and intravenous feeding was seldom resorted to. Later the passage of the tube was delayed until spasms were well controlled, sometimes for as long as 48 hours after admission. Intravenous feeds by intermittent scalp vein infusions were given if the passage of a tube was long delayed or if signs of dehydration developed. When tube fed, expressed breast milk was usually given, but in the event of an artificial feed being necessary either "Kledon" or "Carnation Milk" was used. Intravenous fluids usually consisted of invert sugar or paediatric glucose saline.

Nursing: The infants were kept in a darkened room and all external stimuli reduced to a minimum. Where possible nursing procedures were carried out at periods of maximum sedation. The infants were usually placed in the head down position but frequent changes of position and turning were carried out when spasms were adequately controlled. Inevitably there was variation in nursing efficiency particularly with changes in staff, a nurse seldom staying in the unit for longer than 1 to 3 months. As will be indicated later a more permanent and efficient nursing team was available during the I.P.P.R. trial.

Care of the wound: Approximately half an hour after the initial sedation the umbilicus was irrigated with hydrogen peroxide, any foreign material removed, and merthiolate applied. Tetanus antitoxin was not

injected around the stump and umbilectomy not performed.

Non-neonatal patients:

Procedure on admission: The patient was put to bed in a quiet darkened room and a test dose of tetanus antitoxin given followed by the appropriate sedative.

Tetanus antitoxin: All the patients received a subcutaneous test dose of 500 i.u. of tetanus antitoxin. Thirty minutes later 100,000 i.u. was given intramuscularly and in all patients over the age of 10 years the same dose was repeated after a further 30 minutes but given intravenously.

Chemotherapy: Procaine penicillin 600,000 units twice daily was given to all patients over the age of 10 years, and half that amount to smaller children. If signs of clinical pneumonia developed 500,000 units of soluble penicillin was given four to six-hourly according to age. In later trials streptomycin or a broad spectrum antibiotic was added if pneumonia developed while on treatment with penicillin.

Feeding: Patients who were unable to swallow were fed by an oral or nasal gastric tube in the early part of the series. Later tube feeding was largely replaced by intravenous feeding. It was found that patients who were unable to take feeds orally when spasms were severe were often able to do so a few days later when these were well controlled, intravenous fluids being given in the interim.

Nursing: Whenever possible nursing procedures were carried out approximately 1 hour after sedation.

Care of the wound: The wound was irrigated with hydrogen peroxide and foreign and necrotic material removed. In patients with post-abortal tetanus the products of conception were removed digitally or with an ovum forceps, if present in the vagina or protruding through the cervix.

Wound excision or more extensive surgery was not undertaken in the present series.

TRIAL I : Non-neonatal patients

A randomized comparison of chlorpromazine and barbiturate

Drug dosage : Barbiturate. Phenobarbitone sodium was given intramuscularly in doses of 3 to 6 gr. three- to six-hourly according to the age of the patient and the frequency and severity of reflex spasms. When sedation was required urgently amylobarbitone sodium 0.25 - 1.00 Gm. was given either intramuscularly or intravenously.

Chlorpromazine. This was given intramuscularly in doses of 50 - 150 mg. four- to six-hourly according to the age of the patient and the frequency and severity of reflex spasms. When sedation was required urgently the intravenous route was used. Promethazine was given to a few patients in an attempt to reduce the high dosage of chlorpromazine sometimes required but was soon abandoned.

In all patients drugs were given orally only during convalescence.

Results : In table 11 the two treatment groups are compared and the chief clinical features of the individual cases presented in tabular form in appendix I.

TRIAL II : Non-neonatal patients

A randomised comparison of chlorpromazine and a chlorpromazine barbiturate mixture

Drug dosage : Chlorpromazine. The dosage schedule was identical to that in the first trial except that an upper limit of 1,000 mg. of the drug was set for any twenty-four hour period, because toxic symptoms had been experienced in the previous trial.

Chlorpromazine-barbiturate combination. Patients in this group were given 50 mg. chlorpromazine and 200 mg. phenobarbitone sodium on admission intramuscularly. Thereafter chlorpromazine dosage was fixed at 50 mg. four-hourly, additional sedation being achieved with barbiturate as required. Proportionate doses were given to small children.

Results : In table 11 the two treatment groups are compared and the chief clinical features of the individual cases presented in tabular form in appendix I.

TABLE 11

COMPARISON OF TREATMENT GROUPS NON-NEONATAL PATIENTS TRIALS I AND II

	TRIAL I		TRIAL II	
	Chlor-promazine	Barbiturates	Chlor-promazine	Chlorpromazine-Barb. comb.
No. of cases	23	21	29	27
Average age (days)	18	22.5	13	21
Average incubation period (days)	7.9	8.5	9.7	11.3
Average period of onset (hr.)	32	28.5	38.2	63
Average admission time (hr.)	78.2	55.6	62	66.7
Severity:				
Severe (% of total in brackets)	15(65%)	13(62%)	24(83%)	16(59%)
Moderate	7	6	4	7
Mild	1	2	1	4
Site of wound:				
Leg	10	11	14	7
Arm	2	-	-	3
Trunk	-	-	1	-
Head	3	2	2	2
Uterus	-	1	1	3
Multiple	3	2	5	3
No wound	5	5	6	9
Bronchopneumonia	5	6	3	3
Poor control of spasms	3	5	7	4
Feeding:				
oral	12	5	19	20
Tube	7	6	1	-
Intravenous	2	7	6	7
Not fed	2	3	3	-
Survival time (days)	3.5	2.5	3.0	3.0
Deaths:				
Among all cases	10(43%)	11(52%)	15(52%)	9(33%)
Among severe cases	10(67%)	11(85%)	15(63%)	8(50%)

TRIAL I : Neonatal patients

A randomized comparison of chlorpromazine and barbiturate

Drug dosage : Barbiturate. Phenobarbitone sodium was given intramuscularly in doses of 1 gr. according to the frequency and severity of reflex spasms. Initially this was usually necessary four- to six-hourly but less frequently after the second or third day.

Chlorpromazine. This was given intramuscularly in 20 - 25 mg. doses four-hourly initially, but less frequently as spasms were controlled.

Results : In table 12 the two treatment groups are compared and the chief clinical features of the individual cases presented in tabular form in appendix 5.

TRIAL II : Neonatal patients

A randomized comparison of chlorpromazine and a combination of barbiturate and chloral hydrate

Drug dosage : Barbiturate-chloral hydrate combination. These patients were treated in the first twenty-four hours with phenobarbitone sodium only in doses of 1 gr. intramuscularly, up to a maximum of five doses, the aim being to achieve sedation rapidly to facilitate the passage of a stomach-tube. Thereafter no further phenobarbitone was given and control was attempted with chloral hydrate in doses of

TABLE 12

COMPARISON OF TREATMENT GROUPS NEONATAL PATIENTS TRIALS I AND II

	TRIAL I		TRIAL II	
	Chlor-promazine	Barbiturate	Chlor-promazine	Barbiturate - Chl. hydr.
No. of cases	14	17	20	20
Average age (days)	7.0	7.0	5.7	8.3
Average incubation period (days)	5.8	5.8	5.2	6.8
Average period of onset (hr.)	10.5	18.1	6.8	6.8
Average admission time (hr.)	31	37.5	18.4	36.2
Severity:				
Severe	14	17	20	19
Moderate	0	0	0	1
Mild	0	0	0	0
Bronchopneumonia	3	5	1	6
Poor control of spasms	6	4	18	3
Respiratory failure	0	5	1	10
Feeding:				
Oral	0	0	-	-
Tube	13	16	11	17
Intravenous	0	0	-	-
Not fed	1	0	9	3
Survival time (days)	2.6	2.1	1.8	3.7
Deaths	13(93%)	12(71%)	19(95%)	18(90%)

2 gr. given not more frequently than four-hourly by the stomach tube left in situ.

Chlorpromazine. This was given four-hourly intramuscularly in 20 - 25 mg. doses as in the previous trial.

Results : In table 12 the two treatment groups are compared and the chief clinical features of the individual cases presented in tabular form in appendix 5.

TRIAL III

A randomized comparison of tracheotomy with a conservative method

Criteria for selection:

It was felt that there was sufficient doubt of the value of tracheotomy, particularly with the nursing facilities available in this unit to confine the trial to those patients whose prognosis was poor if treated conservatively. Only selected cases having frequent severe reflex spasms were therefore admitted to two trials, one on neonatal and the other on non-neonatal patients. Treatment schedules were standardized as before, and chlorpromazine and barbiturate were used in combination for control of spasms. Severity was assessed by two members of the team in consultation, a card opened, and if chosen a tracheotomy was performed within 48 hours of admission.

Non-neonatal patients:

Conservatively treated group: The dosage schedule of chlorpromazine and barbiturate was similar to that used in patients treated with this combination in the second trial.

Tracheotomy treated group: With the exception of the tracheotomy, drug dosage and general management was similar to that used in patients treated conservatively. Initially the operation was performed under general anaesthesia but later local analgesia was used. A metal tracheotomy tube was inserted through a window cut in the trachea, if possible at the level of the third and fourth rings. The inspired air was not humidified but oxygen bubbled through water at room temperature was administered when required. Secretions from the trachea were aspirated by means of an electric suction pump two-hourly, or less frequently if necessary, using a soft rubber catheter. Patients were turned frequently and postured by raising or lowering the foot of the bed.

Results: The clinical features of patients in the two treatment groups are compared in table 13 and the chief clinical features of the individual cases presented in tabular form in appendix 3.

Neonatal patients:

Conservatively treated group: Chlorpromazine was administered intramuscularly in doses of 12½ - 25 mg. with phenobarbitone sodium in doses of ½ - 1 gr., the combination being given when necessary according to the frequency and severity of spasms.

TABLE 13

COMPARISON OF TREATMENT GROUPS NON-NEONATAL TRIAL III

	Tracheotomy	Conservative
Number of patients	8	7
Average age (years)	21.3	26.9
Average incubation period (days)	9.5	7.8
Average period of onset (hr.)	32.1	30.6
Average admission time (hr.)	34.5	28.3
Site of wound:		
Leg	2	-
Arm	1	-
Trunk	-	-
Head	2	3
Uterus	1	3
Multiple	1	-
No wound	1	1
Bronchopneumonia	1	2
Poor control of spasms	3	3
Feeding:		
Oral	1	-
Tube	-	-
Intravenous	6	6
Not fed	1	1
Average survival time (days)	4.4	4.7
Deaths	6(75%)	6(85.7%)

Tracheotomy treated group: With the exception of the tracheotomy, drug dosage and general management were similar to that used in patients treated conservatively. The tracheotomy was performed after heavy sedation, the tissues overlying the trachea being infiltrated with 1% procaine hydrochloride so as to produce local analgesia, and a number 16 or 18 Parker tracheotomy tube inserted through a window cut in the trachea. Care of the tracheotomy was similar to that in non-neonatal patients.

Results: In table 14 the two treatment groups are compared and the chief clinical features of the individual cases presented in tabular form in appendix 7.

TRIAL IV

A randomized comparison of I.P.P.B. with a conservative method

Criteria for selection:

As in trial III only patients having frequent severe reflex spasms whose prognosis was thought to be poor if treated conservatively were selected for trial. Other criteria such as incubation period, period of onset and admission time were taken into account when in doubt, but usually only to exclude patients from trial. At no time were patients having moderately severe spasms admitted to the trial even though other criteria suggested a poor prognosis.

TABLE 14

COMPARISON OF TREATMENT GROUPS NEONATAL TRIAL III

	Tracheotomy	Conservative
Number of cases	13	17
Average age (days)	6.0	7.2
Average incubation period (days)	5.2	5.8
Average period of onset (hr.)	7.7	9.0
Average admission time (hr.)	20.8	34.9
Bronchopneumonia	4	12
Poor control of spasms	5	3
Respiratory failure	3	10
Feeding:		
Oral	-	-
Tube	3	3
Intravenous	5	10
Not fed	5	4
Survival time (days) (in deaths under 14 days)	4.8	5.9
Deaths:		
Within 48 hours	6	3
After 14 days	-	3
Mortality %	100	100

The assessment of severity and the decision to admit a patient to the trial was made by at least two members of the team in consultation. Although it was laid down initially that a period not exceeding 48 hours would be allowed for assessment of severity, in practice a decision was made and the patient admitted to trial in a much shorter period. During this period of observation only phenobarbitone was used for sedation as chlorpromazine was thought to have made secretions tenacious and difficult to aspirate in 2 patients treated with I.P.P.R. before the start of the trial.

As in previous trials, treatment groups were randomised and separate trials conducted on neonatal and non-neonatal patients. Despite the strict criteria of severity adopted, the number of patients fulfilling these criteria always far exceeded the number of respirators available, so that continuation of the trial was thought to be justified even when it became apparent that a lower mortality was likely in one of the groups.

Standardised treatment

The dosage of tetanus antitoxin, penicillin and the care of the wound was standardised as in previous trials. Because of the high mortality from bronchopneumonia among early neonatal patients treated with I.P.P.R., gamma-globulin 2 ml. intramuscularly was given on admission to case number 514 and all subsequent infants in both groups (Smythe and Bull, 1959).

Feeding methods: Although expressed breast milk or occasionally an artificial feed was given by intragastric tube to all infants, feeds were usually started later in those treated conservatively because of difficulty in passing a tube until spasms were controlled. In non-neonatal patients, intravenous, tube or oral feeding was used as in previous trials. Initially all non-neonatal patients treated with I.P.P.R. were fed by nasal tube from the start, a "Complan" mixture being given, but later the intravenous route was used for the first 48 hours.

Supportive care differed in the two groups. Patients were treated in two separate small wards with the same medical staff but different nursing staff in attendance. Nurses attending to both groups were, however, selected for their efficiency and remained in the unit for a period of at least 6 months. With rare exceptions, at least 2 nurses and usually 4 were in constant attendance on those patients treated with I.P.P.R. On only one occasion was more than 3 respirators used simultaneously, although quite frequently as many as 6 convalescing patients, some of whom still had tracheotomies, were present in the ward and required attention. Those cases of tetanus treated conservatively were kept in a separate room during the acute stage in the care of a trained nurse with some assistance from a nurse-aid. As many as 8 patients, the majority of whom were infants, were sometimes treated in this ward at one time.

The management of patients treated conservatively

Non-neonatal patients: Chlorpromazine 50 mg. four- to six-hourly and phenobarbitone sodium gr. 3 were given by the intramuscular route when required for control of spasms as in Trial II.

Neonatal patients: Acetylpromazine 5 - 10 mg. and phenobarbitone sodium ½ - 1 gr. were given by the intramuscular route when required for the control of spasms.

Tracheotomies were not performed on any of the patients in the conservative group.

The Management of Patients treated with I.P.P.R.

Non-neonatal patients

Ventilation: The usual routine adopted for the institution of I.P.P.R. was to inject by the intravenous route 25 to 50 mg. succinylcholine with thiopentone sodium 250 to 500 mg., to allow intubation of the larynx with a cuffed Magill tube. Artificial ventilation was then provided either by a Radcliffe Mark V positive-pressure pump (Russell and Schuster, 1953) or a Smith-Clarke positive-negative respirator (Smith-Clarke and Galpine, 1955). Thereafter tubocurarine chloride was injected intramuscularly in 30 mg. doses so as to maintain total paralysis. The frequency with which this was given was left in part to the discretion of the nursing staff, the indications being excessive muscular twitching and attempts at spontaneous respiration. The alveolar

ventilation required was calculated in the first instance from a Radford Nomogram (Radford et al., 1954; Radford, 1955), the rate of respiration being chosen according to age. For this purpose a rough estimate was made of height and weight. Ventilation was subsequently checked by measurement of minute volume. Later adjustments were made according to the clinical condition of the patient and the level of arterial pCO2 obtained by a rebreathing method (Campbell and Howell, 1960; Sykes, 1960) using a modified Haldane apparatus (Campbell, 1960). However, the frequency with which the latter was estimated in any given patient varied with the number of patients being treated with I.P.P.R. at the time and the staff available.

The initial inflation pressures used ranged from 10 to 14 cm. of water but rose to as high as 24 cm. of water in one patient, although a maximum of 18 cm. of water was otherwise not exceeded. Most patients were deliberately overventilated, a minute volume ranging from 8 to 10 litres with an arterial pCO2 below 35 mm. Hg. being usual for an adult.

Inflation pressures, tube temperature, blood pressure and pulse rate were recorded half-hourly, and body temperature four-hourly.

Curare dosage: This varied considerably from case to case as well as in the individual patient. The total daily dosage ranged from 90 - 480 mg., children usually requiring less curare than adults. There was no apparent correlation between the severity of tetanus and the dosage of curare

required. Although the latter appeared to decrease towards the end of treatment with I.P.P.R. in some patients, this was an inconstant finding.

Humidification: Humidifiers incorporated in the respirators were used to humidify the air delivered to the patient. The tube temperature, measured at a point as close to the patient as possible, was kept at 95 to 100 degrees F. by permanently leaving a thermometer inserted through a hole made in the delivery tubing.

The airway: A high tracheotomy was performed within 24 hours of starting I.P.P.R. A cuffed Oxford tracheotomy tube (Spalding and Smith, 1956) was inserted through a window cut in the trachea and the patient ventilated by this route. The cuff was released two-hourly with the patient in the head-down position, but the tube was not changed unless it became defective. Dislodgment of the tube was a problem and will be discussed later.

Physiotherapy and suction: After vigorous percussion to the chest secretions were aspirated half-hourly from the lungs using a soft rubber catheter. The patient was turned and the foot of the bed elevated or lowered. Nurses were trained to auscultate the chest to determine the effectiveness of physiotherapy and suction. During physiotherapy, while disconnected from the respirator, the lungs were inflated intermittently with oxygen.

Sedation: Amylobarbitone sodium 250 mg. was administered intramuscularly every 4 to 8 hours to induce sleep.

the problem was more complex. Hypothermia sometimes as low as 84 degrees F. was a constant terminal feature and heavy sedation often necessary, so that tetanus intoxication of the brain stem could not be implicated with certainty as the cause of death. Convincing evidence of cardiac failure was not found either clinically or at necropsy. Studies of electrocardiographic changes in patients suffering from tetanus treated along conventional lines have usually shown abnormal but non-specific alterations (Veronesi, 1956; Garcia-Palmieri and Ramirez, 1957b). Recently an action of tetanus toxin on the myocardium, with electrocardiographic and histological evidence of myocarditis has been reported in some cases of tetanus treated with I.P.P.B. (Lassen et al., 1954; Allady et al., 1960). These findings together with records on patients in the present series will be discussed later.

Conclusions

An analysis of the causes of death in this series based on clinical and necropsy findings in conservatively treated patients seen before I.P.P.B. was introduced into the unit, shows that, in a few, death was due to pneumonia or asphyxiation.

In the majority it was associated either with inadequate control of reflex spasms or with respiratory failure, which probably resulted from a direct action of tetanus toxin on the medullary centres.

THERAPEUTIC TRIALS IN THE PRESENT SERIES

More than half of the 550 patients in the present series have been studied in a number of randomised therapeutic trials to assess the place of chlorpromazine, tracheotomy and total paralysis with I.P.P.R. The remainder were treated as "off series" cases. Some of these were used for preliminary studies of various drug combinations or of tracheotomy or I.P.P.R. Others were patients excluded from series by reason of having had treatment before admission; or because the diagnosis at the time of admission was in doubt. Many patients were not admitted to the tracheotomy and I.P.P.R. trials because they were not sufficiently severe, or had refused tracheotomy, or because a respirator was not available at the time.

The relative numbers in these different groups are shown in table 19.

In each of the trials all treatment other than the sedative or procedure under investigation was standardised and the patients allocated at random to one or other of the two regimes being compared. In the first two trials all patients irrespective of severity were admitted to the trial provided they had not received treatment before admission which might prejudice the assessment of the drugs being compared. The tracheotomy and I.P.P.R. trials were confined to patients suffering from severe tetanus.

TABLE 10

DISTRIBUTION OF PATIENTS IN CLINICAL TRIALS

NON-NEONATAL PATIENTS

Trial	Treatment Groups				Total
Trial I	Chlorpromazine	23	Barbiturate	21	44
Trial II	Chlorpromazine	29	Barbiturate -Chlorpromazine	27	56
Trial III	Tracheotomy	8	Conservative	7	15
Trial IV	I.P.P.R.	8	Conservative	8	16
"Off Series"	Miscellaneous				90
					221

NEONATAL PATIENTS

Trial	Treatment Groups				Total
Trial I	Chlorpromazine	14	Barbiturate	17	31
Trial II	Chlorpromazine	20	Barbiturate -chloral hydr.	20	40
Trial III	Tracheotomy	13	Conservative	17	30
Trial IV	I.P.P.R.	25	Conservative	25	50
"Off Series"	Miscellaneous				178
					329

Standardised Treatment

As far as possible the dosage of tetanus antitoxin, chemotherapy, feeding, nursing care and care of the wound were standardised throughout. Certain minor variations occurred from time to time particularly in the frequency with which intravenous feeding was used, the type of artificial feed given to neonatal patients, and the chemotherapy used for complications such as pneumonia, but there was no conscious bias for one or other of the treatment groups being compared.

Neonatal patients:

Procedure on admission: The infant was undressed, placed in a bassinet in a quiet darkened room and the frequency and severity of reflex spasms noted. It was then sedated with the appropriate sedative, and left alone for a period of 30 minutes before a more complete examination or any further nursing procedures were performed. Oxygen was administered by funnel if spasms were severe.

Tetanus antitoxin: Fifty thousand i.u. of tetanus antitoxin was given, using the intramuscular route only, and without any preliminary test dose.

Chemotherapy: Benethamine penicillin 300,000 units was injected intramuscularly every third day. The treatment in the event of the development of clinical pneumonia was not constant. During the first trial 500,000 units of soluble penicillin was given six-hourly but subsequently the tendency was to substitute streptomycin 0.5 gm. daily in combination with half the above dose of soluble penicillin. Tetracycline, erythromycin

or chloramphenicol were used when the above antibiotics proved ineffective.

Feeding: Here too there was some variation. The initial practice was to pass a tube by the nasal or oral route as soon as possible after the first dose of sedative, and intravenous feeding was seldom resorted to. Later the passage of the tube was delayed until spasms were well controlled, sometimes for as long as 48 hours after admission. Intravenous feeds by intermittent scalp vein infusions were given if the passage of a tube was long delayed or if signs of dehydration developed. When tube fed, expressed breast milk was usually given, but in the event of an artificial feed being necessary either "Kledon" or "Carnation Milk" was used. Intravenous fluids usually consisted of invert sugar or paediatric glucose saline.

Nursing: The infants were kept in a darkened room and all external stimuli reduced to a minimum. Where possible nursing procedures were carried out at periods of maximum sedation. The infants were usually placed in the head down position but frequent changes of position and turning were carried out when spasms were adequately controlled. Inevitably there was variation in nursing efficiency particularly with changes in staff, a nurse seldom staying in the unit for longer than 1 to 3 months. As will be indicated later a more permanent and efficient nursing team was available during the I.P.P.R. trial.

Care of the wound: Approximately half an hour after the initial sedation the umbilicus was irrigated with hydrogen peroxide, any foreign material removed, and merthiolate applied. Tetanus antitoxin was not

injected around the stump and umbilectomy not performed.

Non-neonatal patients:

Procedure on admission: The patient was put to bed in a quiet darkened room and a test dose of tetanus antitoxin given followed by the appropriate sedative.

Tetanus antitoxin: All the patients received a subcutaneous test dose of 500 i.u. of tetanus antitoxin. Thirty minutes later 100,000 i.u. was given intramuscularly and in all patients over the age of 10 years the same dose was repeated after a further 30 minutes but given intravenously.

Chemotherapy: Procaine penicillin 600,000 units twice daily was given to all patients over the age of 10 years, and half that amount to smaller children. If signs of clinical pneumonia developed 500,000 units of soluble penicillin was given four to six-hourly according to age. In later trials streptomycin or a broad spectrum antibiotic was added if pneumonia developed while on treatment with penicillin.

Feeding: Patients who were unable to swallow were fed by an oral or nasal gastric tube in the early part of the series. Later tube feeding was largely replaced by intravenous feeding. It was found that patients who were unable to take feeds orally when spasms were severe were often able to do so a few days later when these were well controlled, intravenous fluids being given in the interim.

Nursing: Whenever possible nursing procedures were carried out approximately 1 hour after sedation.

Care of the wound: The wound was irrigated with hydrogen peroxide and foreign and necrotic material removed. In patients with post-abortal tetanus the products of conception were removed digitally or with an ovum forceps, if present in the vagina or protruding through the cervix.

Wound excision or more extensive surgery was not undertaken in the present series.

TRIAL I : Non-neonatal patients

A randomised comparison of chlorpromazine and barbiturate

Drug dosage : Barbiturate. Phenobarbitone sodium was given intramuscularly in doses of 3 to 6 gr. three- to six-hourly according to the age of the patient and the frequency and severity of reflex spasms. When sedation was required urgently amylobarbitone sodium 0.25 - 1.00 Gm. was given either intramuscularly or intravenously.

Chlorpromazine. This was given intramuscularly in doses of 50 - 150 mg. four- to six-hourly according to the age of the patient and the frequency and severity of reflex spasms. When sedation was required urgently the intravenous route was used. Promethazine was given to a few patients in an attempt to reduce the high dosage of chlorpromazine sometimes required but was soon abandoned.

In all patients drugs were given orally only during convalescence.

Results : In table 11 the two treatment groups are compared and the chief clinical features of the individual cases presented in tabular form in appendix I.

TRIAL II : Non-neonatal patients

A randomized comparison of chlorpromazine and a chlorpromazine barbiturate mixture

Drug dosage : Chlorpromazine. The dosage schedule was identical to that in the first trial except that an upper limit of 1,000 mg. of the drug was set for any twenty-four hour period, because toxic symptoms had been experienced in the previous trial.

Chlorpromazine-barbiturate combination. Patients in this group were given 50 mg. chlorpromazine and 200 mg. phenobarbitone sodium on admission intramuscularly. Thereafter chlorpromazine dosage was fixed at 50 mg. four-hourly, additional sedation being achieved with barbiturate as required. Proportionate doses were given to small children.

Results : In table 11 the two treatment groups are compared and the chief clinical features of the individual cases presented in tabular form in appendix I.

TABLE II

COMPARISON OF TREATMENT GROUPS NON-NEONATAL PATIENTS TRIALS I AND II

	TRIAL I		TRIAL II	
	Chlor-promazine	Barbiturates	Chlor-promazine	Chlorpromazine-Barb. comb.
No. of cases	23	21	29	27
Average age (days) ?yrs.	18	22.5	13	21
Average incubation period (days)	7.9	8.5	9.7	11.3
Average period of onset (hr.)	32	28.5	38.2	63
Average admission time (hr.)	78.2	35.6	62	66.7
Severity:				
Severe (% of total in brackets)	15(65%)	13(62%)	24(83%)	16(59%)
Moderate	7	6	4	7
Mild	1	2	1	4
Site of wound:				
Leg	10	11	14	7
Arm	2	-	-	3
Trunk	-	-	1	-
Head	3	2	2	2
Uterus	-	1	1	3
Multiple	3	2	5	3
No wound	5	5	6	9
Bronchopneumonia	5	6	3	3
Poor control of spasms	3	5	7	4
Feeding:				
oral	12	5	19	20
Tube	7	6	1	-
Intravenous	2	7	6	7
Not fed	2	3	3	-
Survival time (days)	3.5	2.5	3.0	3.0
Deaths:				
Among all cases	10(43%)	11(52%)	15(52%)	9(33%)
Among severe cases	10(67%)	11(85%)	15(63%)	8(50%)

TRIAL I : Neonatal patients

A randomised comparison of chlorpromazine and barbiturate

Drug dosage : Barbiturate. Phenobarbitone sodium was given intramuscularly in doses of 1 gr. according to the frequency and severity of reflex spasms. Initially this was usually necessary four- to six-hourly but less frequently after the second or third day.

Chlorpromazine. This was given intramuscularly in 20 - 25 mg. doses four-hourly initially, but less frequently as spasms were controlled.

Results : In table 12 the two treatment groups are compared and the chief clinical features of the individual cases presented in tabular form in appendix 5.

TRIAL II : Neonatal patients

A randomised comparison of chlorpromazine and a combination of barbiturate and chloral hydrate

Drug dosage : Barbiturate-chloral hydrate combination. These patients were treated in the first twenty-four hours with phenobarbitone sodium only in doses of 1 gr. intramuscularly, up to a maximum of five doses, the aim being to achieve sedation rapidly to facilitate the passage of a stomach-tube. Thereafter no further phenobarbitone was given and control was attempted with chloral hydrate in doses of

TABLE 12

COMPARISON OF TREATMENT GROUPS NEONATAL PATIENTS TRIALS I AND II

	TRIAL I		TRIAL II	
	Chlor-promazine	Barbiturate	Chlor-promazine	Barbiturate - Chl. hydr.
No. of cases	14	17	20	20
Average age (days)	7.0	7.0	5.7	8.3
Average incubation period (days)	5.8	5.8	5.2	6.8
Average period of onset (hr.)	10.5	18.1	6.8	6.8
Average admission time (hr.)	31	37.5	18.4	36.2
Severity:				
Severe	14	17	20	19
Moderate	0	0	0	1
Mild	0	0	0	0
Bronchopneumonia	3	5	1	6
Poor control of spasms	6	4	18	3
Respiratory failure	0	5	1	10
Feeding:				
Oral	0	0	-	-
Tube	13	16	11	17
Intravenous	0	0	-	-
Not fed	1	0	9	3
Survival time (days)	2.6	2.1	1.8	3.7
Deaths	13(93%)	12(71%)	19(95%)	18(90%)

2 gr. given not more frequently than four-hourly by the stomach tube left in situ.

Chlorpromazine. This was given four-hourly intramuscularly in 20 - 25 mg. doses as in the previous trial.

Results : In table 12 the two treatment groups are compared and the chief clinical features of the individual cases presented in tabular form in appendix 5.

TRIAL III

A randomized comparison of tracheotomy with a conservative method

Criteria for selection:

It was felt that there was sufficient doubt of the value of tracheotomy, particularly with the nursing facilities available in this unit to confine the trial to those patients whose prognosis was poor if treated conservatively. Only selected cases having frequent severe reflex spasms were therefore admitted to two trials, one on neonatal and the other on non-neonatal patients. Treatment schedules were standardized as before, and chlorpromazine and barbiturate were used in combination for control of spasms. Severity was assessed by two members of the team in consultation, a card opened, and if chosen a tracheotomy was performed within 48 hours of admission.

Non-neonatal patients:

Conservatively treated group: The dosage schedule of chlorpromazine and barbiturate was similar to that used in patients treated with this combination in the second trial.

Tracheotomy treated group: With the exception of the tracheotomy, drug dosage and general management was similar to that used in patients treated conservatively. Initially the operation was performed under general anaesthesia but later local analgesia was used. A metal tracheotomy tube was inserted through a window cut in the trachea, if possible at the level of the third and fourth rings. The inspired air was not humidified but oxygen bubbled through water at room temperature was administered when required. Secretions from the trachea were aspirated by means of an electric suction pump two-hourly, or less frequently if necessary, using a soft rubber catheter. Patients were turned frequently and postured by raising or lowering the foot of the bed.

Results: The clinical features of patients in the two treatment groups are compared in table 13 and the chief clinical features of the individual cases presented in tabular form in appendix 3.

Neonatal patients:

Conservatively treated group: Chlorpromazine was administered intramuscularly in doses of 12½ - 25 mg. with phenobarbitone sodium in doses of ½ - 1 gr., the combination being given when necessary according to the frequency and severity of spasms.

TABLE 13

COMPARISON OF TREATMENT GROUPS NON-NEONATAL TRIAL III

	Tracheotomy	Conservative
Number of patients	8	7
Average age (years)	21.3	26.9
Average incubation period (days)	9.5	7.8
Average period of onset (hr.)	32.1	30.6
Average admission time (hr.)	34.5	28.3
Site of wound:		
Leg	2	-
Arm	1	-
Trunk	-	-
Head	2	3
Uterus	1	3
Multiple	1	-
No wound	1	1
Bronchopneumonia	1	2
Poor control of spasms	3	3
Feeding:		
Oral	1	-
Tube	-	-
Intravenous	6	6
Not fed	1	1
Average survival time (days)	4.4	4.7
Deaths	6(75%)	6(85.7%)

Tracheotomy treated group: With the exception of the tracheotomy, drug dosage and general management were similar to that used in patients treated conservatively. The tracheotomy was performed after heavy sedation, the tissues overlying the trachea being infiltrated with 1% procaine hydrochloride so as to produce local analgesia, and a number 16 or 18 Parker tracheotomy tube inserted through a window cut in the trachea. Care of the tracheotomy was similar to that in non-neonatal patients.

Results: In table 14 the two treatment groups are compared and the chief clinical features of the individual cases presented in tabular form in appendix 7.

TRIAL IV

A randomized comparison of I.P.P.R. with a conservative method

Criteria for selection:

As in trial III only patients having frequent severe reflex spasms whose prognosis was thought to be poor if treated conservatively were selected for trial. Other criteria such as incubation period, period of onset and admission time were taken into account when in doubt, but usually only to exclude patients from trial. At no time were patients having moderately severe spasms admitted to the trial even though other criteria suggested a poor prognosis.

TABLE 14

COMPARISON OF TREATMENT GROUPS NEONATAL TRIAL III

	Tracheotomy	Conservative
Number of cases	13	17
Average age (days)	6.0	7.2
Average incubation period (days)	5.2	5.8
Average period of onset (hr.)	7.7	9.0
Average admission time (hr.)	20.8	34.9
Bronchopneumonia	4	12
Poor control of spasms	5	3
Respiratory failure	3	10
Feeding:		
Oral	-	-
Tube	3	3
Intravenous	5	10
Not fed	5	4
Survival time (days) (in deaths under 14 days)	4.8	5.9
Deaths:		
Within 48 hours	6	3
After 14 days	-	3
Mortality %	100	100

The assessment of severity and the decision to admit a patient to the trial was made by at least two members of the team in consultation. Although it was laid down initially that a period not exceeding 48 hours would be allowed for assessment of severity, in practice a decision was made and the patient admitted to trial in a much shorter period. During this period of observation only phenobarbitone was used for sedation as chlorpromazine was thought to have made secretions tenacious and difficult to aspirate in 2 patients treated with I.P.P.R. before the start of the trial.

As in previous trials, treatment groups were randomized and separate trials conducted on neonatal and non-neonatal patients. Despite the strict criteria of severity adopted, the number of patients fulfilling these criteria always far exceeded the number of respirators available, so that continuation of the trial was thought to be justified even when it became apparent that a lower mortality was likely in one of the groups.

Standardised treatment

The dosage of tetanus antitoxin, penicillin and the care of the wound was standardised as in previous trials. Because of the high mortality from bronchopneumonia among early neonatal patients treated with I.P.P.R., gamma-globulin 2 ml. intramuscularly was given on admission to case number 514 and all subsequent infants in both groups (Smythe and Bull, 1959).

Feeding methods: Although expressed breast milk or occasionally an artificial feed was given by intragastric tube to all infants, feeds were usually started later in those treated conservatively because of difficulty in passing a tube until spasms were controlled. In non-neonatal patients, intravenous, tube or oral feeding was used as in previous trials. Initially all non-neonatal patients treated with I.P.P.R. were fed by nasal tube from the start, a "Complan" mixture being given, but later the intravenous route was used for the first 48 hours.

Supportive care differed in the two groups. Patients were treated in two separate small wards with the same medical staff but different nursing staff in attendance. Nurses attending to both groups were, however, selected for their efficiency and remained in the unit for a period of at least 6 months. With rare exceptions, at least 2 nurses and usually 4 were in constant attendance on those patients treated with I.P.P.R. On only one occasion was more than 3 respirators used simultaneously, although quite frequently as many as 6 convalescing patients, some of whom still had tracheotomies, were present in the ward and required attention. Those cases of tetanus treated conservatively were kept in a separate room during the acute stage in the care of a trained nurse with some assistance from a nurse-aid. As many as 8 patients, the majority of whom were infants, were sometimes treated in this ward at one time.

The management of patients treated conservatively

Non-neonatal patients: Chlorpromazine 50 mg. four- to six-hourly and phenobarbitone sodium gr. 3 were given by the intramuscular route when required for control of spasms as in Trial II.

Neonatal patients: Acetylpromazine 5 - 10 mg. and phenobarbitone sodium $\frac{1}{2}$ - 1 gr. were given by the intramuscular route when required for the control of spasms.

Tracheotomies were not performed on any of the patients in the conservative group.

The Management of Patients treated with I.P.P.R.

Non-neonatal patients

Ventilation: The usual routine adopted for the institution of I.P.P.R. was to inject by the intravenous route 25 to 50 mg. succinylcholine with thiopentone sodium 250 to 500 mg., to allow intubation of the larynx with a cuffed Magill tube. Artificial ventilation was then provided either by a Radcliffe Mark V positive-pressure pump (Russell and Schuster, 1953) or a Smith-Clarke positive-negative respirator (Smith-Clarke and Galpine, 1955). Thereafter tubocurarine chloride was injected intramuscularly in 30 mg. doses so as to maintain total paralysis. The frequency with which this was given was left in part to the discretion of the nursing staff, the indications being excessive muscular twitching and attempts at spontaneous respiration. The alveolar

ventilation required was calculated in the first instance from a Radford Nomogram (Radford et al., 1954; Radford, 1955), the rate of respiration being chosen according to age. For this purpose a rough estimate was made of height and weight. Ventilation was subsequently checked by measurement of minute volume. Later adjustments were made according to the clinical condition of the patient and the level of arterial pCO2 obtained by a rebreathing method (Campbell and Howell, 1960; Sykes, 1960) using a modified Haldane apparatus (Campbell, 1960). However, the frequency with which the latter was estimated in any given patient varied with the number of patients being treated with I.P.P.R. at the time and the staff available.

The initial inflation pressures used ranged from 10 to 14 cm. of water but rose to as high as 24 cm. of water in one patient, although a maximum of 18 cm. of water was otherwise not exceeded. Most patients were deliberately overventilated, a minute volume ranging from 8 to 10 litres with an arterial pCO2 below 35 mm. Hg. being usual for an adult.

Inflation pressures, tube temperature, blood pressure and pulse rate were recorded half-hourly, and body temperature four-hourly.

Curare dosage: This varied considerably from case to case as well as in the individual patient. The total daily dosage ranged from 90 - 480 mg., children usually requiring less curare than adults. There was no apparent correlation between the severity of tetanus and the dosage of curare

required. Although the latter appeared to decrease towards the end of treatment with I.P.P.R. in some patients, this was an inconstant finding.

Humidification: Humidifiers incorporated in the respirators were used to humidify the air delivered to the patient. The tube temperature, measured at a point as close to the patient as possible, was kept at 95 to 100 degrees F. by permanently leaving a thermometer inserted through a hole made in the delivery tubing.

The airway: A high tracheotomy was performed within 24 hours of starting I.P.P.R. A cuffed Oxford tracheotomy tube (Spalding and Smith, 1956) was inserted through a window cut in the trachea and the patient ventilated by this route. The cuff was released two-hourly with the patient in the head-down position, but the tube was not changed unless it became defective. Dislodgment of the tube was a problem and will be discussed later.

Physiotherapy and suction: After vigorous percussion to the chest secretions were aspirated half-hourly from the lungs using a soft rubber catheter. The patient was turned and the foot of the bed elevated or lowered. Nurses were trained to auscultate the chest to determine the effectiveness of physiotherapy and suction. During physiotherapy, while disconnected from the respirator, the lungs were inflated intermittently with oxygen.

Sedation: Amylobarbitone sodium 250 mg. was administered intramuscularly every 4 to 8 hours to induce sleep.

Routine investigations: The peripheral blood was examined and the blood urea and serum electrolytes were estimated in all patients with variable frequency, and the plasma carbon dioxide content in most. Facilities were not available for measuring blood pH. An electrocardiogram (E.C.G.) was taken on each patient; and in a few serial records were obtained. Radiographs of the chest were taken on most patients but their value was limited. When atelectasis occurred vigorous physiotherapy was found adequate to achieve re-expansion of the lung without resort to bronchoscopy.

The duration of total curarisation: This ranged from 10 to 18 days in patients who recovered. With one exception (case 220) earlier attempts at assessment of the progress of the disease by decreasing the paralysis were not made.

The return of spontaneous respiration: As soon as definite attempts at spontaneous respiration were being made the patient was disconnected from the respirator for increasing periods with occasional assistance to respiration by manual inflation using an air-oxygen mixture. Recently (cases 220 and 221) succinylcholine given by continuous infusion has been used to maintain paralysis for 12 hours after curare had been discontinued with the purpose of achieving a more rapid return to spontaneous respiration.

Trismus, generalised rigidity and in some patients, reflex tetanic spasms returned on stopping curare. Chlorpromazine or barbiturates

were usually given orally at this stage in small doses to reduce rigidity. The rubber cuffed tracheotomy tube was replaced by a metal one when once satisfactory spontaneous respiration had been re-established. Removal of the metal tube was delayed until trismus and pharyngeal spasm had decreased sufficiently to permit swallowing without difficulty.

Neonatal patients

Ventilation: Succinylcholine 10 to 30 mg. was given intramuscularly, the lungs inflated with oxygen using an anaesthetic bag and face mask, a laryngoscope passed and a size 00 flexometallic tube introduced through the larynx. Artificial ventilation was commenced at a rate of 30 to 40 respirations per minute at an inflation pressure which appeared to produce an adequate tidal volume. A negative-pressure phase was usually, but not invariably, introduced when the Smith-Clarke machine was used. Ventilation was subsequently controlled either by clinical assessment alone, or in some patients with the aid of measurements of arterial pCO2 using a re-breathing technique (Sykes, 1960). It was found that adequate ventilation was possible in infants with both the Radcliffe Mark V and Smith-Clarke machines. There was no apparent advantage with the use of the negative-pressure phase of the latter machine. The cam-operated valves incorporated in these machines made a modification such as that described by Smythe and Bull (1959) who used an earlier model Radcliffe pump with a Stott valve, unnecessary in our babies. Total paralysis was maintained by injecting d-tubocurarine chloride 3 mg. intramuscularly. As in non-neonatal patients indications

for repetition of the dose were muscular twitching and attempts at spontaneous respiration.

Although initial inflation pressures in most infants were similar to those used in non-neonatal patients, in some, pressures as high as 20 cm. of water were required from the outset (case 532). Marked overventilation was usual as indicated by the arterial pCO2 levels which were often well below 30 mm. Hg. Inflation pressures rose steadily during I.P.P.R., the increase possibly being related to the high incidence of pulmonary infection and atelectasis which occurred.

Inflation pressure, tube temperature and pulse rate but not blood pressure were recorded half-hourly as in non-neonatal patients, and body temperature four-hourly.

Curare dosage: As in non-neonatal patients there appeared to be an increase in curare dosage towards the end of the first week, and although there was usually a reduction in its requirement towards the end of treatment with I.P.P.R., this was inconstant. Maximum daily doses ranged from 6 mg. (case 503) to 48 mg. (case 539). There appeared to be no correlation between the severity of tetanus and the curare dosage required. It is of interest that both infants who required very low dosage of curare were hypothermic (cases 503 and 504). Muscular twitching was a considerable problem in one infant (case 521) despite high curare dosage, and a striking feature in all infants seen early in the series as muscle tone returned after curare had been discontinued.

Humidification: The air, often with oxygen admixture, which was delivered to the patient was humidified by the humidifiers incorporated in the machines. It was found that because of its small volume, cooling of the gas occurred before reaching the infant. It was therefore necessary to increase the temperature of the humidifier and lag the delivery tube, thus reducing cooling to a minimum. However, this created a problem when the infant was disconnected from the machine, a greater volume of air passing through the tube so that overheating occurred unless the opening of the delivery tube was stopped with a cork during suction. Nevertheless an attempt was made to keep the temperature, which was measured in the delivery tube as close to the baby as possible, between 95 and 100 degrees F.

The airway: A high tracheotomy was performed within 24 hours. A size 00 or 0 cut-down plain latex armoured tube was used as a tracheotomy tube. This was inserted through a window or vertical incision in the trachea at the level of the second and third rings and positioned to ensure equal ventilation of both lungs. The free end of the tube was attached to the vertical limb of a suction T-piece, the other end of the vertical limb being occluded by a screw-cap which could be removed for suction. The free end of the horizontal limb of the suction T-piece was attached to a metal connection on the delivery tubing of the respirator. The tracheotomy tube was held in position by a brass clamp and harness secured around the infants neck and shoulders so as to prevent dislodgment of the tube (figure 8).

Figure VIII - Oedema of the face in tetanus neonatorum treated with I.P.P.R.

Physiotherapy and suction: After vigorous physiotherapy to the chest performed half-hourly or more frequently if necessary, secretions were aspirated from the lungs with the infant in the head down position, using a soft rubber Jaques catheter (size 3 E.G.). The infant was turned from side to side and physiotherapy and suction repeated until such time as the lungs sounded clear of secretions on auscultation. Nurses became very efficient at this technique and learnt to recognize such complications as pneumonia, atelectasis or displacement of the tracheotomy tube down the right bronchus, by auscultation of the chest and the detection of cyanosis.

Sedation: Unless the curare dosage was high or a marked tachycardia occurred, infants were not sedated during the course of I.P.P.R. With the return of rigidity or mild reflex spasms after curare was discontinued, however, phenobarbitone, chloral hydrate or phenergan were usually given but in low dosage.

Routine investigations: The frequency with which special investigations were undertaken varied considerably. There were none that were essential to treatment. Radiographs of the chest were taken quite frequently to confirm clinical evidence of pneumonia or atelectasis, but the disappointing quality of the films limited their value. Detailed electrolyte balances were attempted on two early cases but difficulty in collecting urine and stool specimens, and inability of the routine laboratory to perform studies of blood chemistry using micro-methods, lead to these attempts being abandoned. These studies had, however, shown that as in non-neonatal patients uraemia

was a complication so that frequent blood urea estimations were made on all infants during the latter half of the trial. Electrocardiographic tracings were taken infrequently during the early part of the series but were done on each of the last 11 patients treated with I.P.P.R., with serial records in some. Haemoglobin and white cell counts were done routinely and serum proteins estimated on 4 oedematous infants.

The duration of total curarisation: This was maintained for as long as 28 days in 1 infant (case 495), the first patient treated with I.P.P.R., but a period of 12 to 16 days was considered optimum.

The return of spontaneous respiration: In the early part of the series when once attempts at spontaneous respiration were being made, usually within 8 to 12 hours of stopping curare, the infant was disconnected from the respirator for increasing periods and allowed to breathe spontaneously. Assistance to respiration was given intermittently if necessary by manual inflation with oxygen until such time as respiration was adequate. During the second half of the trial a technique which we have called "assisted respiration" was developed. Curare was discontinued somewhat earlier than in previous patients (eleventh to twelfth day), but respiration still assisted mechanically during the third week while allowing the infant to breathe spontaneously, the screw cap on the suction connection being removed for that purpose. The rate of ventilation was halved enabling the infant to take one breath spontaneously

for each taken in phase with the respirator. Appropriate adjustments were made to the machine so as to maintain an adequate inflation pressure.

Rigidity usually returned within 72 hours of stopping curare. This was followed by reflex spasms of variable severity in most patients, although in a partially curarised patient they were sometimes difficult to detect. The latex armoured tube was replaced by a metal tracheotomy tube within 72 hours of stopping curare. Rigidity was severe in all infants so that feeding by intragastric tube was usually necessary for 2 to 4 weeks after stopping curare. Attempts at removing the tracheotomy tube were not made until the infant was able to suck from bottle, breast or Belleroy feeder. Rigidity and reflex spasms were sufficiently severe to cause embarrassment to respiration in some infants and careful physiotherapy and suction were still required during the third and fourth weeks. The time of removal of the tracheotomy tube varied from 21 to 227 days after admission.

Results: Results in non-neonatal and neonatal patients are compared, and the clinical features presented in tables 15 and 16 and appendices 4 and 8 respectively. The difference between the two treatment groups in the neonatal trial was significant ($P < 0.1$, X^2 test).

"OFF SERIES" CASES

Non-neonatal patients: A combination of chlorpromazine and phenobarbitone sodium was used for the control of spasms in the majority of patients who were not treated on any of the randomised trials. The dosage schedule

TABLE 15

COMPARISON OF TREATMENT GROUPS

NON-NEONATAL PATIENTS TRIAL IV

	I.P.P.R.	Conservative
No. of cases	8	8
Average age (days)	15.9	15.9
Average incubation period (days)	8	4.4
Average period of onset (hr.)	25.1	23.2
Average admission time (hr.)	31.5	40.7
Postabortal	2	1
Survival time (days)	8.4	1.9
Deaths	4	6
Within 48 hrs.	Nil	3
After 14 days	Nil	Nil
Mortality %	50	75

TABLE 16

COMPARISON OF TREATMENT GROUPS

NEONATAL PATIENTS TRIAL IV

	I.P.P.R.	Conservative
No. of cases	25	25
Average age (days)	6	6.6
Average incubation period (days)	4.9	5.4
Average period of onset (hr.)	5.9	5.9
Average admission time (hr.)	19.5	25.0
Premature infants (under 5½ lbs.)	6	4
Survival time (days)	22.8	4.6
Deaths	11	21
Within 48 hrs.	-	2
After 14 days	8	0
Mortality %	44	84

used was similar to that in the chlorpromazine-barbiturate group in Trial II. Chlorpromazine or barbiturate alone, or acetylpromazine either alone or in combination with barbiturate, were used to control spasms in the remainder, with the exception of 2 cases (cases 204 and 205) who were treated with I.P.P.R.

Acetylpromazine was selected for clinical trial in 8 cases of severe tetanus (cases 147 to 154). On admission the drug was given intramuscularly in 10-50 mg. doses depending on the age of the patient and the frequency and severity of reflex spasms. Thereafter 20 - 25 mg. doses were usually given at four- or six-hourly intervals, but higher dosage was sometimes necessary or phenobarbitone sodium 3 - 6 gr. was added to achieve control. Chlorpromazine and barbiturate were substituted in combination, in 2 patients (cases 148 and 150), in 1 because acetylpromazine had produced toxic effects, and in the other because all available supplies of the drug had been used.

Tracheotomy was performed on 6 patients not included in any of the trials.

The clinical features in "eff series" patients seen before the start of Trial IV trial are summarised in tabular form in appendix 2.

Neonatal patients: The majority were treated with either chlorpromazine or acetylpromazine in combination with barbiturate, in the doses employed

for the control of spasms in the conservative groups in trials III and IV respectively. In 7 infants (cases 425 - 431) paraldehyde ½ - 1 ml. was combined with chlorpromazine 12½ - 25 mg., both drugs being given intramuscularly.

In 4 patients (cases 432 - 435) tracheotomy was performed as a preliminary to the start of Trial III. In 4 others (cases 495 - 498) I.P.P.R. was used, either as a preliminary to the start of Trial IV, or for the purpose of investigating certain aspects of the technique. Two patients treated with I.P.P.R. (cases 499 and 500) were admitted when only one member of the team was available to assess severity and therefore did not fulfil the criteria for admission to the trial.

The clinical features of these patients seen before the start of the I.P.P.R. trial are summarised in tabular form in appendix 6 and those treated with I.P.P.R. in appendix 8.

DISCUSSION

Results of the therapeutic trials in both neonatal and non-neonatal patients show that only in the neonatal I.P.P.R. trial was the difference in mortality rate between treatment groups statistically significant (Lawrence et al., 1958; Adams et al., 1959). Differences in mortality rate between groups in the other trials were relatively small, but these trials were well controlled and limited conclusions based on the results obtained therefore seem justified. Since all patients, irrespective of severity, were included in the first two trials an assessment of the severity of the groups being compared is necessary using the criteria previously suggested.

Clinical trials comparing conservative methods of treatment

Non-neonatal patients

In the first trial the overall mortality rate in the chlorpromazine-treated group (43%), was lower than that in the barbiturate-treated group (52%), a difference which was emphasized if severe cases only were compared (67% compared with 82%). Both groups appeared to be of similar severity when criteria such as incubation period, period of onset and severity of reflex spasms were compared. The average admission time in the chlorpromazine-treated group was substantially longer than in the barbiturate-treated group, largely as a result of the exceptionally long admission time of 10 days in 2 patients with moderately severe tetanus. The incidence of bronchopneumonia and other complications was

similar in the two groups. In the second trial the overall mortality rate in the chlorpromazine-barbiturate group (33%) was lower than in the group treated with chlorpromazine alone (52%). Although there were a larger number of severe cases in the chlorpromazine group, if a comparison was made of mortality rates in severe cases only it remained lower in the combined treatment group (50% compared with 63%), but the difference less marked. There were no significant differences in complications between groups, the incidence of bronchopneumonia being similar. One patient (case 84) in the chlorpromazine-treated group was edentulous, had repeated episodes of respiratory obstruction owing to the tongue falling back, and died despite tracheotomy.

Although comparison of treatment groups in different trials is not strictly valid it will be noted that the overall mortality rate in the chlorpromazine-treated group in the second trial was higher than in the first (52% compared with 43%). However, a similar mortality rate for severe cases (63% compared with 67%) suggested that the difference was due to the larger number of patients with severe tetanus in the second trial.

When used alone in the first trial barbiturate or chlorpromazine were sometimes required in large doses before spasms could be controlled. One patient who died (case 13), had to be given a maximum daily dose of 48 gr. barbiturate intramuscularly to achieve control. The maximum daily dose in a patient who recovered in this group was 25 gr. (case 9). All 3

patients who required more than 1,000 mg. chlorpromazine on any single day died (cases 22, 26 and 27), but control of reflex spasms was usual with smaller doses, and appeared to be accomplished more readily than with barbiturate and with less central depression. Both patients who died as a result of laryngospasm were in the barbiturate-treated group.

In the chlorpromazine-treated group in the second trial dosage was fixed at a maximum of 1,000 mg. for any twenty-four hour period. Barbiturate was added in 2 patients (cases 53 and 72), both of whom died shortly afterwards. In the group treated with chlorpromazine and barbiturate in combination, the maximum daily dose of the former was 700 mg. (case 78), and of the latter 21 gr. (case 77) both in patients who died. The usual dosage found adequate for control of spasms at the height of the disease was 300 mg. chlorpromazine and 9 gr. phenobarbitone, although in most cases of only mild or moderate severity little barbiturate was necessary. Spasms were poorly controlled at the time of death in 10 patients, 6 in the chlorpromazine-treated group and 4 in the group treated with barbiturate and chlorpromazine in combination. Five patients had laryngeal spasms, 3 of whom recovered. Prompt relief of laryngeal spasm occurred in all after the intravenous administration of chlorpromazine. One of the 3 recoveries (case 68), however, died of a second attack of tetanus 3 months after the first admission. There was no significant difference in the survival time (time between admission and death) in the two groups.

After the conclusion of the second trial the combination of chlorpromazine and barbiturate was used on all non-neonatal patients treated before the start of the I.P.P.R. trial, with the exception of those submitted for trial of acetylpromazine and a few mild cases treated with chlorpromazine alone. Since some severe cases were selected during this period for trial of tracheotomy or acetylpromazine, figures of mortality rate or severity cannot be compared with other groups. Clinical impression, however, confirmed the earlier finding of the superiority of chlorpromazine and barbiturate in combination, to either drug used alone.

Despite the use of this combination, control of spasms was not always achieved, so that acetylpromazine, because of experimental evidence of its greater potency (Laurence and Webster, 1958), was tried in 8 selected patients in whom reflex spasms were severe. Although it was thought likely that a combination with barbiturate would prove more effective, acetylpromazine was used alone as far as possible so that its action might best be observed. In 5 of the 8 patients with severe tetanus so treated control of reflex spasms was most effective. This was achieved in 4 patients with a maximum daily dose not exceeding 150 mg., but 1 patient (case 148) considered to have been one of the most severe cases in the whole non-neonatal series to recover, required 420 mg. on the fourth day to control spasms, and then only at the expense of side-effects. Spasms were poorly controlled in 2 patients who died, and the third appeared to die of respiratory failure. The series was small and although all were

having frequent severe reflex spasms, it should be noted that in 3 of the 5 recoveries the period of onset was over 48 hours and the prognosis therefore relatively good. On clinical grounds, however, there was little doubt of the value of acetylpromazine in suppressing tetanic spasms and reducing muscular rigidity. In fact, in 2 patients (cases 149 and 150) marked stiffness or reflex spasms returned on stopping or reducing the dose of the drug.

Assessment of the relative value of acetylpromazine and chlorpromazine in the control of reflex spasms is difficult. When used alone in the average case having frequent severe reflex spasms, a total of 400 to 900 mg. chlorpromazine was usually necessary. In cases thought to be of comparable severity who were treated with acetylpromazine, only 40 to 200 mg. of the drug was required for control, thus confirming experimental evidence of its greater potency.

A striking difference between groups was the frequency with which patients treated with chlorpromazine, or a chlorpromazine barbiturate combination, were able to take fluids orally when compared with those treated with barbiturate alone (see table 11). The observations made by Barr (1958) on the widening of the interdental distance after the injection of chlorpromazine were frequently confirmed on patients in this series. Patients whose jaws were tightly clenched when admitted, were often able

to take fluids orally within half an hour of the administration of the drug. Furthermore, when swallowing proved difficult, the passage of a gastric tube was facilitated by the prior administration of chlorpromazine. This is emphasised by the relative infrequency with which the intravenous route was resorted to in the first trial when compared with the barbiturate group, intravenous feeding in this trial only being used when attempts to pass a gastric tube had failed. Experience with the use of chlorpromazine led to changes in the management of patients who were unable to swallow in subsequent trials. Rather than persist in attempts to pass a tube on patients with dysphagia, short-term intravenous feeding was employed since it was realised that patients treated with chlorpromazine need only be tided over a critical period of a few days before the ability to swallow returns. There are several reasons for abandoning tube feeding if such an alternative method is possible. Although the principle was adopted of attempting to pass a tube only after maximal sedation, this manoeuvre often provoked severe spasms. Furthermore, when left in situ, the tube acted as an irritant, stimulated the production of secretions and partially obstructed the airway. Particularly impressive was the ease with which patients with severe tetanus treated with acetylpromazine were able to take fluids orally, neither tube nor intravenous feeding being required in those who recovered. The ability of chlorpromazine or acetylpromazine to facilitate oral feeding would alone seem to be sufficient to recommend their use in the conservative management of tetanus.

Patients sedated with chlorpromazine or acetylpromazine were more co-operative and easier to nurse than those heavily sedated with barbiturate, an important practical advantage if nursing facilities are inadequate. This advantage was lost, however, when high dosage was necessary and mental confusion occurred so that the combination of either of these drugs with phenobarbitone was preferred, because of lower toxicity.

Neonatal patients

In the first trial the overall mortality rate in the barbiturate-treated group was considerably lower than in the chlorpromazine-treated group (7% compared with 93%). Average age, incubation period, period of onset, and admission time were similar in the two groups. Although severe spasms were seen in all patients, the admission time in 2 of the recoveries in the barbiturate group (cases 227 and 232) were 7 and 4 days respectively, and the prognosis therefore relatively good. The incidence of broncho-pneumonia was slightly higher when patients were treated with barbiturate. In the second trial, although the mortality rate using barbiturate and chloral hydrate (90%) was slightly less than in the chlorpromazine-treated group (93%), one patient was only moderately severe and the average incubation period and admission time was longer than in the chlorpromazine group. The incidence of bronchopneumonia was higher in the barbiturate-chloral hydrate group and one infant (case 274) in this group died on the thirty-sixth day, prolonged tube feeding having produced ulceration of the oesophagus with erosion into the trachea and respiratory obstruction.

In the chlorpromazine-treated group in the first trial a maximum daily dose of more than 200 mg. of the drug was used in over half the patients with reasonable control of spasms, but only one recovered. It was thought that the high dosage of chlorpromazine used might have been responsible for death in some of these patients. In the barbiturate-treated group better control of spasms was achieved, although the survival time was short. One patient who recovered (case 237) required a maximum daily dose of 6 gr. and a total dose of 38 gr. phenobarbitone, the only patient to whom more than 5 gr. of the drug was given in any twenty-four hour period.

In the chlorpromazine treated group in the second trial lower doses were used, and with one exception (case 257), all were given a maximum daily dose below 200 mg. chlorpromazine. With this dosage control of spasms was poor and the average survival time short. Phenobarbitone was added, with temporary control, in one patient (case 269) having continuous spasms. In the barbiturate-chloral hydrate group, it was found that a dose exceeding 5 gr. phenobarbitone sodium in the first 24 hours had to be given to 2 patients before a tube could be passed for the administration of chloral hydrate, the maximum daily dose of which was 13 gr. (case 277). To achieve control of spasms chlorpromazine was added in 2 patients on the second day (cases 265 and 286). The average survival time was considerably longer and spasms were

controlled more effectively in the group treated with barbiturate and chloral hydrate than in the chlorpromazine group. The use of higher doses of chlorpromazine in the first trial resulted in better control of spasms and a longer average survival time than in the chlorpromazine treated group in the second trial, but mortality rates were high in both groups (table 12). Although mortality rates were lower and control of spasms better with the use of barbiturate alone or in combination with chloral hydrate, on the whole, death associated with inadequate control of spasms was replaced by death from respiratory failure.

Because of the impression that better control was achieved in 3 infants in the second trial to whom both chlorpromazine and barbiturate were given, and because of the success with its use in non-neonatal patients, this combination was tried in a large number of cases not included in any of the randomised trials. Preliminary results were encouraging and the combination was therefore used to control spasms in a later trial of tracheotomy in selected severe cases. The overall mortality rate in 94 patients, including those treated with tracheotomy, was 61%. The average survival time was long and spasms were usually controlled.

Acetylpromazine was used alone in 3 very severe cases because of its greater potency when compared with chlorpromazine in experimental tetanus (Lawrence and Webster, 1958). Although given in high dosage of up to 125 mg. intramuscularly in 1 infant, it failed to control spasms

and all died within 24 hours. When combined with barbiturate, however, control of spasms was very effective and 3 of 22 selected severe cases recovered. Of a further 12 patients similarly treated 6 recovered, 4 of whom were having only moderately severe reflex spasms.

A maximum daily dose of 100 mg. chlorpromazine or 40 mg. acetylpromazine combined with 3 gr. barbiturate was seldom exceeded. In most patients only half this dosage was usually required for the initial control of spasms. Once this had been achieved, 5 mg. acetylpromazine or 12½ mg. chlorpromazine, with ½ gr. phenobarbitone given once or twice daily or even on alternate days was adequate. However, despite good control of spasms and an increase in the survival time, death usually occurred from respiratory failure. Chlorpromazine was combined with paraldehyde in a small number of patients (cases 425 to 431), in the hope of preventing possible drug-induced respiratory failure. With this combination control of spasms was less rapid, but an identical picture of respiratory failure was observed.

Few definite conclusions can be drawn with regard to the relative effectiveness of the different treatment groups. None of the differences in mortality are statistically significant. When used alone, chlorpromazine would seem to be of little value in the treatment of our severe cases of neonatal tetanus. It is difficult to reconcile findings in the present

series with those of Gelfand (1955 and 1957) who successfully treated 8 of 25 patients using chlorpromazine alone for the control of spasms. Differences in severity or supportive care between his patients and those in the present series seem the likely explanation.

The lowest mortality rate occurred in patients treated with barbiturate alone, but the group was small and in retrospect it is likely that at least 2 patients were of only moderate severity in terms of the criteria subsequently adopted. The combination of a phenothiazine derivative with barbiturate, although having a slightly higher mortality rate than barbiturate alone, has been preferred because of its ability to control spasms more effectively and therefore prolong survival time. Acetylpromazine was thought superior to chlorpromazine in this respect, some confirmation for this view being obtained from a comparison of conservatively treated patients in the tracheotomy and I.P.P.R. trials. In the tracheotomy trial there were no recoveries using a chlorpromazine-barbiturate combination, whereas in the conservative group in the I.P.P.R. trial with the same criteria of severity for selection, 4 of 25 patients recovered using acetylpromazine and barbiturate in combination. As already mentioned improvement in nursing standards occurred with the start of the I.P.P.R. trial and may have contributed to these results. With better supportive care it is probable that mortality could have been reduced, particularly in the phenothiazine barbiturate groups, by saving some of those infants in whom the survival time was prolonged. A similar opinion has been expressed by Levin and Reef (1960) as a result of their experience

with an intravenous 'cocktail' containing chlorpromazine, promethazine and pethidine.

It is likely that better supportive care would facilitate the use of prolonged intravenous feeding which has been advocated by some authors (Earle and Mellen, 1958; Levin and Reef, 1960). It has been tried in a large number of patients in this series but practical difficulties were considerable. Overhydration with severe oedema occurred in some hypothermic infants, even when far less than the normal daily requirement was given. One such infant after a total of 800 ccs of fluid had been given intravenously over a four-day period, became grossly oedematous and died 2 days later. Necropsy revealed bilateral bronchopneumonia, pulmonary oedema and oedema of liver and brain, with free fluid in the abdomen. Levin and Reef have stressed the need for careful control of electrolytes during the period of intravenous feeding. Difficulty in obtaining blood samples, lack of micro-methods for estimating electrolytes and blood urea, as well as the technical difficulties of maintaining a continuous infusion, have made this method impracticable in this unit, although it may well be the method of choice where nursing and ancillary services are better.

Toxic effects of chlorpromazine: Numerous reports have appeared in the literature on the toxicity and side-effects of chlorpromazine. Of these jaundice is the commonest and is said to occur in about 1% of patients treated for more than one week (British Medical Journal, 1957; Melrose and Ray, 1959). Shay and Siplet (1957, 1958) believed that sensitisation of the liver to chlorpromazine occured in about 25% of such patients but that only a proportion become overtly jaundiced. They incriminated the presence of a chlorine atom at the carbon-2 position on the promazine molecule, the antigenicity apparently being destroyed if the chlorine atom is replaced by an acetyl group as in acetylpromazine. Jaundice is independent of the dosage used and usually appears between the second and the fourth week. There is probably no relation to previous hepatic damage, and it appears to be an allergic reaction to the drug; an intra-hepatic biliary stasis with a picture resembling obstructive jaundice being produced (Werther and Korelitz, 1957; Graham, 1957). Although the period of jaundice is usually brief, lasting for a few weeks only, it may persist for 3 months or longer (Brink and Buckley, 1957), and permanent damage can occur (Melrose and Ray, 1959). Jaundice was only seen in 1 non-neonatal patient in this series, although it may well have been missed in pigmented patients treated in a darkened room. So-called physiological jaundice was seen in a few infants but late jaundice did not develop in any of these who recovered. Liver function tests were performed on some non-neonatal patients but no evidence of hepatic damage which could be ascribed to the use of

chlorpromazine or acetylpromazine was found. The relative frequency with which these drugs disturb hepatic function has not been investigated.

The literature on agranulocytosis caused by phenothiazine derivatives has been reviewed by Korst (1959). Although rare, it is the most serious complication likely to occur and appears to be due to idiosyncrasy. Blood counts have not been performed as a routine on our patients, but there is no reason to believe that agranulocytosis occurred.

It is of interest that Lambo (1957) has suggested that there may be a racial hypersensitivity to chlorpromazine, people of European stock being far more likely to develop allergic toxic effects than Africans or Asians.

Three non-neonatal patients (cases 24, 26 and 27) became confused on high dosage of chlorpromazine and 1 developed a Parkinsonian tremor. Acetylpromazine produced similar mental symptoms, with urinary and faecal incontinence, in 1 patient (case 148). Neurotoxic symptoms were found in 40% of a group of schizophrenics treated with chlorpromazine, even in dosage as low as 150 mg. daily (Hall and Swain (1956)). While this incidence is much higher than generally accepted (Beckman, 1958), and probably related to the underlying mental state, a similar picture to that seen in our patients has been reported by Packard and his colleagues (1958) in 1 of 2 cases of tetanus treated with chlorpromazine.

There is some evidence, based on animal experiments, that

chlorpromazine in large doses makes tetanus worse (Lawrence, 1960). However, this does not seem to have occurred in our patients where the use of larger doses resulted in better control of spasms. It is uncertain whether the high dosage of chlorpromazine given in an attempt to control spasms, particularly in neonatal patients, was a contributory cause of death.

Other side-effects such as tachycardia and hypotension were observed, but it was only necessary to reduce the dose of the drug because of the tachycardia on one occasion, and postural hypotension posed no problem in bed-ridden patients. Painful sterile abscesses producing pyrexia and possibly stimulating spasms occurred in both neonatal and non-neonatal patients. More severe complications such as thrombophlebitis, sloughing and even gangrene may occur after the intramuscular injection of chlorpromazine (Hodges, 1959), but were not seen in any of the patients under review. Careful rotation of injection sites, dilution of the solution and the lower dosage required in the combination groups, have helped to reduce the incidence of this complication, although it remains a problem.

Few series have been published with which our findings in non-neonatal patients can be compared. Shanker and Mehrotra (1959) reported a lower mortality rate in a group of patients treated with chlorpromazine when compared in a randomized trial with a group treated with paraldehyde

(14.3% compared with 38.5%). They considered that "100 mg. of chlorpromazine, given immediately, followed by 100 or 50 mg. 12-hourly, may just be enough to control the spasms in adults." If not they added paraldehyde in doses of 4 - 6 ml. intramuscularly, but do not state the frequency with which this was necessary. Their series was small but their claim that a chlorpromazine-paraldehyde combination is superior to paraldehyde alone seems justified. However, it is doubtful whether the combination of paraldehyde with chlorpromazine rather than barbiturate with chlorpromazine as used in the present series, can account for their better results.

Johnstone (1958) was unimpressed with the ability of chlorpromazine to control spasms when used alone in 2 patients, or when combined with barbiturate in a further 18 cases of tetanus. However, the dosage used was small and it cannot therefore be said to have had a fair trial. Vakil (1960) after using a chlorpromazine-barbiturate combination extensively in tetanus claimed a mortality rate of 25%, and concluded that this combination "provided a more satisfactory control of hypertonia and spasms with lower doses of both the drugs." Packard and his colleagues (1958) were unable to control spasms adequately in a case of severe tetanus, despite chlorpromazine 50 mg. six-hourly with added barbiturate given intramuscularly. They were, however, impressed with its use when given with sodium amylobarbitone by continuous intravenous infusion in larger doses in a second patient, as much as 950 mg. chlorpromazine with added barbiturate being necessary in one day. In an addendum to their paper

they mention success in 3 subsequent severe cases using this regime which included tracheotomy. The administration of chlorpromazine by continuous intravenous infusion has not been tried in the present series, mainly because of the added nursing attention which would be required.

Although the combination of chlorpromazine or acetylpromazine with barbiturate is considered to be an effective and simple method of treatment in the majority of non-neonatal patients, approximately half of those having severe reflex spasms died. Death was still associated in some patients with inadequate control of spasms and in others with an appearance of respiratory failure.

In table 17 the overall mortality rate in 217 neonatal patients treated before I.P.P.R. was first used in the unit is compared with that in other large series published recently. With the exception of the report by Earle and Mellon (1958), the similarity of results with different conservative methods of treatment suggests that there is little to choose between the drugs used. Earle and Mellon treated 32 consecutive cases of tetanus neonatorum with a chlorpromazine-barbiturate combination, given by continuous intravenous infusion with the addition of cortisone in 14 patients, and reported the remarkably low mortality rate of 25%. In the present series, because severe and irreversible respiratory depression was too often the only alternative to death from inadequate control of spasms, a reduction in mortality rate to that achieved by Earle and Mellon did not seem possible by any conservative means.

TABLE 17

COMPARISON OF MORTALITY WITH THAT IN OTHER LARGE SERIES (NEONATAL PATIENTS)

Series	No. of Cases	Sedative used	Mortality
Present series	217	acetylpromazine chlorpromazine barbiturate etc.	82.5%
Jelliffe(1950)	25	paraldehyde chloral hydrate	96%
Spivey et al. (1953)	26	barbiturate	77%
Loh Siew Gek (1951)	174	paraldehyde chloral hydrate	92%
Sarreuy et al. (1956)	20	chlorpromazine barbiturate relaxant	80%
Pinheiro (1957)	256	barbiturate chloral hydrate myanesin	84%
Tompkins (1958)	141	paraldehyde chloral hydrate barbiturate	89.6%
Earle and Mellon (1958)	32	barbiturate chlorpromazine	25%
Levin and Reef (1960)	53	barbiturate i.v. cocktail	75.5%

In most small series results are better. Some reports such as that of Lorenz (1957), have come from areas where tetanus neonatorum is uncommon and medical facilities good, so that better supportive care may have accounted for the superior results. However, it has been shown earlier that mortality is relatively low in infants aged 10 days or more on admission, and it is likely that some cases reported are of lesser severity than usual and the prognosis therefore relatively good irrespective of the treatment used(Block and Foster, 1949; Dietrich, 1951; Friedlander, 1951; Symonds, 1960). Spivey and his colleagues (1953) pointed out that in Vinnard's series (1945) in which 5 of 11 cases recovered, incubation periods ranged from 8 to 12 days, and suggested that this might have accounted for the lower mortality than in their own series from the same hospital. In this respect it is of interest to note that in a series of 4 cases reported by Kao (1951), all of whom recovered, the ages on admission ranged from 10 to 14 days. In a previous communication by the same author Kao (1949), reporting a series of 8 cases of tetanus neonatorum, the only 2 patients who recovered were aged 11 and 21 days.

It would therefore seem, from an analysis of the clinical trials in the present series as well as from reports in the literature, that cases of tetanus neonatorum who recover using conservative methods of treatment are usually of lesser severity. Furthermore, recovery is largely independent of the type of sedative used. It has been shown that the majority of patients

who die once spasms are controlled die of respiratory failure, and although some may recover with better supportive care, little reduction in mortality can be expected using conventional methods of treatment.

Clinical trials comparing tracheotomy with a conservative method of treatment

Of the 8 non-neonatal patients on whom tracheotomies were performed 2 recovered, compared with 1 of 7 patients treated conservatively. The groups were similar as indicated by the criteria of severity adopted and the incidence of complications (see table 13). In one patient on whom a tracheotomy had been performed a large quantity of mucopus was found at necropsy to occlude the left main bronchus with partial collapse of the left lung. The 3 patients who recovered appear to have been less severe than those who died as indicated by a comparison of incubation period, period of onset and admission time.

All neonatal patients in both treatment groups died. Tracheotomies were performed on 13, and 17 were treated conservatively. There were no significant differences between groups although the conservative group would appear to be slightly less severe. Better control of spasms was possible in those patients treated conservatively and the survival time was correspondingly longer. Two patients in this group died of marasmus and bronchopneumonia on the thirty-seventh and the forty-second days, when the only remaining feature of tetanus was

mild generalised rigidity. It is likely that the lower incidence of pneumonia in the group treated with tracheotomy is due to the shorter survival time rather than the prevention of pulmonary infection by this procedure. Although it would have been preferable to have performed tracheotomy under general anaesthesia with preliminary intubation, on the whole with adequate sedation and local analgesia spasms were surprisingly few. It was thought unlikely that failure to use a general anaesthetic influenced the relative mortality between groups.

On the basis of these results it would appear that in our patients suffering from severe tetanus, simple tracheotomy (tracheotomy without assisted respiration), does not materially reduce mortality and may be contra-indicated in neonatal patients. It must be emphasized, however, that this applies only to the type of case selected and the particular circumstances under which these trials were conducted. Lack of adequate physiotherapy, humidification of inspired air and special nursing facilities, are probable deficiencies. The trials were stopped at this stage because it was thought that no significant differences were likely to emerge. Severe cases were thereafter usually treated on the I.P.P.R. trial and only a few selected patients submitted for tracheotomy.

It is impossible to determine whether tracheotomy was responsible for the recovery of the 2 non-neonatal patients so treated in trial III. However, in 2 patients not treated on any of the clinical trials tracheotomies were performed because excessive secretions were producing

obstruction. Its effect was impressive in both and probably life-saving.

Case 118. B.B., an African Male, aged 4 years, had a septic laceration of the penis of 18 days duration. Reflex spasms were not observed at any stage but trismus and opisthotonus were marked with mild rigidity of abdominal and limb muscles. The cerebro-spinal fluid was normal. Respiratory obstruction due to excessive secretions and pharyngeal spasm developed on the third day despite treatment with chlorpromazine 150 mg. and phenobarbitone sodium gr. 6. Tracheotomy produced considerable relief of these symptoms although he became stuporous and his temperature rose to 104 degrees F. Thereafter he gradually improved and made a complete recovery.

Case 177, S.M., an Indian female, aged 8 years, had trodden on a thorn 4 days before admission. Trismus was marked with rigidity and opisthotonus, but generalised reflex spasms were never observed. Opisthotonus and pharyngeal spasm became increasingly severe, with profuse secretions in the pharynx and trachea, pyrexia, increasing dyspnoea and loss of consciousness. Chlorpromazine 150 mg. daily intramuscularly with added barbiturate produced no improvement. A tracheotomy was performed, a number 6 cuffed rubber Oxford tracheotomy tube inserted through a window cut in the trachea and large quantities of purulent secretions aspirated. Her immediate improvement was

striking. By the following day respiration was unembarrassed and she responded to questioning. Recovery from tetanus was complete but a stenosis of the trachea developed.

With the exception of those patients treated on the tracheotomy and I.P.P.R. trials and those described above the procedure has been performed on 8 other patients in the series. Six, 3 neonatal and 3 non-neonatal patients, were very severe and it is likely that their only chance of survival lay in treatment with muscle relaxants and I.P.P.R. One recovered but the extent to which tracheotomy contributed to her recovery is uncertain, and one, in whom severe kwashiorkor was a complicating factor, died 7 days after the tracheotomy had been performed, although initial benefit from the procedure had occurred.

Based on this limited experience it is considered that simple tracheotomy is likely to be of most benefit in those non-neonatal patients who have pharyngeal and laryngeal spasms with excessive secretions. Among the indications for tracheotomy usually given are: the absence of cough and swallowing reflexes; laryngeal obstruction; excessive tracheobronchial secretions; prolonged spasms of the muscles of respiration preventing adequate ventilation; unrelieved trismus and coma from oversedation (Hersen et al., 1951; Ablett, 1956; Wilson, 1956). It is difficult to assess in retrospect the frequency with which these indications occurred in our patients. It is possible that the use of chlorpromazine and acetylpromazine reduced the frequency with which tracheotomy was indicated in the present

series. Their ability to facilitate oral feeding in non-neonatal patients without impairing consciousness, as well as their effectiveness in the treatment of laryngeal spasms have already been referred to, properties which are likely to reduce the need for tracheotomy. Several authors have noticed that the dosage of sedatives required can usually be reduced following a tracheotomy (Creech et al., 1950; Herson et al., 1951; Forbes and Auld, 1955; Galloway and Wilson, 1955). While experience in the few cases of moderate severity treated with tracheotomy in the present series has confirmed this finding, the need for sedation in very severe cases did not appear to be reduced by this procedure.

It has been emphasized that tracheotomy should be performed early rather than late (Creech et al., 1950; Forbes and Auld, 1955). Recently, in the present series, an attempt has been made to select for tracheotomy those patients most likely to benefit from the procedure. Considerable difficulty has been experienced, however, in making such a selection early in the course of the illness. Some patients, whose progress had appeared to be satisfactory, have developed laryngeal or pharyngeal spasms for the first time as late as the end of the first week. In others, admitted during the period of onset, the first spasm has been a laryngeal one which on occasion has proved fatal. Three patients have died in this way during the past year. Two occurred despite the prompt institution of resuscitative measures, including intravenous

chlorpromazine, and in one, a cardiac massage. Although a short admission time and very severe trismus disproportionate to the duration of symptoms may suggest the impending onset of severe generalised or laryngeal spasms, it is difficult to see how all such deaths can be prevented unless tracheotomy is performed as a routine, such as is practised by Landes and his colleagues (1959).

Creech and his colleagues (1957) although using tracheotomy almost as a routine state that "it may be that the most important feature of these newer measures is that they complicate the care of the tetanus patient to the point where constant nursing attention, the really significant factor in therapy, must be provided". While it would appear that tracheotomy has an undoubted place in the treatment of tetanus, the frequency with which it should be performed will depend largely on the supportive care available, since in the absence of adequate supportive care the advantages to be gained by the procedure may be lost.

While the randomised trials in the present series are of little value in assessing the place of this procedure in the treatment of tetanus, they show that in both neonatal and non-neonatal tetanus there exists a group of patients in whom such measures are ineffective. Furthermore, as in severe conservatively treated patients, death usually occurs either from respiratory failure or from inadequate control of spasms.

Clinical trials of the use of I.P.P.R.

Non-neonatal patients: Four of the 8 non-neonatal patients suffering from severe tetanus who were treated with I.P.P.R. recovered, compared with 2 of 8 patients treated conservatively. The trial is still in progress and the numbers small, so that the conclusions which can be drawn with regard to the relative effectiveness of the two methods of treatment on the basis of these results are limited.

Both groups appear to be of similar severity when criteria such as period of onset and admission time are compared (see table 15), although the incubation period was longer in the group treated with I.P.P.R. In only one patient were these criteria favourable (case 208), a patient who died while being treated with I.P.P.R. Of the remainder all had a period of onset of 48 hours or less, or an incubation period of less than 7 days, where this was known. Tetanus followed an abortion in two adults treated with I.P.P.R. both of whom recovered, whereas the only patient suffering from postabortal tetanus treated conservatively, died. The length of survival after admission was considerably longer in patients treated with I.P.P.R. All who were so treated lived for 6 days or more, whereas all treated conservatively died within 4 days.

Neonatal patients: In neonatal patients the difference in favour of I.P.P.R. was more striking. Eleven of the 25 patients so treated died, compared with 21 of an equal number treated conservatively (44% compared with 84%). A difference which is significant ($P < .01$, X^2 test).

Both groups appear to be of similar severity when criteria such as average age on admission, incubation period, period of onset and admission time are compared (see table 16). A comparison of survival time further emphasises the superiority of I.P.P.R. Of the 11 patients treated with I.P.P.R. who died, 8 survived for more than 2 weeks, whereas the longest survival time in a patient treated conservatively was 11 days.

The difference in mortality rate between groups was even greater when 40 patients had been admitted to the trial (33% compared with 90%). All deaths among neonatal patients treated with I.P.P.R. at this stage, with the exception of a premature baby who weighed 3½ pounds on admission (case 534, figure 9), had occurred during the early part of the trial (see table 18). Furthermore 10 infants with severe tetanus treated consecutively using this method, had recovered (including "off series" cases 499 and 500). In non-neonatal patients 3 consecutive deaths occurred early in the trial before results improved (see table 19).

It was considered likely that the initial lack of success, followed by a later improvement in results, could largely be attributed to the development of increased skill in the technique of I.P.P.R. particularly by the nursing staff. This is confirmed by the following analysis of the causes of death in these patients.

Figure IX - Tetanus neonatorum in a premature infant (Case 53A) treated with I.P.P.R.

TABLE 18

NEONATAL PATIENTS TREATED WITH I.P.P.R. IN ORDER OF ADMISSION TO HOSPITAL*

Case No.	Duration of curarisation (days)	Duration on respirator (days)	Removal of trach. tube (days)	Survival time (days)	Result	Max. blood urea (mg.%)	Cause of Death
495	28	28	-	29	D	-	Bronchopneumonia
496	13	13	-	13	D	-	Unknown
503	4½	4½		4½	D	-	Bronchopneumonia
504	6½	6½		6½	D	-	Bronchopneumonia
505	14	21		34	D	-	Gastroenteritis
506	13	17		18	D	-	Bronchopneumonia
510	16	20	140	-	R	-	-
497	6	15	-	26	D	-	Atelectasis
498	11	14	-	29	D	45	Atelectasis
514	14	17	227	-	R	-	-
515	3	3	-	3	D	-	Bronchopneumonia
518	18	18	-	29	D	-	Atelectasis
519	16	19	43	-	R	-	-
520	13	15	186	-	R	-	-
521	16	17	34	-	R	-	-
524	14	14	38	-	R	-	-
525	14	23	still in	-	R	44	-
499	13	14	52	-	R	57	-
500	13	15	51	-	R	43	-
526	13	19	23	-	R	68	-
530	12	17	29	-	R	55	-
532	12	17	28	-	R	35	-
534	12	35	-	44	D	41	Atelectasis
536	12	18	28	-	R	65	-
537	13	20	31	-	R	66	-
539	10	16	36	-	R	35	-
541	11	18	-	18	D	120	Lateral sinus thrombosis
546	12	16	-	16	D	39	Atelectasis
548	11	22	32	-	R	30	-
549	12	21	-	41	D	56	Atelectasis
550	11	38	-	38	D	84	Unknown

* Cases 495 to 500 "off series"

TABLE 19

NON-NEONATAL PATIENTS TREATED WITH I.P.P.R. IN ORDER OF ADMISSION TO HOSPITAL

Case No.	Duration of curarisation (days)	Duration on respirator (days)	Removal of trach. tube (days)	Survival time (days)	Result	Max. blood urea (mg.%)	Cause of Death
204	18	18	26	-	R	-	-
206	8	8	-	8	D	-	Anoxia following dislodgment of tracheotomy tube
208	6	6	-	6	D	46	Asphyxia caused by inadequate aspiration of secretions
210	6	6	-	7	D	145	Pulmonary embolism
212	12	13	27	-	R	118	-
215	6	6	-	9	D	188	? Mechanical fault in spirometer ? Uraemia
214	12	13	25	-	R	105	-
218	10	12	20	-	R	93	-
220	12	13	-	13	D	56	Haemorrhage
221	11	12	25	-	R	43	-

Causes of death in patients treated with I.P.P.R.: In a previous section it has been shown that death in the majority of our patients who were treated conservatively, was associated with inadequate control of reflex spasms or with respiratory failure. Pneumonia occurred frequently but was seldom more than a contributory cause of death.

It is apparent that with the technique of I.P.P.R. used reflex spasms are abolished and respiratory failure should not occur. However, a central action of toxin may have circulatory as well as respiratory effects. Furthermore as already mentioned Lassen and his colleagues (1954) have suggested that death might occur in some patients with severe tetanus treated with I.P.P.R. as a result of an action of tetanus toxin on structures other than the central nervous system. Alhady and his colleagues (1960), after treating 10 patients, 8 of whom died, considered that death was inevitable in some cases of tetanus due to further effects of tetanus toxin emerging, of which the most important appeared to be direct damage to the myocardium. In support of their view they reported electrocardiographic abnormalities in several of their patients and in one histological changes in the myocardium resembling the acute toxic myocarditis found in diphtheria. They attributed episodes of hypotension to this action of tetanus toxin rather than to complications of technique. Similarly Gleason and Low (1957), who lost 6 of 7 patients treated with I.P.P.R., considered that "it may yet be shown that in some patients damage to the medullary centres by the toxin is so severe as to preclude the likelihood of survival, despite all forms of treatment."

They noted fluctuation of blood pressure and variation of pulse rate, but state that they were unable to obtain adequate electrocardiographic control in their patients. Hollaret (1959) has encountered disturbances of blood pressure and pulse rate with circulatory collapse in approximately half of 65 cases of tetanus which he treated with maximal curarisation, and his figures of mortality strongly correlated with the occurrence of these vegetative disturbances. Powell and his colleagues (1958) thought the severe circulatory collapse which occurred in one of their patients to be probably due to "a true tetanus toxaemia, not relieved until more antitetanic serum was given." Stirnemann and Brenzimann (1957) mentioned many complications when treating tetanus with this technique, including fluctuations of blood pressure and pulse rate, hypokalaemia, diffuse myocardial damage and post-tetanic tetraplegia, which they considered might be due to overwhelming tetanus toxaemia.

The extent to which these complications can be attributed to the action of tetanus toxin rather than to complications of the technique of total curarisation and I.P.P.R. is difficult to determine. At least one such complication, bone marrow depression, for which the action of tetanus toxin had been suggested as a possible cause (Lassen et al., 1954), was subsequently shown to be probably due to the prolonged use of nitrous oxide anaesthesia (Lassen et al., 1956; Wilson et al., 1956).

In 4 of the 5 non-neonatal patients who died in the present series, death was related directly or indirectly to faulty technique. One

patient (case 206) died 3 days after having had a cardiac arrest when the tracheotomy tube was accidentally dislodged during physiotherapy. Three electrocardiograms taken on successive days were normal. In another patient (case 206) death occurred as a result of asphyxia when secretions were inadequately aspirated from the lungs. In a third (case 220) an ulcer of the trachea eroded an aberrant innominate artery with sudden death from haemorrhage on the fourteenth day. An electrocardiogram taken on the second day, following an anoxic episode, showed symmetrical T wave inversion in leads V1 to V6, but these had returned to normal 3 days later. A patient who was not treated on the trial (case 205) died as the result of a mechanical fault in the spirometer included in the circuit of the Smith-Clarke respirator. An electrocardiogram taken 3 days previously showed abnormal peaking of P waves with the pattern of an incomplete right bundle branch block. Severe uraemia at the time of death may have been a contributory cause. The remaining patient died of massive pulmonary embolism on the eighth day. This complication, which can probably be attributed to the total immobilisation of the legs during treatment with I.P.P.R., occurred in 2 of the 4 deaths in a series of 9 patients so treated reported by Lawrence and Sando (1959).

Only 2 of the first 11 neonatal patients treated with I.P.P.R. in the unit recovered. The course during treatment with I.P.P.R. was usually stormy. The tracheostomy or endotracheal tubes were frequently dislodged during physiotherapy with episodes of severe anoxia. Gross

bilateral pneumonia, which was attributed to infrequent and unsterile suction technique and inadequate physiotherapy, was the immediate cause of death in 4 of these patients. In one baby (case 515) overheating of the water in the humidifier passed unnoticed and pulmonary damage probably accounted for her early death from pneumonia. Despite these complications the survival time was considerably longer in these infants when compared with conservatively treated patients.

The steps taken to combat the pneumonia will be described later, but that they were effective is apparent from an analysis of the 6 remaining neonatal deaths in the series. In 4 of these severe atelectasis was a feature at necropsy, and death appeared to be due either to the inefficient aspiration of secretions or, in one (case 549), the accidental dislodgment of the tracheotomy tube. Three of these deaths were in premature infants (cases 518, 534 and 549) and occurred 29, 44 and 41 days after admission respectively. In the two remaining neonatal deaths muscle tone failed to return after curare had been discontinued. In one (case 541) the course on treatment with I.P.P.B. was characterised by marked oedema and bronchopneumonia. Death occurred on the eighteenth day and a marantic thrombosis of the left lateral sinus with cerebral softening found at necropsy accounted for the paralysis. In the other infant (case 550), however, the cause of the flaccid paralysis could not be found at necropsy, the central nervous system being completely normal. The possibility of damage to the cervical cord during physiotherapy was considered but no evidence for any such injury could be found. Anoxia or

an action of tetanus toxin on the central nervous system have been suggested by Smythe and Bull (1959) as possible causes for a similar flaccid paralysis seen in their cases of tetanus neonatorum treated with I.P.P.R. In support of the latter possibility, they pointed out that Brenmiemann and Stirnemann (1956) had produced a total flaccid paralysis experimentally in animals after the injection of large doses of tetanus toxin. In a later paper Stirnemann and Brenmiemann (1957) mentioned the occurrence of this complication, which they called a post-tetanic tetraplegia, in several of their patients. A similar flaccid paralysis was not noticed in any other infants treated with I.P.P.R. in this series. However, it may have accounted for the low dosage of curare required to maintain total paralysis in some (cases 503, 504). It is of interest that one of these babies (case 503) had multiple extrasystoles and cyanosis from the start of I.P.P.R. Although an electrocardiogram was not done on this infant, in 11 others treated with I.P.P.R. later in the trial in whom records were taken, minor elevation or depression of the S-T segment, occasionally with T wave inversion, were the only abnormalities noted. Similar changes were seen in 10 patients treated conservatively. The interpretation of electrocardiograms in African patients is difficult, particularly the significance of T wave inversion and deviations of the S-T segment (Grusin, 1954; Powell, 1959), and the limits of normality in our neonatal patients are unknown. However, none of these tracings suggested acute myocardial damage (Reid, 1960). It is impossible to determine whether the tachycardia or extrasystoles seen in our patients were related in any

way to an action of tetanus toxin, either on the myocardium, or on the central or autonomic nervous system, and whether death could have resulted from this cause. However, routine histological examination of the myocardium initially, and a more detailed one on patients dying during the second half of the trial, has failed to reveal any abnormality resembling the acute myocarditis described by Alhady and his colleagues.

In one patient (case 548) multiple extrasystoles appeared to be related to overventilation, and in another electrocardiographic changes could be attributed to an anoxic episode (case 220). Recognising that these investigations on our patients have been limited, it is difficult to attribute any of these changes to an action of tetanus toxin on the myocardium or to express an opinion as to whether or not such an action occurs. However, the fact that 10 consecutive cases of severe tetanus neonatorum recovered and that faulty technique could usually be held responsible for death, suggests that inevitable death from an action of tetanus toxin on the brain stem or myocardium if it occurred in our patients must have been infrequent.

Problems of the technique of I.P.P.R.: Smith (1958) has emphasised the problems of management in a patient, totally paralysed, who cannot move, breathe, eat or communicate. As has been shown in a previous section, the majority of our patients died because of faulty technique, and it was not until these problems of technique had been recognised and dealt with by the establishment of a simple but effective routine for manage-

ment that mortality was reduced.

Problems of ventilation: Both the Radcliffe Mark V and the Smith-Clarke machines provided adequate ventilation with no apparent advantage from the use of a negative-pressure phase in either neonatal or non-neonatal patients. It is of interest that the inflation pressures required were no lower in infants than in adults, and were much higher than those used by Smythe and Bull (1959). Accidental loosening of connections such as the water trap on the Radcliffe pump was a considerable problem initially and sometimes resulted in severe anoxic episodes, but as nurses gained experience in this technique, attention to these problems became a routine.

Problems of the airway: Dislodgment of the tracheotomy or endotracheal tubes, often with severe anoxia, particularly in neonatal patients, was a frequent occurrence during the early part of the series. The effective immobilisation of these tubes was one of the most difficult technical problems. Although the Oxford tracheotomy tube used in non-neonatal patients was seldom dislodged because of its acute angulation, when this occurred nurses found it difficult to replace. Dislodgment of the tube was more likely to occur if physiotherapy was given while the patient was connected to the respirator, so that the lungs were usually inflated manually during this procedure. Difficulty was also experienced in enforcing a routine for the release of the cuff of the tracheotomy tube. At times this was over inflated, and on one occasion herniated around the lower end

of the tracheotomy tube producing obstruction to the airway (case 212).

In infants the shortened plain latex armoured tube proved an effective tracheotomy tube. In sizes 00 or 0, the tube fitted snugly into the trachea without leakage. Despite its immobilization with a clamp and harness dislodgment sometimes occurred, particularly during physiotherapy, but during the latter half of the trial this has been infrequent. The tube was changed on 2 or 3 occasions during the course of I.P.P.R., either because kinking prevented the insertion of suction catheters or because the latex became perished at the junction with the suction connection.

Ulceration of the trachea: This was a common finding at necropsy in non-neonatal patients, an annular area of ulceration occurring approximately one inch below the tracheotomy opening. Possible causes were thought to be over-inflation of the cuff of the tracheotomy tube producing pressure necrosis; constant trauma from suction catheters, and movement of the tube within the trachea during physiotherapy. Erosion into an artery was responsible for the death of one patient (case 220) and in another, not treated with I.P.P.R., but in whom a cuffed tracheotomy tube was used because of excessive secretions, a stenosis occurred approximately three-quarters of an inch below the opening in the trachea and necessitated a permanent tracheotomy (case 177). Patients treated with I.P.P.R. who recovered invariably complained of severe retrosternal pain, and in one (case 221) pieces of slough were aspirated from the trachea

during convalescence. Measures taken to prevent ulceration included careful attention to inflation of the cuff, and emphasis on gentle but rapid suction technique using a catheter with a rounded end rather than one with the tip cut off.

In neonatal patients an area of ulceration on the postero-lateral wall of the trachea extending as far as the carina was often found at necropsy. Squamous metaplasia of the ciliated columnar epithelia of the lower trachea and both main bronchi, predominantly on the right side, was found on histological examination. While actual stenosis could not be demonstrated it was thought that overgrowth of the epithelium producing partial obstruction might have occurred particularly in premature infants.

The prevention of pulmonary complications: As already indicated pneumonia appeared to be the cause of death in most infants treated with I.P.P.R. during the early stages of its use in the unit. Factors which were considered responsible for its later prevention included the use of vigorous and intensive physiotherapy to the chest; the development of a sterile suction technique; an effective method of immobilisation of the tracheotomy tube so as to prevent its dislodgment and contamination; and possibly, the routine administration of gamma globulin.

Physiotherapy was intensified. It was so vigorous during the latter half of the trial that multiple fractures of the ribs in infants were a constant finding at necropsy, and their presence was suspected in

many who recovered. Manual inflation with oxygen by producing full expansion of the lungs assisted physiotherapy; prevented anoxia during suction; and, as already mentioned, by preventing traction on the tracheotomy tube reduced the danger of its dislodgment. The fact that massive collapse seldom occurred and bronchoscopy was not considered necessary is some indication of the effectiveness of the technique of physiotherapy developed.

Suction catheters and pressure tubing for attachment to the suction pump were wrapped in a sheet of "porter" plastic, the whole pack being autoclaved in a paper bag and kept ready for use. All personnel in the ward wore face masks and the need for sterility, comparable to that used during surgical operations, was impressed on the nursing staff.

Pseudomonas pyocyaneus and Staphylococcus aureus were the organisms most frequently cultured from pus aspirated from the trachea when pulmonary infection developed during the course of I.P.P.R. Many antibiotics were tried; chloramphenicol being found the most effective in resistant infections. Purulent secretions sometimes heralded the development of a pneumonia, this sign usually occurring before pyrexia, leucocytosis, or clinical or radiological changes in the lungs. The early use of a broad spectrum antibiotic under these circumstances was thought to have limited or prevented pneumonia in some instances.

The duration of curarisation and I.P.P.R.: As a result of previous experience in the management of tetanus in patients treated conservatively, we aimed at continuing I.P.P.R. until the dangers of severe reflex spasms and respiratory failure were thought to have passed. Frequent, severe reflex spasms had not been observed after 14 days in any patient with severe tetanus, treated conservatively, who had recovered. Since it was considered that some patients selected for treatment with I.P.P.R. were likely to be more severe than any who had recovered when treated conservatively, I.P.P.R. was continued in our first 2 patients (cases 204 and 495) for 18 and 29 days respectively. In case 204 reflex spasms and rigidity did not return after curare was discontinued and it was thought that its duration had been excessive.

Subsequent experience suggested that a period of curarisation of 10 to 12 days in non-neonatal patients might be adequate. Reflex spasms with severe rigidity usually returned within 72 hours of stopping curare but on clinical grounds it was thought that the drug exerted some effect for several days longer. It is of interest that Smith and his colleagues (1956) found a curare-like substance in the urine 7 days after curarisation had been discontinued.

Often the reasons given for continuing curarisation are the return of reflex spasms or fluctuations in blood pressure and circulatory collapse (Smith et al. 1956). In our experience fluctuation in blood pressure was usually related to inadequate ventilation when attempts at

spontaneous respiration commenced and the patient started breathing out of phase with the respirator. It usually stabilised as soon as respiration was adequate, so that instead of considering this to be an indication for recommencing curarization we have persisted in our attempts to re-establish spontaneous respiration, provided reflex spasms were not severe. The marked rigidity, opisthotonus and occasional reflex spasms which occurred in our patients might have prompted some other workers to continue curarization, but the frequency of complications of technique in our hands made a short duration of total paralysis expedient. Our experience of the conservative management of tetanus suggests that rigidity, no matter how severe, and mild or moderate reflex spasms, particularly in patients who have a tracheotomy, are of little consequence.

Whether death from respiratory failure or circulatory collapse due to a postulated action of tetanus toxin on the brain stem will occur in some patients after the tenth or twelfth day is uncertain, but this did not happen in any of our non-neonatal patients. Apnoeic attacks were a common occurrence in infants during the third and fourth weeks, but were usually mechanical and reversible.

Although the re-establishment of adequate spontaneous respiration despite rigidity and spasms has been possible, our experience of the hazards encountered at this stage has been similar to that of other workers (Gumner et al., 1956; Wilson, 1956). In an attempt to allow return of spontaneous

respiration with less distress to the patient, we have tried using succinylcholine to maintain total paralysis for 12 hours after stopping curare in 2 non-neonatal patients. The possibility, however, of the development of a prolonged response to succinylcholine when given in high dosage (Ramsay et al., 1956; Wylie and Churchill-Davidson, 1960), limited the usefulness of this method.

Assistance to respiration for several days after stopping curare in neonatal patients using the method already described, has been of benefit. They readily adapted their breathing to the respirator and by taking alternate breaths spontaneously, gradual re-education of respiration was possible.

In one non-neonatal patient (case 220) an attempt was made to discontinue curare before the tenth day but severe reflex spasms necessitated continued curarisation. With the criteria of severity which we have used for selection of patients for I.P.P.R., a period of curarisation of less than 10 to 12 days would seem to be inadequate.

Problem of removal of the tracheotomy tube: In non-neonatal patients we have had little difficulty in removing the tracheotomy tube, although with the extensive ulceration sometimes found it is likely that stenosis may occur. However, in infants this has been a considerable problem, confirming the experience of Smythe and Bull (1959). Failure to remove the tube has prolonged their stay in hospital and thus over-burdened the

unit with convalescent patients who run the risk of frequent episodes of pulmonary infection and atelectasis. Several infants have died due to blockage of the tracheotomy tube, trachea or bronchi by secretions, when mild residual rigidity remained as the only sign of tetanus. In one (case 498) death occurred from respiratory obstruction a few hours after the tube had been removed, and in others replacement of the tube as an emergency has caused considerable trauma.

Several factors were thought to have been operative in preventing the permanent removal of the tracheotomy tube. Weakening of the tracheal rings as a result of infection; the removal of cartilage during the operation; and pressure necrosis from the tube, may have resulted in their collapse causing obstruction during subsequent attempts at normal respiration. Collapse of overlying soft tissue into the opening in the trachea was thought to be another possibility. Crooke (1954) suggested that the collapse occurred above the tracheotomy opening due to loss of strength of the trachea and the negative pressure during inspiration. Another factor which he emphasised was loss of the natural ability or inclination to breathe through the larynx. Blockage of the tube by granulation tissue such as described by Smythe and Bull was not seen.

The type of opening made in the trachea seemed to have a bearing on the ease with which the tube could be permanently removed. Initially a window was cut in the trachea and in 4 of these infants the tube could not

be removed for 140 days or more (see table 18). In the latter half of the series (case 526 et seq.) a vertical incision through the tracheal rings was made and the tracheotomy tube removed within 36 days in all who recovered. However, one disadvantage of the use of this incision is the greater difficulty experienced in replacing the tracheotomy tube should it become dislodged before a track has formed. In view of recent success it is hoped that the problem of removal of the tube may not be as formidable as previously supposed.

When considerable difficulty has occurred we have found it advisable to wait for the infant to outgrow the tracheotomy, allowing short attempts at spontaneous respiration periodically to assess progress.

Complications

In addition to those already discussed, four complications occurred commonly, irrespective of the treatment used, but to a variable degree. They were hypothermia, oedema, uraemia and spinal fractures. Investigation of these problems has been inadequate but an attempt will be made to indicate their frequency and, in some, to suggest possible causes.

Hypothermia: In infants treated conservatively the temperature fell to subnormal levels as spasms were controlled, hypothermia being a prominent feature of the clinical picture of a flaccid, gasping and often oedematous infant dying of respiratory failure. While it is likely that the hypothermia

was largely due to the well recognised action of phenothiazine derivatives in lowering body temperature (Courvoisier et al., 1953), it was also seen, although to a lesser degree, in patients treated with other sedatives. Immobility probably contributed to the terminal hypothermia, since muscular activity is an important factor in the maintenance of body temperature. Immobility would seem to be responsible for the rapid development of hypothermia seen in some patients treated with I.P.P.R. (see figure 10) since curare by producing muscle paralysis causes a fall in body temperature (Bell, Davidson and Scarborough, 1959). It is of interest that the temperature returned to normal in such cases towards the end of the first week despite the continuation of total paralysis, compensatory mechanisms for the control of body temperature presumably becoming operative. However, in recent cases intensive warming has reduced the severity of the hypothermia. Whether a central action of tetanus toxin on the brain stem was a factor in the production of hypothermia is uncertain; hyperpyrexia usually being seen in cases of non-neonatal tetanus where medullary involvement is suspected.

Oedema and Uraemia: Oedema varied in degree from mild peri-orbital oedema to extensive involvement of the face, limbs and trunk. It was sometimes severe in hypothermic flaccid babies dying of respiratory failure who were treated conservatively. The cause of the oedema is obscure. Anoxic damage to the capillary endothelium (Potter, 1952) together with immobility in these flaccid infants would seem the most likely explanation. However, there is evidence that loss of plasma

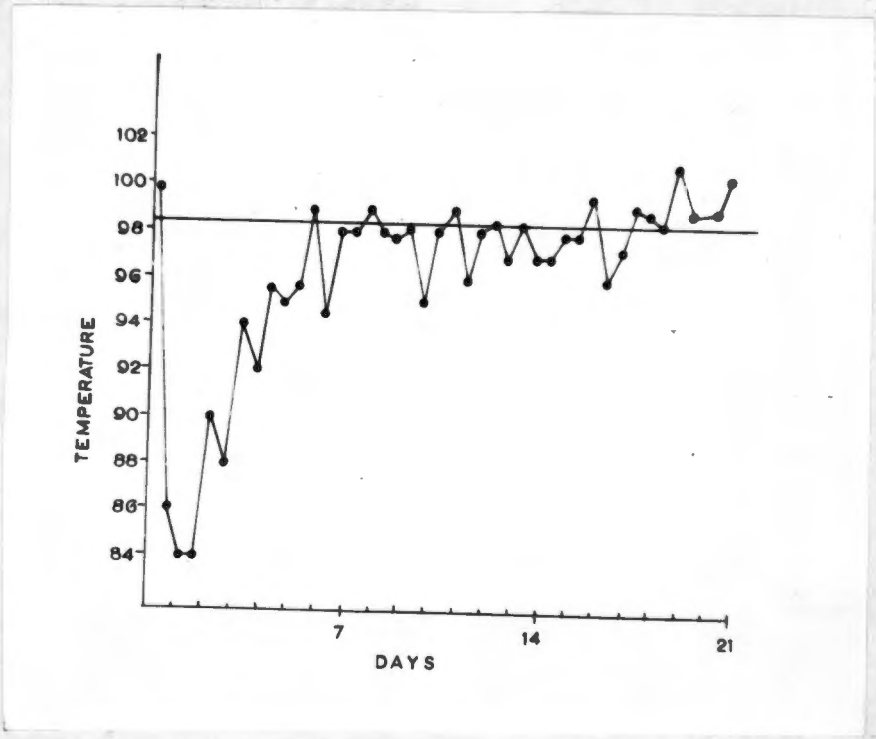


Figure X - Temperature chart to illustrate hypothermia in a case of tetanus neonatorum treated with I.P.P.R.

into the extravascular spaces occurs as a result of prolonged hypothermia (Wylie and Churchill-Davidson, 1960) and oedema is commonly seen in neonatal cold injury (Rowe et al., 1960). On clinical grounds it was thought unlikely to be of cardiac or renal origin, but investigations to exclude these possibilities have been inadequate. Electrocardiograms showed no evidence of acute myocarditis or anoxic cardiac damage and blood urea and electrolytes, while elevated on occasions, were usually normal; but have been estimated infrequently. Serum proteins were within the range found in 30 normal infants born in this hospital (see table 20) and, in the few patients in whom it was examined, the urine was normal or showed only a trace of albumin.

In infants treated with I.P.P.R. the oedema was often extensive (see figure 8), a finding similar to that of Smythe and Bull (1959). During the early part of the trial most infants were not weighed until their treatment with I.P.P.R. had already commenced, but in subsequent cases a rapid gain in weight during the first 24 or 48 hours was demonstrated. While the initial gain in weight may have been due in part to rehydration, oedema often developed simultaneously, both increasing during the first week. A loss of weight usually occurred between the seventh and tenth days with the simultaneous disappearance of oedema. We have shown in some patients, in whom the measurement of urinary output was successful, that a diuresis occurred at this stage. In some infants enlargement of the liver occurred

TABLE 20

NEONATAL PATIENTS

SERUM PROTEINS - ELECTROPHORETIC PATTERNS* AND MAXIMUM BLOOD UREA

Case No.	Total	A:G Ratio	Alb.	Glob.	α1	α2	β	γ	Max. blood urea (mg.%)
I.P.P.R. 530	6.4	.88 : 1	3.0	3.4	0.6	1.0	0.9	0.9	54
	7.5	.70 : 1	3.1	4.4	0.9	1.2	1.2	1.1	
532	6.9	.57 : 1	2.5	4.4	1.0	0.7	0.7	2.0	35
	6.9	.50 : 1	2.3	4.6	0.5	0.9	1.2	1.2	
534	5.8	.71 : 1	2.4	3.4	0.9	0.6	0.7	0.9	41
537	6.4	.68 : 1	2.6	3.8	0.7	0.7	1.2	1.2	66
CONSERVATIVE 531	6.8	.94 : 1	3.3	3.5	0.5	0.7	0.7	1.6	36
	6.3	.80 : 1	2.8	3.5	0.6	0.7	1.0	1.2	
533	6.2	.74 : 1	2.6	3.6	0.7	0.9	0.7	1.3	57
	5.8	.61 : 1	2.2	3.6	0.7	1.0	0.8	1.1	
535	6.7	.67 : 1	2.7	4.0	0.5	0.7	0.6	1.1	28
538	6.0	.87 : 1	2.8	3.2	0.5	0.8	0.9	1.0	122
543	7.3	.66 : 1	2.9	4.4	0.7	1.2	1.2	1.3	-
469	6.7	.91 : 1	3.2	3.5	0.5	1.0	0.9	1.1	25
470	7.5	.74 : 1	3.2	4.3	0.6	1.1	1.0	1.6	-
479	6.1	.60 : 1	2.3	3.8	0.5	0.9	0.9	1.5	36
481	6.0	.50 : 1	2.0	4.0	0.7	0.8	1.2	1.3	52
482	6.0	.76 : 1	2.6	3.4	0.6	0.7	1.05	1.05	-
Mean values	6.5	.71 : 1	2.7	3.8	0.65	0.9	0.9	1.2	
✓ Mean values 30 normal neonates	6.9	.72 : 1	2.9	4.0	0.6	0.8	0.9	1.6	

* albumin and globulin values in g./100 ml.

	Total	Albumin	Globulin
Range in tetanus neonatorum	5.8 - 7.5	2.0 - 3.3	3.2 - 4.6
✓ Range in 30 normal neonates	5.5 - 8.0	1.5 - 3.8	3.1 - 5.2

✓ Chisholm and Joubert (1960)

following the start of treatment with I.P.P.R. While on the whole this was associated with the development of oedema, often oedema was gross but hepatic enlargement minimal or absent. Similarly while the blood urea usually rose with the appearance of oedema this was not constant. The rapidity with which oedema and weight gain developed in patients treated with I.P.P.R. suggests that it is due to the mechanical effects of positive-pressure respiration producing a reduction in venous return, an increased capillary pressure and the passage of plasma into the tissues (Astrup et al., 1954). In one patient (case 496) enlargment of the liver appeared to regress with the introduction of a negative-pressure phase, which has been shown to have some direct effect in increasing the venous return to the heart (Mushin et al., 1959). However, oedema and elevation of the blood urea have been seen in our patients despite its use; and other factors such as anoxia, hypothermia and immobility are probably also operative.

In non-neonatal patients treated with I.P.P.R. uraemia was a frequent finding but oedema did not occur. Glossop and Low (1957) and Lawrence and Sando (1959) often observed this complication and it has been reported in other cases of tetanus treated with I.P.P.R. (Wilson et al., 1956; Smith et al., 1956). Glossop and Low considered that it was caused by a "combination of impaired renal function together with excess urea production", and pointed out the danger of excessive protein intake in a patient who might have an increased catabolism due to tetanus.

In some of our patients treated conservatively elevated blood urea levels have been found, possibly from this cause, although dehydration due to inadequate fluid intake is the more likely. In 3 patients (cases 205, 210 and 212) the uraemia was severe and prolonged, with a rise in serum electrolytes. Initially all had been given a high protein diet which may have precipitated the uraemia, although in one (case 212) there was evidence of previous renal damage possibly related to a criminal abortion. In two others (cases 214 and 215) the blood urea, which was elevated initially, rapidly fell to normal after rehydration and a restricted protein intake. Because of partial ileus in these patients who were fed by an intragastric tube, in two treated subsequently (cases 220 and 221) rapid rehydration was accomplished by the administration of intravenous fluids during the first 48 hours, and neither uraemia nor ileus have occurred.

Circulatory collapse which has been a feature in other series, when observed in our non-neonatal patients has been related either to anemia (case 206) or severe pulmonary embolism (case 210). Smythe and Bull (1959) observed circulatory failure in their neonatal patients who died of tetanus. While we have seldom recorded blood pressures in infants, clinically we have only noted this complication terminally in association with severe pneumonia.

Spinal fractures: Although a common complication, until recently few reports of spinal fractures in tetanus had appeared in the English

language (Roberg, 1937; Rand, 1938; Dietrich et al., 1940; Quinlan, 1954; Robertson, 1955; Veronesi, 1956; Colangelo, 1959). Dietrich and his colleagues emphasized their frequency after finding radiological evidence of vertebral compression in 9 of 13 children who had recovered from tetanus. Figure II illustrates the extensive vertebral fractures which occurred in some patients in the present series, and in table 21 the incidence of vertebral lesions is related to age and severity of tetanus. The absence of lesions in patients with mild tetanus and their frequency if tetanus is severe, indicates a relationship to the severity of reflex spasms. However, deformity was surprisingly frequent in children and adolescents in whom spasms were of only moderate severity.

Roberg has distinguished an adult and a juvenile type of deformity. In the former, true fracture of the spine with fragmentation of bony structure occurs whereas in the juvenile type, kyphosis with or without compression of the vertebral bodies is more common. He suggested that this was due to brittleness of the vertebrae in older patients. No attempt has been made in the present analysis to make this distinction, but only true fractures or compression of the vertebrae have been included. The nature of the deformity was similar to that usually described. Wedge-shaped compression with indentation of the anterior border was seen most commonly, and when very severely affected the density was increased or actual comminution occurred. In some patients fractures extended from the third to the ninth thoracic vertebrae but usually only two or three

Figure XI - Radiograph showing compression fractures with wedging of thoracic vertebrae.

TABLE 21

INCIDENCE OF VERTEBRAL FRACTURES IN NON-NEONATAL PATIENTS

Age (years)		Mild	Moderate Spasms	Severe Spasms
1 - 10	No. X-rayed	6	9	13
	No. with Fractures	-	3	7
11 - 20	No. X-rayed	1	5	26
	No. with Fractures	-	4	17
21 - 40	No. X-rayed	3	8	12
	No. with Fractures	-	-	5
over 40	No. X-rayed	3	2	1
	No. with Fractures	-	1	-
TOTAL	No. X-rayed	13	24	52
	No. with Fractures	-	8	29
	%	0	33	56

were involved. As is usually found the fifth and sixth thoracic vertebrae were involved most frequently.

Roberg, and Dietrich and his colleagues, considered that the cause of the deformity was mechanical, but their reasons given for the site of selection differed. Quinlan (1954) felt that a combination of their theories gave a satisfactory explanation, the simultaneous contraction of flexor and extensor muscles resulting in a longitudinal compression of the spine with an increase in thoracic curvature. He suggested that the apex of the curve was higher than normal during generalised spasms, thus accounting for its localisation at the level of the fifth thoracic vertebra.

The high incidence during adolescence confirms the findings of both Veronesi and Roberg. In only 2 of 32 neonatal patients whose spines were examined radiologically have deformities of the vertebrae been observed, although kyphosis and scoliosis were common while rigidity persisted. Radiological examination of patients with severe spinal deformity has been repeated at intervals for periods of up to two years after the illness and no improvement in the deformity noted. Laurance (1956) suggested that this complication might occur less frequently in patients treated with muscle relaxants, and it is of interest that in only 1 of the 5 non-neonatal patients treated with I.P.P.R. who recovered, was compression of vertebrae observed. The finding of vertebral fractures at necropsy in some of our patients in whom the course of the disease was

short further indicates that they can develop rapidly.

Other complications occasionally seen included serum sickness and, in 4 patients, frank haemoptysis for which no cause could be found.

One patient (case 68) died of a second attack of tetanus, and active immunisation was commenced in all subsequent cases before discharge from hospital.

The place of I.P.P.R. in the treatment of tetanus

Non-neonatal patients: Although the number of patients treated with I.P.P.R. was relatively small and the difference in mortality between groups not significant, our clinical impression that some patients, who would otherwise have died, have been saved by this technique is similar to that of other workers. Particularly impressive is the recovery of both patients with postabortal tetanus treated with I.P.P.R., compared with only 1 of 12 whom we have treated using other methods. Only when a larger number of patients have been treated on the trial will final assessment be possible. However, if recent success following improvement in technique is maintained, a significant difference in mortality in favour of I.P.P.R., as in neonatal tetanus, should emerge.

It is difficult to compare our results to date with those elsewhere, or to determine from a review of the literature how effective I.P.P.R. has been in the treatment of severe tetanus. Bodman (1954) used the incubation period and period of onset to assess the severity

of 4 cases of tetanus, treated in this way, reported by Lassen and his colleagues (1954) and considered that similar results could have been expected using conservative methods. However, as has been shown in an earlier section, these criteria are not absolute and it is not possible with their use to compare accurately results in our patients with those elsewhere or to determine the effectiveness of I.P.P.R. in other series. Although they provide a good general guide to prognosis it cannot be said in any given case that treatment with I.P.P.R. was life-saving because the period of onset or incubation period was short.

In addition comparison with other series is made difficult by the differences of technique and methods of selection used. The technique of maximal curarisation used in the present series has been based on that described by Honey (1954), Smith (1956) and their colleagues, and by Hellaret (1956). In addition to the use of muscle relaxants, some workers have anaesthetised their patients by the continuous or intermittent administration of nitrous oxide (Lassen et al., 1954, 1956; Andersen et al., 1955; Wilson et al., 1956; Lawrence and Sando, 1959) while others have produced hypothermia (Hossli, 1956; Stirnemann and Brenninkmeyer, 1957). Many have continued to use failure of conservative treatment as the indication for the institution of I.P.P.R. (Kirkpatrick et al., 1956; Gleason and Law, 1957; Powell et al., 1958; Lawrence and Sando, 1959; Alhady et al., 1960) and their claims of success might therefore have more justification than any based on results in the present series. It is difficult to compare

our results with those of Stirnemann and Brenninann (1957) who treated 9 patients, 5 of whom recovered, with curarisation and artificial respiration because many of their patients were over the age of 50 years, the incidence of complications high and the required period of curarisation long - up to 34 days in one patient. Wellaret (1959) reporting on his experience of 136 cases of tetanus, 65 of whom were treated with maximal curarisation and artificial respiration, stated that his figures of mortality correlated strongly with the occurrence of vegetative disturbances. Fourteen of the first 18 patients in whom these were a feature died, although subsequently his results improved. Smith (1958) and his fellow workers at Oxford treated 7 patients with I.P.P.R. 3 of whom died; and Garland and Ablett (1958) have reported 3 deaths in their last 8 patients treated with this regime. Many of these reports have come from specialised units and the cases have been selected; however, together with claims of success in large numbers of single case reports and small series (Ramsay et al., 1956; Gunner et al., 1956; Weisser and Neiditsch, 1957; Dwyer and Lazarus, 1957; Wilton et al., 1958; Wilkens, 1958; Schiller, 1958) they would appear to indicate that I.P.P.R. has a definite place in the management of severe tetanus.

The infrequency, among our non-neonatal patients, of circulatory collapse and hyperpyrexia, which have occurred in most of the series mentioned above, might indicate that we have not, as yet, treated with I.P.P.R. any who have brain stem involvement. It would therefore seem

that the only definite conclusion that can be drawn from our results to date is that severe tetanus can be treated successfully with I.P.P.R. even though medical and ancillary services are limited, provided a separate unit is established. Apart from possible differences in severity, the lower mortality in the present series when compared with that of Gleaspy and Low (1957) and Albady and his colleagues (1960) who treated tetanus under conditions similar to our own, may have been due to the fact that we were able to establish a permanent unit in which I.P.P.R. was constantly being practised. Another possibility is the difference used in the method of selection of patients for this technique. These workers waited until conservative treatment was about to fail before instituting I.P.P.R. so that we may have had the advantage of commencing treatment before severe pulmonary infection, dehydration and electrolyte imbalance had occurred.

The effectiveness of the criteria used for the selection of a group of patients suffering from severe tetanus who were unlikely to benefit from conservative methods of treatment is apparent from the high mortality among those treated conservatively in trials III and IV. An analysis of the 19 fatal cases among 56 patients admitted to the unit after the introduction of I.P.P.R. is of value in further assessing the usefulness of these criteria. Eleven of the 19 who died were treated with I.P.P.R. or formed part of the conservative control group. Two others fulfilled the criteria for inclusion in the I.P.P.R. trial but because a respirator was not available at the time this was not possible.

The 6 remaining patients who died formed part of a group of 34 who were not considered sufficiently severe for admission to the I.P.P.R. trial. Three were admitted during the period of onset and died during one of their first episodes of severe laryngeal or generalised spasms (see appendix 4). As already mentioned routine tracheotomy during the period of assessment for I.P.P.R. might have saved these patients, although one died while being admitted to the unit. The only alternative to routine tracheotomy whereby these deaths during the period of assessment might have been prevented, would have been by the constant supervision of the patient by a medical officer seated at the bedside with facilities to perform an immediate tracheotomy if indicated (Mollaret, 1959). Unfortunately both these procedures are impracticable in a unit such as this. A short admission time of 7 hours and the rapid development of severe trismus did, however, suggest the impending onset of severe tetanus in one patient (case 179) and it is in such cases that early tracheotomy might be indicated if the institution of I.P.P.R. is contemplated.

Of the 3 remaining patients who died, one had mild tetanus (case 194) but death occurred on the eleventh day despite tracheotomy, bronchiectasis being a complicating factor; one (case 173) was of moderate severity and died on the thirteenth day, bronchopneumonia and pulmonary tuberculosis being contributory causes; and in the third patient (case 188)

although severe reflex spasms which developed on the day after admission were well controlled, death occurred on the seventh day despite tracheotomy, coma and pulmonary collapse being a feature terminally. I.P.P.R. might have been indicated in the last patient, but it is difficult to see when it should have been instituted, or how the two remaining patients whose tetanus was either mild or moderate could have benefited from this procedure, death having been due to complications rather than the disease itself.

From this analysis it would appear that the criteria which we have adopted, based on the severity of reflex spasms, will be adequate for the selection of the majority of patients in whom treatment with I.P.P.R. may be indicated. However, as shown in table 9, this selection often cannot be made at the time of admission to hospital. In cases of doubtful severity the incubation period, period of onset and admission time are of value in the early assessment of prognosis. In some patients in whom spasms are severe they may suggest a favourable outcome, and in others, although apparently mild, the impending onset of severe tetanus.

Of the 34 patients not considered to be sufficiently severe for admission to the I.P.P.R. trial 28 recovered. In 2 patients tracheotomy was performed but the treatment of the remainder was relatively simple. Several developed severe reflex spasms but the majority were of mild or moderate severity and in all the combination of chlorpromazine and barbiturate was most effective. By simplifying the management of patients with tetanus of mild or moderate severity, as well as a proportion

having severe reflex spasms, the use of this combination will allow the medical and nursing facilities available to be concentrated on a few patients in whom simple tracheotomy is indicated and on a larger group whose best chance of survival may well lie in treatment with I.P.P.R. in a specialised unit. However, irrespective of the circumstances under which these more complicated methods of treatment are practised, careful assessment of prognosis is essential in every patient to avoid, as emphasised by Adams (1958) the overtreatment of milder cases.

Neonatal patients: Clinical trials on neonatal patients in the present series leave no doubt of the superiority of treatment with I.P.P.R. to any of the conservative methods used. Its use is indicated in all but a small minority of infants who do not have frequent severe reflex spasms. Using this criterion selection can be made in most infants at the time of admission to hospital (see figure 5). However, the prospect of having to treat up to 100 cases of tetanus neonatorum annually in this unit by this exacting and complicated regime has prompted the consideration of ways of making the greatest possible use of conservative methods of treatment and if possible of simplifying the technique.

Simplification of the technique has, however, not been possible. Prolonged endotracheal intubation was tried in two patients (cases 495 and 497) but both died and gross distortion of the laryax was present at necropsy. Reduction in the duration of curarization has only been

possible, in the infants selected, by assisting respiration during the third week when apnoeic attacks are otherwise common. A further reduction, below 10 to 12 days, is unlikely to be of benefit because heavy sedation would be required for control of spasms.

By allowing trial of conservative treatment before instituting I.P.P.R. a proportion, even of severe cases (16% of the conservatively treated group in trial IV) might avoid treatment with I.P.P.R. However, it is likely that if failure of conservative treatment is used to select patients for I.P.P.R. the mortality from this technique will increase since, by the third or fourth day when respiratory failure occurs, pneumonia has often already developed (see figures 6 and 7). It is therefore advisable to institute I.P.P.R. as soon as possible after admission rather than to allow serious anoxia and pulmonary infection to develop during trial of conservative treatment. Possible exceptions, even in patients having severe reflex spasms, are those infants over the age of 8 days (provided they are not born in hospital) or in whom the incubation period, period of onset or admission time are prolonged. In a small minority in whom reflex spasms at the time of admission to hospital are infrequent or absent, trial of conservative treatment is definitely indicated as the prognosis in such cases is relatively good.

Smythe and Bull (1959) in the only series of neonatal tetanus treated with I.P.P.R. with which these findings can be compared likewise concluded that this procedure was an improvement on previous methods of

treatment. They considered that in some cases tracheotomy alone or with I.P.P.R., using mephenesin as the relaxant so as to allow spontaneous respiration, might suffice, but that in the more severe cases treatment with curare would be preferable. The good results achieved in the present series are thought to be due to the use of total curarisation but when advocating this technique the problems encountered initially must be emphasised. Because of these problems it may well be shown that this method of treatment is only effective in a unit where a large number of cases are being seen and constant practice in the use of the technique is being obtained by the medical and nursing staff. Once a routine is established and a team of nurses has become expert in the technique of physiotherapy and suction, the medical attention required is surprisingly little, the unit having been successfully run with only one medical officer in charge of its immediate management for a period of three months.

However, in order to treat all the infants suffering from severe tetanus neonatorum admitted annually to this hospital it would be necessary to increase the unit to three times its present size, and it is apparent that the method of treatment, while effective, has considerable practical disadvantages.

The only rational approach to the treatment of the disease lies in its prevention. Attempts have been made by the local authorities to instruct the African and Indian population in simple methods of hygiene at the time of delivery, emphasis being placed on the dangers of tribal

customs of applying foreign material to the cord (Stephen, 1960). In non-neonatal patients the importance of active immunisation has been repeatedly emphasised (Amick and Alexander, 1957; Fulford, 1960). The active immunisation of mothers during pregnancy in an attempt to produce protective antibody levels in their newborn infants has been suggested (Rogers, 1944) and its transplacental transmission demonstrated experimentally (Ten Broeck and Bauer, 1922-23). Whether this will ever be possible is however doubtful. The number of antenatal clinics which cater for the Indian and African population is limited and most patients who do attend such clinics present themselves for examination at a stage of pregnancy when it is probably too late to produce protective passive immunity in the newborn. The large number of hospital-born infants who have contracted the disease during the past year gives rise to considerable concern. As already suggested it is likely that these infants contracted tetanus at home after discharge from hospital, the development of tetanus in hospital-born infants who have been discharged prematurely having been well documented (Spivey et al., 1953; Amick and Alexander, 1957). So great has this problem become that it would seem that the use of prophylactic tetanus antitoxin should be considered before discharge from hospital, as well as in infants delivered at home under circumstances which suggest the possibility of infection.

Until such time as the educational and socio-economic status of primitive, underprivileged communities has improved to the extent where these measures can be effective in prevention, the need for the

establishment of special units, such as described in the present series, is indicated for the treatment of tetanus neonatorum with I.P.P.R. (figure 12).

Although this would seem to be a more effective method of treatment than that advocated by Sims and Hartigan, the extent to which it can be applied will likewise require further assessment by "contemporaneous observers".

Figure XII - Severe tetanus treated with I.P.P.R.

SUMMARY

The literature relating to the more controversial aspects of the treatment of tetanus is reviewed as an introduction to a study of 550 cases of tetanus admitted to a special unit at King Edward VIII Hospital, Durban, over a four-year period. Most of these patients, 329 of whom were suffering from tetanus neonatorum, were investigated in a series of therapeutic trials to assess the place of chlorpromazine, acetylpromazine, tracheotomy and curarisation with intermittent positive-pressure respiration (I.P.P.R.).

The high local incidence, particularly of tetanus neonatorum, is emphasized and it is shown to be second only to prematurity as a cause of neonatal death in this hospital.

It is pointed out that diagnosis in these patients was seldom difficult although atypical forms occurred.

An analysis is made of different criteria of severity to determine their relative value as a guide to prognosis for the selection of patients for total paralysis and I.P.P.R., and for comparing randomised groups. The occurrence of frequent severe generalised reflex spasms is shown to be the most important criterion indicating a poor prognosis. If the incubation period, period of onset and admission time are short they usually indicate a poor prognosis but all three should be assessed together. A long admission time and period of onset usually indicate a

good prognosis but a long incubation period is of less value in this respect. The outcome varies little with the presence of a wound or its site, unless the uterus is the portal of entry when the prognosis is grave. In non-neonatal patients the severity of reflex spasms at the time of admission to hospital is not a good guide to prognosis, but in infants the disease is usually so severe and the onset so rapid that this provides a good indication of the probable outcome. It is emphasised that in the patients under review none of these criteria proved absolute and, in particular, single criteria may be misleading.

An attempt is made to determine the cause and mechanism of death in 179 neonatal and 71 non-neonatal patients who died before the introduction of I.P.P.R. into the unit. A few patients died of bronchopneumonia or asphyxia. In the majority, although the exact cause was unknown, death was associated with inadequate control of reflex spasms or respiratory failure, the latter probably resulting from a direct action of tetanus toxin on the medullary centres.

The design of 4 randomised trials on neonatal and non-neonatal patients is described together with the technique of I.P.P.R. used. All treatment other than the drug or procedure under investigation was standardised and patients allocated at random to one or other of the two treatment groups being compared. In the first two trials all patients irrespective of severity were admitted to the trial provided they had not received treatment before admission which might prejudice the assessment of the

drugs being compared. Subsequent trials in which the value of tracheotomy alone or with I.P.P.R. was assessed were confined to patients suffering from severe tetanus.

In non-neonatal patients in the first trial the mortality rate was lower in patients treated with chlorpromazine (43%) than in those treated with barbiturate (52%). In the second trial a combination of chlorpromazine and barbiturate using a lower dosage of each appeared to be superior to chlorpromazine alone (mortality rate 3% compared with 52%). However, these differences were not significant.

Experimental evidence that the potency of acetylpromazine is greater than that of chlorpromazine was confirmed clinically in the treatment of 8 selected severe cases of non-neonatal tetanus.

The effectiveness of these phenothiazine derivatives in the control of reflex spasms and in facilitating oral feeding and simplifying nursing care is emphasised.

In neonatal patients the mortality was high irrespective of the treatment used, but a combination of chlorpromazine or acetylpromazine with barbiturate was preferred because of their ability to control spasms effectively and prolong survival time. The overall mortality rate of 82.5% in neonatal patients treated before the introduction of I.P.P.R. into the unit is shown to be similar to that in most large series.

Tracheotomy failed to reduce significantly the mortality in

either neonatal or non-neonatal patients in whom this procedure was compared with a conservative control group in selected severe cases; all the neonatal patients in both groups died. Success with its use in a few selected non-neonatal patients in whom respiratory obstruction was a feature confirmed favourable reports of the value of this procedure.

In the fourth trial treatment with total curarisation and I.P.P.R. was compared in both non-neonatal and neonatal patients with a conservative method using chlorpromazine or acetylpromazine in combination with barbiturate for the control of reflex spasms. Four of 8 non-neonatal patients treated with I.P.P.R. recovered compared with 2 of 8 patients treated conservatively. Eleven of 25 neonatal patients treated with I.P.P.R. died compared with 21 of an equal number treated conservatively (44% compared with 84%), a significant difference in mortality ($P < .01$, X 2 test).

The causes of death in cases of tetanus treated with I.P.P.R. are discussed and it is shown that pulmonary infection and faulty technique rather than a postulated action of the toxin on the brainstem or myocardium, was responsible for death in our patients.

Problems of the technique of I.P.P.R. in the present series are discussed and the importance of vigorous physiotherapy and a sterile suction technique emphasized.

The frequency of complications such as uraemia, and in neonatal

patients oedema and hypothermia, is indicated and possible causes suggested. The incidence of spinal fractures and the relationship to the severity of reflex spasms is discussed.

It is considered that should our recent success with the use of I.P.P.R. in non-neonatal patients be maintained, a significant difference in mortality in favour of I.P.P.R. will emerge, confirming favourable reports of other workers.

It is suggested that specialised units for the treatment of tetanus neonatorum with I.P.P.R. should be established but that the only rational approach lies in its prevention.

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APPENDICES

ABBREVIATIONS USED IN TABLES

TREATMENT

Total intramuscular dose recorded with maximal daily dose in brackets.

A or Acetylprom.	-	Acetylpromazine.
B or Phenobarb. sod.	-	Phenobarbitone sodium.
C or Chlorprom.	-	Chlorpromazine.
P	-	Paraldehyde.
T	-	Tracheotomy.

RACE and SEX

AM - African male
IF - Indian female

FEEDS

O - oral
T - tube
N.F. - not fed
i.v. - intravenous

RESULT

D - died
R - recovered
Bpn - bronchopneumonia
PTB - pulmonary tuberculosis

SEVERITY

S - severe spasms
Mod. - moderate spasms
Mild - no spasms

HOSP. NO. [redacted]
CASE NO. [redacted] NAME [redacted] RACE [redacted] AGE [redacted] SEX [redacted]

Physician Professor Adams

Treatment group Soluble phenobarbitone and chlorpromazine

Date of hosp. admission 11.6.58 6.30 p.m.

Date of wound 12.6.58

Site of wound Extraction of teeth at home in kraal using a pair of pliers.

Nature of wound

Wound sepsis

Surgical treatment, date and nature

Date of first tetanus symptom [redacted] Trismus.

Incubation period (i.e. time from wound to first symptom) [redacted] days

Prophylactic antitoxin, date, dose

Previous active immunisation, details

Condition on admission

General physique Good

Tetanus Frequent severe spasms spontaneously Trismus++++ Abdomen++++ Neck++ Back+

Intercurrent disease

Date & time of onset of reflex spasms (i.e. convulsive jerks superimposed on tonic rigidity) 13.6.58

Period of onset (i.e. time hours & days from first symptom to onset of reflex spasms under 48 hours

Any other modifying factors Rx Ramsbottom Hospital

Complications during course of tetanus Compression fractures of spine D4 - D7.

2554

Fate Recovered. Discharged: 17.7.58.

Date of first getting up

Cause of death X

Local

TREATMENT

Chlorpromazine

21.6.58	100 mgm.
22.6. to 30.6.	50 mgm.4-hourly
1.7.	200 mgm.
2.7.	150 mgm.
3.7.	150 mgm.
4.7.	200 mgm.
	3500 mgm. i.m. total
	1500 mgm. orally
	5000 mgm. total

Soluble phenobarbitone

21.6.58	gr. 3
22.6.	gr.12
23.6.	gr. 9
24.6.	gr. 6
25.6.	gr. 6
26.6.	gr. 6
28.6.	gr. 3
29.6.	gr. 3
30.6.	gr. 6
	gr. 54 total

Oral chlorpromazine

5.7. to 12.7.	200 mgm. daily.
	1600 mgm. total

Temperature on admission: 98.4°F.

CLINICAL COURSE & COMMENT:

Tetanus was severe with marked stiffness and severe spasms occurring spontaneously and on slight disturbance. Only mild opisthotonos. Well relaxed after sedation and was able to take fluids orally throughout. Drowsy on 3rd day, but this disappeared when soluble phenobarbitone dosage was reduced. Passed urine normally but was constipated for the first seven days. Spasms continued until the fifteenth day.

HOSP. NO. 435/59
CASE NO. [redacted] NAME [redacted] RACE Africans AGE 7 days SEX Male

Physician Professor Adams

Treatment group Acetylpromazine & Soluble phenobarbitone.

Date of hosp. admission 31.1.59 4 p.m.

Date of wound One of twins, born at home, Cole Manor 24.1.59. Breech delivery but

Site of wound } Septic otherwise no difficulty. Cord cut with razor blade.

Nature of wound } umbilicus Wood & iron house, cement floor.

Wound sepsis

Surgical treatment, date and nature

Date of first tetanus symptom 31.1.59 Twins noticed to suck 9 a.m.

Incubation period (i.e. time from wound to first symptom) 6 days

Prophylactic antitoxin, date, dose

Previous active immunisation, details

Condition on admission

General physique Weight 6 lbs. 5 ozs.

Tetanus Frequent severe spasms when disturbed.

Intercurrent disease Ophthalmia neonatorum

Date & time of onset of reflex spasms (i.e. convulsive jerks superimposed on tonic rigidity) 31.1.59 a.m.

Period of onset (i.e. time hours & days from first symptom to onset of reflex spasms 2 ½ hours

Any other modifying factors

Complications during course of tetanus

Fate Died 10.2.59 7 a.m.

Date of first getting up

Cause of death Respiratory failure

Local

31.1.39	10 mg.
2.2.	20 mg.
3.2.	20 mg.
4.2.	10 mg.
5.2.	10 mg.
	70 mg. i.m. total

Daily maximum 20 mg.

31.1.39	gr. ½
2.2.	gr. 1
3.2.	gr. 1
4.2.	gr. ½
5.2.	gr. ½
	gr. 3½ i.m. total

Daily maximum 1 gr.

AUTOPSY:

Liver - congested.
Lungs - inhalation pneumonia.

SURVIVAL TIME: 9½ days

TEMPERATURE ON ADMISSION: 99°F.

CLINICAL COURSE & COMMENT:

Well relaxed with control of spasms after initial dose of sedative. Did not require further sedation until the 3rd day when spasms again became severe. Temperature fluctuated between 91° and 95°F. Scalp vein infusion given on the morning of the fourth day of 5% Glucose in 0.2 N saline to a total of 640 cos. between 4th and 9th days. Urinary output 60 - 70 cos/day. In spite of this the infant became oedematous. Cold, flaccid and gasping on the 7th day and had several episodes of respiratory failure thereafter. Kept alive on coramine and intragastric oxygen. No further spasms observed before death.

APPENDIX I

TRIAL I & II NON-NEONATAL PATIENTS

TRIAL ONE. NON-NEONATAL PATIENTS

BARBITURATE TREATED GROUP

Case Number	Age, race and sex	Incubation period (days)	Period of onset (hrs.)	Admission time (hrs.)	Feeding	Phenobarb. sod. (gr.)	Wound	Fractures	Severity	Result	Survival time	Autopsy and comment
1	19 IF	12	-	48	0	33(6)	Uterus	-	Mild	R	-	The only post-abortal case to recover.
2	7 IF	4	24	72	T i.v.	12(6)	Nil	-	S	D	29 hrs	Respiratory failure ? oversedation.
3	60 IM	13	6	12	i.v.	21(15)	Leg ulcer	-	S	D	60 hrs	Bronchopneumonia
4	34 AM	?	24	24	NF	6(6)	Nil	-	S	D	3 hrs	Spasms not controlled, laryngospasm.
5	7 IM	11	4 d.	72	T	11(5)	Leg	-	Mod.	R	-	-
6	43 AM	5	4 d.	72	0	43(21)	Head	-	Mod.	R	-	-
7	6 AF	5	6	36	i.v.	53(18)	Foot	-	S	D	4 days	Bronchopneumonia and pulmonary tuberculosis.
8	5 IF	7	36	36	i.v.	40(15)	Leg	-	S	D	6 days	Diffuse bronchopneumonia
9	29 AM	14	72	24	i.v.	111(25)	Multiple	-	Mod.	R	-	-
10	26 AM	?	4 d.	72	0	45(9)	Nil	-	Mod.	R	-	-
11	40 AF	7	10	24	NF	3(3)	Head	-	S	D	6 hrs	Laryngospasm, oedema of glottis.
12	10 IM	42	13	17	T	53(18)	Leg	-	S	D	3 days	-
13	12 AM	3	10	10	T	136(48)	Leg	-	S	D	5 days	Scattered areas of bronchopneumonia.
14	15 AM	5	0	3	i.v.	71(38)	Leg	-	S	D	66 hrs	Spasms not controlled, bronchopneumonia.
15	29 AM	10	0	48	T	78(12)	Leg burn	-	Mod.	R	-	-
16	5 AF	?	?	-	NF	9(9)	Nil	-	S	D	12 hrs	Spasms not controlled.
17	27 IF	10	-	3	T	10(6)	Foot	NAD	Mild	R	-	-
18	16 IF	6	0	30	0	27(9)	Leg	T4 to 7	S	R	-	Laryngospasm, collapse L. lung.
19	11 IM	11	24	48	0	3(3)	Foot	T5 to 7	Mod.	R	-	-
20	45 AM	14	0	24	i.v.	38(17)	Multiple	-	S	D	49 hrs	Bronchopneumonia. Prophylatic A.T.S. given.
21	21 AF	?	0	38	T	115(17)	Nil	-	S	R	-	-

TRIAL ONE. NON-NEONATAL PATIENTS

CHLORPROMAZINE TREATED GROUP

Case Number	Age, race and sex	Incubation period (days)	Period of onset (hrs.)	Admission time (hrs.)	Feeding	Chlorprom. (mg.)	Wound	Fractures	Severity	Result	Survival time	Autopsy and comment
22	38 AM	4	72	48	T	3480(2020)	Foot	-	S	D	3 days	Abscess deep to injury
23	3 AM	?	?	10 d.	O	45(15)	Nil	-	Mild	R	-	Kwashiorkor. Bronchopneumonia.
24	40 AM	3	4 d.	48	T	2600(600)	Hand	-	Mod.	R	-	Delirium and Parkinsonian tremor.
25	15 AM	4	6	10 d.	T	225(225)	Foot	-	Mod.	R	-	-
26	21 AM	?	36	48	i.v.	6125(1400)	Leg	-	S	D	7 days	Drowsy, confused. Blood urea 116 mg.%.
27	27 AF	6	9	30	T	4000(1300)	Foot	-	S	D	6 days	Confused.
28	56 AF	21	60	8 d.	T	775(350)	Multiple	T5 & 6	Mod.	R	-	Bronchopneumonia. Amoebic dysentery.
29	5 IF	35	24	48	O	1175(200)	Arm	-	Mod.	R	-	-
30	12 AM	11	6	24	O	3650(600)	Multiple	-	S	R	-	-
31	27 AF	?	2	4 d.	O	4300(950)	Nil	-	S	R	-	-
32	16 AM	?	30	30	O	3250(900)	Nil	-	S	D	6 days	Bronchopneumonia.
33	6 AM	?	5	21	O	700(300)	Nil	-	S	D	55 hrs	Bronchopneumonia. Poor control of spasms.
34	14 IM	9	48	48	T	1350(600)	Foot	-	S	R	-	-
35	8 IM	3	10	30	NF	100(100)	Leg	-	S	D	6 hrs	Poor control of spasms
36	5 AM	?	0	33	O	400(200)	Nil	-	S	D	40 hrs	Bronchopneumonia.
37	36 AF	60	48	72	i.v.	2550(900)	Foot	-	S	D	4 days	Pulmonary oedema ? over hydration.
38	19 AF	9	48	48	T	2400(500)	Head	-	S	R	-	-
39	8 IM	14	10	17	NF	300(300)	Head	-	S	D	8 hrs	Haemophilia. Poor control of spasms.
40	21 IM	10	0	8 d.	O	400(300)	Head	N.A.D.	S	R	-	-
41	26 IM	23	5	72	O	1000(600)	Leg	-	Mod.	R	-	-
42	7 AF	4	6	6	O	1000(550)	Leg	-	S	D	4 days	Drowsy, delirious. Blood urea 94 mg.%.
43	2 AF	5	6 d.	5 d.	O	150(100)	Multiple	T4,5, 6 & 7	Mod.	R	-	-
44	12 IM	35	48	4 d.	O	500(250)	Leg	N.A.D.	Mod.	R	-	-

TRIAL TWO. NON-NEONATAL PATIENTS

CHLORPROMAZINE TREATED GROUP

Case Number	Age, race and sex	Incubation period (days)	Period of onset (hrs.)	Admission time (hrs.)	Feeding	Chlorprom. (mg.)	Wound	Fractures	Severity	Result	Survival time	Autopsy and comment
45	3 IF	?60	1	36	0	812(237)	Multiple		S	D	3½ days	Early hypostatic pneumonia.
46	3 AM	?	-	?	0	25(25)	Leg burn	None	Mild	R		
47	5 IF	?	48	6 d.	0	200(150)	Otitis media	None	Mod.	R		
48	17 IM	4	9	48	i.v.	500(200)	Foot		S	D	4 days	Respiratory failure.
49	10 AM	?	24	6 d.	0	450(150)	Multiple	None	S	R		
50	11 IM	?	0	28	0	650(250)	Nil		S	D	2½ days	Spasms not controlled. Early Bronchopneumonia.
51	13 IF	9	7	11	T	1350(300)	Foot		S	D	10 days	Respiratory failure
52	3 AM	8	0	5 d.	0	525(150)	Multiple	None	S	R		
53	8 AM	?	0	37	i.v.	1975(400)	Nil		S	D	7 days	Laryngeal spasms. Barbiturate added.
54	28 AF	15	5 d.	5 d.	0	3850(600)	Multiple	None	S	R		
55	9 AM	?	4	5	0	575(150)	Trunk	None	Mod.	R		
56	6 AF	?	48	48	NF	200(100)	Nil		S	D	32 hrs.	Purulent bronchitis. Spasms not controlled.
57	9 IM	6	6	18	NF	350(200)	Foot		S	D	34 hrs.	Purulent bronchitis. Died unexpectedly.
58	10 IF	18	0	11	0	1050(300)	Foot		S	D	3 days	Moderate bronchopneumonia.
59	7 IF	14	?	6	NF	100(100)	Foot		Mod.	D	16 hrs.	Face in pillow ? asphyxia.
60	13 IF	?	7 d.	5 d.	i.v.	4500(450)	Nil	None	S	R		Laryngospasm, serum sickness, quadriparesis.
61	15 IF	10	48	3 d.	0	3675(425)	Foot	T3-9	S	R		Reaction to A.T.S.
62	42 AF	9	4 d.	4 d.	0	4350(600)	Foot	None	S	R		
63	28 IF	?	3 d.	24	i.v.	3350(600)	Foot ulcer	None	S	R		Post-operative. Laryngeal spasms.
64	16 IM	18	4 d.	4 d.	0	3600(600)	Foot	T3	S	R		
65	7 IF	7	48	9 d.	0	700(275)	Leg	None	Mod.	R		
66	7 AM	7	12	3 d.	0	800(500)	Head		S	D	40 hrs.	Spasms not controlled.
67	10 AM	42	17	48	0	3000(400)	Multiple	T5-9	S	R		
68	38 IF	11	43	3	i.v.	7300(650)	Uterus		S	D	6 days	Laryngeal spasms. Recovered to die of second attack 3 months later.
69	14 IM	?	26	3 d.	0	4000(600)	Nil	T8-10	S	R		
70	10 AM	?	?	?	0	350(350)	Nil		S	D	13 hrs.	Spasms not controlled.
71	8 AF	7	24	48	0	675(675)	Thigh		S	D	26 hrs.	Spasms not controlled.
72	19 AM	5	5	5	i.v.	1000(1000)	Foot		S	D	29 hrs.	Spasms not controlled. Barbiturate added.
73	3 IM	7	72	26	0	250(100)	Foot		S	D	50 hrs.	Necropsy, congestion only.

TRIAL TWO. NON-NEONATAL PATIENTS

CHLORPROMAZINE BARBITURATE COMBINATION TREATED GROUP

Case Number	Age, race and sex	Incubation period (days)	Period of onset (hrs.)	Admission time (hrs.)	Feeding	Chlorprom. (mg.)	Phenobarb. sod. (gr.)	Wound	Fractures	Severity	Result	Survival time	Autopsy and comment
74	18 AM	?	-	6 d.	0	400(250)	3(3)	Multiple	-	Mild	R		
75	29 AM	30	6	48	0	1700(300)	78(18)	Arm	none	S	R		
76	2 AF	15	11	29	0	25(25)	5(1)	Foot	none	Mod.	R		
77	27 AM	6	28	28	i.v.	1500(400)	87(21)	Multiple		S	D	4 days	Spasms not controlled. Fractured skull. P.T.B.
78	17 AM	?	?	?	0	1000(700)	6(3)	Nil		S	D	38 hrs	Confluent bronchopneumonia.
79	4 IM	14	-	48	0	600(100)	2(2)	Foot	none	Mild	R		
80	36 AM	13	8 d.	24	0	900(300)	13(4)	Foot	none	Mod.	R		Prophylactic A.T.S. 3,000 units given.
81	23 AM	?	72	3½ d.	0	2250(300)	27(9)	Nil	T4-6	S	R		
82	57 AM	?	24	48	0	950(300)	27(9)	Nil		S	D	3½ days	Purulent brenchitis. Bronchopneumonia.
83	10 IM	?	46	65	i.v.	775(150)	31(9)	Multiple	T3-9	S	R		
84	28 IF	4	24	15	i.v.	650(300)	24(15)	Uterus		S	D	55 hrs	Poor control of spasms, obstructed, tracheotomy performed, respiratory failure.
85	15 IF	?	15	24	i.v.	1200(300)	76(25)	Uterus		S	D	4 days	Spasms not controlled. Purulent bronchitis.
86	29 AM	17	6 d.	4 d.	0	2300(300)	30(6)	Leg	none	Mod.	R		
87	11 AM	?	72	5 d.	0	2300(300)	21(6)	Nil	T6-8	Mod.	R		
88	8 AM	9	9	13	i.v.	425(150)	15(7½)	Finger		S	D	4 days	Necropsy congestion only.
89	61 AM	?	-	?	0	650(300)	33(6)	Foot	none	Mild	R		Post-operative.
90	11 IM	?	?6 d.	?	0	1850(300)	18(6)	Nil	T5&6	S	R		
91	34 AM	17	?5 d.	5 d.	0	1800(300)	9(3)	Head	none	Mod.	R		
92	11 IM	?	5 d.	5 d.	0	2350(300)	9(3)	Nil	T5-7	S	R		
93	10 IM	8	21	40	0	750(300)	19(6)	Thigh		S	D	2½ days	F.B. in wound. Respiratory failure
94	19 IF	7	48	48	i.v.	1350(500)	21(6)	Uterus		S	D	3½ days	Pelvic abscess. Laryngospasm controlled. Respiratory failure.
95	38 AM	9	72	72	0	2100(300)	3(3)	Arm	none	Mod.	R		
96	12 IM	19	8	30	0	1750(300)	15(3)	Foot	T5-8	S	R		
97	29 AF	?	-	48	0	850(300)	3(3)	Nil	-	Mild	R		
98	10 AM	?	6 d.	4 d.	i.v.	1650(175)	20(3)	Nil	T6&7	S	R		
99	14 AM	?	24	9 d.	0	3300(300)	48(9)	Nil	T5-9	S	R		
100	13 IM	10	41	26	0	200(200)	3(3)	Head		Mod.	D	25½ hrs	F.B. in wound. Moderate with laryngospasm, early bronchopneumonia.

APPENDIX II

OFF SERIES BEFORE START OF I.P.P.R. NON-NEONATAL PATIENTS

(INCLUDING ACETYLPROMAZINE GROUP)

(CFF SERIES). NON-NEONATAL PATIENTS

Case Number	Age, race and sex	Incubation period (days)	Period of onset (hrs.)	Admission time (hrs.)	Feeding	Treatment	Wound	Fractures	Severity	Result	Survival time	Autopsy and comment
101	49 AF	5	3 d.	6 d.	O	C	Foot	-	S	R		
102	60 IF	5	10	2 d.	i.v.	C	Foot	-	S	D	3 days	No necropsy. ? respiratory failure.
103	24 IM	?	-	24	O	C	Multiple	-	Mild	R		
104	3 IM	4	?	± 6	NF	C	Head	-	S	D	13¾hrs	Urticaria following A.T.S., laryngospasm, atelectasis.
105	4 AM	-	?	3 d.	Oral	C + B	Nil	T 7	S	R		
106	8 AM	-	?	?	O	C + B	Nil	T4 & 5	Mod.	R		
107	48 AM	6	20	23½	NF	C + B	Trunk	-	S	D	14 hrs	Followed nephrectomy. Bronchopneumonia, hypernephroma. Spasms not controlled.
108	37 AM	18	-	-	O	C	Head	-	Mild	R		Followed mastoidectomy.
109	13 AF	10	?24	?24	T	C + B	Multiple burns	-	S	R		Prophylactic A.T.S. given. 25% burn.
110	19 AF	-	7 d.	6 d.	i.v.	C	Nil	-	S	R		Haemoptysis ? cause.
111	12 IF	30	48	36	O	C + B	Foot	T 6	S	R		
112	56 AM	15	-	4 d.	O	C + B	Foot	-	Mild	R		
113	14 AM	10	18	4 d.	O	C + B	Foot	T4 - 8	S	R		Very severe spasms.
114	14 AM	?	48	11 d.	O	C + B	Multiple	T5-8	S	R		
115	18 AM	12	48	2 d.	O	C + B	Arm burn	none	S	R		Haemoptysis ? cause.
116	7 IM	30	4 d.	2 d.	O	C	Foot	none	S	R		
117	30 AM	6	48	3 d.	O	C + B	Head	T4-7	S	R		Spasms until 15th day. Dental extraction with pliers.
118	4 AM	18	-	-	i.v.	C + B + T	Trunk	-	Mild	R		Respiratory obstruction. Tracheotomy performed.
119	10/12 IF	-	-	5 d.	O	C + B	Nil	-	Mild	R		
120	28 IM	15	72	-	O	C + B	Hand burn	-	S	R		
121	42 IF	4	24	17	NF	C + B + T	Uterus	-	S	D	36 hrs	Post abortal. Tracheotomy for laryngospasm. Respiratory failure.
122	45 AM	14	48	2 d.	O	C + B	Multiple legs	none	Mod.	R		
123	19 AM	?	72	11 d.	O	C + B	Foot ulcer	none	S	R		
124	44 AM	9	48	30	i.v.	C + B	Foot	-	S	D	5 days	Laryngeal & pharyngeal spasms, severe bronchopneumonia. Prophylactic A.T.S. given.
125	6 AM	2 mths.	40	24	O	C + B	Foot	none	S	R		? serum sickness.
126	10 IM	10	-	5 d.	O	C + B	Foot	none	Mild	R		
127	49 AM	-	-	2 d.	O	Misc.	Nil	-	Mild	R		Severe local tetanus of leg in addition.
128	9 AM	?	24	24	-	C + B	Multiple	-	S	D	24 hrs.	Respiratory failure.

(OVF SERIES). NON-NEONATAL PATIENTS.

Case Number	Age, race and sex	Incubation period (days)	Period of onset (hrs.)	Admission time (hrs.)	Feeding	Treatment	Wound	Fractures	Severity	Result	Survival time	Autopsy and comment
129	?45 AM	?	-	3 d.	i.v.	C + B	Leg	-	Mild	D	5 days	Debility, bronchopneumonia. Appeared older than 45.
130	15 AM	-	40	24	i.v.	C + B	Nil	None	S	R		Severe laryngeal & generalized spasms. Haemoptysis ? cause.
131	22 AM	?	-	?48	0	C	Nil	-	Mild	R		
132	21 IF	7	72	15½	i.v.	C + B	Uterus	-	S	D	3 days	Postabortal. Respiratory failure.
133	31 AF	?	-	3 d.	0	C + B	Leg	-	Mild	R		
134	11 AM	10	-	10 d.	0	C + B	Leg	-	Mild	R		Note long admission time.
135	15 AM	3	12	2 d.	0	C + B	Foot	T4 - 9	S	R		? A.T.S. neuropathy.
136	11 IM	17	40	24	0	C + B	Leg	-	S	D	2 days	Sudden death ? respiratory failure. Necropsy: congestion only.
137	10 IF	2	48	24	0	C + B	Foot	-	Mod.	R		
138	10 AM	17	48	3 d.	-	C + B	Foot	-	S	D	1 day	Toxic, gangrene of toes ? septicaemia, bronchopneumonia.
139	16 AM	-	-	2 d.	0	C	Nil	-	Mild	R		
140	5 AM	-	-	36	i.v.	C + B	Nil	-	Mild	D	50 hrs.	Respiratory failure. CO_2 content 14 mEq/L. P.T.B.
141	6 IM	-	15½	14	0	C + B	Nil	-	S	D	29 hrs.	Necropsy macroscopically normal. ? respiratory failure.
142	54 IM	12	-	24	i.v.	C + B	Hand burn	-	Mild	D	10 days	Pharyngeal spasm, blood chemistry normal. Bronchopneumonia. Severe atheroma.
143	45 AM	10	-	48	i.v.	Misc.	Head	-	Mild	R		
144	52 IM	?	-	5 d.	0	C + B	Leg ulcer	None	Mild	R		
145	11 AM	4	?6 d.	3 d.	0	C + B	Foot	T4 - 6	Mod.	R		
146	32 AM	12	-	2 d.	0	C + B	Head	None	Mild	R		

(OFF SERIES). NON-NEONATAL PATIENTS.

ACETYLPROMAZINE TREATED GROUP

Case Number	Age, race and sex	Incubation period (days)	Period of onset (hrs.)	Admission time (hrs.)	Feeding	Acetylprom. (mg.)	Phenobarb. sod. (gr.)	Wound	Fractures	Severity	Result	Survival time	Autopsy and comment
147	16 IF	21	55	72	0	575(100) 8 days		Head	T4-9	S	R		Good control of spasms.
148	19 AM	?	36	48	0	2140(420) 6 days		Nil	T4-9	S	R		Spasms controlled until 7th day on very high dosage. Confused, hallucinated & incontinent. Chlorprom. and phenobarb. substituted.
149	18 AM	13	42	72	0	1205(150) 12 days		Foot	None	S	R		Spasms controlled, but returned on reducing dose on 7th day.
150	15 AM	?	72	5 d.	0	400(80) 6 days		Nil	T4-6	S	R		Drug stopped 7th day, spasms returned, chlorpromazine & barbiturate substituted.
151	4 AM	?	12	26	0	135	6	Nil		S	D	32 hrs.	Spasms not controlled.
152	9 AM	10	48	72	i.v.	95	5½	Legs		S	D	38 hrs.	Spasms controlled. Terminal hyperpyrexia & respiratory failure.
153	6 AM	7	12	22	i.v.	150(80)	6(6)	Foot		S	D	39 hrs.	Spasms not controlled, respiratory failure, bronchopneumonia.
154	12 IF	28	72	4 d.	0	690(80) 13 days		Multiple	None	S	R		Spasms controlled, disappeared on 8th day, but returned with dysphagia on stopping drug. Prophylactic A.T.S. given.

APPENDIX III

TRIAL III NON-NEONATAL PATIENTS (TRACHEOTOMY)

TRIAL THREE. NON-NEONATAL PATIENTS

TRACHEOTOMY AND CONSERVATIVE GROUPS

TRACHEOTOMY

Case Number	Age, race and sex	Incubation period (days)	Period of onset (hrs.)	Admission time (hrs.)	Feeding	Chlorprom. (mg.)	Phenobarb. sod. (gr.)	Wound	Fractures	Severity	Result	Survival time	Autopsy and comment
155	50 AM	4	36	30	i.v.	1100(300)	39(15)	Hand		S	D	4 days	Respiratory failure. Purulent bronchitis. Prophylactic A.T.S. given.
156	8 AF	8	33	12	i.v.	1325(225)	43(7)	Foot		S	D	7 days	Respiratory failure. Moderate Bronchopneumonia.
157	12 IM	7	12	12	i.v.	1050(300)	12(4)	Foot		S	D	4 days	Purulent bronchitis. Collapse L. lung. Spasms not controlled.
158	21 AM	7	12	14	i.v.	550(300)	21(12)	Head		S	D	43 hrs.	Pus deep to wound. Spasms not controlled.
159	2½ IF	?	20	40	NF	150(100)	4½(3)	Nil		S	D	17 hrs.	Spasms not controlled.
160	30 AF	?	40	48	i.v.	2900(300)	33(9)	Uterus		S	D	9 days	Septic pedunculated fibroid. Debilitated.
≡ 161	7 IM	13	?60	3 d.	i.v. T	1825(225)	15(3)	Multiple feet	T5-8	S	R		Surgical emphysema of neck & chest.
≡ 162	40 AM	18	44	48	0	3200(300)	9(3)	Head	T4-6	S	R		Marked sinus tachycardia ? chlorpromazine.

CONSERVATIVE

163	34 IF	?	12	12	i.v.	650(300)	33(15)	Uterus		S	D	44 hrs.	Respiratory failure. Purulent bronchitis.
164	10 AF	?	12	24	i.v.	500(225)	13(4½)	Nil		S	D	3 days	Spasms not controlled. Bronchopneumonia.
165	26 AM	5	43	28	i.v.	850(300)	33(18)	Head		S	D	4 days	F.B. deep to wound. Bronchopneumonia. Spasms not controlled.
166	34 IF	8	25	16	i.v.	350(300)	12(9)	Uterus		S	D	28 hrs.	Respiratory failure.
167	6 AF	14	?	?	i.v.	2100(225)	6(3)	Head	T4-7	S	R		Dental extraction.
≡ 168	50 AM	8	3 d.	3 d.	i.v.	3950(300)	30(6)	Head		S	D	17 days	Debilitated. I.v. feeding prolonged.
≡ 169	28 AF	4	20	18	NF	300(300)	21(21)	Uterus		S	D	26 hrs.	Admitted during period of onset. Fulminating. Spasms not controlled.

≡ Treated after the start of the I.P.P.R. trial.

APPENDIX IV

TRIAL IV NON-NEONATAL PATIENTS (I.P.P.R.)

(INCLUDING OFF SERIES AFTER START OF I.P.P.R.)

Case No. 204 Hosp. No. I.466/59 [redacted]
Date of Admission: 10.7.59 Date of Discharge: 14.8.59

Age, race and sex: 15 years. Coloured male.
Incubation period: 10 days.
Period of onset: 7 hours.
Admission time: 8 hours.
Wound: Pustule right heel.

Artificial respiration: This was maintained on a Radcliffe Mark V pump.

Inflation pressures - 10 to 13 cm. of water.
Respiratory rate - 20 per minute.
Minute volume - 4 to 5 L.

Curare Dosage: 6,480 mg. intramuscularly total (18 days)
Maximum daily dose 480 mg. (8th day)

Investigations: Electrolytes and blood urea normal.

Temperature: Ranged between 96 and 101°F.

Clinical Course: I.P.P.R. was instituted 24 hours after admission. Secretions from the lungs were thick and purulent initially but became mucoid on the third day after humidification and physiotherapy. Progress was satisfactory until the eighth day when an erythematous papular rash appeared which was attributed to penicillin. Pneumonia developed on the eighteenth day but responded to treatment with streptomycin. Curare was stopped on the nineteenth day and the patient was able to breathe spontaneously without distress when disconnected from the pump later that day. The tracheotomy tube was removed on the twenty-sixth day and the patient discharged 8 days later.

Comment: The absence of rigidity and spasms during convalescence in this patient suggests that the duration of I.P.P.R. was excessive.

Case No. 205 Hosp. No. 40579/59 OFF SERIES
Date of Admission: 25.12.59 Date of Death: 3.1.60

Age, race and sex: 34 years. African male.
Incubation period: 6 days.
Period of onset: 20 hours.
Admission time: 16 hours.
Wound: Septic abrasions to knuckles of right hand.

Artificial respiration: This was maintained on a Smith-Clarke respirator.
Inflation pressures - 10 to 13 cm. of water. A negative phase (-4 cm. of water) was introduced intermittently.
Respiratory rate - 16 to 18 per minute.
Minute volume - 8 to 10 L.
$PaCO_2$ - 34 to 38 mm. Hg.

Curare Dosage: 1,170 mg. intramuscularly total (6 days)
Maximum daily dose 270 mg. (4th day)

Investigations: Electrolytes - serum sodium 135 to 152 mEq/L.
potassium 4.9 to 6.1 mEq/L.
chlorides 103 to 115 mEq/L.
Blood urea - 68 to 188 mg.%.

Temperature: Fluctuated between normal and 101°F. Survival time: 9 days

Necropsy: Erosion of the trachea below the tracheotomy opening.
Histology: Lungs showed congestion and atelectasis.

Clinical Course: This patient admitted during the period of onset had very severe generalised and laryngeal spasms, and death appeared imminent despite conservative treatment with chlorpromazine and amylobarbitone sodium. I.P.P.R. was instituted on the third day but progress was unsatisfactory from the outset. The blood urea was raised and the E.C.G. showed a pattern of right heart strain. He died suddenly on the tenth day, 6 hours after curare had been stopped. It was subsequently found that as a result of a mechanical fault in the spirometer included in the circuit of the Smith-Clarke respirator, a water trap had formed and the expired air could not escape.

Comment: Death followed a mechanical fault in the spirometer in this patient with severe tetanus. Uraemia may have been a contributory cause.

Case No. 206 Resp.No. I.A881/59 I.P.P.R. SERIES
Date of Admission: 19.7.59 Date of Death: 27.7.59

Age, race and sex: 8 years. Indian male.
Incubation period: Unknown.
Period of onset: 18 hours.
Admission time: 9½ hours.
Wound: Multiple healing abrasions on the feet.

Artificial respiration: This was maintained on a Radcliffe Mark V pump.

Inflation pressures	- 10 to 13 cm. of water.
Respiratory rate	- 23 per minute.
Minute volume	- 4 L.
$PaCO_2$	- 32 to 41 mm. Hg.

Curare Dosage: 1,170 mg. intramuscularly total (8 days)
Maximum daily dose 180 mg. (2nd and 4th days)

Investigations: Electrolytes and blood urea normal.

Temperature: Fluctuated between normal and 101°F. Survival time: 7½ days

Necropsy: There was no evidence of inflammation or ulceration of the trachea. Left sided haemorrhagic pleurisy.

Clinical Course: Progress was satisfactory on I.P.P.R. until the fourth day when the tracheotomy tube was accidentally dislodged during physiotherapy. This passed unnoticed for several minutes resulting in severe anoxia and cardiac arrest. A cardiac massage was performed and the heart restarted. The pupils were widely dilated and failed to react to light. Electrocardiograms on successive days were normal. The blood pressure fell to 80 mm. Hg. on the seventh day and the patient died on the following day.

Comment: Death occurred in this patient 4 days after an episode of severe anoxia.

Case No. 208 Hosp. No. 25202/59 I.P.P.R. SERIES
Date of Admission: 17.8.59 Date of Death: 23.8.59

Age, race and sex: 9 years. African male.
Incubation period: 14 days.
Period of onset: ? 3 days.
Admission time: 3 days.
Wound: Laceration right elbow.

Artificial respiration: This was maintained on a Smith-Clarke respirator.
Inflation pressures - 10 to 13 cm. of water with a negative phase (-2 to -6 cm. of water).
Respiratory rate - 16 per minute.
Minute volume - 5 to 6 L.

Curare Dosage: 1,065 mg. intramuscularly total (6 days)
Maximum daily dose 240 mg. (5th and 6th days)

Investigations: Electrolytes and blood urea normal.

Temperature: Fluctuated between 95 and 100°F. Survival time: 6 days

Necropsy: Both main bronchi were filled with mucopurulent secretions.

Clinical Course: I.P.P.R. was instituted 8 hours after admission when reflex spasms were frequent and severe. Progress was satisfactory although secretions from the lungs were profuse and frequent suction was required. Early on the seventh day he became cyanosed and died despite inflation with oxygen.

Comment: Death appears to have been due to faulty technique in this patient, spasms were frequent and severe although other criteria suggested a good prognosis. He died from asphyxia following secretions which should have been aspirated.

Case No. 210 Hosp. No. 30234/59 I.P.P.R. SERIES
Date of Admission: 28.9.59 Date of Death: 5.10.59

Age, race and sex: 33 years. African male.
Incubation period: 5 days.
Period of Onset: 4 hours.
Admission time: 48 hours.
Wound: Laceration of foot.

Artificial respiration: This was maintained on a Radcliffe Mark V pump.
Inflation pressures - 14 to 18 cm. of water.
Respiratory rate - 16 to 18 per minute.
Minute volume - 7 to 10 L.
$PaCO_2$ - 34 to 42 mm. Hg.

Curare Dosage: 1,260 mg. intramuscularly total (6 days)
Maximum daily dose 240 mg. (2nd day)

Investigations: Electrolytes - serum sodium 121 to 143 mEq/L.
potassium 5.4 to 7.8 mEq/L.
chlorides 102 to 121 mEq/L.
Blood urea - 107 to 145 mg.%.

Temperature: 100.9°F. on admission. This rose to 103°F. on the sixth day.

Survival time: 7 days.

Necropsy: A large embolus occluded the left main pulmonary artery with a smaller earlier infarct in the right lung. There was ulceration of the trachea approximately 1" below the opening in the trachea.

Clinical Course: Bilateral rhonchi with increasing pyrexia and rusty purulent sputum developed in this patient on the third day. A pulmonary infection was suspected but an x-ray of the chest was normal. The cuff of the tracheotomy tube burst on the sixth day, the blood pressure fell to 50 mm. Hg. systolic two hours later with aspiration of bright red blood from the lungs. The hypotension responded to noradrenaline but the patient died suddenly early on the eighth day.

Comment: Death was due to pulmonary embolism in this patient. Uraemia was a feature but in error the kidneys were not examined histologically.

Case No. 212 Hosp.No. I. 7770/59 I.P.P.R. SERIES
Date of Admission: 15.11.59 Date of Discharge: 24.12.59

Age, race and sex: 25 years. Indian female.
Incubation period: 6 days.
Period of onset: Under 30 hours.
Admission time: 23 hours.
Wound: Uterus. Abortion 6 days before admission following a fall 2 days previously.

Artificial respiration: This was maintained on a Radcliffe Mark V pump.
Inflation pressures - 12 to 14 cm. of water.
Respiratory rate - 16 to 20 per minute.
Minute volume - 7 to 10 L.
P_aCO_2 - 22 and 24 mm. Hg. (isolated readings)

Curare dosage: 1,380 mg. intramuscularly total (12 days)
Maximum daily dose 210 mg. (10th day)

Investigations: Hb 5.2 g.% rose to 12.7 g.% on the 5th day after transfusion of 5½ pints of blood.
Blood urea - uraemic for the first 2 weeks, 118 mg.% maximum on the fifth day.
Electrolytes - serum sodium, potassium & chlorides high during the first week.
Plasma CO_2 content - 13.6 to 24.1 mEq/L.
Urinary S.G. - 1010 for the first 2 weeks; diuresis on the eighth day.
X-ray spine normal.

Temperature: Fluctuated between normal and 103°F.

Clinical course: I.P.P.R. was commenced on the second day. The course was uneventful until the fourth day when the tracheotomy tube was dislodged during physiotherapy. This was replaced without severe anoxia. After inflating the cuff the chest movement ceased and on removing the tracheotomy tube it was found that the cuff had perished and herniated around the lower end of the tube, causing obstruction. Protein was restricted because of the uraemia with a diuresis between the eighth and tenth days, and a fall in the serum electrolytes. Curare was discontinued on the thirteenth day and although irregular spontaneous respiration was possible after 12 hours assistance from the respirator was required until the following day. Marked rigidity with trismus and occasional reflex spasms were noted on the sixteenth day. Oral feeding was possible on the twenty-fourth day and the tracheotomy tube was removed 3 days later.

Comment: Uraemia and difficulty with the tracheotomy tube and uraemia were problems in the management of this patient suffering from severe post-abortal tetanus, who recovered on treatment with I.P.P.R.

Case No. 214 Hosp. No. 40729/59 I.P.P.R. [redacted]
Date of Admission: 27.12.59 Date of Discharge: 1.2.60

Age, race and sex: 21 years. African female.
Incubation period: Less than 7 days.
Period of onset: Less than 24 hours.
Admission time: 12 hours.
Wound: Uterus.

Artificial respiration: This was maintained on a Radcliffe Mark V pump.
Inflation pressures - 10 to 14 cm. of water.
Respiratory rate - 16 per minute.
Minute volume - 7 to 10 l.
$PaCO_2$ - 28 to 43 mm. Hg.

Curare Dosage: 2,460 mg. intramuscularly total (12 days)
Maximum daily dose 300 mg. (9th day)

Investigations: Blood urea 105 mg.% on second day;
36 mg.% on fourth day.
Serum electrolytes normal.
Hb 9 g.% on admission; 12.9 g.% after transfusion of 2 pints of packed cells.
CO_2 17.6 to 22.1 mEq/l.
X-ray spine normal.

Temperature: Fluctuated between 100 and 102°F.

Clinical course: I.P.P.R. was instituted shortly after admission. Secretions were thick and tenacious initially. There was retention of urine requiring catheterisation on the second day. Oral feeds were discontinued because of a paralytic ileus with marked abdominal distension on the fifth day. Curare was stopped on the eleventh day, spontaneous respiration being possible for a short period 9 hours later. Severe rigidity gradually returned (trismus $\frac{1}{2}$") with profuse sweating. The patient was noted to have a right third nerve palsy which had not been present previously. Severe retrosternal pain probably due to tracheitis was a persistent complaint at this stage. The tracheotomy tube was removed on the twenty-fifth day and the patient discharged 12 days later. When seen 2 weeks later the third nerve palsy had disappeared.

Comment: Treatment on I.P.P.R. was successful in this patient suffering from severe post-abortal tetanus. Her raised blood urea which soon returned to normal and a third nerve palsy, are points of interest.

Case No. 218 Hosp. No. 5689/60 I.P.P.R. SERIES
Date of Admission: 18.2.60 Date of Discharge: 25.3.60

Age, race and sex: 13 years. African female.
Incubation period: Unknown.
Period of onset: 35 hours.
Admission time: 48 hours.
Wound: Purulent otitis media.

Artificial respiration: This was maintained on a Radcliffe Mark V pump.

Inflation pressures	- 12 to 19 cm. of water.
Respiratory rate	- 20 per minute.
Minute volume	- 3 to 6.1 L.
$PaCO_2$	- 20.4 to 40.3 mm. Hg. mean 28.9 mm. Hg.

Curare dosage: 1,135 mg. intramuscularly total (10 days)
Maximum daily dose 210 mg. (9th day)

Investigations: Electrolytes

serum sodium	- 130 to 148 mEq/L.
potassium	- 4.4 to 5.9 mEq/L.
chlorides	- 100 to 117 mEq/L.
Blood urea	- 93 mg.% before the start of I.P.P.R., fell to 41 mg.% on the fifth day.

X-ray spine - compression fracture T_4 - 7.

Temperature: There was a low-grade pyrexia until the end of the third week.

Clinical course: I.P.P.R. was started 3 hours after admission in this patient who appeared dehydrated. She was given 2,250 cc. of fluids by tube in the first 19 hours. The abdomen became distended, a paralytic ileus having developed which necessitated intravenous feeding from the third to the seventh days. Curare was stopped at midnight on the tenth day and thirty-two hours later full spontaneous respiration was possible. Rigidity and moderate reflex spasms returned in the course of the next 3 days but caused little distress. Fluids were taken orally on the nineteenth day and the tracheotomy tube was removed on the following day. At the time of discharge on the thirty-seventh day slight trismus was still present.

Comment: Paralytic ileus was a feature in this patient successfully treated with I.P.P.R. Compression fractures of the spine occurred despite treatment with total paralysis.

Case No. 220 Hosp. No. 384.9/60 I.P.P.L. [redacted]
Date of Admission: 5.6.60 Date of Death: 20.7.60

Age, race and sex: 11 years. African male.
Incubation period: Uncertain.
Period of onset: 6 hours.
Admission time: 20 hours.
Wound: Small septic abrasions of left foot.

Artificial respiration: This was maintained on a Smith-Clarke respirator.
Inflation pressures - 13 to 24 cm. of water.
Respiratory rate - 23 to 26 per minute.
Minute volume - 6.2 to 12 l.
$PaCO_2$ - 26 to 40.3 mm. Hg.

Curare dosage: 2,305 mg. intramuscularly total (12 days)
Maximum daily dosage 300 mg. (6th day)

Investigations: Electrolytes
serum sodium - 119 to 139 mEq/l.
potassium - 3.9 to 5.3 mEq/l.
chlorides - 87 to 97 mEq/l.
Blood urea - 24 to 56 mg.%.
Plasma CO_2 content - 18 to 20.7 mEq/l.

Temperature: Usually elevated 99 to 101°F. Survival time: 13 days

Necropsy: Showed ulceration of the trachea with erosion into the innominate artery and extensive haemorrhage.

Clinical course: There was technical difficulty in performing a tracheotomy on this patient, because a large aberrant artery crossed the trachea anteriorly. Early on the second day the tracheotomy tube was dislodged with an episode of severe anoxia. An E.C.G. taken later that day showed symmetrical T wave inversion in leads V1 - V4 which had returned to normal three days later. A purulent bronchitis and infection of the tracheotomy wound developed on the fifth day. Severe reflex spasms occurred when curare was stopped for 12 hours on the ninth day. Total paralysis was therefore reinstituted for 3 further days. Late on the fourteenth day when spontaneous respiration had been re-established the patient died as a result of a sudden severe haemorrhage into the lungs.

Comment: This patient died of haemorrhage when an ulcer at the lower end of the trachea eroded a large vessel.

Case No. 221 Hosp.No. I.3849/60 I.P.P.R. SERIES
Date of Admission: 5.6.60 Date of Discharge: 24.7.60

Age, race and sex: 7 years. Indian female.
Incubation period: ? 4 weeks.
Period of onset: Under 12 hours.
Admission time: 19½ hours.
Wound: Open septic ulcer foot.

Artificial respiration: This was maintained on a Radcliffe Mark V pump.
Inflation pressures - 14½ to 17 cm. of water.
Respiratory rate - 23 per minute.
Minute volume - 5 to 7.7 L.
$PaCO_2$ - 29.7 to 40 mm. Hg.

Curare dosage: 1,940 mg. intramuscularly total (11 days)
Maximum daily dose 270 mg. (8th day)

Investigations: Electrolytes
serum sodium - 108 to 130 mEq/L.
potassium - 3.6 to 5.4 mEq/L.
chlorides - 92 to 118 mEq/L.
Blood urea - maximum 43 mg.%.
Plasma CO_2 content - 15.5 to 31.5 mEq/L.
X-ray spine - normal.

Temperature: Pyrexial until the end of the third week.

Clinical course: This was uneventful during the first week apart from an infection of the tracheotomy wound. Temperature rose to 105°F. on the tenth day with peri-orbital oedema, probably due to serum sickness. The return of reflex spasms and rigidity caused distress when curare was discontinued, but spontaneous respiration was adequate on the twelfth day. Several mucosal sloughs were aspirated from the trachea. Swallowing commenced on the twenty-first day and the tracheotomy tube was removed on the twenty-fifth day.

Comment: This patient who recovered showed evidence of damage to the mucosa of the trachea.

TRIAL FOUR. NON-NEONATAL PATIENTS — CONSERVATIVE TREATED GROUP

Case Number	Age, race and sex	Incubation period (days)	Period of onset (hrs.)	Admission time (hrs.)	Feeding	Chlorpromazine (mg.)	Phenobarb. sod. (gr.)	Wound	Result	Survival time	Comment
207	9 IM	-	40	20	0	1625	3	Nil	R	-	Fractures T4 - 6
209	11 AM	-	17	3 days	N	3700	9½	Nil	R	-	Fractures T3 - 7
211	6 AM	3½	0	10	Nil	50	1½	Foot	D	1½ hrs	Poor control of spasms
213	50 AM	5	12	8	0	200	12	Leg	D	20 hrs	Poor control of spasms Chronic P.T.B.
215	23 IP	?	24	24	i.v.	500	21	Uterus	D	36 hrs	Septic abortion Poor control of spasms
216	8 IM	5	6	24	i.v.	450	19½	Foot	D	3 days	Poor control of spasms terminally
217	5 IP	?	39	2 days	i.v.	225	4½	Multiple	D	3½ days	Bronchopneumonia ? respiratory failure
219	15 AM	4	48	5 days	i.v.	900	18	Leg	D	2½ days	Early bronchopneumonia Respiratory failure

OFF SERIES. NON-NEONATAL PATIENTS ADMITTED AFTER START OF I.P.P.R.

Cases 170 - 203

28 Recoveries
7 severe
9 moderate
12 mild

Two patients who recovered had a tracheotomy (cases 177, 187) already described in text.

6 Deaths

Case No.	Age, race and sex	Incubation period (days)	Period of onset (hrs.)	Admission time (days)	Treatment	Severity	Survival time	Comment
172	48 AM	30	-	?5	B	S	3 hrs	Died suddenly of severe spasms during assessment of severity despite a cardiac massage.
173	50 AM	13	?4 days	24 hrs	C + B	Mod.	12 days	Complicated by pulmonary tuberculosis and bronchopneumonia.
179	25 AM	±21	29	7 hrs	B	S	29 hrs	Died of laryngeal spasm during period of assessment of severity.
188	17 IM	11	48	?36 hrs	C + B + T	S	6 days	Spasms well controlled. ? Respiratory failure.
194	3 AM	?4	-		C + B + T	Mild	10 days	Complicated by kwashiorkor.
200	49 AF	-	-	?7	Nil	Mild	0	Died on admission of laryngeal spasm.

APPENDIX V

TRIALS I & II NEONATAL PATIENTS

TRIAL ONE. NEONATAL PATIENTS. BARBITURATE TREATED GROUP

Case Number	Age, race and sex	Incubation period (days)	Period of onset (hrs.)	Admission time (hrs.)	Feeding	Phenobarb. sod. (gr.)	Autopsy findings	Result	Survival time	Comment
222	6 AM	4	22	32	T	6(4)	-	D	28	spasms not controlled
223	5 AM	5	6	19	T	8½(3½)	-	D	3 days	respiratory failure
224	6 AF	5	0	24	T	11½ (2)		R		
225	5 AF	4	0	16	T	4½ (2)	Bpn	D	52 hrs	spasms not controlled
226	7 AM	6	24	26	T i.v.	3½(2½)	-	D	48 hrs	
227	13 AF	12	120	7 days	T	13 (3)		R		
228	7 AF	6	0	21	T	26½(3)		R		
229	6 IF	6	25	11½	T	2 (2)	-	D	26 hrs	spasms not controlled
230	9 AM	6	6	72	T	5 (4)	Bpn	D	60 hrs	respiratory failure
231	8 AF	6	8	15	T	4 (2)	Bpn	D	24 hrs	respiratory failure
232	11 AM	7	52	4 days	T	7 (3½)		R		
233	4 IM	4	0	11	T	5½(3)	Bpn	D	47 hrs	
234	7 AF	6	10	17	T	8 (5)	-	D	33 hrs	
235	7 AM	5	15	33	T	8 (5)	-	D	35 hrs	respiratory failure
236	8 AF	6	1	48	T	3 (3)	-	D	15 hrs	spasms not controlled
237	5 IM	5	16	22	T	38 (6)		R		
238	5 AF	5	3	5	T	10½(4)	Bpn	D	7 days	respiratory failure

TRIAL ONE. NEONATAL PATIENTS. CHLORPROMAZINE TREATED GROUP

Case Number	Age, race and sex	Incubation period (days)	Period of onset (hrs.)	Admission time (hrs.)	Feeding	Chlorprom. (mg.)	Autopsy findings	Result	Survival time	Comment
239	6 AM	6	4	24	T	1700(360)		D	10 days	
240	9 AF	8	27	24	T	890(120)		R		
241	8 AF	6	21	45	T	495(325)		D	41 hrs	
242	7 AF	5	0	48	T	530(210)	Bpn	D	3 days	
243	9 AM	8	0	31	T	220(120)		D	41 hrs	spasms not controlled
244	7 AM	6	4	6	T	337(150)		D	48 hrs	spasms not controlled
245	9 AF	7	1	41	T	935(210)		D	5 days	
246	10 AF	7	12	74	T	967(222)		D	5 days	
247	5 AF	5	5	14	T	260(160)		D	24 hrs	spasms not controlled
248	6 AM	5	6	20	T	395(280)		D	31 hrs	
249	4 AM	4	0	9	NF	50(50)	Bpn	D	9 hrs	spasms not controlled
250	7 AM	5	39	42	T	150(150)		D	13 hrs	spasms not controlled
251	6 AF	4	19	41	T	575(575)		D	24 hrs	spasms not controlled
252	6 IF	5	10	15	T	362(237)	Bpn	D	35 hrs	

TRIAL TWO. NEONATAL PATIENTS — CHLORPROMAZINE TREATED GROUP

Case Number	Age, race and sex	Incubation period (days)	Period of onset (hrs.)	Admission time (hrs.)	Feeding	Chlorprom. (mg.)	Autopsy findings	Result	Survival time	Comment
253	6 AF	5	16	24	T	125(125)		D	10 hrs	spasms not controlled
254	4 AF	4	2	21	T	25(25)		D	6 hrs	spasms not controlled
255	5 AM	5	5	8	NF	150(150)		D	12 hrs	spasms not controlled
256	6 AM	6	4	6	T	225(150)		D	48 hrs	spasms not controlled
257	6 AF	5	0	32	T	1475(200)		D	10 days	respiratory failure
258	6 AM	6	0	3	T	75(75)	Bpn	D	7 hrs	spasms not controlled
259	7 AF	6	13	22	T	750(150)		D	7 days	spasms not controlled
260	5 IM	5	0	8	T	50(50)		D	6 hrs	spasms not controlled
261	8 AM	8	0	½	T	825(150)		R		
262	7 AF	6	21	24	NF	75(50)		D	36 hrs	spasms not controlled
263	5 AF	5	0	28	NF	75(75)		D	24 hrs	spasms not controlled
264	4 AF	4	2	7	NF	75(75)		D	12 hrs	spasms not controlled
265	6 AM	5	18	23	T	150(150)		D	23 hrs	spasms not controlled
266	4 IM	4	0	36	NF	75(75)		D	10 hrs	spasms not controlled
267	7 AF	7	10	13	NF	150(150)		D	20 hrs	spasms not controlled
268	5 AF	5	0	13	NF	125(125)		D	19 hrs	spasms not controlled
269	5 AF	4	20	24	T	800(150)	not done	D	6 days	spasms not controlled phenobarbitone added
270	7 AM	5	24	48	T	125(125)		D	17 hrs	spasms not controlled
271	5 AF	3	0	19	NF	100(100)		D	15 hrs	spasms not controlled
272	5 AM	5	0	9	NF	100(100)	not done	D	18 hrs	spasms not controlled

TRIAL TWO. NEONATAL PATIENTS — BARBITURATE & CHLORAL HYDRATE TREATED GROUP

Case Number	Age, race and sex	Incubation period (days)	Period of onset (hrs.)	Admission time (hrs.)	Feeding	Phenobarb. sod. (gr.)	Chloral hydrate (gr.)	Autopsy findings	Result	Survival time	
273	6 AF	5	8	19	T	5	10(6)		D	51 hrs	respiratory failure
274	14 AM	12	0	36	T	3	16(6)		D	35 days	ulcer of trachea with respiratory obstruction
275	9 AM	8	9	32	T	4	37(7)		D	11 days	
276	7 AF	6	0	19	T	4	15(6)	Bpn	D	5 days	respiratory failure
277	8 AM	7	11	23	T	3	43(13)	Bpn	D	6 days	respiratory failure
278	10 AF	6	66	4 days	T	3½	58(12)		R		
279	7 AM	6	6	24	T	5½	44(12)		D	6 days	respiratory failure
280	7 AM	6	5	9	T	4	14(8)		D	54 hrs	respiratory failure
281	13 AF	12	0	20	T	3	14(4)		D	9 days	
282	17 AF	8	0	11 days	T	2	2(2)		R		only moderately severe
283	5 AM	4	0	15	T	7	10(8)		D	3 days	respiratory failure
284	5 AM	4	0	27	T	5	6(4)		D	3 days	respiratory failure
285	5 AM	4	0	4	T	5	10(6)	Bpn	D	4 days	respiratory failure chlorprom. added
286	8 AM	7	4	20	T	5	22(10)	Bpn	D	5 days	respiratory failure chlorprom. added
287	7 IF	6	0	5	T	4	12(10)	Not done	D	2½ days	
288	5 AF	5	0	11	NF	5	Nil		D	26 hrs	spasms not controlled
289	6 AM	5	12	24	T	5	2(2)		D	38 hrs	
290	6 AF	15	8	31	T	5	12(8)	Bpn	D	4 days	respiratory failure
291	7 IF	7	6	21	NF	3	Nil		D	10 hrs	spasms not controlled
292	13 AF	?2	0	24	NF	2	Nil	Bpn	D	8 hrs	spasms not controlled

APPENDIX VI

OFF SERIES BEFORE START OF I.P.P.R. (NEONATAL PATIENTS)

(INCLUDING ACETYLPROMAZINE GROUP)

(OFF SERIES) NEONATAL PATIENTS — BARBITURATE CHLORPROMAZINE COMBINATION TREATED GROUP

Case Number	Age, race and sex	Incubation period (days)	Period of onset (hrs.)	Admission time (hrs.)	Feeding	Chlorprom. (mg.)	Phenobarb. sod. (gr.)	Autopsy findings	Result	Survival time	Comment
293	6 AF	5	0	19	T	950(100)	8(3)		R		
294	7 AM	4	24	18	T	250(50)	4(1)		R		
295	6 AM	5	7	19	T	350(75)	7(2½)	Bpn	D	8 days	respiratory failure
296	5 AM	4	6	24	NF	100	4½	Bpn	D	35 hrs	
297	8 AM	7	24	32	T	325(75)	8(2½)		R		only moderately severe
298	7 AM	6	0	24	T	225(75)	5½(2)	Bpn	D	4 days	respiratory failure
299	12 AF	8	0	5 days	T	100(50)	2½(1½)		D	2 days	
300	6 AM	4	0	24	T	25	1	Bpn	D	23 hrs	respiratory failure
301	6 AF	6	4	12	T	250(75)	7(1½)		R		
302	7 AM	6	24	24	T	300(100)	5½(1)	Bpn	D	6 days	respiratory failure
303	5 AF	4	?	?	T	325(75)	12(3)	Not done	D	9 days	respiratory failure
304	6 AM	6	23	10	T	150(25)	3(1)		D	17 days	cause of death unknown
305	4 AM	4	9	12	T	50	1		D	12 hrs	spasms not controlled
306	6 AM	6	0	16	T	125(50)	6(2)	Bpn	D	5 days	respiratory failure
307	9 AF	9	5	9	T	75	2		D	28 hrs	spasms not controlled
308	8 IM	7	0	3½	T	75(50)	2(2)		D	36 hrs	spasms not controlled
309	7 AM	6	12	28	T	100(50)	3(2)		D	7 days	respiratory failure
310	6 AM	5	0	8	T	100(50)	4(2)		D	3 days	
311	12 AF	8	30	3 days	T	50(25)	1(1)		R		only moderately severe
312	5 AM	3	6	21	T	100(75)	3(2)	Not done	D	25 hrs	spasms not controlled

(OFF SERIES) NEONATAL PATIENTS — BARBITURATE CHLORPROMAZINE COMBINATION TREATED GROUP

Case Number	Age, race and sex	Incubation period (days)	Period of onset (hrs.)	Admission time (hrs.)	Feeding	Chlorprom. (mg.)	Phenobarb. sod. (gr.)	Autopsy findings	Result	Survival time	Comment
313	5 AM	5	0	14	T	250(125)	5½(2½)		D	3 days	
314	7 AF	6	0	24	T	325(100)	7½(2½)	Bpn	D	5 days	
315	6 AM	4	15	18	T	300(75)	9(2)		D	26 days	spasms ceased on 10th day; stiff & marasmic. Spasms restarted 24th day. respiratory failure.
316	9 AF	9	18	48	T	150(100)	4(3)	Not done	D	29 hrs	spasms not controlled
317	5 AM	5	0	11	T	200(125)	5(3)		D	40 hrs	spasms not controlled
318	12 AM	6	7	6 days	T	75(25)	2½(1)		R		only moderately severe
319	5 AM	5	2	8	T	250(75)	7(2)		D	3 days	spasms not controlled
320	5 IF	5	?	?	NF	25	1		D	4 hrs	spasms not controlled
321	9 AM	7	23	24	T	100(50)	3(2)		R		only moderately severe
322	7 AM	7	0	?	T	125(75)	4(2)	Bpn	D	16 days	marasmus, Bpn cause of death
323	11 AF	8	24	2 days	NF	200(75)	5½(2)		D	60 hrs	spasms not controlled
324	7 AM	6	20	22	T	275(100)	6½(3)	Bpn	D	64 hrs	
325	6 AM	4	4	40	T	225(125)	5(2)		D	62 hrs	respiratory failure
326	4 AM	3	12	23	T	75(50)	2½(1)		R		only moderately severe
327	6 AM	3	42	58	T	325(125)	7(2½)	Bpn	D	4 days	respiratory failure
328	5 AM	4	?	?	NF	25	1		D	8 hrs	
329	19 AM	14	24	3 days	T	25	½		R		only moderately severe
330	12 IM	7	-	6 days	T	25(12½)	1(½)		R		no reflex spasms
331	10 AF	5	36	?	T	75(50)	1½(1)		R		only moderately severe
332	6 AM	6	0	18	T	350(87½)	8(2)	Bpn	D	8 days	respiratory failure

(OFF SERIES) NEONATAL PATIENTS — BARBITURATE CHLORPROMAZINE COMBINATION TREATED GROUP

Case Number	Age, race and sex	Incubation period (days)	Period of onset (hrs.)	Admission time (hrs.)	Feeding	Chlorprom. (mg.)	Phenobarb. sod. (gr.)	Autopsy findings	Result	Survival time	Comment
333	7 AM	7	7	3	T	162½(75)	5½(2)	Bpn	D	3 days	respiratory failure
334	5 AF	5	0	4	T	100(50)	4(2)		D	50 hrs	spasms not controlled
335	12 AF	10	-	48	T	125(75)	3½(2)		R		no reflex spasms
336	6 AM	6	12	?	NF	87½(50)	2(1)		D	48 hrs	respiratory failure
337	8 AF	5	25	48	T	100(25)	3(1)		R		
338	6 AM	5	0	12	T	237½(62½)	10(3)	Bpn	D	7 days	respiratory failure
339	9 AM	7	0	36	T	50(12½)	½		R		only moderately severe
340	6 AM	6	-	10	T	37(25)	½		R		no reflex spasms
341	6 AM	6	3	8	NF	125(62)	5(2½)		D	44 hrs	spasms not controlled
342	8 AM	7	6	24	NF	112(50)	4(2)		D	70 hrs	respiratory failure
343	7 AM	6	10	24	T	87(50)	3½(2)		D	45 hrs	spasms not controlled
344	6 AF	5	20	24	NF	87(50)	3½(2)	Bpn	D	66 hrs	
345	6 AM	5	2	19	T	137(50)	5(2)	Not done	D	7 days	respiratory failure
346	6 AF	6	6	14	NF	125(62)	5(2½)	Bpn	D	3½ days	spasms not controlled
347	10 AM	8	-	48	T	25(12)	½		R		no reflex spasms
348	8 AM	7	48	24	T	50(25)	½		D	4½ days	aspiration of feed
349	7 AF	6	19	12	T	87(37)	3½(1)		R		
350	4 AF	3	6	16	NF	12	½		D	20 hrs	
351	7 AM	5	6	48 hrs	T i.v.	37(25)	2(1)		R		only moderately severe
352	5 AF	4	2	18	T	125(37)	4(1½)	Bpn	D	7 days	respiratory failure

(OFF SERIES) NEONATAL PATIENTS

BARBITURATE ACETYLPROMAZINE COMBINATION TREATED GROUP

Case Number	Age, race and sex	Incubation period (days)	Period of onset (hrs.)	Admission time (hrs.)	Feeding	Acetylprom. (mg.)	Phenobarb. sod. (gr.)	Autopsy findings	Result	Survival time	Comment
383	8 AF	8	0	16	NF	20	-		D	3½ hrs	spasms not controlled
384	7 AF	5	15	24	NF	125	-		D	21 hrs	spasms not controlled
385	6 AM	6	19	27	NF	40	-		D	7 hrs	spasms not controlled
386	8 IM	6	0	36	T	280(100)	6½(2)		D	4 days	respiratory failure spasms not controlled
387	6 AM	5	0	23	NF	30	2		D	12 hrs	spasms not controlled
388	5 AM	4	0	13	T	185(70)	9(2½)	not done	D	9 days	respiratory failure
389	7 AM	6	8	16	T	145(85)	5(2½)	not done	D	58 hrs	respiratory failure
390	6 AM	5	12	20	T	90(30)	4½(1½)	Bpn	D	7 days	respiratory failure spasms not controlled
391	7 AM	7	2	12	T	40	2½	Bpn	D	56 hrs	respiratory failure
392	9 AM	8	0	16	T	120(30)	5½(1½)		R		
393	7 AF	7	0	9	T	140(30)	7(1½)		D	9 days	respiratory failure
394	7 AM	6	10	28	T	90(20)	5½(1½)		D	8 days	respiratory failure
395	4 AM	4	12	12	T	70(40)	4½(2)		D	48 hrs	spasms not controlled
396	5 AM	5	0	19	NF	20	1½		D	5½ hrs	spasms not controlled
397	5 AF	4	3	12	NF	10	½		D	23 hrs	spasms not controlled
398	8 AM	7	0	22	T	70(30)	4(1½)	not done	D	4 days	respiratory failure
399	7 AM	7	12	24	T	80(20)	3½(1)		D	7 days	respiratory failure
400	6 AM	4	0	48	T	70(20)	3½(1)		D	5 days	respiratory failure
401	7 AM	6	24	36	i.v.	70(20)	3½(1)	Bpn	D	9 days	respiratory failure
402	7 AM	6	12	24	i.v.	100(30)	5(1½)		D	6 days	respiratory failure

(OFF SERIES) NEONATAL PATIENTS

BARBITURATE ACETYLPROMAZINE COMBINATION TREATED GROUP

Case Number	Age, race and sex	Incubation period (days)	Period of onset (hrs.)	Admission time (hrs.)	Feeding	Acetylprom. (mg.)	Phenobarb. sod. (gr.)	Autopsy findings	Result	Survival time	Comment
403	8 AM	6	20	24	i.v.	120(20)	6(1)	Bpn	D	10 days	respiratory failure
404	11 AM	10	6	30	T i.v.	100(20)	4½(1)		R		chest deformity
405	6 AM	5	6	18	i.v.	80(40)	4(2)	Bpn	D	5 days	respiratory failure
406	5 AM	5	4 days	24	T	70(20)	3(½)		R		mild on admission
407	7 AM	6	0	18	T	80(30)	4½(2)		D	4 days	respiratory failure
408	14 AM	11	48	48	BF	20(10)	1½(1)		R		only moderately severe
409	11 AM	10	0	24	T	30(10)	1½(½)		R		only moderately severe
410	8 AF	7	7	24	i.v.	170(30)	8(1½)		D	11 days	respiratory failure
411	10 AM	6	24	4 days	BF	10	1		R		only moderately severe
412	10 AF	9	48	24	T	60(10)	1½(½)		R		
413	10 AF	7	?	3 days	BF	40(20)	1		R		only moderately severe
414	14 AF	11	0	3 days	BF	10	½		R		spasms ceased rapidly
415	5 AF	5	5	13	i.v.	120(30)	5½(1½)	not done	D	8 days	respiratory failure
416	10 IM	9	0	18	T	50(20)	2½(1)		D	6 days	respiratory failure
417	10 AM	9	2	20	i.v.	50(30)	2½(1½)	Bpn	D	2½ days	respiratory failure
418	8 IF	7	13	20	i.v.	60(20)	4(2)	not done	D	4 days	respiratory failure
419	5 AF	4	16	24	NF	20	2		D	28 hrs	spasms not controlled

(OFF SERIES) NEONATAL PATIENTS — MISCELLANEOUS TREATMENT

Case Number	Age, race and sex	Incubation period (days)	Period of onset (hrs.)	Admission time (hrs.)	Feeding	Treatment	Autopsy findings	Result	Survival time	Comment
420	6 AF	5	0	16	NF	A + C + B		D	20 hrs	spasms not controlled
421	8 AM	7	0	?	i.v.	A + C + B	not done	D	11 days	respiratory failure
422	6 AM	6	4	10	NF	A + C + B		D	6 days	respiratory failure
423	7 AM	6	2	21	NF	A + C + B		D	18 hrs	spasms not controlled
424	7 AM	6	0	18	i.v.	A + B	Bpn	D	4½ days	respiratory failure
425	5 AM	4	6	16	T	C + P		D	66 hrs	respiratory failure
426	7 AM	6	1	15	i.v.	C + P		D	4 days	spasms not controlled
427	6 IM	6	0	13	NF	C + P		D	48 hrs	respiratory failure
428	4 IM	4	6	12	i.v.	C + P	Bpn	D	4 days	respiratory failure
429	5 AM	5	9	14	i.v.	C + P	Bpn	D	4 days	respiratory failure
430	5 AM	4	0	11	T	C + P	Bpn	D	4 days	respiratory failure
431	8 AM	7	12	24	NF	C + P		D	48 hrs	spasms not controlled
432	5 AF	5	0	10	T	C + B + T		D	5 days	respiratory failure
433	5 AM	3	0	40	NF	C + B + T		D	9 hrs	spasms not controlled
434	6 AM	5	12	16	NF	C + B + T		D	16 hrs	spasms not controlled
435	7 AF	7	0	17	NF	C + B + T		D	8 hrs	spasms not controlled
436	10 AF	8	-	48	BF	Chloral only		R		no reflex spasms
437	5 AM	5	0	16	NF	-		D		spasms not controlled died on admission
438	16 AF	16	-	?	BF	C		R		no reflex spasms

APPENDIX VII

TRIAL III NEONATAL PATIENTS (TRACHEOTOMY)

TRIAL THREE. NEONATAL PATIENTS — CONSERVATIVE TREATED GROUP

Case Number	Age, race and sex	Incubation period (days)	Period of onset (hrs.)	Admission time (hrs.)	Feeding	Chlorprom. (mg.)	Phenobarb. sod. (gr.)	Autopsy findings	Result	Survival time	Comment
353	9 AF	7	32	48	i.v.	87(50)	3(1½)	Bpn	D	7½	respiratory failure
354	5 AM	4	12	28	i.v.	125(37)	5½(1½)	Bpn	D	8 days	respiratory failure
355	9 AM	6	24	3 days	i.v.	112(37)	5(1½)	Bpn	D	7 days	respiratory failure
356	8 AF	6	15	21	i.v.	212(50)	8(1½)		D	8 days	respiratory failure
357	6 AF	5	0	18	i.v.	200(62)	8(2½)	Bpn	D	6 days	respiratory failure
358	7 AF	7	0	8	NF	37	1½		D	16 hrs	spasms not controlled
359	7 AM	7	0	13	NF	100(62)	4(2½)	Bpn	D	38 hrs	spasms not controlled
360	5 IM	4	0	34	NF	62	3	Bpn	D	50 hrs	respiratory failure
361	9 AM	7	24	48	T	175(37)	7(1½)	Bpn	D	15 days	Bpn cause of death
362	4 AM	3	0	24	T	225(37)	9(1½)	Bpn	D	37 days	Bpn & marasmus cause of death
363	6 AF	4	0	48	T	112(62)	4½(2)	Bpn	D	7 days	respiratory failure
364	8 AM	7	8	18	T i.v.	237(37)	7(1½)	Bpn	D	42 days	Bpn & marasmus cause of death
365	6 AF	4	6	48	NF	25	1		D	3 hrs	spasms not controlled
366	9 IM	9	0	10	i.v.	150(37)	5(1½)	Bpn	D	9 days	respiratory failure
367	7 AM	5	0	24	T i.v.	112(37)	4(1½)	Bpn	D	9 days	respiratory failure
368	12 AF	7	24	5 days	T i.v.	150(37)	5½(1)		D	11 days	cause unknown
369	6 AF	6	8	12	i.v.	112(50)	4½(2)		D	5½ days	respiratory failure

TRIAL THREE. NEONATAL PATIENTS. TRACHEOTOMY TREATED GROUP

case number	age, sex and wt	Anesthesia period (days)	Period of onset (hrs.)	Admission time (hrs.)	Feeding	Chlorpromazine (mg.)	Penicillin, total and (U.)	Autopsy findings	Result	Survival time	
370	9 AF	7	24	40	? i.v.	237(125)	5(2)		D	6 days	
371	7 AF	6	24	26	i.v.	100(75)	3(2)	Bpn	D	64 hrs	respiratory failure
372	5 AM	5	0	7	i.v.	175(75)	6(2½)	Bpn	D	4 days	respiratory failure
373	4 AM	3½	12	15	NF	75	2½	Bpn	D	19 hrs	spasms not controlled
374	5 AF	4½	0	9	NF	37	1½		D	8 hrs	spasms not controlled
375	9 AM	8	12	35	?	75	3	Bpn	D	13 days	Bpn cause of death
376	6 AM	5	0	15	NF	112(62)	4(2)		D	42 hrs	
377	5 AF	5	6	18	?	150(50)	6(2)		D	13 days	cause unknown
378	5 AM	5	0	9	?	187(37)	7(1½)		D	11 days	respiratory failure
379	6 AM	5	0	24	i.v.	125(62)	5(3)		D	46 hrs	spasms not controlled
380	6 AM	5	12	30	NF	75(50)	3(2)		D	32 hrs	spasms not controlled
381	5 IM	4	7	24	NF	87(37)	3½(1)		D	45 hrs	spasms not controlled Infected in hospital
382	6 AF	5	3	18	i.v.	75(37)	3(1½)		D	4½ days	

APPENDIX VIII

TRIAL IV NEONATAL PATIENTS

(INCLUDING OFF SERIES AFTER START OF I.P.P.R.)

"OFF SERIES" NEONATAL PATIENTS TREATED WITH I.P.P.R.

Case No.	Age (days)	Intubation period (days)	I.P.P.R. (days)	Result	Survival time (days)	Comment
495	7	4	28	D	29	Prolonged endotracheal intubation was tried in this infant who died of bronchopneumonia.
496	12	6	13	D	13	The course on I.P.P.R. was satisfactory, but death occurred at night and the cause was unknown. An enlarged liver regressed after using a negative pressure phase.
497	5	4	15	D	25	Gross distortion of the larynx occurred, treatment with I.P.P.R. having been attempted by prolonged endotracheal intubation.
498	7	5	15	D	29	Death occurred from an anoxic episode 4 hours after the tracheotomy tube was removed.
499	4	4	15	R	-	Treatment with I.P.P.R. was uneventful, the tracheotomy tube being removed on the fifty-second day.
500	5	4	13	R	-	Treatment with I.P.P.R. was uneventful but several anoxic episodes occurred during the third week. The tracheotomy tube was removed on the fifty-first day.

Case No. 503 Hosp. No. 22903/59 I.P.P.R. SERIES
Date of Admission: 27.7.59 Date of Death: 1.8.59

Age, race and sex: 11 days. African male.
Incubation period: 8 days.
Period of onset: About 12 hours.
Admission time: 48 hours.

Artificial respiration: This was maintained on a Smith-Clarke respirator.
Inflation pressures - 15 to 30 cm. of water, with a negative phase (-4 to -6 cm. of water)

Curare dosage: 18 mg. intramuscularly total (4½ days)
Maximum daily dose 6 mg.

Weight: 5 lb. 2 ozs. on admission, 5 lb. 15½ ozs. (5th day).

Temperature: 102°F. on admission; fell rapidly to as low as 80°F. terminally.

Survival time: 4½ days

Necropsy: Suppurative bronchopneumonia.

Clinical course: The progress of this infant was never satisfactory. From the start of I.P.P.R. it became cyanosed and had multiple extrasystoles. The cyanotic attacks continued despite high inflation pressures and the administration of oxygen. On the fifth day the abdomen became distended and the liver edge palpable to 4 cm. below the right costal margin.

Comment: Death in this patient appeared to be due to suppurative bronchopneumonia, cyanotic attacks persisting despite high inflation pressures and the administration of oxygen.

Case No. 504 Hosp.No. 23056/59 I.P.P.R. SERIES
Date of Admission: 28.7.59 Date of Death: 4.8.59

Age, race and sex: 8 days. African female.
Incubation period: 6 days.
Period of onset: 4 hours.
Admission time: 48 hours.

Artificial respiration: This was maintained on a Radcliffe Mark V pump.
Inflation pressures - 12 to 15 cm. of water.

Curare dosage: 57 mg. intramuscularly total (6½ days)
Maximum daily dose 9 mg.

Weight: 4 lbs. 15 ozs. on admission, 5 lb. 10½ ozs. (7th day).

Temperature: Fluctuated between 90 and 96°F., falling to 87°F. terminally.

Survival time: 6½ days.

Necropsy: Suppurative bronchopneumonia with acute tracheitis.

Clinical course: On the third day there was mild oedema of the hands and face and the liver edge was palpable 3 cm. below the right costal margin. Progress was satisfactory until the seventh day when pneumonia developed, secretions from the lungs being scanty and bloodstained. A paralytic ileus developed with increasing abdominal distension and death occurred on the eighth day.

Comment: Death in this premature infant treated with I.P.P.R. appeared to be due to bronchopneumonia. Total paralysis was possible on low dosage of curare.

Case No. 505 I.P.P.R. SERIES

Age, race and sex: 6 days. African female.
Incubation period: 5 days.
Period of onset: Nil.
Admission time: 12 hours.

Artificial respiration: This was maintained on a Radcliffe Mark V pump.
Inflation pressures - 14 to 22 cm. of water.

Curare dosage: 213 mg. intramuscularly total (14 days)
Maximum daily dose 24 mg. (6th to 9th day)

Weight: 7 lbs. 4 ozs. (2nd day), 7 lbs. 13½ ozs. (4th day)
7 lbs. 3½ ozs. (10th day).

Temperature: 99°F. on admission. This fell to 86°F. on the third day and then fluctuated between 90 and 96°F., rising to normal on the 9th day.

Survival time: 34 days.

Necropsy: The lungs were atelectatic. The trachea showed acute inflammation at the site of the tracheotomy and the kidneys areas of scarring and fibrosed glomeruli.

Clinical course: Secretions from the lungs were tenacious at first and difficult to aspirate. On the eighth day an X-ray of the chest showed collapse of the right upper lobe. For 3 days the inflation pressures required were high and additional oxygen was necessary to prevent cyanosis. Curare was discontinued at 5.30 a.m. on the fifteenth day and by that afternoon fine fibrillary muscular twitching had developed. The infant was able to breathe spontaneously when disconnected from the pump for increasing periods until the twenty-first day when no further assistance to respiration was necessary. Generalised rigidity and mild reflex spasms returned. Gastro-enteritis developed on the thirty-second day when secretions became extremely tenacious. Death occurred 2 days later.

Comment: This infant died of gastro-enteritis on the thirty-fourth day during convalescence from severe tetanus.

Case No. 506 Hosp.No. 25305/59 I.P.P.R. SERIES
Date of Admission: 30.7.59 Date of Death: 16.8.59.

Age, race and sex: 5 days. African male.
Incubation period: 3 days.
Period of onset: Nil.
Admission time: 48 hours.

Artificial respiration: This was maintained on a Smith-Clarke respirator, with a negative phase (-4 to -6 cm. of water). Inflation pressures - 22 to 25 cm. of water.

Curare dosage: 87 mg. intramuscularly total (13 days)
Maximum daily dose - 9 mg.

Weight: 8 lbs. 13½ ozs. (2nd day), 9 lbs. 1 oz. (8th day), 8 lbs. 4½ ozs. (15th day).

Temperature: This was 104°F. on admission. It fell rapidly to 88°F. and thereafter fluctuated between 85°F. and 95°F. until the tenth day when it returned to normal.

Survival time: 17 days.

Necropsy: This showed an extensive suppurative bronchopneumonia.

Clinical course: The course of this infant treated with I.P.P.R. was characterised by frequent anoxic episodes due to dislodgment of the tracheotomy tube. On the fourth day secretions from the lungs became purulent and tetracycline was substituted for penicillin. Curare was discontinued on the thirteenth day but attempts at spontaneous respiration were inadequate. Muscular twitching and tetanic spasms occurred until death on the eighteenth day.

Comment: Death was associated with suppurative bronchopneumonia in this infant suffering from severe tetanus neonatorum treated with I.P.P.R. The low dosage of curare required to maintain paralysis is of interest.

Case No. 510 Hosp.No. 24181/59 I.P.P.R. SERIES
Date of Admission: 7.8.59 Date of Discharge: 4.12.59

Age, race and sex: 4 days. African female.
Incubation period: 4 days.
Period of onset: Nil.
Admission time: 12 hours.

Artificial respiration: This was maintained on a Radcliffe Mark V pump.
Inflation pressures - 18 to 21 cm. of water.

Curare dosage: 192 mg. intramuscularly total (16 days)
Maximum daily dose 18 mg. (16th day)

Weight: 6 lbs. 10½ ozs. (2nd day), 7 lbs. 4½ ozs. (6th day)
6 lbs. 8 ozs. (10th day).

Temperature: Fluctuated between 88 and 96°F. until the 10th day when it became normal, but a further period of hypothermia occurred between the 12th and 20th days.

Clinical course: This patient had an episode of anoxia three days after starting I.P.P.R. when the tracheotomy tube was dislodged. Oedema of the face was noticed on the fifth day, which became generalised on the following day. Curare was discontinued for eight hours on the fourteenth day with severe muscular twitching so that total paralysis was recommenced. When curare was withheld once more on the seventeenth day severe twitching recurred, but the infant was able to breathe spontaneously for short periods. When rigidity returned a marked deformity of the thoracic cage was noticed with sternal prominence and lateral concavity. Although rigidity was severe with some opisthotonos typical reflex tetanic spasms did not occur. The latex tube was replaced by a size 16 metal tracheotomy tube on the twenty-sixth day when attempts at sucking commenced. Any attempt at removal of the tracheotomy tube resulted in considerable distress with crying, vomiting and, eventually, cyanosis necessitating its replacement. One hundred and forty days after admission the feed was stopped for a few hours, the infant sedated and the tracheotomy tube successfully removed. When seen six weeks after discharge the lateral rectus palsy and the chest deformity had resolved.

Comment: Considerable difficulty was experienced in removing the tracheotomy tube in this, our first case of tetanus neonatorum to recover after treatment with I.P.P.R.

Case No. 514 Hosp.No. 31136/59 I.P.P.R. SERIES
Date of Admission: 6.10.59 Date of Discharge: 27.5.60

Age, race and sex: 6 days. African female.
Incubation period: 5 days.
Period of onset: Nil.
Admission time: 17 hours.

Artificial respiration: This was maintained on a Smith-Clarke respirator until the 5th day.
Inflation pressures - 16 to 20 cm. of water with a negative phase (-4 cm. of water).

Because of a technical fault in this respirator a change was made to a Radcliffe Mark V pump on the 5th day at an initial inflation pressure of 16 cm. of water.

Curare dosage: 312 mg. intramuscularly total
Maximum daily dose 30 mg. (6th, 8th & 11th days)

Weight: 6 lbs. 13½ ozs. (3rd day), 6 lbs. 8 ozs. (7th day)

Temperature: Fluctuated between 93 and 95°F. until the ninth day with a further period of hypothermia between the thirteenth and sixteenth days.

Clinical course: In this infant a tracheotomy was performed soon after the start of I.P.P.R., a large window being made in the trachea because of technical difficulty. The latex tracheotomy tube was displaced during the night with probable anoxia. Mild oedema of the face was noted on the fifth day. Curare was discontinued on the sixteenth day and the infant allowed to breathe spontaneously for short periods nine hours later, respiration being assisted with intermittent inflation with oxygen. The latex tube was replaced by a metal tracheotomy tube on the twenty-fourth day. Rigidity was extreme and uninfluenced by mephenesin given orally. The tracheotomy tube could not be permanently removed, despite repeated attempts, until 227 days after admission. Numerous episodes of pulmonary infection occurred during this period.

Comment: A case of tetanus neonatorum successfully treated with total curarization and I.P.P.R. Difficulty in removing the tracheotomy tube can probably be attributed to the large incision made in the trachea.

Case No. 513 Hosp.No. 31237/59 I.P.P.R. SERIES
Date of Admission: 7.10.59 Date of Death: 10.10.59

Age, race and sex: 6 days. African female.
Incubation period: 5 days
Period of onset: 5 hours.
Admission time: 12 hours.

Artificial respiration: This was maintained on a Radcliffe Mark V pump.
Inflation pressures - 13 to 25 cm. of water.

Curare dosage: 21 mg. intramuscularly total (3 days)
Maximum daily dose 12 mg. (2nd day)

Weight: Not weighed.

Temperature: 99.6°F. on admission, fluctuated between 93° and 97°F. thereafter.

Survival time: 3 days.

Necropsy: This showed a suppurative bronchopneumonia with inflammation of the trachea and larynx. There was a large pneumoperitoneum with bubbles of air in the mesentery.

Clinical course: As a result of faulty adjustment of the thermostat of the humidifier, this infant sustained a burn of the mouth with probable pulmonary damage soon after starting I.P.P.R. When a tracheotomy was performed shortly afterwards laryngoscopy revealed reddening of the larynx and pharynx. During the subsequent course secretions from the lungs were scanty and increasing inflation pressures were required with progressive distension of the abdomen. For a short while before death the lungs were inflated manually with oxygen.

Comment: Probable pulmonary damage as a result of overheating of the humidifier may have predisposed to pneumonia and death in this infant treated with I.P.P.R. It is thought that the pneumoperitoneum was due to the manual inflation used terminally.

Case No. 518 Hosp. No. 33096/59 I.P.P.R. SERIES
Date of Admission: 23.10.59 Date of Death: 21.11.59

Age, race and sex: 5 days. African male.
Incubation period: 4 days.
Period of onset: 4 hours.
Admission time: 24 hours.

Artificial respiration: This was maintained on a Smith-Clarke respirator.
Inflation pressures - 13 to 23 cm. of water, with a negative phase (-4 cm. of water)

Curare dosage: 264 mg. intramuscularly total (18 days)
Maximum daily dose 27 mg. (16th day)

Weight: 5 lbs. ½ oz. on admission, 5 lbs. 12½ ozs. (3rd day)

Temperature: 103°F. on admission, fell to 92°F. on the 2nd day and returned to normal on the 3rd day.

Survival time: 29 days.

Necropsy: Collapse of the left lung but no apparent obstruction in the left main bronchus. The trachea showed an area of necrosis and acute inflammation.

Clinical course: On the third day after the start of I.P.P.R. mild oedema of the face was noted. The course was uneventful, apart from an episode of diarrhoea, and curare was stopped on the eighteenth day. Adequate spontaneous respiration was possible 16 hours later. Rigidity gradually returned with definite, but moderate, tetanic spasms. The infant was able to suck from a Bellcroy feeder on the twenty-sixth day, but suddenly collapsed and died while being fed 4 days later.

Comment: This premature infant had generalized rigidity but no spasms at the time of death, which was probably due to asphyxia.

Case No. 519 Hosp.No. 33318/59 I.P.P.R. SERIES
Date of Admission: 25.10.59 Date of Discharge: 15.12.59

Age, race and sex: 6 days. African female.
Incubation period: 5 days.
Period of onset: 20 hours.
Admission time: 24 hours.

Artificial respiration: This was maintained on a Radcliffe Mark V pump.
Inflation pressures - 12 to 16 cm. of water.

Curare Dosage: 309 mg. intramuscularly total (16 days)
Maximum daily dose 27 mg. (13th day)

Weight: 7 lbs. 3¼ ozs. on admission, 7 lbs. 12¼ ozs. (3rd day)
7 lbs. 7¼ ozs. (9th day)

Temperature: 100°F. on admission. There were no episodes of hypothermia in this infant.

Clinical course: Spasms only became frequent and severe on the morning after admission when I.P.P.R. was instituted. The course was uneventful, mild oedema of the face being noted for the first time on the sixteenth day. Curare was discontinued on the following day with the development of characteristic muscular twitching noted in previous cases. Spontaneous respiration without assistance from the pump was possible on the nineteenth day but periodic episodes of dyspnoea required manual inflation with oxygen. Rigidity increased and mild but definite tetanic spasms occurred. Breast feeding was possible from the twenty-seventh day. There was a steady gain in weight and the tracheotomy tube was removed with unexpected ease on the forty-third day at the first attempt.

Comment: The course of this infant was uneventful apart from some distress while spontaneous respiration was being re-established.

Case No. 520 Hosp. No. 35601/59 I.P.P.R. SERIES
Date of Admission: 13.11.59 Date of Discharge: 23.5.60

Age, race and sex: 6 days. African male.
Incubation period: 5 days.
Period of onset: 15 hours.
Admission time: 24 hours.

Artificial respiration: This was maintained on a Smith-Clarke respirator.
Inflation pressures - 13 to 21 cm. of water with a negative phase (-4 cm. of water)

Curare dosage: 233 mg. intramuscularly total (13 days)
Maximum daily dose 33 mg. (5th and 8th days)

Weight: 6 lbs. 14 ozs. (2nd day), 6 lbs. 9 ozs. (4th day).

Temperature: 100°F. on admission. This fell to 95°F. on the 4th day but had returned to normal by the 7th day.

Clinical course: Spasms were only moderately severe when this infant was admitted late at night. By the following morning they were frequent and severe and I.P.P.R. was instituted. Mild oedema of the face was noted on the third day. The course was uneventful until the eleventh day when a right apical pneumonia, confirmed radiologically, developed. Curare was stopped on the fourteenth day and the infant was completely free of assistance from the respirator on the following day. Severe rigidity with occasional reflex spasms gradually returned and periods of respiratory distress occurred at this stage which required the administration of oxygen. Feeds were stopped for 9 hours on the sixteenth day because of marked abdominal distension and gastric stasis. Considerable difficulty was experienced with removal of the tracheotomy tube. Its permanent removal was not possible until 186 days after admission.

Comment: Removal of the tracheotomy tube was a considerable problem in this infant who recovered after treatment with I.P.P.R.

Case No. 521 Hosp. No. 35687/59 I.P.P.R. SERIES
Date of Admission: 14.11.59 Date of Discharge: 2.1.60

Age, race and sex: 6 days. African female.
Incubation period: 6 days.
Period of onset: Nil.
Admission time: 10 hours.

Artificial respiration: This was maintained on a Radcliffe Mark V pump.
Inflation pressures - 13 to 19 cm. of water.
$PaCO_2$ - 34 to 48 mm. Hg. (isolated readings)

Curare dosage: 342 mg. intramuscularly total (16 days)
Maximum daily dose 36 mg. (6th day)

Weight: 7 lbs. 10 ozs. on admission, 7 lbs. 12½ ozs. (3rd day), 7 lbs. 1½ ozs. (9th day).

Temperature: This ranged from 97 to 100°F.

Clinical course: The tracheotomy tube was dislodged soon after starting I.P.P.R. in this infant, cyanosis and bradycardia occurring. Mild peri-orbital oedema was noted on the third day. Twitching of the muscles was severe despite high doses of curare and was uninfluenced by the administration of 3 cc. calcium gluconate intramuscularly. Curare was discontinued on the seventeenth day and 12 hours later the infant was able to breathe adequately when disconnected from the respirator. The infant was able to take feeds from the breast on the thirtieth day and 4 days later the tracheotomy tube was permanently removed at the first attempt.

Comment: Severe muscular twitching and the high curare dosage used are of interest in this infant who was successfully treated with I.P.P.R.

Case No. 524 Hosp. No. 39919/59 I.P.P.R. SERIES
Date of Admission: 19.12.59 Date of Discharge: 5.2.60

Age, race and sex: 8 days. African female.
Incubation period: 6½ days.
Period of onset: Nil.
Admission time: 30 hours.

Artificial respiration: This was maintained initially on a Smith-Clarke respirator but because of a mechanical fault a change was made to a Radcliffe Mark V pump on the following day. Inflation pressures - 12 to 18 cm. of water.

Curare dosage: 264 mg. intramuscularly total (14 days)
Maximum daily dose 27 mg.

Weight: 6 lbs. 13¾ ozs. (2nd day), 7 lbs. 1¼ ozs. (6th day), 6 lbs. 8 ozs. (11th day).

Temperature: The temperature fell as low as 80°F. on the 2nd day but returned to normal on the 3rd day.

Clinical course: After the start of I.P.P.R. in this infant a tracheotomy was performed with some difficulty. The window cut in the trachea was made too low so that the latex armoured tracheotomy tube tended to slide down the right main bronchus resulting in repeated cyanotic episodes. Because of this hazard curare was discontinued early. With the establishment of spontaneous respiration on the fourteenth day reflex spasms occurred and rigidity was very severe producing a kypho-scoliosis. The tracheotomy tube was removed on the thirty-eighth day when the infant was able to take feeds from the breast.

Comment: A low tracheotomy complicated management in this infant. The tube tended to slip down the right main bronchus producing cyanotic attacks.

Case No. 525 H/No. I.68/60 I.P.P.R. SERIES
Date of Admission: 4.1.60 Date of Discharge: (still in hospital) 31.8.60

Age, race and sex: 5 days. Indian male.
Incubation period: 4 days.
Period of onset: 7 hours.
Admission time: 12 hours.

Artificial respiration: This was maintained on a Smith-Clarke respirator.
Inflation pressures - 16 to 20 cm. of water with a negative phase (-3 cm. of water)
$PaCO_2$ - 26.8 to 54.2 mm. Hg.

Curare dosage: 163 mg. intramuscularly total (14 days)
Maximum daily dose 30 mg. (4th day)

Weight: 7 lbs. 6 ozs. (2nd day), 7 lbs. 11 ozs. (6th day), 7 lbs. 0 ozs. (10th day).

Investigations: Blood urea 44 mg.%

Temperature: 100°F. on admission. There were no episodes of hypothermia.

Clinical course: The course of this infant on treatment with I.P.P.R. was uneventful; neither hepatomegaly nor oedema being noted. A size 1 cut-down latex armoured tracheotomy tube was eventually necessary to prevent leakage of air past the tube. Curare was discontinued on the fifteenth day and the infant was able to breathe spontaneously on the following day with only a short period of assistance from the respirator. Mild reflex spasms and rigidity returned with several episodes of respiratory arrest. A deformity of the sternum with scoliosis and kyphosis was noted with the return of rigidity. Several episodes of pulmonary infection occurred and to date, eight months after admission, all attempts at removal of the tracheotomy tube have been unsuccessful.

Comment: Although this patient made a complete recovery from tetanus neonatorum removal of the tracheotomy tube is still a problem to date. Respiration was assisted intermittently in this patient until the twenty-third day.

Case No. 526 Hosp. No. 3665/60 I.P.P.R. SERIES
Date of Admission: 1.2.60 Date of Discharge: 7.3.60.

Age, race and sex: 6 days. African female.
Incubation period: 5 days.
Period of onset: 46 hours.
Admission time: 20 hours.

Artificial respiration: This was maintained on a Smith-Clarke respirator. Carbon dioxide retention developed at an inflation pressure of 14 cm. of water and when increased to 20 cm. of water $PaCO_2$ values fell from 50.3 to 39.8 mm. Hg. When inflation pressures were reduced to below 18 cm. of water slowing and irregularity of the heart rate were noted.

Curare dosage: 19¼ mg. intramuscularly total (13 days)
Maximum daily dose 21 mg. (7th, 8th and 11th days)

Weight: 6 lbs. 2 ozs. (3rd day), 6 lbs. 6 ozs. (5th day), 5 lbs. 15½ ozs. (13th day).

Investigations: Blood urea ranged from 43 to 68 mg.%.

Temperature: 101.6°F. on admission. This fell to 96°F. on the 3rd day and returned to normal three days later.

Clinical course: This infant had frequent severe reflex spasms with cyanosis and anoxia. I.P.P.R. was instituted and a tracheotomy performed, a vertical incision being made in the trachea. Diarrhoea developed on the sixth day but responded to treatment with erythromycin. Curare was discontinued on the fourteenth day and assisted respiration commenced on the following day when the infant was able to breathe spontaneously. The tracheotomy tube was removed without difficulty on the twenty-third day.

Comment: The tracheotomy tube was removed early in this the first patient in whom a vertical incision in the trachea was used.

Case No. 530 Hosp.No. 5290/60 I.P.P.R. SERIES
Date of Admission: 15.2.60 Date of Discharge: 21.3.60.

Age, race and sex: 7 days. African female.
Incubation period: 6 days.
Period of onset: 3 hours.
Admission time: 16 hours.

Artificial respiration: This was maintained on a Radcliffe Mark V pump.
Inflation pressures - 13 to 19 cm. of water.
$PaCO_2$ - 16.2 to 43.7 mm. Hg.
Assisted respiration - 13th to 17th days.

Curare dosage: 246 mg. intramuscularly total (12 days)
Maximum daily dose 30 mg. (7th day)

Weight: 7 lbs. 9 ozs. (3rd day), 7 lbs. 3½ ozs. (5th day).

Investigations: Electrolytes
serum sodium - 117 mEq/L.
potassium - 5.1 mEq/L. (3rd day)
Blood urea - maximum 55 mg.% (8th day)

Temperature: There was a low grade pyrexia until the fifth week but no episodes of hypothermia.

Clinical course: Mild peri-orbital oedema was noted for the first time on the third day in this infant. Diarrhoea developed on the tenth day but responded to treatment with chloramphenicol. Curare was stopped on the twelfth day and although rigidity became severe reflex tetanic spasms were not observed. A severe anoxic episode, with bradycardia, occurred on the twenty-sixth day because of blockage of the tracheotomy tube. This was successfully removed on the twenty-ninth day and the infant discharged with mild residual rigidity on the thirty-sixth day.

Comment: Despite an episode of anoxia the tracheotomy tube was removed early in this infant treated with I.P.P.R.

Case No. 532 Hosp. No. 7391/60 I.P.P.R. SERIES
Date of Admission: 5.3.60 Date of Discharge: 9.4.60

Age, race and sex: 6 days. African female.
Incubation period: 5 days.
Period of onset: Under 6 hours.
Admission time: 16 hours.

Artificial respiration: This was maintained on a Smith-Clarke respirator.
Inflation pressures - 15 to 25 cm. of water with a negative phase (-2 to -4 cm. of water)
Assisted respiration - 12th to 16th days.
$PaCO_2$ - 18.8 to 47.5 mm. Hg.

Curare dosage: 189 mg. intramuscularly total (12 days)
Maximum daily dose 24 mg. (9th day)

Weight: 4 lbs. 14 ozs. on admission.

Investigations: Blood urea - maximum 35 mg.%.

Temperature: There was a low grade pyrexia until the week before discharge.from hospital.

Clinical course: The course on treatment with I.P.P.R. was uneventful in this infant. Mild periorbital oedema was noted on the second day. Curare was discontinued on the twelfth day with a gradual return of stiffness and definite reflex tetanic spasms. The tracheotomy tube was removed on the twenty-eighth day and the infant discharged on the thirty-fifth day although some residual stiffness remained.

Comment: This premature infant recovered after treatment with I.P.P.R.

Case No. 534 Hosp.No. 8612/60 I.P.P.R. SERIES
Date of Admission: 16.3.60 Date of Death: 29.4.60

Age, race and sex: 5 days. African male.
Incubation period: 4 days.
Period of onset: 2 hours.
Admission time: 17 hours.

Artificial respiration: This was maintained on a Radcliffe Mark V pump.
Inflation pressures - 9 to 15 cm. of water.
$PaCO_2$ - 16.8 to 47.5 mm. Hg.
Assisted respiration - 19th to 35th days.

Curare dosage: 105 mg. intramuscularly total (12 days)
Maximum daily dose 15 mg. (9th day)

Weight: 3 lbs. 8½ ozs. on admission, 4 lbs. 2½ ozs. (3rd day), 5 lbs. shortly before death.

Investigations: Hb 8.5 g.% (13th day) Platelet count 60,000
Blood urea - maximum 41 mg.% (7th day)

Temperature: There were intermittent periods of hypothermia to a minimum of 95°F.

Survival time: 44 days.

Necropsy: This showed collapse of the left lung with multiple fractures of the ribs. Histological examination revealed a squamous metaplasia of the lining epithelium of the main bronchi.

Clinical course: Soon after I.P.P.R. was instituted a tracheotomy was performed with considerable technical difficulty on this premature infant. Generalized oedema was pronounced on the third day but decreased at the end of the first week. Faecal impaction was a feature. Petechiae were noted on the trunk on the thirteenth day and a transfusion of 40 cc. of whole blood given on the following day. Although curare was discontinued on the twelfth day spontaneous respiration was only possible on the nineteenth day and assisted respiration required until the thirty-fifth day. An episode of anoxia occurred on the forty-second day and a similar episode was thought to be the immediate cause of death two days later. Modified reflex tetanic spasms were present until the thirtieth day and rigidity was still present at the time of death.

Comment: This premature infant died during convalescence while still very weak. Inefficient aspiration of secretions from the lungs may have been the immediate cause of death.

Case No. 536 Hosp.No. 9367/60 I.P.P.R. SERIES
Date of Admission: 23.3.60 Date of Discharge: 29.4.60

Age, race and sex: 7 days. African male.
Incubation period: 6 days.
Period of onset: Nil.
Admission time: 18 hours.

Artificial respiration: This was maintained on a Radcliffe Mark V pump.
Inflation pressures - 11 to 20 cm. of water.
$PaCO_2$ - average 25 mm. Hg.
Range - 14 mm. Hg. to 43.2 mm. Hg.
Assisted respiration - 13th to 18th days.

Curare dosage: 243 mg. intramuscularly total (12 days)
Maximum daily dose 27 mg. (5th and 11th days)

Weight: 6 lbs. 7 ozs. (2nd day), 6 lbs. 11½ ozs. (3rd day)

Investigations: Maximum blood urea 65 mg.% (6th day).

Temperature: 99.2°F. on admission. This fell to 96°F. on the 2nd day but soon returned to normal.

Clinical course: On the third day after starting I.P.P.R. in this infant unexplained tachycardia of up to 200 beats per minute developed. The face became oedematous and the liver edge was palpable 3 cm. below the right costal margin on the sixth day. Secretions from the lungs were purulent on the tenth day, the infection responding to treatment with tetracycline. The tracheotomy tube was removed on the twenty-eighth day and sucking commenced on the following day. At the time of discharge 10 days later residual stiffness was still present.

Comment: The clinical course in this infant who recovered was uneventful. The prompt use of tetracycline when secretions became purulent may have prevented the development of pneumonia.

Case No. 537 Hosp.No. 10645/60 I.P.P.R. SERIES
Date of Admission: 5.4.60 Date of Discharge: 27.5.60

Age, race and sex: 4 days. African female.
Incubation period: 4 days.
Period of onset: Nil.
Admission time: 9 hours.

Artificial respiration: This was maintained on a Smith-Clarke respirator.
Inflation pressures - 15 to 20 cm. of water. A negative phase (-4 cm.) was used intermittently.
Pa CO_2 - 18.2 to 42.4 mm. Hg.
Assisted respiration - 14th to 20th days.

Curare dosage: 201 mg. intramuscularly total (15 days)
Maximum daily dose 24 mg. (5th, 6th and 8th days)

Weight: 6 lbs. 10½ ozs. (2nd day), 7 lbs. 5¾ ozs. (7th day), 6 lbs. (14th day).

Investigations: Maximum blood urea - 66 mg.% (4th day).

Temperature: This fluctuated between 96 and 98°F. during the first week, but thereafter there was a low-grade pyrexia.

Clinical course: This infant was having very severe spasms with marked cyanosis and anoxia before I.P.P.R. was instituted shortly after admission. There was a further episode of anoxia before tracheotomy was performed. Severe oedema was observed on the second day and persisted until the seventh day when secretions from the lungs became purulent. Tetracycline was given with a good response. Reflex spasms and rigidity returned 2 days after curare was discontinued. The tracheotomy tube was removed on the thirty-first day and breast feeding was adequate 12 days later.

Comment: Severe anoxia, oedema and a raised blood urea were points of interest in this infant who recovered after treatment with I.P.P.R. The absence of hepatomegaly should be noted.

Case No. 539 Hosp.No. 11088/60 I.P.P.R. SERIES
Date of Admission: 10.4.60 Date of Discharge: 23.5.60

Age, race and sex: 4 days. African male.
Incubation period: 4 days.
Period of onset: 2 hours.
Admission time: 8 hours.

Artificial respiration: This was maintained on a Radcliffe Mark V pump.
Inflation pressures - 10 to 17 cm. of water.
$PaCO_2$ - 21 to 36 mm. Hg.
Assisted respiration - 12th to 16th days.

Curare dosage: Total dose 345 mg. intramuscularly (10 days)
Maximum daily dose 48 mg. (4th, 7th & 8th days)

Weight: 8 lbs. 6 ozs. on admission, 8 lbs. 10½ ozs. (3rd day).

Investigations: Blood urea ranged from 25 to 35 mg.%.

Temperature: Fluctuated between 97 and 99.6°F. during the first week.

Clinical course: When reflex spasms became severe on the day after admission in this infant I.P.P.R. was instituted. Mild oedema occurred during the first week with little change in weight. A pulmonary infection developed on the eighth day and responded rapidly to treatment with chloramphenicol. The tracheotomy tube was removed on the thirty-sixth day and the infant was taking feeds well from the breast although slightly stiff at the time of discharge one week later.

Comment: The course in this infant, who was successfully treated with I.P.P.R., was uneventful.

Case No. 541 Hosp.No. I.2779/60 I.P.P.R. SERIES
Date of Admission: 22.4.60 Date of Death: 10.5.60

Age, race and sex: 4 days. Indian male.
Incubation period: 3½ days.
Period of onset: Nil.
Admission time: 3 hours.

Artificial respiration: This was maintained on a Radcliffe Mark V pump.
Inflation pressures - 12 to 23 cm. of water.
$PaCO_2$ - 17.5 to 34 mm. Hg.

Curare dosage: 135 mg. intramuscularly total (11 days)
Maximum daily dose 18 mg. (10th day)

Weight: 7 lbs. 2 ozs. on admission, 8 lbs. 7 ozs. (7th day), 7 lbs. 8 ozs. (13th day).

Investigations: The blood urea was normal during the first week but rose steadily to 120 mg. on the 18th day.

Temperature: This was subnormal on occasions during the first week, but thereafter the temperature ranged between 100 and 102°F.

Survival time: 18 days.

Necropsy: This showed a marantic thrombosis of the left lateral sinus, cerebral haemorrhage and softening.
Histology: Acute bronchopneumonia. The trachea and main bronchi showed a squamous metaplasia of the surface epithelium with a small area of ulceration of the trachea.

Clinical course: This infant was markedly oedematous during the first week of treatment with I.P.P.R. A bronchopneumonia developed during the second week which failed to respond to treatment with several antibiotics. After curare was discontinued on the eleventh day, muscle tone failed to return and the infant appeared drowsy. A lumbar puncture revealed markedly xanthochromic fluid. Gastro-enteritis and collapse was followed by death on the nineteenth day.

Comment: In this infant with severe tetanus neonatorum death was due to lateral sinus thrombosis, bronchopneumonia and gastro-enteritis.

Case No. 546 Hosp. No. 14681/60 I.P.P.R. SERIES
Date of Admission: 14.5.60 Date of Death: 31.5.60

Age, race and sex: 5 days. African male.
Incubation period: 5 days.
Period of onset: Nil.
Admission time: 14 hours.

Artificial respiration: This was maintained on a Radcliffe Mark V pump.
Inflation pressures - 12 to 17 cm. of water.
$PaCO_2$ - average 28 mm. Hg.

Curare dosage: 195 mg. intramuscularly total (12 days)
Maximum daily dose 21 mg. (4th day)

Weight: 6 lbs. 10 ozs. on admission, 7 lbs. 6½ ozs. (2nd day).

Investigations: Blood urea - this ranged from 22 to 39 mg.%.

Temperature: This was usually normal, but rose to 106°F. on the 15th day.

Survival time: 16 days.

Necropsy: This showed massive collapse of both lungs. Histologically the trachea and main bronchi showed a squamous metaplasia of the surface epithelium.

Clinical course: After the start of I.P.P.R. this infant gained weight but clinically did not appear oedematous. After an uneventful course curare was discontinued on the thirteenth day, but difficulty was experienced in clearing the lungs of secretions on the following day. Two days later the nurse in charge noticed that breathing had stopped and the heart beats were no longer audible. Attempts at resuscitation failed.

Comment: In this, the third infant treated with I.P.P.R. in whom the main bronchi were examined histologically, squamous metaplasia of the lining epithelium was again noted.

Case No. 548 Hosp.No. 15388/60 I.P.P.R. SERIES
Date of Admission: 21.5.60 Date of Discharge: 5.7.60

Age, race and sex: 9 days. African male.
Incubation period: 8 days.
Period of onset: Nil.
Admission time: 10 hours.

Artificial respiration: Initially this was maintained on a Smith-Clarke respirator, but on the third day the infant was transferred to a Radcliffe Mark V pump.
Inflation pressures - 12 to 17 cm. of water.
$PaCO_2$ - 17.8 to 34.2 mm. Hg.

Curare dosage: 168 mg. intramuscularly total (11 days)
Maximum daily dose - 24 mg. (8th day)

Weight: 6 lbs. 2½ ozs. on admission, 7 lbs. 14 ozs. (5th day), 6 lbs. 14 ozs. (12th day).

Investigations: Maximum blood urea 30 mg.%.

Temperature: This was usually normal, the lowest recorded temperature being 95°F. on the fifth day.

Clinical course: Multiple extrasystoles and severe oedema were a feature in this infant during the first week. Curare was discontinued on the eleventh day and this was followed by severe muscular twitching. Respiration was assisted until the twenty-second day because of very severe rigidity and some reflex spasms. The tracheotomy tube was removed on the thirty-second day, two weeks before discharge.

Comment: Characteristic muscular twitching commonly seen in infants earlier in the series were a feature in this patient who recovered after treatment with I.P.P.R.

Case No. 549 Hosp.No. 17305/60 I.P.P.R. SERIES
Date of Admission: 8.6.60 Date of Death: 19.7.60

Age, race and sex: 6 days. African female.
Incubation period: 5 days.
Period of onset: 12 hours.
Admission time: 13 hours.

Artificial respiration: This was maintained on a Radcliffe Mark V pump.
Inflation pressures - 10 to 16 cm. water.
$PaCO_2$ - 22.3 to 41.8 mm. Hg.
Mean - 34.6 mm. Hg.
Assisted respiration - 13th to 21st days.

Curare dosage: 135 mg. intramuscularly total (12 days)
Maximum daily dose - 21 mg. (8th day)

Weight: 4 lbs. 10 ozs., on admission, 5 lbs. 7 ozs. (4th day), 5 lbs. 0 ozs. (10th day).

Investigations: Maximum blood urea 56 mg.% (4th day).

Temperature: Episodes of hypothermia to as low as 94°F. during the first 4 days; thereafter it was normal or slightly elevated.

Survival time: 41 days.

Necropsy: Showed atelectasis and early bronchopneumonic changes on histological examination of the lungs, but no other abnormality.

Clinical course: The course on treatment with I.P.P.R. was satisfactory. Inflation pressures were low throughout. Rigidity returned with mild reflex spasms after curare had been discontinued. Attempts were made to remove the tracheotomy tube on several occasions after the twenty-seventh day, but all were unsuccessful. Early on the forty-second day the baby was found dead with the tracheotomy tube dislodged.

Comment: Failure to secure adequately the tracheotomy tube in this infant was thought to be responsible for its dislodgment. This passed unnoticed at the time and the infant died.

Case No. 550 Hosp.No. I.4136/60 I.P.P.R. SERIES
Date of Admission: 15.6.60 Date of Death: 23.7.60

Age, race and sex: 5 days. Indian male.
Incubation period: 4 days.
Period of onset: 10 hours.
Admission time: 20 hours.

Artificial respiration: Initially this was maintained on a Smith-Clarke respiretor, but a change made to a Radcliffe Mark V pump on the 6th day.
Inflation pressures - 13 to 20 cm. of water.
$PaCO_2$ - 23.2 to 40.3 mm. Hg.
Mean - 31 mm. Hg.

Curare dosage: 156 mg. intramuscularly total (11 days)
Maximum daily dose - 24 mg. (3 days)

Weight: 6 lbs. 9½ ozs. (2nd day), 7 lbs. 5½ ozs. (4th day), 7 lbs. 15 ozs. (10th day), 6 lbs. 7 ozs. (14th day).

Investigations: Blood urea: This ranged from 58 to 84 mg.%.

Temperature: This was normal until the 4th day. Thereafter it was usually elevated.

Survival time: 38 days.

Necropsy: No macroscopic abnormality was noted. Marked squamous metaplasia of the surface epithelium confined to the trachea was the only abnormality found on histological examination.

Clinical course: On the second day oedema and elevation of the blood urea was noted in this infant treated with I.P.P.R. A pulmonary infection developed on the fifth day but appeared to respond to treatment with antibiotics. It was noted that the bladder did not empty well spontaneously from the ninth day. Curare was discontinued on the twelfth day but there was no return of muscle tone, the infant remaining totally paralysed. There were bizarre ocular and facial movements and all reflexes were absent. A lumbar puncture on the fourteenth day was normal. Although some attempts at respiration were made the infant remained in a state of total flaccidity of all muscles until death on the thirty-ninth day.

Comment: No abnormality could be found at necropsy to account for the flaccid paralysis in this infant who died despite treatment with I.P.P.R.

RESULTS IN 56 CVP SERIES NEONATAL PATIENTS AFTER START OF I.P.P.R.

		Mean	Range
Age (days)		7.7	3 - 23
Sex	Male	23	
	Female	33	
Race	African	51	
	Indian	5	
Incubation period (days)		6.2	3 - 12
Period of onset (hours)		18.9	0 - 96
Admission time (hours)		27.1	8 hrs. - 4 days
Result	Deaths	41	
	Recoveries	15	
Survival time (days)		4.8	1 hr. - 18 days

TETANUS NEONATORUM*

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Despite the high incidence of tetanus neonatorum in South Africa a large series of cases has not been recorded. Friedlander,[1] and Klenerman and Scragg,[2] drew attention to the frequency of the condition in Durban, and there have also been reports from the other large centres.[3-5] During the 3-year period May 1956 to April 1959, 246 cases of tetanus neonatorum were admitted to King Edward VIII Hospital, Durban. Of these, 217, admitted to a special tetanus unit, are the subject of this report.

Race, sex and age. The average age on admission was 7 days. There were 198 African and 19 Indian infants, a ratio of approximately 10 to 1, and males outnumbered females by 129 to 89. The seasonal incidence was not striking, though there was a slight increase during the summer months.

Infection. The organism was rarely isolated, but the umbilicus was always presumed to be the source of infection, though in a few instances it did not appear septic.

Clinical features. The appearance of an established case is unmistakable. The face is pursed up in risus sardonicus and the limbs are partly flexed and stiff, with fists clenched around the thumb and toes plantar-flexed. There is usually some degree of opisthotonus and characteristically stiffness of the abdominal muscles. By placing one hand on the infant's abdomen and the other over the spinal muscles we have found the simultaneous contraction of these antagonistic muscle groups to be a sign pathognomonic of reflex tetanic spasms.

Diagnosis. This picture is so characteristic that we agree with Jelliffe[6] that there is no valid differential diagnosis, and differentiation from conditions causing convulsions in the neonatal period is easy. Some difficulty may occur in the minority of patients (7% in this series) who are not having typical reflex spasms when first seen. Infants suffering from meningitis, birth trauma or sclerema have shown sufficient resemblance to tetanus to be admitted with this diagnosis. Necropsies were performed in all deaths and in none of them was the clinical diagnosis of tetanus disproved.

Treatment. The general principles of treatment remained constant throughout the series. One hour after sedation a single dose of 50,000 international units (i.u.) of antitetanus serum was given intramuscularly. Benethamine penicillin, 300,000 i.u., was injected by the same route and repeated every third day unless signs of pneumonia supervened, when soluble penicillin or a broad-spectrum antibiotic was substituted. Local treatment of the umbilicus was restricted to cleaning with hydrogen peroxide and the application of merthiolate.

Feeding. When spasms had been reasonably well controlled, an intragastric rubber or polyethylene tube was passed by the nasal or oral route and feeds of expressed breast milk given. However, because poor absorption and aspiration of feeds occurred quite commonly, intravenous feeding by intermittent scalp-vein infusion has been recently attempted in a few infants. Most of these were hypothermic and their fluid requirements low, so that overhydration with the development of oedema was a constant danger. Difficulty in providing adequate nutrition during the stage of reflex spasms and rigidity resulted in death from marasmus and bronchopneumonia as late as the 5th or 6th week.

Sedation. Chlorpromazine has been compared with barbiturates and a mixture of barbiturate and chloral hydrate in two random trials which have been reported elsewhere.[7,8] Chlorpromazine (or acetylpromazine, another phenothiazine derivative) was used in combination with a barbiturate in a large number of cases in an attempt to reduce the toxic effects of both drugs. Table I shows the various combinations and the dosage of the drugs used. When once spasms had been controlled, particularly in the phenothiazine-barbiturate groups, the dosage required was usually at the minimum of the daily range.

TABLE I. DRUG COMBINATIONS AND DOSAGES USED

Drug	*Size of Dose (mg. intramuscularly)*	*Daily Range (mg.)*
Chlorpromazine ..	25	100—200
Phenobarb. sod. ..	60	60—300
Phenobarb. sod.* + chloral hydrate..	120 orally	240—720
Phenobarb. sod. .. + chlorpromazine	30—60 12½—25	30—180 12½—100
Phenobarb. sod. .. + acetylpromazine	30—60 5—10	30—180 5— 40

*300 mg. (intramuscularly) maximum for 1st 24 hours.

Tracheotomy. Tracheotomy was performed on 17 patients, 13 of whom were compared in a random clinical trial with a conservative method, a mixture of chlorpromazine and barbiturate for sedation being used in both groups.

DISCUSSION

Incidence. It is difficult to compare accurately the incidence of tetanus neonatorum in Durban and district with that elsewhere. Table II has been constructed from reports in the literature to emphasize the alarmingly high incidence at Durban. Table III shows the figures for the past year for neonatal deaths in King Edward VIII Hospital, Durban, indicating that tetanus is one of the major killers. Because of the rapid period of onset and early death if spasms are uncontrolled, it is likely that many more infants die before reaching hospital.

TABLE II. INCIDENCE OF TETANUS NEONATORUM

Area	*Period under Review*	*No. of Deaths or Cases*
Great Britain[9] ..	1938—47	36 deaths
United States[10] ..	1951—55	370 deaths
Singapore[11]	1946—50	254 cases
Ibadan[12]	1953—56	141 cases
Durban	1956—59	246 cases

Aetiological factors. Though no specific custom or method of delivery can be incriminated, about a third of the mothers gave a history of the application to the umbilicus of a 'black powder' obtained from a witch-doctor, and in a few cases *Clostridium tetani* has been cultured from this substance. Confinement on a mat in a hut or shack with an earthen floor, and the use of an unsterilized razor blade, pair of scissors or sharp reed for cutting the cord, has not surprisingly resulted in umbilical sepsis. However, quite frequently the

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TABLE III. NEONATAL DEATHS AT KING EDWARD VIII HOSPITAL FOR THE YEAR ENDED 30 JUNE 1959

		%
Prematurity	167	26·2
Tetanus	90	14·2
Asphyxia neonatorum and atelectasis	87	13·2
Bronchopneumonia	79	12·4
Gastro-enteritis	72	11·3
Miscellaneous	61	9·6
Haemorrhagic disorders	49	7·7
Cerebral haemorrhage	18	2·8
Meningitis and septicaemia	12	1·9
Total	635	

delivery took place in a location or domestic servant's quarters, and some of the mothers, occasionally with teaching or nursing experience, had obviously made some attempt at an hygienic confinement, or had even been delivered in hospital.

Prognostic criteria and criteria of severity. Spivey *et al.*[13] have used a 7-day incubation period as the critical level for prognosis. In the present series only 7% of deaths had an incubation period greater than 7 days and only 8% a period of onset of more than 24 hours. While a short incubation period and a short period of onset usually indicate a poor prognosis, as many as 24% of the recoveries had an incubation period of less than 6 days, and 30% a period of onset of under 6 hours. The most useful prognostic sign is the severity of reflex spasms on admission; only 1 of 64 cases in which they were *spontaneous* recovered, whereas 12 of the 15 infants who were not having typical spasms on admission survived. In 8 of these, reflex spasms as described above were never observed, but stiffness and facies were so typical that they are classed in a small group corresponding to mild tetanus in non-neonatal patients. The existence of this type of case, as well as another small group in whom spasms were only moderately severe, though together comprising less than 10% of the series, nevertheless emphasize the need to randomize when comparing different treatment groups.

Complications and mechanism of death. We have found considerable difficulty in deciding on the exact cause of death in the majority of cases. In general terms there would appear to be 4 groups, viz:

1. Uncontrolled spasms, usually in those dying within the first 48 hours, anoxia and exhaustion being largely responsible.
2. Respiratory failure, occurring between the 3rd day and the end of the 2nd week; the action of the toxin on the medullary centres, over-sedation and pulmonary infection and atelectasis being factors in its causation.
3. Marasmus with terminal bronchopneumonia between the 3rd and 8th weeks.
4. A miscellaneous group including tracheo-oesophageal fistula from prolonged tube feeding, neonatal peritonitis and aspiration of feeds.

Necropsies on those dying early usually show acute congestion of the lungs and liver with intra-alveolar haemorrhages and cerebral oedema. Histological evidence of bronchopneumonia was present in 37% of deaths, its incidence being directly proportional to the survival time. Two of the infants who recovered showed radiological evidence of compression of the mid-thoracic vertebrae.

Comparison of sedatives used. Table IV shows the mortality, and the average survival time, in those dying within 14 days in the different treatment groups. Experimentally the phenothiazine derivatives have been shown by Laurence and Webster[14] to have a potent antitetanic action in animals, and this has been confirmed clinically in non-neonatal tetanus.[7,8]

TABLE IV. COMPARISON OF DIFFERENT TREATMENT GROUPS

No. of Cases	*Treatment*	*Percentage Mortality*	*Survival Time* (days)*
17	Barbiturate	72	2·2
34	Chlorpromazine	94	2·0
20	Barbiturate + chloral hydrate	90	3·8
77	Chlorpromazine + barbiturate	76	4·0
34	Acetylpromazine + barbiturate	74	5·2
17	Tracheotomy	100	4·1
18	Miscellaneous	92	
217	(Recoveries 38)	82·5	

* Average survival time in deaths under 14 days.

In two clinical trials in the present series phenothiazine derivatives used alone have not been effective in controlling reflex spasms in 75% of cases, even if given in large doses, and the mortality has been high and the survival time short. In this respect we have not been able to confirm the findings of other workers.[15,16] When they have been combined with barbiturates, spasms have been controlled in all but 30% of cases, with some reduction in mortality, but in general death from uncontrolled spasms within the first 48 hours has been replaced by death from respiratory failure a few days later. In Table V our average mortality throughout the series is compared with that in other large series published recently. With one surprising exception,[20] in which full details of cases are not given, the similarity of the results with different conservative methods of treatment suggests that there is little to choose between the sedatives used.

TABLE V. COMPARISON OF MORTALITY WITH THAT IN OTHER LARGE SERIES

Series	*No. of Cases*	*Sedative used*	*Percentage Mortality*
Present series	217	acetylpromazine chlorpromazine barbiturate etc.	82·5
Jelliff *et al.*[17]	26	barbiturate	96
Spivey[13]	25	paraldehyde chloral hydrate	77
Loh Siew Gek[11]	174	paraldehyde chloral hydrate	92
Sarrouy *et al.*[18]	20	chlorpromazine barbiturate relaxant	80
Pinheiro[19]	256	barbiturate chloral hydrate myanesin	84
Tompkins[12]	141	paraldehyde chloral hydrate barbiturate	89·6
Earle *et al.*[20]	32	barbiturate chlorpromazine	25

In an attempt to reduce the mortality from respiratory failure, a random trial was conducted to assess the value of tracheotomy in preventing pneumonia and anoxia. The sedative used was a barbiturate-chlorpromazine combination and tracheotomy was performed under local anaesthesia, a metal tube being inserted through a window cut in the trachea. Oxygen was administered when required by means of a funnel or catheter but without artificial respiration or humidification of the inspired air. Only very severe cases were selected for

trial. Though the mortality was 100% in both groups, the survival time in the conservatively treated group was longer than in those on whom tracheotomy was performed, two cases in the former dying of late complications at 42 and 37 days respectively. It is apparent that some form of assisted respiration is necessary in the treatment or prevention of respiratory failure, and a trial is now in progress of total curarization, tracheotomy, and intermittent positive-pressure respiration. The constant medical and nursing attention required may alone be an important factor in reducing mortality, making it essential to randomize when assessing the value of this form of treatment. While our own and other preliminary findings[5] indicate a striking increase in survival time, care should be taken in confining such a radical procedure to severe cases; even if it is shown to be effective its use on a large scale will be limited by the expense and the need for specially trained personnel.

Preventive treatment. The only practical method of reducing the high death rate from this disease lies in its prevention. While this can only come with radical changes in the educational and socio-economic status of our African and Indian populations, a few measures may be advocated under present circumstances. A campaign by the local authorities should be directed against the current tribal customs of applying foreign material to the cord, and advice given on simple methods of hygiene at the time of delivery. Active immunization of mothers during pregnancy in an attempt to produce protective antibody levels in their newborn infants has been suggested,[21] and transplacental transmission has been demonstrated experimentally.[22] At least 2 inoculations are given at an interval of 6 weeks during pregnancy. Mothers delivered in hospital should be carefully instructed in the care of the cord; the development of tetanus in hospital-born infants who are discharged prematurely has been well documented,[10,13] and has occurred in this series. Lastly, in view of the high incidence and appalling mortality from the disease, it may well be that the administration of prophylactic tetanus antitoxin, which has become a routine in the treatment of surgical wounds, is as strongly indicated in newborn infants at risk in areas where tetanus neonatorum is endemic.

SUMMARY

Over 200 cases of neonatal tetanus have been admitted to a special unit of the Department of Medicine, King Edward VIII Hospital, Durban, during a 3-year period. The alarmingly high incidence of the disease in the area is emphasized, and possible aetiological factors mentioned. The diagnosis, clinical features, prognostic criteria and mechanism of death in these cases are discussed. Various forms of therapy are described, some of which were investigated in randomized clinical trials, and the value of phenothiazine derivatives and other drugs in the suppression of tetanic spasms compared. The literature is briefly reviewed and the problems of therapy discussed, with special reference to the control of reflex spasms and the treatment and prevention of respiratory failure.

In view of the high mortality, public-health measures are urged in an attempt to prevent the disease.

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TETANUS NEONATORUM

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TREATMENT OF TETANUS WITH ACETYLPROMAZINE

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In recent years there have been several reports of the use of chlorpromazine in the treatment of tetanus (ANDERSEN et al., 1955 ; BODMAN et al., 1955 ; GELFAND, 1955, 1957 ; COLE and ROBERTSON, 1955 ; KELLY and LAURENCE, 1956 ; PACKARD et al., 1958) and experience in this department in two clinical trials has confirmed its value (LAURENCE et al., 1958 ; ADAMS et al., 1959). The mortality rate among severe cases has remained high, however, and reflex spasms were not always controlled, particularly in the neonatal age-group.

By comparing the anti-tetanic effect of various drugs on local tetanus in rabbits, LAURENCE and WEBSTER (1958) showed that acetylpromazine has 10 times the activity of chlorpromazine and is much more potent than thiopentone or mephenesin. Its chief use to date has been in psychiatric disorders. This paper records the results of a clinical trial of acetylpromazine on 8 non-neonatal and 25 neonatal patients suffering from severe tetanus. They formed part of a group who had refused tracheotomy in another clinical trial (to be reported later), the object of which is to assess the place of this procedure in the treatment of tetanus.

The general management of all cases was similar to that adopted in previous series, dosages of anti-tetanus serum and prophylactic penicillin being similarly standardized.

Control of reflex spasms

Non-neonatal cases. On admission 10-50 mg. acetylpromazine was given intramuscularly, depending on the age of patient and the frequency and severity of spasms. Thereafter 20-25 mg. were usually given at 4- or 6-hourly intervals, but sometimes a higher dosage was necessary or phenobarbitone was added to control the spasms.

Case 1. This Indian female aged 16 years had an incubation period of about 21 days and a period of onset of reflex spasms (the " period of onset ") of less than 60 hours. She was having frequent severe spasms when disturbed, with marked trismus and rigidity of abdominal and spinal muscles. Fifty mg. acetylpromazine given intramuscularly produced prompt relaxation and almost complete disappearance of spasms. Good control of spasms and rigidity was achieved with 25 mg. at 6- or 8-hourly intervals, and recovery was complete. The total dosage was 575 mg. given over a period of 8 days, with a daily maximum of 100 mg.

Case 2. There was no history of injury in this African male aged 19 years, but the period of onset was short (36 hours). On admission frequent severe spasms were observed to occur spontaneously and when he was disturbed, and as much as 70 mg. 4-hourly was needed for control (4th day). The patient remained mentally alert and sufficiently relaxed to take fluids orally until the 7th day (after a

* I wish to thank Professor E. B. Adams for his encouragement and advice, Dr. D. R. Laurence who suggested using acetylpromazine and Benger Laboratories Ltd. for supplies of the drug ; Dr. N. M. Mann for his assistance, and Dr. S. Disler, medical superintendent, and members of the nursing staff of King Edward VIII Hospital, for their co-operation.

total dosage of 2140 mg.) when he became confused and hallucinated and developed incontinence of urine and faeces. Acetylpromazine was discontinued, but since spasms increased in frequency and severity and swallowing became difficult, chlorpromazine in combination with phenobarbitone was substituted 48 hours later with a favourable outcome.

Case 3. The incubation period was 13 days, and the period of onset 42 hours, in this 18-year old African male. There was marked rigidity and he had severe spasms when disturbed, but by the 4th day both had almost disappeared on 25 mg. acetylpromazine 4-hourly. On the 7th day when the dose was reduced stiffness returned, followed a few hours later by reflex spasms, but these were controlled on resuming the original dosage. A total of 1205 mg. of the drug was given over 12 days without any side-effects, and the patient recovered.

Case 4. This African male, aged 15 years, gave no history of injury. The period of onset was 72 hours. Frequent severe reflex spasms were easily controlled and relaxation was good on 20 mg. acetylpromazine 6-hourly. Oral chlorpromazine and phenobarbitone sodium had to be substituted on the 7th day because all available supplies of the drug had been used. Spasms and stiffness increased in severity over the following 48 hours, and chlorpromazine had to be given by the intramuscular route to achieve control, recovery being complete.

Case 5. There was no history of injury in this African male, aged 4 years ; the period of onset was less than 12 hours. Opisthotonus was severe with frequent tetanic spasms. Acetylpromazine 20 mg. 4-hourly with added phenobarbitone sodium 90 mg. 8-hourly did not control spasms adequately, and the patient died 32 hours after admission.

Case 6. This African male, aged 9 years, had an incubation period of 10 days and a period of onset of 48 hours. When first examined he had stiffness of abdominal and spinal muscles, relatively mild reflex spasms and bilateral bronchopneumonia. There was rapid progression, spasms and opisthotonus becoming severe, and he died 38 hours after admission, a total dose of 95 mg. acetylpromazine and 270 mg. phenobarbitone sodium having been given. The terminal picture was one of respiratory failure and opisthotonus, spasms being relatively well controlled.

Case 7. The incubation period was 7 days, and the period of onset under 12 hours in this African male, aged 6 years. On admission he had trismus, opisthotonus and reflex tetanic spasms with bilateral bronchopneumonia. Spasms rapidly increased in frequency and severity and respiratory distress became marked. Control of spasms was poor on a total dose of 150 mg. acetylpromazine and 400 mg. phenobarbitone sodium, and death occurred 39 hours after admission.

Case 8. This Indian female, aged 12 years, had a long incubation period (27 days) and a long period of onset (72 hours). There was good relaxation and control of spasms after the initial dose of 20 mg. acetylpromazine and fluids were taken well orally. By the 8th day spasms had disappeared. The drug was withheld for a period of 18 hours with marked increase in stiffness, inability to take fluids orally and the development of severe reflex spasms. On restarting acetylpromazine, control was rapidly achieved and a full recovery made, after a total of 690 mg. in 13 days with a maximum daily dose of 80 mg.

Neonatal Cases. All were severe and had typical reflex tetanic spasms. The average incubation period was 6 days, with a range of 4-10 days and the period of onset 24 hours or less in all but one case.

Initially acetylpromazine was used alone in three very severe cases, and although given in high dosage of up to 125 mg. daily, intramuscularly in one case, it failed to control spasms and all died within 24 hours.

In view of the known potentiation of barbiturates by phenothiazine derivatives and the confirmation of this action in tetanus in our previous trials, it was decided to combine phenobarbitone sodium in doses of 30 mg. with 10 mg. acetylpromazine. This combination was required 2 to 4 times daily while spasms were severe, but usually only once a day or even on alternate days after control had been achieved. Of the 22 infants so treated, three recovered and the average survival time of the remainder was 5 days. In a few of these, death occurred early as a result of uncontrolled spasms. In the others the clinical course followed a remarkably constant pattern. Relaxation and control of spasms was usually accomplished within 48 hours. Thereafter there was a period of good control of spasms lasting 2 to 5 days when little sedation was required. Apnoeic attacks, if they occurred, responded to resuscitation. In the terminal stage, sometimes lasting for several days, the infant was cold and flaccid, taking only occasional gasps, death being due to respiratory failure.

Discussion

Although it is encouraging that five of the eight non-neonatal patients recovered, no claims of the efficacy of acetylpromazine are made on the basis of mortality rate. The series is small and although all were considered severe because they were having frequent generalized reflex spasms, it should be noted that in three of the five recoveries the period of onset was over 48 hours and the prognosis therefore relatively good (Cole, 1940 ; Adams, 1958). On clinical grounds, however, there was little doubt of the value of acetylpromazine in suppressing tetanic spasms and abolishing muscular rigidity. In fact, in Cases 3 and 8, marked stiffness and reflex spasms returned on stopping or reducing the dose of the drug. Particularly impressive was the ease with which these patients with severe tetanus were able to take fluids orally, neither tube nor intravenous feeding being required in those who recovered. It is probable that the toxic effects encountered in one patient (Case 2) could have been avoided had barbiturates been given in addition from the commencement of treatment, thus reducing the necessity for such a high dose of acetylpromazine. The only other side-effects noted were a fall of 20 mm. of mercury in the blood pressure and a slight tachycardia ; neither of which produced symptoms.

Assessment of the relative values of acetylpromazine and chlorpromazine in the treatment of non-neonatal tetanus is difficult. Although both are useful drugs experimental evidence of the greater potency of acetylpromazine has been confirmed. In the previous series an adult who had typical moderately severe tetanus received a daily total of 400 to 900 mg. chlorpromazine intramuscularly, whereas cases of comparable severity described here required only 40 to 200 mg. acetylpromazine for control, which would suggest that it has 5 to 10 times the anti-tetanic effect of chlorpromazine.

In neonatal patients the low rate of recovery is similar to that found in most large series. It was possibly adversely affected by selection on the basis of severity. When used alone in three cases acetylpromazine was ineffective in controlling spasms, confirming our previous experience with chlorpromazine in tetanus neonatorum, but the combination with barbiturate was effective, and in the majority of cases control was possible. It cannot be denied that this may only have been achieved at the expense of subsequent drug-induced respiratory failure. Since phenothiazine derivatives do not effect respiration and only small doses of barbiturates were used, it appears more likely that once control of spasms has been achieved these infants die later of tetanus intoxication of the medullary centres. It is here that conservative treatment has its limitations, and trials with neuromuscular block and intermittent positive pressure respiration are planned to prevent and treat the respiratory failure, whatever the cause.

Summary

1) A phenothiazine derivative, acetylpromazine, has been used in eight non-neonatal and 25 neonatal cases of severe tetanus, either alone or in combination with phenobarbitone sodium.

2) It has been shown to be effective in reducing muscular rigidity and controlling reflex spasms, and experimental evidence of greater potency than chlorpromazine has been confirmed.

3) The limitations of this type of therapy in very severe cases with respiratory failure are emphasized.

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TREATMENT OF TETANUS WITH CHLORPROMAZINE AND BARBITURATES

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THIS paper records the results of a clinical trial on 96 patients with tetanus in which chlorpromazine was compared with a combination of chlorpromazine and barbiturates in 56 non-neonatal cases, and with a combination of barbiturates (for the first twenty-four hours only) and chloral hydrate in 40 neonates. The results of treatment in 57 subsequent cases of tetanus neonatorum are also briefly reported.

In a previous trial we allotted 75 patients at random to two treatment groups, using either chlorpromazine or barbiturates to control reflex spasms (Laurence et al. 1958). We showed that there was no significant difference in the outcome between the two groups, but we found chlorpromazine easier to manage. Because large doses of both drugs were sometimes required to control spasms and toxic effects were encountered, we limited the doses of the drugs used in our second trial and made use of the potentiating effect of chlorpromazine on barbiturates. The design of this second trial was the same as that of the first, and feeding, nursing procedures, and treatment with

anti-tetanus serum and with prophylactic penicillin were similarly standardised, but different drug dosages and combinations were used.

Drugs Used to Control Spasms

Non-neonatal Patients

Such patients in the chlorpromazine group received 100 mg. intramuscularly on admission, with subsequent four-hourly doses of 100–200 mg. according to the severity, a limit of 1000 mg. being set for any twenty-four-hour period. Smaller doses were used for those under 10 years of age. Only 3 patients needed more than 600 mg. in any one day, and control of spasms was not difficult.

Every patient in the group treated with the combination of chlorpromazine and barbiturates was given 50 mg. chlorpromazine and 200 mg. phenobarbitone intramuscularly on admission. Thereafter chlorpromazine dosage was fixed at 50 mg. four-hourly, additional sedation being achieved with phenobarbitone sodium as required. Control was usually good and easily effected by this combination, although the daily maximum of 300 mg. chlorpromazine was exceeded in 1 case. Only 3 patients required more than 1·0 g. phenobarbitone sodium in addition to 300 mg. chlorpromazine in any one day.

Occasionally sedation was required urgently. For this purpose in the chlorpromazine group 100 mg. was given intravenously, while intramuscular or intravenous amylobarbitone sodium 0·25–1·0 g. was used in the group treated with the combination of chlorpromazine and phenobarbitone.

Neonatal Patients

Neonates treated with chlorpromazine were given 25 mg. intramuscularly on admission, and thereafter the same dose not more frequently than four-hourly. Control of spasms was often poor on the maximum daily dose of 150 mg. 1 infant needed as much as 200 mg. chlorpromazine, and another 60 mg. phenobarbitone sodium in addition to 150 mg. chlorpromazine to control the spasms.

Those in the barbiturate-chloral group were treated in the first twenty-four hours only with phenobarbitone sodium in 60 mg. doses intramuscularly, up to a maximum of five doses, the aim being to achieve sedation rapidly to facilitate the passage of a stomach-tube. After that no further phenobarbitone was given and control was main-

tained with chloral hydrate in 120 mg. doses given not more frequently than four-hourly by the stomach-tube left in situ. Spasms were poorly controlled in 4 patients, of whom 3 needed additional sedation with phenobarbitone in the first twenty-four hours, and the 4th 50 mg. chlorpromazine to facilitate the passing of the stomach-tube.

Results

As regards severity, our cases were classified as before—" mild " when there was rigidity but no reflex spasms, " moderate " when there were reflex spasms which were either mild or infrequent, and " severe " when frequent severe reflex spasms were present. The main points of difference between cases of tetanus are found in the incubation period, the period of onset of reflex spasms, the age of the patient, and the site of the wound. All of these factors affect the outcome of treatment, and we have listed them in table I, in which the groups are compared.

Analysis of the results in non-neonatal patients shows no statistically significant difference in the outcome between treatment with chlorpromazine and with the mixture of chlorpromazine and barbiturates (overall mortality-rates 52% and 33%, and mortality-rates among severe cases 63% and 50% respectively), and there are no significant differences betwen the two neonatal treatment

TABLE I—COMPARISON OF GROUPS

—	Non-neonates		Neonates	
	Chlor-promazine	Chlor-promazine/ barbiturate combination	Chlor-promazine	Barbiturate/ chloral-hydrate combination
No. of cases ..	29	27	20	20
Average age	13 yr.	21 yr.	5·7 days	7·7 days
Severity:				
Severe	24	16	20	19
Moderate	4	7	0	1
Mild	1	4	0	0
Site of wound:			All umbilicus	
Leg	16	7		
Arm	0	3		
Trunk	1	0		
Head	1	2		
Uterus	1	3		
Multiple	5	3		
No wound ..	5	9		
Av. incubation period (days)	13	11	5·2	6·8
Av. period of onset (hr.)	36	65	6·8	6·8
Deaths:				
Among all cases ..	15 (*52%*)	9 (*33%*)	19 (*95%*)	18 (*90%*)
Among severe cases	15 (*63%*)	8 (*50%*)	19 (*95%*)	18 (*95%*)

groups (overall mortality-rates 95% and 90%, mortality-rates among severe cases 95% and 95%).

Causes of Death

In the non-neonatal series there was clinical evidence of respiratory embarrassment other than that due to pneumonia in 12 patients (21%), 10 of whom died. 5 patients had laryngeal spasms, 3 in the chlorpromazine group. Prompt administration of intravenous chlorpromazine was effective in all 5, but 3 died later. Other evidence of respiratory embarrassment was observed in 8 patients, none of whom survived; 4 were in each treatment group, and 1 had previously had laryngeal spasms. In 4 patients severe or continuous spasms were followed by gasping respiration or by apnœa without definite evidence of laryngeal spasms. There was respiratory obstruction on two successive days in another patient owing to the tongue falling back, and for this reason tracheotomy was performed—the only instance in the whole series. This patient subsequently died after a period of continuous spasms and shallow breathing. In the remaining 3 patients there were either irregular gasping respirations or abrupt cessation of breathing which did not follow repeated spasms.

Evidence of respiratory embarrassment was observed in 13 neonates (33%), all of whom died. Most often there was irregular gasping, and the infants were commonly cold and flaccid as well. Cyanotic attacks also occurred following apnœa rather than laryngeal spasms. Overdosage cannot be excluded as a cause of death in these neonates, but we think it more likely that in the majority death was due to tetanus intoxication of the medullary centres.

Contusion of the brain under a fracture may have con-

TABLE II—SUMMARY OF PULMONARY COMPLICATIONS (NECROPSY MATERIAL)

—	Non-neonates		Neonates	
	Chlorpromazine	Chlorpromazine/barbiturate combination	Chlorpromazine	Barbiturate/chloral-hydrate combination
No. examined ..	16	9	17	17
Bronchopneumonia	4	3	4	6
Purulent bronchitis ..	1	1	..	..
Collapse	3	..	5	3
Ulcer of trachea with obstruction ..	..	..	..	1

tributed to death in 1 of the non-neonatal patients; but at necropsy the main complications were observed in the lungs, as in other series of cases of tetanus. Analysis of the incidence of such complications in the four treatment groups shows no striking differences (see table II). Bronchopneumonia was present in approximately a quarter of the patients given chlorpromazine alone, and in a third of all those treated with the combinations used. Collapse of the lung, usually patchy in distribution and seldom extensive, was more often observed in the chlorpromazine-treated groups. After recovering from tetanus, 1 of the neonatal patients died on the thirty-fifth day from respiratory obstruction caused by prolonged œsophageal intubation which resulted in ulceration of œsophagus into trachea. In at least half of the non-neonatal cases no cause of death was apparent at necropsy, and there was also no apparent cause in nearly half of the neonates.

Discussion

Although the mortality-rate among severe cases of tetanus remains considerable, adequate control of spasms in non-neonatal patients can be achieved with chlorpromazine alone or with a combination of this drug with phenobarbitone sodium in the dosages we have employed. Management is relatively easy, consciousness is not lost, and patients usually remain cooperative. Two-thirds of our patients in both treatment groups were satisfactorily fed by mouth. When a stomach-tube has to be passed or special procedures are necessary, chlorpromazine is a most useful relaxant; and we found it effective in the treatment of laryngeal spasms. Although the mortality-rates were similar whether we used chlorpromazine alone or in combination with barbiturates, we prefer the combination of the two drugs because control of spasms is readily achieved while the toxic effects of either drug used alone are avoided.

In animal experiments it has been found that there is a maximal dose above which anti-tetanus activity is not increased, and indeed the tetanus may be increased at very high doses (Laurence and Webster unpublished). From these experiments it would be expected that in man this critical dose is 200–300 mg. for non-neonates, but it is not possible to suggest a dose for neonates as there is no valid basis for comparison. If chlorpromazine is given more frequently than every two hours, tachyphylaxis (diminish-

ing response to doses repeated at very short intervals) may occur (Laurence and Webster unpublished). This risk of losing therapeutic effect can be avoided by alternating chlorpromazine with phenobarbitone when the severity of the spasm calls for additional sedation.

Prognosis in tetanus seems to be most closely related to the period of onset of reflex spasms (Cole 1940). It is particularly bad when the period of onset is under forty-eight hours, as analysis of our material shows (Adams 1958). This period was very short in our neonatal cases (mean 6·8 hours), and it is not surprising that the mortality-rate was so high. Although control of spasms was poorly achieved among neonates in the trial reported here, and we accept the view that such control is one of the aims of treatment, we are doubtful whether control of spasms alone will save the majority of cases of tetanus neonatorum; for we believe that tetanus intoxication of the medullary centres is probably the most important factor determining the high mortality-rate.

We have subsequently treated 57 consecutive cases of tetanus neonatorum using similar standardised treatment but attempting to control spasms by other methods. 13 of these patients recovered. The average period of onset for this series (10·5 hours) was somewhat longer than in the trial reported above, and the overall mortality-rate (77%) was correspondingly lower. 13 of the most severe cases were selected for preliminary testing of tracheotomy (4 cases) and acetylpromazine, either alone or in combination with sodium phenobarbitone (9 cases); but all 13 died. Given intramuscularly not more frequently than four-hourly in 10 mg. doses, acetylpromazine did not appear to be any better than chlorpromazine. Acetylpromazine was tried because it has been shown to have ten times the activity of chlorpromazine against experimental tetanus (Laurence and Webster 1958). We treated the remaining 44 patients with a combination of chlorpromazine and barbiturate. We usually gave 100 mg. chlorpromazine and 120 mg. sodium phenobarbitone intramuscularly in divided doses over the first twenty-four hours, attempting to control spasms thereafter with half these amounts. All 13 patients who survived were in this group. Because there was selection, we cannot make valid comparisons with the results of our previous trials, but we believe that this combination has some merit for the control of spasms in tetanus neonatorum as it has in non-neonatal

cases. We are accordingly using these drugs to control spasms in all cases in a further trial in which we are attempting to assess the role of tracheotomy in this disease.

Summary

A clinical trial on 96 tetanus patients allotted at random to two treatment groups practised concurrently is reported.

Chlorpromazine was compared with a combination of chlorpromazine and barbiturates in 56 non-neonatal cases, and with a combination of barbiturates (for the first twenty-four hours only) and chloral hydrate in 40 neonates; but in neither group were there statistically significant differences.

The results of treatment in a further 57 cases of tetanus neonatorum are recorded. For 44 of these, a combination of chlorpromazine and barbiturates was used, and 13 very severe cases were subjected to preliminary trials of acetylpromazine and tracheotomy.

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