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TREATMENT OF SEVERE TETANUS

BY

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Tetanus, a largely preventable disease, remains one of the few bacterial infections for which curative therapy is not available and the precise pathology of which is still disputed (Payling Wright, 1956; Abel *et al.*, 1938; Brooks *et al.*, 1955). However, it has been claimed, with considerable justification, that in most cases tetanus is a self-limited disease provided the patient can be tided over the storms of its assault. In some cases the mode of death is obscure, but many patients die from pulmonary causes, either from asphyxia during spasm involving the larynx and respiratory muscles, or from aspiration pneumonia and atelectasis (Creech *et al.*, 1950; Adriani and Kerr, 1955; Garcia-Palmieri and Ramirez, 1957).

The main aim of treatment, therefore, is to support the patient through the acute attack by minimizing muscular spasm and rigidity and by preventing respiratory infection. This involves a carefully integrated plan of management in which sedation and, more recently, muscle relaxants are used.

Many excellent articles have appeared in recent years, reviewing the conflicting views on the pathogenesis and treatment of tetanus (Drew, 1954; Shackleton, 1954; Forbes and Auld, 1955; Ablett, 1956; Creech *et al.*, 1957). Except for the reports of Adriani and Kerr (1955) and of Veronesi (1956), most of the larger series of cases have come from centres with relatively limited resources (Johnstone, 1958), while the application of newer techniques has been reported in smaller numbers, making assessment of their value difficult. Further difficulty in comparing the results of treatment arises because so many factors affect the outcome of tetanus and cases must be divided into prognostic categories, often by elaborate criteria.

The value of tracheostomy is generally accepted, and more recent methods of treatment which have been advocated include continuous or intermittent intravenous mephenesin (Adriani and Kerr, 1955; Veronesi, 1956), or chlorpromazine, promethazine, and pethidine, which has been used extensively in Europe, and full curarization with artificial respiration (van Bergen and Buckley, 1952; Lassen *et al.*, 1954). Other clinics have further complicated the management by using hypothermia (Hossli, 1956).

In a period of five months from June to October, 1957, 14 cases of tetanus were admitted to the Royal Adelaide Hospital, and nine of these were classified as severe. They were treated by full curarization and artificial respiration. These nine cases are reported here with a description of the problems which arose in the use of this technique, and an assessment of its value in the severe case.

Method of Treatment

Each patient was admitted to a sound-proof room, and after skin tests 300,000 units of antitetanic serum was administered, half of it intravenously. Surgical opinion was then obtained on the question of debridement of the entry wound. When it was indicated, tracheostomy was performed under general anaesthesia at the same time as debridement, and a cuffed rubber tube was inserted. The indications for tracheostomy were essentially those of Ablett (1956), and this operation was performed early rather than late. Assessment of the patient's ability to cough effectively was found to be particularly significant. In order to correct the frequent dehydration, to nourish the patient, and to administer drugs, an intravenous drip was inserted, preferably a "polythene" catheter to prevent extrusion during spasms. By this route, in the earlier cases, mephenesin and later chlorpromazine were administered intermittently. Penicillin was given, and the sedatives found to be useful were promethazine, pethidine, chlorpromazine, paraldehyde, and chloral. If tracheostomy had to be performed, sterile tracheal toilets were done. During this time there was continuous nursing surveillance with frequent medical assessment.

If heavy sedation failed to inhibit spasms, especially of the muscles of respiration, curarization was begun with artificial respiration. This involved continuous medical supervision together with expert anaesthetic assistance, particularly during the periods of induction and of decurarization.

The gases were delivered to the patient through the absorber unit of an anaesthetic machine, maintaining a flow of 6 to 8 litres a minute. During the period of initiation and stabilization a mixture of nitrous oxide and oxygen was used and then a variable mixture of compressed air and oxygen, breathing being maintained by the Beaver respirator adjusted to provide positive and negative pressure. Ventilation was mainly controlled according to half-hourly records of blood pressure, pulse rate, the presence or absence of sweating, and cyanosis. These observations were affected by variations in posture, sedation, muscular tone, and infection, as well as by hypoxia and carbon dioxide retention or lack. Twice-daily estimations of venous carbon dioxide combining power gave warning of gross respiratory alkalosis. The *p*H of the blood and plasma was also measured. The latter was found to be more

variable and more sensitive to acute changes in ventilation than the carbon dioxide combining power. Both investigations were repeated when the patient's condition required urgent assessment.

Curarization was instituted by the intravenous route, but maintenance could be effectively achieved by intramuscular injections of between 60 and 90 mg. of D-tubocurarine. The indicationsf or further doses were a rising blood pressure or pulse rate, the appearance of muscular twitches, movement of the tongue, face, or lips, or breathing motions.

Sedation, while the patient was curarized, was intended to produce amnesia and, to some extent, analgesia. It was not necessary to maintain anaesthesia, but in the absence of movement it was sometimes difficult to assess how much sedative to give. Changes in pulse rate and blood pressure were produced by many factors other than the level of sedation, and a method of resolving such doubts was devised by giving nitrous oxide. If administration of this gas reduced the pulse rate and blood pressure to basal levels it was felt that the previous sedation had been inadequate. Several patients had vague memories of events during their period of paralysis, but said that these were not distressing. The sedatives used during curarization were promethazine and pethidine, given alternately.

One of the objects of this method was to keep the respiratory tract free of infection. The cuffed tube prevented inhalation of pharyngeal contents but inevitably produced superficial ulceration of the tracheal mucosa, which, however, healed when the tube was withdrawn. To minimize this effect, the cuffed tube was released for five minutes every two hours after pharyngeal toilet had been done with the patient in the head-down position Lung complications were prevented by frequent postural changes and the foot or head of the bed was raised, as indicated by the clinical detection of areas of collapse or persistent rhonchi. Secretions were removed by means of a sterile lubricated Tiemann catheter. This was aided by heavy percussion on the chest wall and by compression at the end of the expiratory phase. When the secretions were tenacious, "alevaire" was used and sodium bicarbonate was instilled into the tube two-hourly. With the above technique bronchoscopy was not necessary, and quite dense opacities were cleared (see Fig. 1). The chest was radiographed daily, the lungs being held inflated.

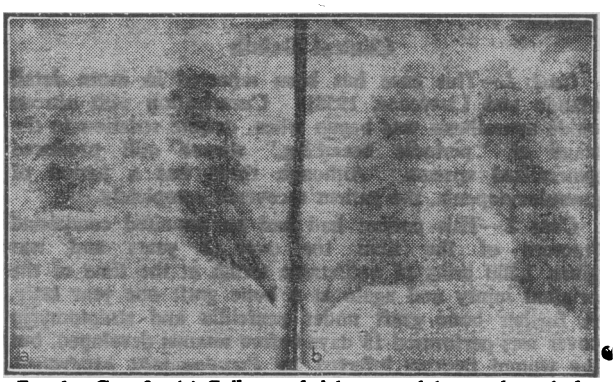

FIG. 1.—Case 2. (*a*) Collapse of right upper lobe on eleventh day of illness. (*b*) Fifty-five minutes later, after percussion and aspiration.

Tracheal secretion was cultured daily, prophylactic antibiotics being changed according to the sensitivity of pathogenic bacteria found. Masks were worn by all those attending the patient.

The ideal time for decurarization was when the patient could tolerate tracheal suction and could cough without developing generalized spasm. It was determined by trial. The period required varied from 18 to 72 hours, a careful watch being maintained for evidence of persistent severe tetanic activity. Some patients became restless, tending to breathe against the machine, and we found that the ideal sedative then was nitrous oxide given for short periods, together with manual control of respiration.

During the period of curarization the patient was nourished through an intragastric polythene tube, and, although gastric contents sometimes regurgitated through the relaxed cardia, tracheal aspiration was

Details of Cases

Case	Age and Sex	Incubation Period (Days)	Time of Onset (Hours)	Focus of Infection: Site	Focus of Infection: Treatment	Tracheostomy (Hours after Admission)	Curarization: Begun after Admission	Curarization: Total Period	Complications	Result
1	57 M	14	40	Tip of index finger	Amputation of distal phalanx	12	20 hours	15 days	Granulocytopenia	Cured
2	26 M	15	43	Infected ununited compound fracture of tibia and fibula; bone graft	Knee-level amputation	31	2 days	17 ,,	Surgical emphysema, mediastinitis, hyperglycaemia, lung abscess	
3	16 M	8	30	Nail in sole of foot	Excision of wound	20	2 ,,	16 ,,	—	
4	?32 M	14	?	"40% full-thickness burns of legs and buttocks	Excision of sloughs	6 (after onset of disease)	3 hours (after onset)	4 ,,	Severe burns 14 days before tetanus occurred	Death: "Toxaemia from burns and tetanus"
5	34 F	14 ?5	36	Infected abortion	Hysterectomy	4	37 hours	3 ,,	Thrombophlebitis right leg	Death: "Massive pulmonary embolus"
6	5 M	5	20	Splinter in thigh	Excision of wound	20	22 ,,	10 ,,	Hypernatraemic uraemia, Hyperglycaemia	Cured
7	32 M		?60		—	8	24 ,,	7 ,,	Anuria, Acute tubular necrosis	Death: "Uraemia (generalized haemorrhagic tendency)
8	16 M		30		—	8	24	12 ,,	Congenital "cerebral palsy," Granulocytopenia	Cured
9	47 M	5	36	Splinter in paronychia of finger	Amputation of distal phalanx	8	72	10 ,,	Chronic bronchitis, Bilateral basal pneumonia. ?*Ps. pyocyanea* septicaemia	Death. "Multiple pulmonary emboli"

prevented by the cuffed tube. Voiding occurred spontaneously or urine could be expressed manually and collected by continuous "sheath" drainage. Physiotherapy was given twice daily and frequent skin toilets were performed. Brief details of the cases are summarized in the Table.

Clinical Details

Case 1.—This case has been reported in more detail (Sando and Lawrence, 1958). Curarization with nitrous oxide anaesthesia was begun when, despite sedation to the stage of "periodic breathing," stimuli still produced generalized spasms. Although there was a period of granulocytopenia, the patient recovered completely.

Case 2.—This patient had had an ununited compound fracture of the tibia for over 2 years and was given 1,500 units of antitetanic serum at the time of the original injury and again at a bone graft one year later. A further bone graft under penicillin and streptomycin cover was performed 15 days before tetanus developed, but the wound became infected by *Pseudomonas pyocyanea*. The case apparently had a long incubation period and at first did not seem to be particularly severe. In fact, the tetanic process was prolonged and severe. The wound debridement was inadequate, and tracheostomy, which was done under local anaesthesia, was left too late, so that pneumonia was already present. Fifteen days after curarization had begun a staphylococcal abscess formed at the right lung base followed by a total empyema with massive collapse of the lung. After a prolonged convalescence the patient had his amputation stump refashioned and his empyema decorticated. He remains well. Sugar and acetone were present in the urine on admission, and blood-sugar levels rose to 240 mg. per 100 ml. Levels of 120–130 mg. per 100 ml. were maintained with 25 units of soluble insulin every six hours. As soon as the tetanic process abated, however, despite the persistent lung infection, the blood-sugar level fell to the normal range and glucose-tolerance curves were consistently normal.

Case 3.—By the time this patient arrived the routine was better organized, and, despite the short incubation period, this patient had a less troublesome course and a rapid convalescence

Case 4.—This patient developed tetanus while being treated for extensive deep burns and had been given 1,500 units of antitetanic serum when admitted to hospital 14 days previously. He had particularly brief time of onset, but was apparently well controlled by curarization until he died suddenly, no cause of death being found at necropsy. In this patient, massive administration of antitetanic serum caused anaphylaxis with tight bronchospasm. Although suxamethonium chloride was given, the chest could not be inflated manually until adrenaline was administered intravenously. Had emergency measures, including an anaesthetist and equipment for endotracheal intubation not been immediately available, this patient would have died of anaphylatcic shock.

Case 5.—This patient had induced an abortion, using a syringe, five days before she was admitted to hospital. Hysterectomy and tracheostomy were completed five hours after she was admitted, and her early progress was satisfactory. In this case, as in Cases 3 and 7, curarization became necessary when tracheal aspiration began to produce apnoea and anoxic spasm despite sedation, intravenous mephenesin, and chlorpromazine. The patient died very suddenly, only four days after her operation, with a massive pulmonary embolus.

Case 6.—This boy, aged 5, was transferred from the Adelaide Children's Hospital. He had a short incubation period and time of onset. The sixth to the eighth day of his illness was stormy, with periods of tachycardia, cyanosis, and hyperpyrexia. There were anaesthetic ventilatory problems and he had a hypernatraemic hyperchloraemic uraemia probably associated with excessive protein intake. Having weathered this storm, he improved quite rapidly, but was left with a mild tracheal stridor from granulation tissue for some months after his tracheostomy had healed. Meteorism and retention of faeces due to D-tubocurarine caused abdominal distension, made ventilation difficult, and obstructed venous return. This was relieved by neostigmine without precipitating further spasms. During the period of neostigmine effect, suxamethonium chloride was substituted for tubarine.

Case 7.—It seemed that this patient would not have had particularly severe tetanus, but he had been having spasms at home for 48 hours before admission and could not swallow. He was severely dehydrated and was given intravenous fluid, chlorpromazine, and mephenesin while hydration was re-established. However, 12 hours after admission his blood urea nitrogen was 52 mg./100 ml. and the serum potassium 6 mEq/l. Anuria persisted despite strict fluid and protein restriction, and dialysis was not available. No blood pigments were seen spectroscopically in the small amount of urine passed, but necropsy showed renal tubular necrosis with many dark tubular casts.

Case 8.—This patient had congenital cerebral palsy with marked speech defect, involuntary movements, and spasticity. He was admitted to hospital after several typical tetanic spasms and became anoxic during a severe spasm in the casualty department. Chlorpromazine, 20 mg. intravenously, rapidly relieved the spasm and anoxia. Curarization was effective, but when this was discontinued after 12 days he became very restless, with generalized rigidity and choreathetotic movements, which it was felt were due to a combination of resolving tetanus and his congenital disability. The best sedative during this period of hyperkinesia was nitrous oxide, as tolerance developed to other drugs, and we were forced to administer this gas for considerable periods, particularly during the three days after discontinuing curare. It was used for short periods during the next three days, and a blood picture done at this stage showed a red-cell count of 3,200,000/c.mm.; haemoglobin, 9.2 g./100 ml.; platelets plentiful; leucocytes 2,300/c.mm (polymorphs 11%, lymphocytes 83%, monocytes 1%, eosinophils 5%). Nitrous oxide was discontinued, 3 pints (1.7 l.) of blood was transfused and, as in Case 1, there was a rapid and dramatic response over the succeeding seven days, the leucocyte count rising to 12,900/c.mm. (see Fig. 2). The patient had also been having a number

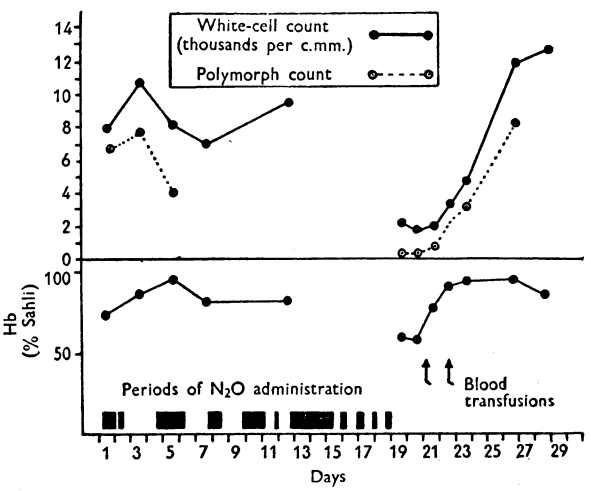

FIG. 2.—Blood picture in Case 8.

of other drugs, including phenobarbitone, pethidine, promethazine, chlorpromazine, methenesin, and paraldehyde. Although they were discontinued when the granulocytopenia developed, most of these drugs were

administered again later without any evidence of bone-marrow toxicity. After a period of pyrexia the restlessness and rigidity gradually subsided and the patient was cured of tetanus.

Case 9.—This man, who had recurrent bronchitis, had a short incubation period and time of onset. The white-cell count on admission was 32,000/c.mm., but his chest infection remained under control during the early management. However, three hours after beginning curarization he collapsed with hypotension and loud variable heart murmurs. He required noradrenaline for 20 hours; the blood pressure then recovered and his condition seemed satisfactory, although the leucocytosis persisted. Repeated blood cultures were negative, but *Ps. pyocyanea* was recovered from the heart blood at necropsy. A second transient episode of collapse occurred on the seventh day. Hyperglycaemia was also present during the first 10 days. On the tenth day D-tubocurarine was discontinued, tetanic activity by then having subsided. A thrombosis of the right femoral vein then became apparent, and, despite anticoagulant therapy, the left leg also became involved, congestive cardiac failure occurred, and after a further episode of collapse and anoxia he lapsed into a state resembling "coma vigil." He steadily deteriorated, and died 22 days after admission. Necropsy showed multiple pulmonary emboli of varying ages, and it would appear that the episodes of collapse described above were the result of recurrent incidents. There was no conclusive evidence of septicaemia and the heart valves were intact.

Discussion

The above group is too small to allow of definite conclusions, and the mortality (44%) was of the same order as that in many reported series of cases of severe tetanus. However, two of the four fatal cases had severe complications unrelated to the technique. Case 4 had extensive deep burns, while in Case 7 death occurred from renal failure. The former may have been an example of the fulminating case in which therapy proves useless because of the toxic effects on the brain-stem nuclei (Baker, 1942; Cole, 1953; Woolmer, 1954).

Two patients (Cases 5 and 9) died of pulmonary embolism, the former three days after beginning curarization, while the latter probably had his first embolus only three hours after D-tubocurarine was given. Another case of tetanus, in a man aged 75, was treated at this time. Curarization was not required, but he died some days after the tetanic process had abated. Necropsy showed several pulmonary infarcts and a terminal pulmonary embolus. Previous authors have not reported pulmonary embolism in cases of tetanus, but Hossli (1956) describes two cases with severe tetanus successfully treated by curarization and hypothermia. Both developed extensive thrombophlebitis, one of them having a thrombosis of the inferior vena cava. The flaccid paralysis induced by D-tubocurarine could contribute to the occurrence of venous thrombosis, which may be a complication of this method of treatment. However, this seems unlikely to have caused the first episode of presumed pulmonary embolism in Case 9, while both the infected abortion and the subsequent hysterectomy may have precipitated peripheral thrombosis in Case 5.

As may be seen from the Table, all of the surviving cases could be classed as severe, especially Cases 3, 6, and 8 which, it is suggested, fall into the group mentioned by Cole (1953) in which the use of relaxants saved life.

Lassen *et al.* (1954) reported that prolonged nitrous oxide anaesthesia may produce depression of bone marrow. The events in Case 1, as previously reported (Sando and Lawrence, 1958), appear to support this theory. For this reason, in succeeding cases nitrous oxide was used only for short periods during the induction of curarization, and to reduce restlessness during the period of decurarization, a function which it subserves very well. As described above, granulocytopenia and anaemia were observed also in Case 8, and although the situation was confused by the administration of other drugs the prompt response to the cessation of nitrous oxide provides further support for Lassen's suggestion. It is also significant that in both cases the depression was rapidly reversible. Thus, although nitrous oxide has a place in management, it should be used with care, and any prolonged use of the gas would require a careful watch on the blood picture.

A further interesting observation was hyperglycaemia, which was severe enough in Cases 2, 6, and 9 to warrant the use of insulin. The glycosuria experienced by these patients was often associated with ketosis and abated with decreasing tetanic activity. A review of the records of the last 44 cases of tetanus admitted to this hospital showed that in 11 cases a positive Benedict test of the urine was recorded. (Five of these patients had been given paraldehyde.) Jacono *et al.* (1953) showed decreased glucose tolerance in 14 cases of tetanus, of which only one had glycosuria. They suggested adrenal cortical stimulation as a cause. No ready explanation of this phenomenon is available, but damage to cells at the base of the brain or brain stem might be suggested.

In the cases reported from Nigeria by Glossop and Low (1957), paralysis and intermittent positive-pressure respiration were instituted when the patients were in advanced or fulminating stages of the disease, and most of them were azotaemic. High blood-urea levels were present in Cases 1, 4, 6, 7, and 9 of our group, but returned to normal in each patient who survived. The provocation of hypernatraemic hyperchloraemic uraemia in Case 6 by high-calorie high-protein feeding again emphasizes the need stressed by Wilson and Care (1955) for careful supervision of metabolic and electrolyte therapy in paralysed patients.

As numerous writers have pointed out, the time-honoured treatment of tetanus by massive sedation further depresses both the respiratory centres and cough, one of the most important defences of the lungs, thus increasing the likelihood of pulmonary complications in a chest already rigid from the effects of the tetanus toxin. We have been impressed in severe cases by the occurrence of apnoea in response to stimuli even after tracheostomy, heavy sedation, and mephenesin, and hence the need for a method which avoids such anoxic periods, eliminates the distressing spasms, and allows control of pulmonary secretions and infection.

In the fatal cases of this series, necropsy revealed the extent to which the lungs weer kept free from infection. There was superficial ulceration of the trachea and main bronchi, but there were no areas of consolidation or collapse in the lungs of Cases 4, 5, and 8. However, a purulent bronchopneumonia was present in Case 9, in which the patient died 10 days after curare was discontinued, and in Case 2, in which the patient survived and developed a pulmonary abscess. In both patients pulmonary infection was present before

curarization began, and was apparently controlled during the period of D-tubocurarine administration.

Doubts have been expressed about the value of the more exacting and complicated techniques in treating severe cases of tetanus (Creech *et al.*, 1957), but we feel that, as Cole (1953) suggests, they will save a group of patients who previously would not have survived. The best results are obtained by experienced teams who have a planned routine, as Adriani and Kerr (1955) and Veronesi (1956) have shown, but their papers, despite convincing evidence of the value of intermittent relaxant drugs, reveal a group of cases that cannot be controlled adequately by their techniques. Thus, although Veronesi reports the excellent overall mortality rate of 18.9% in his last 236 cases, the death rate of the severe cases with a "time of onset" (Cole and Spooner, 1935) of less than 48 hours was still 44%. Chlorpromazine has been shown to be useful in the management of the disease, and its final place has yet to be assessed. Recent reports stress the use of very large doses (Hossli, 1956; Packard *et al.*, 1958). By measuring the degree of trismus we were able to show that chlorpromazine relaxes hypertonus in tetanus. It was particularly valuable when given intravenously as an "emergency" treatment of generalized tetanic spasm in Case 8. However, using relatively small intravenous doses, we found its action was short-lived, and Laurence *et al.* (1958) describe a case in which severe spasms could not be arrested by 50 mg. intravenously.

Thus there remains a group of patients in whom tracheostomy, paralysis, and artificial respiration would appear to be necessary. The use of this method has not so far been reported in a large series of cases, and the reduction in mortality in those which have been published is not impressive. This must partly be due to its use only in small numbers of severe cases, so that the staff treating the patients have not had an extensive experience of the many problems involved.

This technique eliminates the exhausting painful spasms and rigidity, making the patient more comfortable and less apprehensive. It allows nursing procedures and skin toilet to be done more effectively by eliminating the strain of working as silently as possible in a darkened room. The recurrent crises of apnoea and spasm which characterize other methods of management do not occur, and physiotherapy and adequate tracheal aspiration can be performed without precipitating further spasms.

Constant medical supervision, an essential part of this technique, is both an advantage and a disadvantage in a busy general hospital. Crises still occur, but they tend to be mechanical and reversible, involving the cuffed tracheostomy tube and respiratory or biochemical disturbances. (A large ancillary staff, including radiology, biochemistry, bacteriology, and haematology personnel, is also involved.)

Although this series is not large, we feel that the technique of paralysis and mechanical artificial respiration has a real place in the management of tetanus. It is indicated in the fulminating case or in the severe case when sedation and other relaxant agents fail to control reflex spasms and thoracic rigidity. Like tracheostomy, it should not be left until pulmonary infection is established or the patient is *in extremis*, but should be begun as soon as it is evident that simpler measures will not adequately control the tetanic process.

Summary

The treatment of nine cases of severe tetanus by paralysis with D-tubocurarine and artificial respiration is described. Four patients died, two of them from pulmonary emboli and another in acute renal failure. Several other complications occurred, including bone-marrow depression, thought to be related to prolonged nitrous oxide administration, and hyperglycaemia

This technique relieves the distressing muscular hypertonus of tetanus and prevents spasms. It allows adequate pulmonary ventilation and aspiration to be performed, thus avoiding the respiratory complications which commonly result from the rigid thorax and inadequate cough of patients with severe tetanus. Feeding and nursing are made easier.

However, because of its complexity, the method should be reserved for fulminating cases or for those in which sedatives and other relaxant agents do not prevent reflex spasms. It requires careful continuous medical supervision and skilled anaesthetic control.

Tetanus in the more advanced communities should be treated by special units with adequate facilities, and paralysis with artificial respiration should be available for the severe case.

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Medical Memoranda

Addiction to Carbromal

Carbromal (α-bromo-α-ethylbutyrylcarbamide) is incorporated in a variety of proprietary preparations which are available freely without prescriptions to the general public as safe sedatives. The present case is reported in order to draw further attention to the possible serious consequences of overdosage and to the difficulties of dealing with addiction to it under the existing regulations.

CASE HISTORY

The patient, a married woman, was first admitted to hospital in June, 1949, when aged 54. Her husband and neighbours had observed that she had been taking about 30 tablets of "persomnia" (each containing carbromal 195 mg. and bromvaletone 65 mg.) daily for some months and had become lethargic, confused, and ataxic. Her doctor had already formed the opinion that she was a persomnia addict and had sought psychiatric advice, but no mental disease had been found.

On admission she was drowsy, but showed no localizing sign and no rash. Her recovery was uneventful except for the occurrence of a transient tremor of her hands. Samples of her urine and stomach contents taken on admission showed a considerable excess of bromine.

After discharge she continued to take persomnia in spite of her husband's efforts to prevent this, and was also known to take fairly large quantities of alcohol. Her mental condition showed progressive deterioration and she neglected her housework, which was done by her husband until he left her in the spring of 1958. Thereafter she was largely fed by her neighbours.

She was readmitted in June, 1958, having been found on the floor of the house with the room in disorder. Her doctor had removed several containers of persomnia tablets from her house some days previously. Clinical examination again gave negative findings, and she recovered within a few days. Psychiatric opinion remained that she had no mental disorder which justified restraint.

A very similar cycle of events recurred five time between July and September, although her doctor had contacted all local pharmacists and requested them not to supply her with persomnia. She consistently refused prolonged hospital or convalescent-home treatment, would not accept admission to local authority accommodation, nor was it found possible to force her to do so under the National Assistance Act.

At noon on December 11 she was noted by a neighbour to be in her usual state, and was found dead in bed the following morning.

At necropsy no organic change of any significance was found. Analysis of her blood, urine, and cerebrospinal fluid showed bromide concentrations of 132 mg., 110 mg., and 105 mg. per 100 ml. respectively. Her stomach contained 850 ml. of fluid, the level of bromine being approximately 125 mg. per 100 ml., precise estimation proving technically difficult. No evidence of barbiturate or of salicylate was found in any of the body fluids.

At the inquest a verdict of accidental death due to carbromal (persomnia) intoxication was recorded.

DISCUSSION

The more serious effects of carbromal overdosage include acute and chronic mental symptoms (Magnussen, 1947; Stroh, 1955), addiction (Barker, 1958; Seager and Foster, 1958; Young, 1958), and death (*Pharm. J.*, 1958a, 1958b), while drug eruption is another complication even with normal dosage (Borrie, 1955; Prosser Thomas, 1958; Young, 1958).

In the present instance the patient took persomnia tablets in large numbers for at least 10 years. Her resultant mental disturbances were well known, not only to those concerned with her medical care but also to the police and to her neighbours. Several hospital admissions were required for the more severe acute toxic episodes, which mainly occurred after she had been left by her husband, who previously had removed an enormous number of persomnia tablets from the house. Nothing effective could be done for her, as she always denied taking persomnia or other drugs, refused to co-operate with every endeavour to control her addiction, and continued to obtain the drug despite the efforts to stop her.

Considerable concern is now felt in this country about the unrestricted sale of carbromal and bromvaletone. The Ethical Committee of the Pharmaceutical Society has recommended that these drugs be included in Part I of the Poisons List and First and Fourth Schedules to the Poisons Rules (*Pharm. J.*, 1958c). The Poisons Board was unable to accept this recommendation, and this decision was upheld by the Home Secretary, but the matter has been referred to the Interdepartmental Committee on drug Addiction by the Minister of Health (*Brit. Med. J.*, 1958; *Pharm. J.*, 1958d).

This case emphasizes some of the difficulties of dealing with carbromal addiction under existing regulations, and it is to be hoped that measures will soon be adopted which will improve the present position.

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