are due to Dr. Joseph Seifter, of Wyeth, Philadelphia, for the generous supply of paritol, and to Mr. Kibben Williams for his able technical assistance.

REFERENCES

- Basu, D. P., and Stewart, C. P. (1950). *Edinb. med. J.*, **57**, 596.
 Besterman, E. M. M., and Evans, J. (1957). *Brit. med. J.*, **1**, 310.
 Block, W. J., Barker, N. W., and Mann, F. D. (1951). *Circulation*, **4**, 674.
 Bloor, W. R. (1939). *Physiol. Rev.*, **19**, 557.
 Brown, W. D. (1952). *Quart. J. exp. Physiol.*, **37**, 215.
 Constantinides, P., Cairns, A., and Werner, A. (1954). *Arch. int. Pharmacodyn.*, **99**, 334.
 — and Saunders, P. (1958a). *A.M.A. Arch. Path.*, **65**, 360.
 — (1958b). *Ibid.*, **65**, 499.
 — and Wood, A. (1956). *Ibid.*, **62**, 369.
 — Szasz, G., and Darrach, M. (1955). *Canad. J. Biochem.*, **33**, 226.
 — and Harder, F. (1953). *A.M.A. Arch. Path.*, **56**, 36.
 Fischer, R., Bircher, J., and Reich, T. (1953). *Schweiz. med. Wschr.*, **83**, 509.
 Forbes, J. C., and Petterson, O. M. (1953). *Proc. Soc. exp. Biol. (N.Y.)*, **83**, 665.
 Friedman, M., and Byers, S. O. (1953). *J. exp. Med.*, **97**, 117.
 Glazko, A. J., Strong, J., and Kazenko, A. (1954). *Fed. Proc.*, **13**, 55.
 Graham, D. M., Lyon, T. P., Gofman, J. W., Jones, H. B., Yankley, A., Simonton, J., and White, S. (1951). *Circulation*, **4**, 666.
 Gutmann, N., and Constantinides, P. (1955). *A.M.A. Arch. Path.*, **59**, 717.
 Hahn, P. F. (1943). *Science*, **98**, 19.
 Horlick, L., and Duff, G. L. (1954). *A.M.A. Arch. Path.*, **57**, 417.
 Korn, E. D. (1958). In *Chemistry of Lipides as Related to Atherosclerosis*, A Symposium, edited by I. H. Page, p. 169. Thomas, Springfield, Ill.
 Lever, W. F., Herbst, F. S. M., and Hurley, N. A. (1955). *A.M.A. Arch. Derm. Syph.*, **71**, 150.
 Schuler, W., Müller, G., and Maier, F. (1957). *Schweiz. med. Wschr.*, **87**, 787.
 Sollmann, T. (1957). *A Manual of Pharmacology*, 8th ed., p. 573. Saunders, Philadelphia.
 Sperry, W. M., and Webb, M. (1950). *J. biol. Chem.*, **187**, 97.
 Waldron, J. M., and Friedman, M. H. F. (1948). *Fed. Proc.*, **7**, 130.
 Youngburg, G. E., and Youngburg, M. V. (1930). *J. Lab. clin. Med.*, **16**, 158.

"The triennial reports of the [joint Bethlem Royal Hospital and Maudsley] hospital have two objects. The first is the provision of statistics relating to the medical administration of the hospital departments. The second is the provision of demographic, social, and diagnostic data on the patient population attending the hospital. While these two objects have much in common, there is a basic difference between them. The administrator is concerned with the amount of work done by the various departments of the hospital in providing treatment for its patients. This work is most conveniently assessed by taking into account the total number of admissions of patients to (or their discharges from) a department during a given time. On the other hand, statistics relating to demography, social factors, and diagnoses need for the most part to be based on the number of individual patients that attend the hospital, irrespective of the number of occasions on which they are admitted. As compared with previous reports, the present report puts rather more emphasis on the clinical and rather less on the administrative aspects of the data. One of the principal objects of this change is to allow the presentation of data concerning the whole population attending the hospital. Most of the published data on the statistics of mental illness in Great Britain deal only with in-patients. But psychiatric hospitals are becoming increasingly concerned with out-patient care and treatment. Moreover, because of changes in administration and in treatment, many cases that a few years ago would have been treated as in-patients are now treated as out-patients. There is consequently an increasing need for clinical statistics on all patients under care at psychiatric hospitals and not merely on the in-patients. It is in the belief that hospital statistics of this kind will have a growing value that the present editor has emphasized the clinical aspects of the data." (*Triennial Statistical Report: Years 1955-7*. Bethlem Royal Hospital and the Maudsley Hospital.)

TOTAL PARALYSIS REGIME IN SEVERE TETANUS

BY

S. M. A. ALHADY, M.B., F.R.C.S., F.R.C.S.Ed.
Surgeon

D. P. BOWLER, M.D., M.R.C.P., D.T.M.&H.
Paediatrician

H. A. REID, M.B., F.R.C.P.Ed., D.T.M.&H.
Physician

AND

L. T. SCOTT,* B.M., F.F.A.R.C.S., D.A.
Anaesthetist

The General Hospital, Penang, Malaya

In an era of remarkable therapeutic advances the search for an effective treatment of severe tetanus has been disappointing. In New Orleans, Creech *et al.* (1957) demonstrated a small and steady decline in mortality over the past fifty years, but were unable to relate this fall to the many changes in treatment. In Malaya tetanus is common: from 1952 to 1956 an average of 20 patients with tetanus (excluding neonatal tetanus) have been admitted each year to the Penang General Hospital. About one-third of these victims were children. The mortality was 40%, varying yearly from 20% to 50%. We soon recognized that patients with mild tetanus recover with conservative treatment.

Our concern in this paper is confined to non-neonatal severe cases—patients who develop generalized spasms that stop respiration despite conservative treatment. In 1957 we started treating such patients with the total paralysis regime (T.P.R.), consisting of tracheostomy, total paralysis of skeletal muscles, and intermittent positive- or positive/negative-pressure artificial respiration. In reviewing our experience with this treatment, the two main questions we wish to consider are: (1) How may severe tetanus be recognized at the outset? (2) Is the T.P.R. effective in treating severe tetanus?

Material and Methods

All patients aged over 6 with tetanus were admitted under the charge of one of us (S. M. A. A.), those aged 6 or less under the charge of D. P. B. During the 16 months June, 1957, to September, 1958, a total of 40 consecutive cases were seen (excluding neonatal tetanus) and 11 were selected for treatment with T.P.R. One subject died during tracheostomy on the day of admission and has not been included in the series. Details of age, site of infection, incubation period, onset period (the time between the first symptom and the first spasm whether local or generalized), duration of T.P.R., and result in the 10 patients are given in the Table.

All patients received antiserum (50,000 to 100,000 units), intramuscular chlorpromazine (50-100 mg. four- or six-hourly), intravenous thiopentone, and crystalline penicillin. Four patients in addition had promethazine, 25 mg. 12-hourly, and sodium amylobarbitone, 200 mg. six-hourly. If feasible, the wound causing the infection was excised at a suitable interval after starting the antiserum. When it seemed that this conservative treatment was failing, all consultants met to assess the

*Now at the Vale of Leven Hospital, Alexandria, Dunbartonshire.

Details of Cases

Case No.	Age	Site of Infection	Incubation Period in Days	Period of Onset in Hours	Duration of T.P.R. in Days	Result
1	14	Foot	13	24	12	Lived
2	31	Uterus	5	—	7	Died
3	11	Foot	4	24	11	Lived
4	44	Toe	7	>48	5	Died
5	6	Knee	9	<24	6	"
6	2	Middle ear	6	36	2	"
7	42	Uterus	3	12	3	"
8	6	Middle ear	?6	>36	5	"
9	29	Foot	2	12	6	"
10	4	Leg	3	24	5	"

case. In some instances T.P.R. was instituted immediately, but in others we first tried intensifying the conservative treatment. When this also failed T.P.R. was started. In 9 of the 10 cases the chief indication for T.P.R. was one or more spasms severe enough to stop respiration despite the treatment given. In Case 2, however, T.P.R. was induced on admission in view of the known severity of post-abortion tetanus. In Case 4 T.P.R. was begun three hours after admission, in Case 7 one week after admission, and in the other seven cases within 24 to 48 hours of admission.

General Management of T.P.R.

The general management of the respiration unit was the combined responsibility of us four consultants. Our registrars and house staff were available for duty with the unit, thus providing a doctor on immediate call throughout the period of treatment. One consultant was always on 10-minute call and was responsible for the care of the patient during his spell of duty. A medical and nursing plan was recorded, and was amended as experience suggested. The unit was located in a side-ward under the general direction of the ward sister. Additional nursing staff was posted to the ward to provide one staff-nurse and one second-year nurse with the patient throughout the 24-hour period. We managed to build up a nucleus of nursing staff familiar with the management of these cases; the majority took great pride in the special experience and responsibility which this exacting work requires. To minimize staff disturbance one of us (D. P. B.) at a later date started the nursing of children on T.P.R. in the open ward. The sister and senior staff-nurse (both with prior experience of T.P.R.) supervised junior nurses who managed the regime. The system worked well and obviated the need for additional nursing staff.

When it was decided to use T.P.R., atropine was given intravenously followed by thiopentone and suxamethonium. After oral intubation a high tracheostomy was done and a cuffed endotracheal tube suitably shortened was inserted through the tracheostome. We tried various types of tube, but prefer ordinary endotracheal tubes with a short cuff. It lies more comfortably in the neck than would at first seem likely and is not prone to kink. L-shaped tubes have not in our experience been satisfactory. Magill's suction T-piece connexions of light metal with rubber cap are suitable connectors. We experimented with many devices to secure the tracheostomy tube, but have come to the conclusion that it is best to use only a length of tape tied behind the neck and to disconnect the tube from the machine during the few seconds in which the patient is being turned over in nursing procedures. The passing of a gastric tube in an

unrelaxed subject with tetanus is dangerous and may precipitate a severe general spasm, vomiting, and subsequent inhalation of vomit. We prefer to delay passing the "polythene" stomach-tube until the tracheostomy has been done.

As soon as respiration returned after the initial dose of suxamethonium, full curarization was obtained by intravenous D-tubocurarine. Thereafter paralysis was maintained by giving D-tubocurarine intramuscularly together with hyaluronidase. This was fully effective, but there was a delay of 7 to 10 minutes before maximum effect was reached. The most reliable indication for a further dose of relaxant was the faintest twitching movement of the trachea on gentle manipulation of the tracheostomy tube. A second useful sign was a flicker of diaphragmatic movement at the end of inspiration. Twitching movements of the fingers mentioned by Powell *et al.* (1958) occur later, and by the time they are evident there is usually a reduction in respiratory minute-volume due to increased resistance in the thorax. The dosage of D-tubocurarine varied from 4 to 30 mg. every one to two hours, and was remarkably constant in individual patients.

Because prolonged sedation is itself a hazard the use of narcotic drugs was kept to a minimum. In early cases sodium amylbarbitone, 0.2 g. six-hourly, was given via the gastric tube. It seems unlikely this dosage could account for the amnesia which the two survivors had for the duration of the T.P.R. Both these patients during the first few hours after stopping the T.P.R. were restless when breathing spontaneously (though the minute-volume was satisfactory), but fell promptly asleep when the machine was started again. In Cases 6, 9, and 10 all sedation was stopped once T.P.R. was started. Fluid and nutritional requirements were given every two hours via the gastric tube as a milk mixture fortified according to the patient's age and weight. During the first 24 hours of T.P.R. the amount per feed was progressively increased from (in adults) 55 to 230 ml.; thereafter the 24-hour total was 2.75 litres, supplying 2,600 calories, 75 g. of protein, 3 g. of sodium, 5 mg. of aneurine, 5 mg. of riboflavine, 125 mg. of ascorbic acid, 50 mg. of nicotinic acid, and 0.6 g. of ferrous sulphate.

Intermittent positive-pressure respiration (I.P.P.R.) was provided by a Radcliffe respirator. In Cases 1 to 5 this was of the single-phase type. Generally speaking, we did not find the flutter-valves of this machine satisfactory. For a given pressure each valve would give a different minute-volume, though valves with silicon rubber were more consistent. The "perspex" casing of the valve tended to crack after some days' handling. In the last five patients the newer Radcliffe respirator providing a negative phase and having cam-operated valves was used. This machine was much more satisfactory.

A respiratory rate appropriate to the age of the patient was chosen and the respiratory pressure was then adjusted to provide the desired minute-volume, which was usually higher than that indicated by the nomogram of Radford (1955). In patients on T.P.R. there is a continuous fluctuation in pulmonary function. Variation in the resistance of thoracic muscles with the degree of curarization, and the constant tendency for secretions to accumulate, interfere with ventilation. In our experience frequent clinical appraisal, particularly of sweating, blood-pressure, pulse, chest auscultation,

and minute volume as recorded by the machine, gave adequate indication of any failure in ventilation, etc.

Biochemical estimations were made and chest radiographs taken, but these were of no significant help in the minute-to-minute management of the patient. The nursing staff soon learnt to appreciate these clinical observations (including chest auscultation), and if matters were not righted by turning, suction, percussion, and compression of the chest, their instructions were to inform the doctor on call. Patients were turned every two hours as a routine. Tracheal and bronchial toilet, using a Tiemann catheter, was done as indicated, usually by the nursing staff, who also percussed and squeezed the chest to assist drainage. A "wet chest" is

disastrous in T.P.R. (or, for that matter, in tetanus generally), and in preventing this our watchword soon became "keep the patient off his back." The semi-prone or occasional lateral positions promote drainage of secretions by gravity and prevent infection. Apart from penicillin for the tetanus infection, no antibiotics were given as a routine. When hypotension developed, individual patients were given steroids, noradrenaline, and other drugs as indicated in the case-summaries.

Results

Only two patients out of the 10 survived (see Table). In Case 10 we probably stopped T.P.R. prematurely;

but in six cases lethal hypotension developed, usually when everything appeared to be progressing satisfactorily. Some of the salient clinical features are outlined in the case-summaries.

Case 1.—A Chinese boy aged 14 was admitted on June 27, 1957, with generalized spasms not interfering with respiration. Despite conservative treatment the spasms became more severe, and T.P.R. was started on June 28. A temperature of 105° F. (40.6° C.) was recorded that day, but thereafter progress was satisfactory and hypotension did not develop. However, the first electrocardiogram (E.C.G.), on June 29, showed symmetrical T inversion in leads V4R to V3. In the second record, on July 3, T was upright in V2 and V3 (see Fig. 1). The serum potassium was 5 mEq/l. and serum sodium 135 mEq/l. T.P.R. was stopped on July 10, but for the next 48 hours, after cessation of D-tubocurarine, respiration required assistance. Mild generalized spasms continued for three days but were controlled by chlorpromazine. The tracheostomy tube was removed on July 13, the tracheostome had healed by July 19, and the patient was discharged well on August 7.

Case 2.—An Indian woman aged 31 had a procured abortion on July 6, 1957, developed trismus on July 11, and was admitted on July 12. T.P.R. was instituted immediately, and her condition remained satisfactory until July 15, when the B.P. dropped to 60/40. A noradrenaline drip raised the diastolic B.P. to 80, but the systolic remained at 100 or less. The first E.C.G., on July 16, showed upright T waves in all chest leads. The second, on July 18, showed symmetrical T inversion in V3R to V4, maximal in V3. Meanwhile hypotension became increasingly resistant to noradrenaline despite progressively increasing the dose so that the concentration was 192 mg. in 540 ml. (at 30 drops a minute) on July 19, when she died. A third E.C.G. taken 15 minutes

FIG. 1.—Case 1. First E.C.G., on second day of T.P.R. (top row, June 29) shows inverted T waves which become upright in V2 and V3 four days later (bottom row, July 3). The patient recovered.

FIG. 2.—Case 2. T.P.R. was started July 12, 1957: hypotension started February 15, 1957: diastolic B.P. was raised by noradrenaline, and the first E.C.G. (top row, July 16) shows upright T waves. Two days later, when hypotension had become increasingly resistant to noradrenaline, T is inverted in right chest leads. The third E.C.G., 15 minutes before death (bottom row, July 19) shows gross conduction defect.

FIG. 3.—Case 5. T.P.R. was started October 12, 1957: hypotension developed October 16. E.C.G.s on October 17 (top) and 18 (bottom) show that T inversion became progressively more marked in chest leads. Patient died on October 18.

before death showed wide biphasic complexes indicating gross conduction defect (see Fig. 2).

Case 3.—An Indian boy aged 11 was admitted on July 20, 1957, and T.P.R. was started on July 22, when conservative treatment had failed and spasms were stopping respiration. Progress was satisfactory and hypotension did not supervene. The first E.C.G., on July 25, showed symmetrical T inversion 4.5 mm. deep in V1 and biphasic T waves in V2 to V4. The second record, on July 29, showed upright T waves in V2 to V4. T inversion in V1 was only 1 mm. deep. T.P.R. was stopped on August 2, and though generalized stiffness continued there were no spasms. The tracheostomy tube was removed on August 9, the tracheostome had healed by August 12, and the patient was discharged fully recovered on August 24.

Case 4.—An Indian man aged 44 was admitted with generalized spasms on September 13, 1957. Initially, conservative treatment appeared successful, but later on September 13 a violent spasm stopped respiration and caused collapse of the patient. T.P.R. was therefore started, and progress was satisfactory until 2.45 p.m. on September 16, when the B.P. dropped to 80/50. Intravenous digoxin, 0.5 mg., was given, and the B.P. rose to 110/90 (noradrenaline was not given). The first E.C.G., on the morning of September 16, was taken when the B.P. was normal, and it showed a 1-mm. horizontal depression of ST segment in V5 and V6. Oral digoxin was continued, 0.25 mg. 12-hourly. Thereafter there were fluctuating irregularities in the pulse, and at 8.30 a.m. on September 18 hypotension again supervened. It was not relieved by noradrenaline, and the patient died at 5.30 p.m. A second E.C.G., at 3.30 p.m., showed a 2-mm. S-T elevation in V1 and V2 but no other significant change.

Case 5.—A Chinese boy aged 6 was admitted on October 12, 1957, and T.P.R. was started later that day. Hypotension developed at 5.30 p.m. on October 16 and remained resistant to noradrenaline and intramuscular cortisone, 50 mg. six-hourly, until his death at 9 p.m. on October 18. The first E.C.G., on October 17, showed symmetrical T inversion in V3 to V6. The second E.C.G., on October 18, showed further deepening of T inversion and extension to involve all chest leads (see Fig. 3).

Case 6.—An Indian boy aged 2 years was admitted on March 25, 1958. T.P.R. with the newer positive-negative Radcliffe respirator was started on March 26, when spasms interfering with respiration occurred despite conservative treatment. Progress appeared satisfactory until the evening of March 28, when, without obvious cause, he suddenly died. His blood-pressure was normal 45 minutes before death.

Case 7.—A Chinese woman aged 42 was admitted on June 9, 1958, after an abortion. Tracheostomy was performed shortly after admission, but otherwise the conservative regime was followed until June 16, when increasing spasms culminated in respiratory arrest. T.P.R. was therefore started. On June 17 the pulse was irregular, and next day hypotension supervened, continuing despite intramuscular cortisone and repeated intravenous methylamphetamine hydrochloride until the patient died on June 19. No E.C.G. records were obtained, but necropsy showed toxic myocarditis (see Fig. 4).

Case 8.—A Malay girl aged 6 was admitted on July 28, 1958, with trismus of uncertain duration. Spasms which started 36 hours after admission continued despite conservative treatment. The CO₂ combining power had dropped to 18 mEq/l. on July 30, when T.P.R. was started. On July 31 it had risen to 25 mEq/l., and thereafter remained normal. Daily serum sodium and potassium levels remained within the normal range. On August 3 there were episodic pulse irregularities, and on August 4 hypotension developed at 6.30 p.m. There was no significant improvement with noradrenaline, and the patient died at 9.30 p.m. E.C.G. records obtained on July 29 and 31 and August 1 and 3 showed a monophasic R wave in

FIG. 4.—Case 7. Patient died after three days' T.P.R. and two days' hypotension. Heart showed a toxic myocarditis. Interstitial oedema and infiltration with mononuclear and occasional plasma cells. A few muscle fibres showed fragmentation, cellular reaction being minimal. ($\times 500$.)

V4R and V3R. R exceeded S in V1, but there were no significant changes in serial records.

Case 9.—A Malay man aged 29 was admitted on August 8, 1958, and T.P.R. was started on the 10th. Hypotension lasted from 3 to 10 a.m. on August 14, but then responded to methylamphetamine. Thereafter the pulse was irregular for brief episodes. Hypotension recurred on August 16 between 8.30 and 9 a.m. and again at 6.30 p.m., the patient dying at 7.10 p.m. E.C.G. records were taken on August 10, 14, and 16. They were normal. Unfortunately no record was obtained during a hypotensive phase. Daily serum potassium and sodium on August 10 to 16 were normal.

Case 10.—A Chinese boy aged 4 was admitted on September 2, 1958, but, despite intensifying the conservative regime, spasms increased and CO₂ combining power fell to 16.5 mEq/l. on September 3, when T.P.R. was started. On September 4 it rose to 22 mEq/l. and thereafter remained normal. Control of tetanus toxæmia was satisfactory, but amoebic and Sonne dysentery developed. The infection responded to emetine and sulphonamide. On September 8 T.P.R. was stopped. Progress appeared satisfactory, though chlorpromazine was still required to control occasional spasms. However, on September 17 bronchopneumonia was evident, and the patient died the following day. Thirteen E.C.G. records were taken between September 3 and 11. The fourth record, on September 5, and the eighth, on September 8, showed deep symmetrical T inversion in V4. In the other 11 records T was upright in this lead.

Electrocardiography

Serial E.C.G.s were obtained during T.P.R. in all except Cases 6 and 7. Standard, unipolar, and eight chest leads (V4R to V6) were taken as a routine, but in Cases 8 and 10 leads V3R and V3 or V4 were often omitted as the chest was too small. In Case 9 the three records were normal, but the E.C.G.s were not taken when hypotension was present. In Case 8 there was a monophasic R in V4R and V3R, and R exceeded S in V1 though there were no significant changes in serial records (again no record was obtained during hypotension). Gailani *et al* (1958) found similar E.C.G. changes in patients with muscular dystrophy. They excluded pulmonary hypertension and

right heart enlargement by cardiac catheterization and attributed the changes to conduction defect in the myocardium. In Case 8 this pattern of right ventricular dominance may therefore have been due to tetanus toxæmia.

In Case 4 there was only a 1-mm. ST depression in left chest leads. The second record, taken five hours after terminal hypotension started and two hours before death, showed ST elevation in V1 and V2. In the two patients who recovered (Cases 1 and 3) and in another who died (Case 10) there were fluctuating T-wave inversions, mostly in right chest leads (see Fig. 1). In Case 10 it is possible the fluctuating T inversion in V4 was due to slight alteration in location of the electrodes. But as the records were all taken by the same technician under the supervision of one of us (H. A. R.) and as unequivocally abnormal changes occurred in other patients, we think this explanation unlikely. The position of the patient was also investigated as a factor in causing pattern changes. Consecutive records were taken with the patient lying flat on his back, on the left, and then the right side. There was no significant difference between the records. In Cases 2 and 5 the E.C.G.s became progressively and grossly abnormal (see Fig. 3). In Case 2 the record taken 15 minutes before death showed wide biphasic complexes (see Fig. 2).

Pathology

In Malaya, owing to religious and social customs, it is difficult to obtain consent for necropsies. Permission, however, was granted in Cases 2, 5, 7, and 10. In Case 2 there was slight lung oedema and in Case 10 a diffuse purulent bronchopneumonia. The heart was macroscopically normal in both cases, but microscopy was not done. In Case 5 macroscopic and microscopical findings were not remarkable. No significant histological abnormality was seen in the myocardium or lungs. In Case 7 the uterus was enlarged, but other viscera, including the lungs, appeared normal to the naked eye. Histologically there were inflammatory and necrotic changes in the decidua of the uterus. The brain appeared normal. The liver showed moderate fatty degeneration. In the myocardium there was oedema of the interstitial tissue with a scanty cellular infiltration of mononuclear cells and a few plasma cells. Some of the small nerves were degenerated and infiltrated by the same cells. There was necrosis of a few muscle fibres, the cellular reaction to this being very slight. Dr. A. T. H. Marsden remarked that the acute toxic myocarditis was similar to that found in diphtheria (see Fig. 4).

Discussion

Two vital factors in tetanus are often overlooked—the toxin dose and the speed with which it becomes fixed to susceptible structures. Payling Wright (1958) has reminded us of animal assays showing a thousand or more lethal doses of toxin in the tissues surrounding the wound. He remarks that in man, who ranks among the more highly susceptible mammals to tetanus, the same great excess may be present. E. A. Wright (1954) showed experimentally that tetanus toxin was rapidly fixed to cells of guinea-pig brain stems. More than half the dose injected was fixed within two hours. Undoubtedly the toxin dose is the paramount factor determining the fate of human victims who have not

previously been inoculated with toxoid (and this comprises the great majority of patients in Malaya). In a fortunate minority the toxin dose is small, the illness mild, and the subject recovers with no more treatment than is required to relieve discomfort. In the opposite group the toxin dose is overwhelming and death is inevitable. A third category remains in which treatment can sway the issue. This category may be divided into moderate cases in which conservative treatment as outlined should succeed and severe cases in which it will fail. It is in the latter group that we hope T.P.R. might be effective.

For the clinician, however, a major difficulty lies in allocating individual patients to one of these four groups—mild, moderate, severe, or inevitably fatal—so that appropriate treatment may be given with minimum delay. The traditional method of assessing severity by the duration of incubation and onset period may not in our experience (Reid *et al.*, 1958) be reliable in individual cases shortly after admission. Though these two measurements are valuable in retrospective analysis of series of cases, there are exceptions which vitiate their application to the individual patient. Thus we have seen fatal cases with incubation periods of four weeks and onset periods as long as nine days. Patients with incubation periods of only two or three days and onset period as short as 24 hours have recovered uneventfully. We have known a patient die in hospital during the first spasm five days after the onset of symptoms.

Though all cases in the present series were severe by these criteria, with the possible exception of Case 4 (where the onset period was uncertain), we came to rely more and more on accurate observation of hypertonus and spasms as the index of severity. Satisfactory definition of these terms is a fundamental difficulty in tetanus and makes comparison of results in different series treacherous. Both hypertonus and spasms may be generalized or localized, involving one part of the body more than another. The stimulus required to put a muscle or group of muscles into tetanic spasm varies from subject to subject and the duration may be less than a second or more than a minute.

We use the term "hypertonus" to describe the constant background of stiffness, whether involving single muscles such as the masseters a group such as the abdominal or neck muscles, a limb, or the whole body. A "spasm" is a sudden spasmodic increase in muscle tone, localized or generalized, spontaneous or induced, lasting a few seconds or more than a minute. We classify tetanus as mild when there is only hypertonus, moderate when spasms do not stop respiration, and severe when one or more spasms arrest breathing. Though this classification is based on substantial clinical experience, we recognize that it is arbitrary and far from infallible—as instanced by the apparently mild case in which the patient died during the first spasm. We are unable to distinguish the inevitably fatal from the severe in the early stages. But we think a spasm stopping respiration despite conservative treatment is the most reliable indication for adopting T.P.R.

The use of T.P.R. was based on the assumption that tetanus killed through the direct or indirect effects of hypertonus and spasms; that tetanus is a self-limiting disease from which the patient will recover if he can be kept alive until the disease burns itself out.

Originally we did not think tetanus toxin affected vital structures other than motor-nerve cells. However, with T.P.R. one can prolong survival and see further effects of tetanus emerging. We now believe there is a direct action on the myocardium.

We think the two patients who recovered (Cases 1 and 3) would have died if we had persisted with conservative treatment, and that T.P.R. was effective in saving their lives. It might also be regarded as effective in Case 10, as the tetanus toxæmia was waning when the patient died from lung infection 10 days after stopping T.P.R.

The results in the remaining seven patients can only be described as disappointing. Was the toxin dose so overwhelming that death was inevitable? The common feature in these cases has been the development of hypotension two or five days after the start of T.P.R. This has usually occurred when all was going well. In Case 2 the hypotension persisted for four days until death, but in the other cases it was episodic, lasting half to several hours. All the patients except in Case 6 died in a hypotensive phase. It seems unlikely the treatment was responsible. The extensive experience gained in western Europe from the treatment of respiratory insufficiency in poliomyelitis by I.P.P.R.—often for months at a time—shows without doubt that man can accommodate himself to this regime if it is properly managed. We do not think that technical mismanagement was an important factor in our bad results. Theoretically, I.P.P.R. may diminish return of blood to the heart by increasing the pressure in the chest. It might be thought that this mechanical factor rather than the tetanus toxin was responsible for the hypotensive phases. But hypotension did not occur in two patients recovering, and they were subjected to I.P.P.R. longer than the other three patients.

Secondly, the introduction of a negative-pressure phase in the last five cases did not prevent hypotension. Heavy sedation may be a contributory factor in the deaths of tetanus patients. But in later cases we have not given sedatives. Yet lethal hypotension still occurred. Foldes (1957) showed that excretion of D-tubocurarine may be slow. The initial recovery from its effects is due to a redistribution through extracellular spaces, and the ultimate elimination proceeds slowly, by renal excretion and liver action. With continued administration a point of saturation might be reached after which the plasma concentration would rapidly rise. Depression of vital centres might then result if there is concomitant electrolyte upset. But in the two patients receiving the most prolonged D-tubocurarine administration (Cases 1 and 3) recovery ensued without hypotension. Furthermore, no biochemical or E.C.G. evidence of significant electrolyte upset was observed.

An important observation in Case 4 was the effect of intravenous digoxin—the blood-pressure promptly rose from 80/50 to 110/90, though no vasoconstrictors were given. According to Goodman and Gilman (1955) digitalis affects systolic blood-pressure largely by its action on the heart and not by any significant effect on the blood vessels or vasomotor centre. In Case 2 noradrenaline raised the diastolic blood-pressure to a normal level yet the systolic blood-pressure remained low. To maintain this partial response steady increase in dosage was necessary until enormous amounts had to be given—30 drops a minute of a

solution with 192 mg. per 540 ml. These observations suggest the hypotension was due to central myocardial failure rather than to peripheral arteriolar relaxation. Fluctuating irregularities of the pulse and the E.C.G. findings support this concept. Whenever an E.C.G. was taken during the hypotension it was abnormal.

In Cases 2 and 5 the records became progressively abnormal. At necropsy in Case 5 the myocardium was histologically normal. This, of course, does not exclude lethal biochemical changes. In Case 7, however, microscopy revealed an acute toxic myocarditis. Lassen *et al.* (1954) recorded histological evidence of myocarditis in one of their four patients treated by I.P.P.R. But the patient had septicaemia, and the myocarditis might well have been caused by this rather than by the tetanus toxæmia. In Cases 5 and 7 there was no clinical or post-mortem evidence suggesting significant infection other than tetanus. We conclude that the myocardium may be directly damaged by the toxin in severe tetanus. This effect may nullify therapeutic measures such as T.P.R. But not necessarily so: there were E.C.G. changes in both our patients who survived, and in one of the cases reported by Lassen *et al.* (1954) the patient had E.C.G. changes of supraventricular paroxysmal tachycardia yet recovered.

As a result of our experience we consider T.P.R. is indicated in cases of severe tetanus but that in such cases it will be effective to only a limited extent. It will save a few patients who would die if treated by more conservative methods. However, we are as yet unable at the outset to distinguish the patients who may be saved from the ones with a higher toxin dose where death is inevitable.

Summary

Tetanus may be mild, moderate, severe, or inevitably fatal. Our clinical experience suggests it may be classified as severe (or, maybe, inevitably fatal) when a tetanic spasm stops respiration.

Ten patients with severe tetanus were treated by the total paralysis regime (T.P.R.), consisting of tracheostomy, curarization, and intermittent positive- or positive/negative-pressure respiration. Two of the patients were saved by T.P.R. and therefore only limited effectiveness can be claimed for the regime.

In inevitably fatal cases survival can be prolonged by T.P.R. so that further effects of tetanus toxin emerge. Of these, the most important appears to be direct damage to the myocardium.

We thank Dr. A. T. H. Marsden for the histology reports. Professor R. Kirk for the photomicrograph, and the many doctors and nurses who helped in the respiration unit.

REFERENCES

- Creech, O., Glover, A., and Ochsner, A. (1957). *Ann. Surg.*, **146**, 369.
- Foldes, F. F. (1957). *Acta anaesth. scand.*, **1**, 63.
- Gailani, S., Danowski, T. S., and Fisher, D. S. (1958). *Circulation*, **17**, 583.
- Goodman, L. S., and Gilman, A. (1955). *The Pharmacological Basis of Therapeutics*, 2nd ed., p. 682. Macmillan, New York.
- Lassen, H. C. A., Børneboe, M., Ibsen, B., and Neukirch, F. (1954). *Lancet*, **2**, 1040.
- Powell, K. J., Brimblecombe, F. S. W., and Stoneman, M. E. R. (1958). *Ibid.*, **1**, 713.
- Radford, E. P. (1955). *J. appl. Physiol.*, **7**, 451.
- Reid, H. A., Bowler, B. P., and Scott, L. T. (1958). *Brit. med. J.*, **1**, 772.
- Wright, E. A. (1954). *J. Path. Bact.*, **68**, 131.
- Wright, G. P. (1958). *Proc. roy. Soc. Med.*, **51**, 997.