Ps. pyocyanea infection as reviewed by Stanley (1947).

According to the tables of mortality probabilities in burns, Case 3 had less than a 5% chance of survival under modern burn therapy. He responded well from the start, even before the administration of cortisone. He did not develop any evidence of pulmonary oedema, despite the fact that on the second day he received 15,500 ml. of fluid (Fig. 2). He did, however, develop marked peripheral oedema, making it necessary by the third day to split the body cast. This oedema probably accounts for the marked positive fluid-balance at this time. Cortisone therapy was begun on the fourth day and continued to the twenty-seventh day. Eosinophil counts were found to be depressed on the tenth, twelfth, and twenty-fourth days (Fig. 3). The cortisone dosage was tapered off on the nineteenth and finally stopped on the twenty-seventh day. The very high counts on the following days may indicate that the endogenous production of corticoids was somewhat depressed. The patient experienced a remarkable state of well-being, almost euphoria, during the period of cortisone administration and after its cessation. Also, he managed a sizeable calorie intake, averaging over 4,000 calories daily and on three occasions reaching 7,000 calories. Although it has been reported (Ragan *et al.*, 1950) that too much cortisone may delay wound-healing, no such difficulty was encountered in this case, despite the fact that the first graft was made during the period of cortisone administration.

Summary

Three cases of severe burn are presented in which routine burn therapy was supplemented by the administration of cortisone acetate.

The first patient, who suffered a 55% burn, died despite cortisone therapy. He had a normal histological distribution of lipid material in the adrenal cortices at necropsy.

The second patient, who suffered a 30% burn, received cortisone from the third to eighth days, during which period she was remarkably well. Her condition deteriorated clinically after the initial change of burn dressings on the tenth day. She died on the twenty-fourth day, death apparently being due to sepsis. The finding of markedly decreased sudanophilic material in her adrenal cortices suggests adrenal exhaustion at the time of death.

The third patient, who suffered a 70% burn, has done well. He received cortisone from the fourth to twenty-seventh days and displayed a remarkable state of well-being and a keen appetite. This unusual recovery may be related to the cortisone therapy.

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REFERENCES

- Brown, A. (1946). *J. Path. Bact.*, **58**, 367.
 Brown, W. A., Farmer, A. W., and Franks, W. R. (1948). *Amer. J. Surg.*, **76**, 594.
 Bull, J. P., and Squire, J. R. (1949). *Ann. Surg.*, **130**, 160.
 Cain, A. J., and Harrison, R. G. (1950). *J. Anat.*, **84**, 196.
 Crassweller, P. O., Farmer, A. W., and Franks, W. R. (1950). *British Medical Journal*, **2**, 242.
 Hawk, P. B., Oser, B. L., and Summerson, W. H. (1947). *Practical Physiological Chemistry*, 12th ed., p. 699. London.
 Lund, C. C., and Browder, N. C. (1944). *Surg. Gynec. Obstet.*, **79**, 352.
 Ragan, C., Howes, E. L., Plotz, C. M., Meyer, K., Blunt, J. W., and Lattes, R. (1950). *Bull. N.Y. Acad. Med.*, **26**, 251.
 Sayers, G. (1950). *Physiol. Rev.*, **30**, 253.
 — and Sayers, M. A. (1949). *Ann. N.Y. Acad. Sci.*, **50**, 522.
 Shuman, C. R., and Finestone, A. J. (1950). *Proc. Soc. exp. Biol.*, **N.Y.**, **73**, 248.
 Sprague, R. G., Power, M. H., Mason, H. L., Albert, A., Mathieson, D. R., Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F. (1950). *Arch. intern. Med.*, **85**, 199.
 Stanley, M. M. (1947). *Amer. J. Med.*, **2**, 253, 347.

AN UNUSUAL COMPLICATION OF MYANESIN THERAPY IN THE TREATMENT OF TETANUS

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"Myanesin" (α - β -dihydroxy- γ -(2-methylphenoxy)-propane; mephenesin) was introduced into clinical use by Berger and Bradley (1947), and was first used for relief of spasm in two cases of tetanus by Belfrage (1947), with encouraging results. Torrens, Edwards, and Wood (1948) treated a moderately severe case of tetanus with a combination of intramuscular and intravenous injections of myanesin, giving 22 g. in nine days, with considerable benefit to the patient. Davison, Ward, and Pask (1949) also treated two cases. The first case, after a period of treatment with curare and sedatives, was given intermittent intravenous injections of myanesin and recovered. The second was more seriously affected, and myanesin was used from the beginning of treatment. When it was found that a single intravenous injection controlled the spasms for only about 30 minutes, an intravenous glucose-saline drip was set up and myanesin added in varying amounts according to the condition of the patient. After 26½ hours of continuous myanesin treatment haemoglobinuria was observed and the myanesin was discontinued, but the patient immediately relapsed and died from violent spasms two hours later. Macdonald (1949) combined intravenous myanesin with intravenous thiopentone, giving 1–1.5 g. myanesin and 0.5–0.75 g. thiopentone in each 600 ml. of glucose-saline. In 23 days he gave a total of 40 g. myanesin and 32.75 g. sodium thiopentone. No haemoglobinuria occurred, and the patient, a child aged 8, recovered. Godman and Adriani (1949) used the American oral preparation "tolserol" in eight cases of tetanus; all but one of their cases were mild. They found that in doses ranging from 62.5 to 750 mg. in children, and up to 3,500 mg. in adults, it was an extremely satisfactory relaxing agent.

Case Reports

The following are reports of two cases of tetanus in which oral myanesin was used. Rectal thiopentone was also given in the first case.

Case 1.—A man aged 38, an inmate of a colony for mental defectives but of fairly high mental grade, was employed as an agricultural labourer. He gave no history of recent injury. On March 12, 1950, he complained of a painful stiff neck, which was thought to be due to fibrositis; he remained in bed but had no special treatment. The pain increased in severity and spread from the neck to the trunk and legs, and on the morning of March 16 he had a generalized convulsion. He was admitted to hospital, under the care of M. L. N. and J. D. R., at 2.30 p.m. on that day. On examination he was seen to be a well-built muscular man; there was no external injury, and he was fully conscious, flushed, and sweating profusely. There was rigidity of the neck and shoulder muscles with trismus and risus sardonicus. The erector spinae, the anterior abdominal muscles, and all muscles of the legs were in persistent spasm, and clonic contractions of the legs occurred on attempts to flex the knees. The arms were unaffected. No abnormalities were found in the heart, lungs, or central nervous system.

It was decided to treat the patient with a combination of myanesin and rectal thiopentone. At 3.50 p.m. 1 g. of myanesin dissolved in 10 ml. sterile water was given intravenously. Within two or three minutes complete relaxation had occurred, and the change in expression of the patient was most striking as his anxious frown and "risus" relaxed. The patient was given 250,000 units of tetanus antitoxin intramuscularly, and appeared to be comfortable, but by 5 p.m. generalized rigidity had recurred and a further 1 g. myanesin was given intravenously and 2 g. myanesin in tablet form by mouth. Again the intravenous myanesin had a rapid effect, but within half an hour spasms had recurred. At 5.50 p.m. the first dose of 2 g. sodium thiopentone was given per rectum; within 10 minutes the patient had completely relaxed and fallen asleep, but he was disturbed by several sneezing attacks (which are not unknown under light thiopentone narcosis), though these did not precipitate any tetanic spasms. At 8 p.m. there was again generalized rigidity, and the patient was given a further 1 g. myanesin intravenously. He was now ordered 2 g. myanesin by mouth and 0.5 g. sodium thiopentone per rectum, both every two hours. These were given regularly between 11.30 p.m. and 9.30 a.m. the next morning. At 8.50 p.m., about two hours after his third injection of myanesin, he passed

Relationship of muscle tone to myanesin and thiopentone dosage in Case 1.

"port-wine" urine, and the next two specimens of urine, passed at 3.30 a.m. and 4.30 a.m., were also heavily stained. Spectroscopic examination confirmed the presence of haemoglobin, but the specimen passed at 9 a.m. was clear both to the naked eye and on spectroscopy; there was no recurrence of haemoglobinuria.

The following day there was only moderate neck stiffness and the patient was able to speak and swallow without difficulty; he had, however, developed a cough with purulent sputum and there were scattered rales and rhonchi on both sides of the chest. The same dosage of myanesin and rectal thiopentone was continued, but the myanesin elixir was substituted for the tablets. During the day there were only two spasms, both affecting the right leg. The chest condition worsened. Through a misunderstanding the myanesin was omitted during the second night in hospital, though three doses of rectal thiopentone were given. At 7.30 a.m. on the third day the patient had a severe generalized spasm with opisthotonos. Rectal thiopentone was given, followed by oral myanesin, and complete relaxation was obtained within 10 minutes. After this there was no return of major spasms, though rigidity of the neck and abdominal muscles recurred from time to time; this was easily controlled by oral myanesin. The accompanying Graph shows the time-relationship between the spasms and muscular rigidity and the dosage of myanesin and sodium thiopentone.

In spite of decreased dosage of sedatives, the chest condition deteriorated rapidly and the patient died on the evening of his fifth day in hospital. The total dosage of myanesin was 3 g.

intravenously and 40 g. by mouth. Altogether 11 g. sodium thiopentone was given per rectum.

At necropsy the body was reported to be that of a well-nourished male. A healing abrasion was present over the left scapula, and there were several splinters in the hands—one 4 mm. long with a surrounding inflammatory reaction and deeply embedded. Anaerobic cultures from this splinter were negative for *Cl. tetani*. No abnormalities were noted in the heart, the central nervous system, or the alimentary system. The lungs showed suppurative bronchitis with early hypostatic pneumonia. The kidneys showed some evidence of old-standing chronic nephritis; otherwise the urinary tract was normal.

Case 2.—A man aged 45 was admitted under the care of G. R. R. on June 7, 1950, at 8.45 p.m. Six days previously while pushing a wooden tomato-stake into the ground he drove a splinter into his left antecubital fossa. He immediately boiled a pair of forceps, pulled out the splinter, dressed the small puncture wound with "dettol," and applied a bandage. Four days later, in the morning, while driving his bus, his back became stiff. The following day, 36 hours before admission, he noticed that his "gums were stiff"; there was some difficulty in chewing. On the day of admission he complained that while walking "something seems to run up and down my spine, and every now and then everything seems to stiffen up—throat, jaws, and back." For the last 12 hours he had been unable to swallow anything.

He was a well-built muscular man, alert and euphoric. He was lying quietly on his back with a stiff neck. There was no neck retraction. His spine was rigid and he was unable to sit up. He was edentulous and could separate his gums by only $\frac{1}{2}$ in. (1.58 cm.). There were no other abnormal signs, except for the presence of a small unhealed puncture-wound in the left antecubital fossa which appeared moist and unhealthy. There was no lymphangitis nor were there palpable lymph nodes.

A diagnosis of tetanus was made and treatment instituted as follows: Antitetanic serum, 100,000 units intravenously and 50,000 units intramuscularly, was given and sodium penicillin, 250,000 units six-hourly, begun. Myanesin, 1 g. in 20 ml. distilled water, was then given intravenously at 11.10 p.m. Within 30 seconds the patient smiled, said he had not felt so well for days, and asked for a drink. He sat up in bed and could bend his neck so that his chin almost reached his chest. His trismus disappeared and he could separate his gums by about $1\frac{1}{2}$ in. (3.75 cm.). He was then given 2 g. of myanesin in 2 oz. (57 ml.) of the elixir by mouth. He took one sip and complained of a burning sensation in the mouth; the elixir was therefore diluted with an equal quantity of water. He still found it rather hot and sipped it slowly. At the fifth sip he clutched his throat, had a violent attack of coughing, and, with his eyes bulging and tears streaming down his cheeks, rapidly became greatly distressed. The paroxysm lasted about two minutes, and on his recovery he said, "It went down the wrong way, doctor." It was noticed that though he had stopped coughing a rattling noise was coming from the trachea. From then on until his death signs in the chest became progressively more prominent. The patient was encouraged to finish his elixir and was given a further 2 oz. half an hour later. With this second dose there was again a paroxysm of coughing. With neither of these paroxysms was there any return of spasticity. At 12.30 a.m. he was taken to the theatre and his wound excised under nitrous oxide, oxygen, and "trilene" anaesthesia. A swab from the wound failed to yield any *Cl. tetani* on culture. Unfortunately the tissue removed was not examined. More myanesin was then given—2 oz. of the elixir at 2 a.m. and 4 a.m., the latter dose being swallowed slowly and with difficulty. At 5.15 a.m. abdominal cramps and dysphagia necessitated a further 1 g. myanesin in 20 ml. distilled water intravenously. Relaxation was immediate, and at 6 a.m. the patient managed to drink a further 2 oz. of the elixir. At 9 a.m. he objected to the elixir, so crushed tablets (2 g.) were substituted. At 9.15 a.m. he tried to cough up some mucus, became intensely cyanosed, and had a generalized clonic convulsion with loss of consciousness. Mucus was sucked from his pharynx, and after artificial respiration and the administration of oxygen with 5% carbon dioxide he

recovered. Postural drainage then produced a good deal of thick mucopus. Numerous rales could now be heard at both bases and in the left axilla. At this stage lumbar puncture yielded normal fluid. The urine was clear. At 11.15 a.m. a further 2 g. crushed tablets of myanesin was prescribed, but he was unable to swallow the powder, and it was noticed that some of the previous dose was still adhering to the tongue and the pillars of the fauces. It was therefore decided to give 1 g. myanesin intravenously and then pass a stomach tube. However, every effort to pass a Ryle's tube or an oesophageal catheter (12E) resulted only in tracheal intubation. It is noteworthy that this caused no distress or cough. The attempt was then abandoned. A further 1 g. myanesin was given intravenously at 3 p.m., and soluble phenobarbitone 3 gr. (0.2 g.) intramuscularly as he had not slept since admission. A quarter of an hour later he again started to cough, became cyanosed, and had clonic convulsions. Resuscitation failed, and he died.

At necropsy the brain was intensely congested, but apart from this appeared normal. The trachea and bronchi contained a moderate amount of mucopurulent fluid, and there was marked congestion of both lungs with bronchopneumonia at the bases. The heart showed no macroscopic abnormality. The liver was congested. The spleen and kidneys appeared normal.

Discussion

Cole and Spooner (1935) describe four degrees of severity of tetanus. In the second degree there is generalized tonic rigidity; in the third the tonic rigidity passes on to the stage of reflex spasms. Our Case 1 corresponds to the third category, and according to those authors this bears a poor prognosis. Case 2 corresponds to the second category, in which the prognosis is better; but the short incubation period in this case indicates a severe attack. Both patients responded extremely well to intravenous myanesin, and in the first case the oral myanesin was of considerable value in controlling spasm.

In the first patient it appeared that during the last three days of his illness the tetanic symptoms were under control and required only small doses of antispasmodics and sedative, but he had already developed signs of bronchitis by the second day in hospital, and it seems likely that he was too heavily sedated during his first 15 hours of treatment. It is not thought that the myanesin was responsible for the development of the chest complication, as even when given intravenously it did not depress respiration. The two drugs appeared to have a synergistic action, as when both drugs were given the patient was easily controlled; but when, as during the second night in hospital, the myanesin was withheld, a very violent spasm occurred (see Graph). Both drugs were easily administered. The sodium thiopentone was given rectally in 10% solution. The patient could swallow freely, or the elixir could easily have been given by tube.

With the second patient, although the elixir was diluted with an equal quantity of water after the initial sip, it still burnt his throat and he was unable to swallow it as a draught. After a few minutes he found that the solution no longer burnt him. This we now believe to have been due to the local analgesic action of the elixir on the pharynx. It was at this stage that there was the first violent fit of coughing: quite clearly some of the elixir entered the trachea. From this point a rapidly progressive purulent bronchitis developed. With the second dose further elixir was inhaled. The substitution of powdered tablets for the elixir, coming at a time when swallowing was again difficult, resulted in the powder adhering to the tongue and the mucous membrane of the mouth and fauces, where it exerted its local analgesic action. It was this analgesia that accounted for the stomach tube passing straight into the trachea at every attempt without producing any cough or distress. It is probable that during this period saliva

containing dissolved and undissolved myanesin was trickling down the trachea. This would account for the very rapid development of the severe bronchitis in a man with no previous chest history who was receiving penicillin and was nursed sitting upright throughout his illness.

The asphyxial attacks seemed to be due to mucopus being coughed up and accumulating at the back of the pharynx. The presence or absence of laryngeal spasm could not be determined, but it was noticed that there was no trismus or neck stiffness. The convulsions followed the intense cyanosis and were presumably anoxaemic in nature rather than tetanic.

Myanesin has two properties. It causes muscle relaxation by an action on the central nervous system: this may be a depressant action on the reflex excitability of the spinal cord. Its second property, on which no emphasis has been placed in the literature to date, is its local analgesic action. This we believe to be important, and indeed consider it to be directly responsible for the fatal outcome in Case 2. In view of this local analgesic property we feel that myanesin should not be given by mouth to patients with tetanus, in which dysphagia is a common occurrence.

A suggested scheme of treatment would be to begin with an intravenous injection of myanesin, 1 g. in 20 ml. distilled water. This should cause relaxation and enable a Ryle's tube to be passed into the stomach. Two ounces of myanesin elixir could then be given via the tube and repeated half an hour later. In the early stages two-hourly doses of 2 oz. (57 ml.) myanesin elixir by stomach tube would probably be needed, and it might be necessary also to give 0.5 g. thiopentone per rectum. Later the dose of myanesin could cautiously be reduced and the time interval between doses increased. It is felt that the intravenous preparation is of considerable value in the rapid control of severe spasms. The risk of haemoglobinuria after oral myanesin appears to be remote, as it did not recur in our patient after a further 40 g. by mouth, nor did Godman and Adriani (1949) report it in any of their eight cases. In those cases in which oral intubation is difficult or poorly tolerated myanesin could be given in doses of 1 g. intramuscularly.

It is stressed that myanesin should be used solely as an adjunct to treatment with antitetanic serum, penicillin, and local wound excision. The patient should be sedated as little as possible and nursed in the sitting position.

Summary and Conclusions

Two fatal cases of tetanus treated with myanesin are described. The first case also received rectal thiopentone.

Investigation showed that myanesin, given intravenously and orally, is a useful relaxant and controls tetanic spasms satisfactorily; and that when used in therapeutic doses it does not depress respiration.

Myanesin has a local analgesic action and should never be given in powder form by mouth. The elixir should not be given when there is dysphagia. When administered intravenously the risk of haemoglobinuria is diminished by adequate dilution, and may be ignored.

In the second case death occurred from lung complications due to the inhalation of myanesin elixir.

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REFERENCES

- Belfrage, D. H. (1947). *Lancet*, 2, 889.
 Berger, F. M., and Bradley, W. (1947). *Ibid.*, 1, 97.
 Cole, L., and Spooner, E. T. C. (1935). *Quart. J. Med.*, 1, 295.
 Davison, M. H. A., Ward, A. B., and Pask, E. A. (1949). *British Medical Journal*, 1, 616.
 Godman, H. E., and Adriani, J. (1949). *J. Amer. med. Ass.*, 141, 754.
 Macdonald, W. B. (1949). *Med. J. Aust.*, 2, 538.
 Torrens, J. A., Edwards, P. M., and Wood, M. W. W. (1948). *Lancet*, 2, 807.