TABLE VIII.—Deaths Not Directly Attributable to Tetanus

Group A		Group B	
<i>Mild to Moderate</i>			
P.U.O.; sudden death more than 1 week after tetanus symptoms controlled	1	Overt kwashiorkor and multiple abscesses	1
Bronchopneumonia	2	Staphylococcal septicaemia, severe bronchopneumonia, Hb 30%, and dehydration on admission..	1
		Purulent laryngo-tracheobronchitis on admission; died within 36 hours	1
		Died suddenly at home on day of discharge from hospital	1
<i>Severe</i>			
Bronchopneumonia and cardiac failure	1		

Comment on Action of Diazepam

Diazepam appeared to be of most value in cases of tetanus in which tonic spasm of muscles was marked but convulsive spasms were infrequent. It was effective in relieving trismus and opisthotonos in the majority of cases, at the dose of 4.4 mg./kg./24 hours.

The oral route of administration was used almost exclusively in this trial and appeared to be perfectly satisfactory. Our limited experience of the intramuscular route of administration does not suggest that this has any special advantage over oral administration.

The intravenous route of administration was tried on a few occasions and did not appear to produce a dramatic onset of action of the drug.

No toxic effects attributable to diazepam were observed in either neonates or older children. The lower temperatures revealed among neonates who received diazepam, however,

suggest that it tends to induce hypothermia. Mortality was not adversely affected by this action of the drug.

Summary and Conclusions

Results of therapeutic trial of diazepam in tetanus are reported. The trial included 149 patients—104 neonates and 45 older children. Patients were randomly allocated into two treatment groups, one of which received diazepam in addition to the standard treatment used in both groups.

In neonatal tetanus the mortality rate was unaffected by the use of diazepam, but the drug was of value in relieving tonic muscle spasm, in particular trismus.

A significant number of patients who received diazepam had minimum temperatures of 95°F. (35°C.) and lower, but did not appear to be adversely affected by this.

In older children with tetanus the overall mortality rate was lower among those who received diazepam than among those who did not, but the difference is not statistically significant. As in neonates, the drug was of value in relieving tonic spasm but did not seem to have any direct effect on convulsive spasms.

Findings in this trial indicate that diazepam is a useful drug in the management of tetanus, principally because of its ability to reduce tonic muscle spasm. Its use appears to be free of toxic effects or unpleasant side-actions. In older children it may have favourably influenced mortality from the disease.

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Experience with Diazepam in Tetanus

D. FEMI-PEARSE,* M.B., M.R.C.P.ED., D.T.M.&H.

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The mortality from tetanus is still high in many parts of the world (Jelliffe, 1950; Johnstone, 1958; Tompkins, 1958, 1959; Adams *et al.*, 1959; Smythe, 1963; Kloetzel, 1963). However, an encouraging report by Ellis (1963) claimed that in the Leeds Tetanus Unit there had been no deaths among 36 cases treated in the previous four years; all except two mild cases were treated with curare (total paralysis) and positive-pressure artificial respiration. Such a method of treatment is beyond the scope of most hospitals in the developing countries, where there are, among other problems, shortages of equipment and expert medical personnel. Simpler methods of treatment therefore continue to be tried.

Cole and Robertson (1955) and Gelfand (1955) reported the successful abolition of spasms by chlorpromazine in tetanus patients. Kelly and Laurence (1956) substantiated this finding by abolishing spasms in rabbits having experimental tetanus, and proceeded to treat a 2½-year-old boy successfully with the drug.

Weinberg (1964) successfully treated severe tetanus in a 6½-year-old boy weighing 17.4 kg. with diazepam in doses varying

between 30 and 40 mg. every 24 hours. Hendrickse and Sherman (1965), in a preliminary report of a therapeutic trial of diazepam and chlorpromazine in neonates and children, found diazepam to be useful in tetanus, but could not draw definite conclusions because of the small number in their series.

Prior to its use in tetanus, diazepam had been found useful in treating skeletal-muscle spasms associated with conditions such as overriding fractures of the femur and tibia (Kestler, 1963); stiff-man syndrome (Howard, 1963); cervical and lumbar disc protrusion (Bain, 1964); and in the relief of spasticity in patients with upper-motor-neurone lesions (Leavitt *et al.*, 1963).

Diazepam is a tranquillizer and muscle-relaxant of the 1,4-benzodiazepine group. We have used this drug in the treatment of tetanus at the Lagos University Teaching Hospital with a view to assessing its value and shortcomings in the management of the disease. This paper describes our present experience.

Materials and Methods

Forty-two patients (19 males and 23 females) with tetanus were studied. Their ages ranged from 4 days to 50 years. Twenty-nine received diazepam from the time of admission,

* Department of Medicine, Lagos University Teaching Hospital, P.M.B. 12003, Lagos, Nigeria. Present address: University of Rochester School of Medicine and Dentistry and Strong Memorial Hospital, Rochester, New York.

while the other 13 were treated with chlorpromazine and sodium amytal for at least 24 hours without arrest of spasms, before being treated with diazepam.

All the patients received 10 mg. of diazepam intravenously or intramuscularly to start with. Subsequent doses were administered parenterally or as a syrup either by mouth or through nasogastric and gastrostomy tubes.

Some patients also received a barbiturate orally or parenterally (phenobarbitone in 21 and sodium amytal in 4), depending on the degree of control of spasms and rigidity achieved. Doses of barbiturate (phenobarbitone or sodium amytal) varied up to a maximum of 200 mg. six-hourly for periods of two days to two weeks.

The clinical course of all patients was recorded on a special form, and sedation was varied in the light of the patient's progress.

All cases were graded on admission according to the criteria of Jenkins and Luhn (1962): Mild, without convulsions; moderate, convulsions easily induced; severe, spontaneous convulsions not easily controlled.

Standard Management

The following standard management was made available to all cases.

1. Antitetanus serum (A.T.S.), 50,000 units intravenously or intramuscularly in adults following test dose (20,000 units in children).
2. Parenteral penicillin for seven days at least, as well as any other antibiotic specifically indicated.
3. Feeding: glucose-saline solutions orally or parenterally; high-protein fluids orally or through nasogastric or gastrostomy tubes.
4. Appropriate surgical treatment—for example, dilatation and curettage in uterine tetanus.
5. Blood transfusion—when necessary.
6. Haemoglobin genotype and sickling test on admission.
7. Regular determination of haemoglobin and blood counts, blood urea, electrolytes, liver-function and urine tests.
8. Stool examination for ova and deworming on admission, especially for ascaris.
9. Regular blood-gas estimations when indicated by Astrup pH-meter, or Campbell and Howell's rebreathing technique for measuring mixed venous PCO_2 .
10. Tracheostomy or gastrostomy when necessary.
11. Intermittent positive-pressure respiration with curarization if required, usually as a last resort.

Results

Most of our patients were adolescents and young adults (see Table) with moderate or severe tetanus. Of the 42 cases 17 (40%) were treated with diazepam alone. The remaining 25 had diazepam with varying amounts of a barbiturate orally or parenterally (phenobarbitone, 30 to 200 mg. six-hourly, or sodium amytal, 60 to 200 mg. six-hourly), and also for periods varying from two days to two weeks. Twenty-one patients received phenobarbitone and four received sodium amytal.

Age Distribution of 42 Patients

Age in Years:	0-1	1-10	11-20	21-30	31-40	41+
No. of patients	2	6	17	10	4	3

The response to intravenous diazepam was remarkable. Within two minutes of injecting the drug reflex spasms stopped, the limbs became flaccid, and the board-like abdominal wall softened. Case 1 is typical of the muscle-relaxant response obtained after intravenous diazepam. The addition of a bar-

biturate in 25 cases sustained the effect of diazepam and produced longer duration of abolition of spasms. All the patients received diazepam for periods ranging from two to six weeks.

In three of the 42 cases diazepam failed to stop reflex spasms. These three patients died. There were three other deaths, making a total of six. The fourth death resulted from an accident: the tube conveying humidified oxygen was tightly connected to the tracheostomy tube and the patient was denied exit for expiration. She died of pneumothorax (necropsy finding).

The fifth death was that of a man aged 50 with a long history of cigarette-smoking. He had copious secretions in his chest, which he could not expectorate, complicated by bronchospasm. A tracheostomy was performed. Later his arterial PCO_2 rose to 106 mm. Hg and he improved with respiratory support by a ventilator without curare. Two weeks after admission he died of massive pulmonary embolism from thrombosis of the right femoral vein and bullous emphysema of the left lung (necropsy findings).

The sixth death was that of a woman aged 23, who died of multiple pulmonary atelectasis and pulmonary embolism (necropsy findings) after 23 days in hospital.

Gastrostomy was carried out in 12 (28%) cases and tracheostomy in 16 (38%). Four patients (Cases 3, 4, 5, and 6) showed behavioural changes, which disappeared on discontinuing diazepam.

Most of those who received diazepam alone were drowsy, but were easy to rouse. During the convalescent phase patients were ambulant on as much as 60 mg. every 24 hours, and most of them did not complain of any side-effects. Two patients had diplopia on doses of 60 and 120 mg. daily. We have monitored respiration clinically and by measuring the tidal volume, and have not encountered respiratory depression due to diazepam.

Haematological and laboratory examinations, including haemoglobin, blood count, blood urea, liver-function tests, including transaminases, and urine tests did not reveal any abnormality that could be attributed to diazepam. This agrees with the observation of Randall *et al.* (1961).

Dosage Schedule

The accompanying Chart shows the dosages in relation to body-weight per 24 hours of 30 of the patients whose weights were known.

In the mild cases the dosage range was 0.7 to 4 mg./kg./24 hours, in moderate cases 2.4 to 8.5 mg./kg./24 hours, and in severe cases 3 to 40 mg./kg./24 hours. The mean dosages for the three grades of severity were 2.4, 4.3, and 9.3 mg./kg./24 hours respectively.

A female neonate weighing 3 kg. had a maximum dosage of 5 mg. of diazepam every hour—that is, 40 mg./kg./day—for

three days. The total duration of diazepam administration was three weeks.

The case of a 57-kg. man who had 30 mg. of diazepam syrup hourly at the peak of tetanus—that is, 720 mg. daily—with occasional addition of sodium amytal without any side-effects has been described (Femi-Pearse and Fleming, 1965). This dose represents the highest daily dosage yet described.

Illustrative Case Reports

Case 1.—A girl aged 12, weight 45 kg., was admitted on 18 July 1965 with neck stiffness, trismus, and opisthotonos. Grading: moderate tetanus. No portal of entry found. Sedated with chlorpromazine, 100 mg., alternating with sodium amytal, 200 mg., every three hours intramuscularly. She deteriorated, with uncontrolled spasms, and was transferred to the intensive care unit on 23 July. Tracheostomy was performed because of laryngeal spasms, tight chest, and retention of secretions. Every slight stimulus, even the gust from the revolving electric fan, provoked strong spasms. At 2 p.m. the next day the temperature (axillary) rose to 104° F. (40° C.) pulse to 130, and respirations to 50. This trend has been observed to be ominous in tetanus (Smythe, 1963). At 3 p.m. the same day (24 July) 10 mg. of diazepam diluted in normal saline was administered intravenously at a slow rate. Two minutes after its completion there was a remarkable muscle-relaxation; the limbs were flaccid, and neck retraction and opisthotonos had become markedly less. There was not a single spasm for 45 minutes, and afterwards mild spasms recurred at five-minute intervals. Subsequently diazepam was administered as a syrup through a nasogastric tube in a dose of 15 mg. every two hours, supplementary parenteral diazepam, 10 mg., being given when needed. At 6 p.m. the same day the temperature, pulse, and respirations had fallen to 98.4° F. (36.9° C.), 110/min., and 25/min. respectively. The relaxed state was maintained throughout. She also had parenteral sodium phenobarbitone, 100 mg. p.r.n. She was on diazepam for 21 days, and her total stay in hospital was 41 days.

Case 2.—A man aged 22 was admitted on 20 August 1965 with mild tetanus which rapidly became severe, with powerful spasms, within a few hours. The management with diazepam and its eventual rejection was as follows. At 9 a.m. on August 20 diazepam, 10 mg. intravenously and 10 mg. intramuscularly, was given. Spasms stopped for 30 minutes. Subsequently 20 mg. of diazepam syrup was given through nasogastric tube two-hourly. He still had moderate spasms. Tracheostomy was performed at 11.30 p.m. Diazepam, 15 mg. intramuscularly, was given every hour. He had still more severe spasms. At 9 a.m. the next day sodium amytal, 100 mg. intramuscularly, was given two-hourly for four doses. He still had more spasms. At 6.15 p.m. he was given curare and intermittent positive-pressure respiration. No more spasms occurred. He died of sudden circulatory collapse during the morning of 23 August.

Subsequent case reports show the side-effects which we have observed in four of our patients on diazepam.

Case 3.—A girl aged 18, weight 56.4 kg., was admitted with uterine tetanus on 21 August 1965. Grading: mild, sedated with 20 mg. of diazepam intramuscularly every two hours for the first 24 hours and later with 10 mg. of syrup two-hourly. After two weeks in the ward she was observed to be unduly happy, free, uninhibited, and talkative. She stopped the young house-officers for a chat, held their hands, and made dates with them. She just had to be avoided. She was observed in this state for five days, after which diazepam was stopped. Seventy-two hours later she was as quiet as other patients. Her mental status prior to acquiring tetanus was said to be normal.

Case 4.—A woman aged 23, weight 51 kg., was admitted on 2 October 1965 with severe uterine tetanus. She was sedated with diazepam syrup, 15 mg. two-hourly, for 35 days. For another week this dose was increased to 30 mg. two-hourly for rigidity. During the last two weeks in the intensive-care unit, with spasms entirely abolished and with only tonic rigidity to overcome, she lay mute, motionless, and completely detached. She would not respond to simple commands such as "Shut your eyes," "Raise up your arm." There were no smiles in response to jokes about recovery. However, she seemed conscious throughout. From 48 to 72 hours after

withdrawing diazepam she was beginning to smile, move her limbs, and sit up in bed.

Case 5.—A youth aged 18, weight 50.4 kg., was admitted on 10 November 1965 with moderately severe tetanus. Sedation was with diazepam syrup, 20 mg. four-hourly, and phenobarbitone syrup, 100 mg. eight-hourly. Spasms were well controlled. On 20 November he was noisy, disorientated for space, time, and person, had had delusions and visual hallucinations. His arterial PCO_2 was 51 mm. Hg and bicarbonate (HCO_3) 20.5 mEq/l. He had vigorous physiotherapy to his chest and diazepam was reduced to 10 mg. intramuscularly eight-hourly. Intramuscular injections had to be given because of severe pharyngeal spasms on attempting to pass a nasogastric tube. He also had sodium phenobarbitone, 100 mg. intramuscularly eight-hourly. Forty-eight hours after diazepam had been reduced, although his sensorium was still clouded and he was still restless, he was aware that he was in hospital, he recognized the nurses, and he knew the time of day. Diazepam was discontinued on 22 November. His recovery was complete.

Case 6.—A youth aged 17, weight 62.5 kg., was admitted on 18 August 1965 with moderate tetanus. He was sedated with diazepam syrup, 20 mg. two-hourly, and phenobarbitone, 60 mg. eight-hourly. After 20 days he developed visual hallucinations. Both drugs were stopped and chlorpromazine was given to control rigidity. Hallucinations disappeared on stopping diazepam and phenobarbitone.

Discussion

In action diazepam is qualitatively similar to chlordiazepoxide (Librium), of which it is an analogue, but is more potent in most laboratory tests and in initial clinical trials. Diazepam is reported to be about five times as potent as chlordiazepoxide as a tranquillizer and muscle-relaxant in animals and ten times as strong as an anticonvulsant (Randall *et al.*, 1961). Recently chlordiazepoxide in large dosage has been used in tetanus and found to be useful (Phillips, 1965).

Though the mode of action of diazepam has not been completely elucidated, it has been suggested that the drug depresses the spinal internuncial neurones (Weinberg, 1964), the ascending reticular activating system, and the amygdala (Hernández-Peón *et al.*, 1964; Arrigo *et al.*, 1965). In action diazepam resembles chlorpromazine, which is also known to depress the spinal internuncial neurones and the reticular formation (Dasgupta and Werner, 1955).

Case 1 is typical of the muscle-relaxant response from diazepam. Though no other case has shown the spectacular fall in temperature, pulse, and respiratory rate of Case 1, the muscle-relaxant effect of the drug has been constant in 39 cases. In three cases diazepam failed to stop reflex spasms, and these patients eventually died. Hendrickse and Sherman (1965) have commented that diazepam is not very effective in controlling reflex spasms during the early phase of treatment.

In our cases the effect of 10 mg. of diazepam intravenously was remarkable. The abolition of spasms and emergence of flaccidity within two minutes of the injection may last for an hour, or less, as in Case 1. This experience accords with that of Gastaut *et al.* (1965), who have used intravenous diazepam in the control of status epilepticus and within a few minutes achieved complete abolition of convulsions. The addition of phenobarbitone helped to sustain the muscle-relaxant effect of diazepam in our cases.

We have taken measurements in at least 10 patients to show the muscle-relaxant action on the masseters. Measurements between the free edges of the lower and upper incisors on maximal voluntary opening of the mouth before and after 10 mg. of diazepam intravenously showed that in tetanus patients the value increased by 50% to 100% within five minutes of injecting the drug and was sustained for about an hour.

The rise in temperature, pulse, and respiratory rate in Case 1 when spasms were uncontrolled merits some comment. Hyperpyrexia and tachycardia in tetanus have been attributed to the direct effect of the tetanus toxin on the brain stem (Montgomery, 1961), to underventilation (Smythe, 1963), and to

pyogenic septicaemia (Spalding and Smith, 1963). In Case 1 pneumonia, septicaemia, or toxic damage to the brain stem could not have responded so spectacularly to intravenous diazepam. Very severe spasms provide a most likely explanation for the pyrexia, tachycardia, and increased respiratory rate, the abolition of which brought about the remarkable changes. This response is physiological.

Respiratory depression is an undesirable side-effect in the management of tetanus and has not been observed with diazepam. Circulatory depression has also been absent. The drug, used alone, produces varying grades of sedation from drowsiness to peaceful sleep without complete loss of consciousness.

The varying dosage level of 0.7 to 4 mg./kg./day in mild cases, 2.4 to 8.5 mg./kg./day in moderate cases, and 3 to 40 mg./kg./day in severe cases suggests that adjustment of dosage to meet individual needs is essential. While dosages are being adjusted in difficult cases it should be borne in mind that failure can occur with diazepam.

Side-effects have been reported but none yet has been alarming. Leavitt *et al.* (1963) have encountered drowsiness, orthostatic hypotension, and excessive flaccidity. Two of our patients complained of diplopia, and no apparent weakness of eye movement was observed on examination. Payne and Ishmael (1963) mentioned the case of a woman who complained of feeling "drunk," with ataxia and diplopia, while she was taking diazepam 40 mg./day. Our patients were on 60 and 120 mg./day respectively.

Four of our patients exhibited rather severe behavioural changes. The euphoria, talkativeness, and amorous approaches of Case 3, the akinetic mutism of Case 4, and the disorientation and hallucination of Cases 5 and 6 disappeared within 48 to 72 hours of stopping diazepam.

The confusion and hallucination of Case 4 was quite severe and prompted electrolyte and blood-gas estimations. The serum sodium, potassium, and chloride were normal. The arterial PCO_2 of 51 mm. Hg and bicarbonate (HCO_3) of 20.5 mEq/l. constituted a respiratory and metabolic acidosis of a mild degree. It did not seem likely that the acid-base change *per se* was responsible for the mental changes observed. However, Milne (1965) has commented that such changes may have a profound influence on the efficacy and toxicity of drugs by altering the concentrations in the extracellular and intracellular compartments. Hendrickse and Sherman (1965) did not observe any side-effects that could be attributed to diazepam in neonates and children; the recognition of behavioural changes in that age group may not be easy. Kloetzel (1963) has observed disorientation and hallucinations in uncomplicated tetanus, but this has not been our experience in Lagos.

A 22-year-old man had a diuresis while on parenteral diazepam, 20 mg. two-hourly, and later 15 mg. of syrup two-hourly.

The absence of toxic effects in the 3-kg. neonate on 40 mg./kg./day and the 57-kg. man on 720 mg. daily reaffirms the wide margin of safety with diazepam acclaimed by Randall *et al.* (1961). Administration of the drug in such large doses as are used in tetanus must continue for some time before firm conclusions can be drawn about the margin of safety of the drug in ill patients.

Since the reports of Cole and Robertson (1955), Gelfand (1955), and Kelly and Laurence (1956), chlorpromazine has remained the mainstay of sedation in most centres treating large numbers of tetanus cases. At Ibadan Tompkins (1959) found a combination of chlorpromazine and phenobarbitone to be

superior to any other sedative. In view of the experience acquired so far with diazepam, a clinical trial of chlorpromazine and diazepam has begun. Since this report is in no way comparative we can only conclude that where chlorpromazine has not been satisfactory diazepam has been of immense value and is a useful addition to the short list of muscle-relaxants available in the management of tetanus.

Summary

Forty-two cases of tetanus were treated with diazepam (Valium). There were three failures which ended fatally and three other deaths—a total of six. The drug is recommended as a useful addition to the small range of muscle-relaxants available for the care of tetanus. It is free from respiratory and circulatory depression and from toxic damage to the bone-marrow, liver, and kidneys.

The average dosages for mild, moderate, and severe cases were 2.4, 4.3, and 9.3 mg./kg./24 hours respectively. Phenobarbitone was a useful adjuvant.

Four cases with reversible behavioural changes probably due to diazepam are described.

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