

## THE EFFECTS OF INTRASPINAL INJECTION OF MAGNESIUM SALTS UPON TETANUS.

By S. J. MELTZER AND JOHN AUER.

(From the Rockefeller Institute for Medical Research, New York.)

In several investigations, some <sup>1</sup> of which have already been published, the writers studied the effects of magnesium salts upon the animal body. The starting point for the investigations was the idea that magnesium salts may have a specific relation to the inhibitory processes of the vital functions. Among the results which have been obtained thus far may be mentioned: (1) deep anæsthesia produced in several species of animals by subcutaneous injections of magnesium salts; (2) the same effect produced with smaller doses of the salts given intravenously; (3) interruption of conductivity by local applications of magnesium salts to nerve trunks; (4) production of anæsthesia by intraspinal injection of magnesium salts. The last effect has a special bearing upon the subject of this paper and hence it will be dwelt upon at greater length.

The first experiments were made upon dogs, cats, and rabbits in which it was found that an injection of a solution of magnesium salts into the lumbar region of the spinal canal caused anæsthesia and paralysis from the pelvis down. The effects were, however, very variable. In a certain number of experiments there was no effect or the animals failed to recover from the paralysis, or succumbed to the injection. The effects became more uniform as soon as monkeys were used for the experiments. On the basis of our experiments on these animals we can state in a general way that a dose of 0.06 to 0.07 gram of magnesium sulphate to one kilo body weight injected through the fourth

<sup>1</sup> S. J. Meltzer and John Auer, *Am. Jour. of Phys.*, 1905, xiv, 366.

“ “ *Am. Jour. of Phys.*, 1906, xv, 387.

“ “ *Am. Jour. of Phys.*, 1906, xvi, 233.

“ “ *Medical Record*, 1905, lxviii, 965.

S. J. Meltzer and Haubold, *Jour. of Am. Med. Assoc.*, 1906, xli, 647.

lumbar intervertebral space definitely produces, sooner or later, anæsthesia and paralysis more or less pronounced, from which the animal recovers in eight to twenty hours. Repeated at proper intervals this dose caused in many of the monkeys the same general effects without recognizable harmful after-results. This dose or one a little larger caused in some instances more pronounced effects; the paralysis spread upward and the animal became, in time, generally anæsthetic. Even from these profound effects the animals recovered completely in the above-mentioned time. A still larger dose produced, in a comparatively short time, a respiratory paralysis from which the animal died without convulsions. But even in these cases artificial respiration through a tracheal tube, begun while the heart-beat was still present, would soon restore life, and if continued long enough the animal would begin again to breathe spontaneously. A dose of the salts which is just sufficient to paralyze the respiration is practically without effect upon the heart-beat and blood pressure, that is, without direct effect. To affect the heart and blood pressure much larger doses are required. This statement may be taken as the rule, from which there are a number of exceptions.

Using our experience with monkeys as the basis, spinal anæsthesia has already been employed upon human beings. It may be stated here that in human beings a dose of 0.03 gram of magnesium sulphate per kilo produces, after some time, deep anæsthesia accompanied by considerable relaxation of all the muscles, lasting from five to eight hours. The respiration is sometimes reduced, but the pulse and blood pressure remain nearly normal.

In view of the fact that the intraspinal injection of magnesium salts affected profoundly the central nervous system and especially the functions of the spinal cord, it occurred to us that certain pathological states depending upon an abnormal activity of the cord might be influenced by these injections. The first conditions to claim our attention were strychnine poisoning and tetanus. We intend in this communication to report the results obtained in our studies upon experimental tetanus.

To produce tetanus we used tetanus toxin. We had again to

contend with the difficulty of selecting proper animals. The animals which have hitherto been employed in tetanus experiments, namely mice or guinea-pigs, were useless for our study, since they could not be relied upon to bring out uniform results. Hence we resorted to monkeys. The cost of monkeys precludes their free use, and furthermore, we did not find in the literature any definite statement of the degree of susceptibility of monkeys to tetanus toxin.

Our studies are, therefore, limited in extent, and we cannot claim to have solved all the problems which the subject suggests. Nevertheless our experiments throw some light upon what we may expect from intraspinal injections of magnesium salts in the treatment of tetanus. One of the questions which seemed fundamental was: Could the intraspinal injections of magnesium salts bring about complete relaxation of the tonically contracted muscles of the tetanic state? Previous experiments had shown us that spinal injections in normal animals produced complete paralysis. But in this case we had only to deal with suppression or interruption of normal impulses, not especially of an inordinate strength. In tetanus, on the other hand, one has not only to deal with a greatly hyperæsthetic cord which, as in strychnine poisoning, causes on slight peripheral stimulation maximal clonic contractions of many muscles, but, unlike any other state, the condition is one of continued contraction of many groups of muscles which are not infrequently in a state of maximum tonicity. Hence we asked ourselves: Will the intraspinal injection be capable of conquering the extraordinary hyperæsthesia of the cord and the exaggerated tonic impulses?

Another question which we asked ourselves was whether the injections would be able to paralyze the muscles implicated in the production of opisthotonus and trismus, in other words, muscles which are innervated by cerebral and cervical nerves, without at the same time reaching the respiratory centre.

To these questions we can now give positive answers. We have seen, more than once, an animal in an exquisite state of tetanus with trismus, opisthotonus, etc., with strong hyperæsthesia and frequent clonic convulsions, lie absolutely relaxed and free from

all tetanic symptoms after receiving a single dose of magnesium sulphate (0.08 gram per kilo), while at the same time respiration, heart-beats, etc., were normal; and later the animal recovered completely from the effects of the magnesium salt. Intraspinal injections of magnesium salts are capable, therefore, of abolishing completely, at least temporarily, both tonic and clonic tetanic contractions; and certain doses also affect the muscles of the neck and face without implicating the respiratory functions.

Acting upon an hypothesis which we do not intend to discuss in this paper, we endeavored to ascertain whether these intraspinal injections are capable of retarding the development of the tetanic symptoms. To obtain an answer to this question we had to begin the magnesium injections soon after introducing the tetanus toxin. The discussion of the outcome of these experiments will be deferred until the actual protocols of some of the experiments have been given.

*Protocols of Experiments.<sup>2</sup>*

Series I. Tetanus toxin 4/100 of a mgr. fatal on the third day for 100 grams of guinea-pig. Hence it equals 1 m.l.d. for guinea-pigs. April 30, 1906, 4 P.M., injected into the right gluteal region of 4 monkeys 2 m.l.d. (8/100 of a mgr.) tetanus toxin for each 100 grams of body weight.

Monkey A, 2828 grams, control. May 2, 12 M. (44 hours after injection), animal very active, possibly slight stiffness of right leg. May 3, 2 P.M. (70 hours after injection), right hind leg definitely stiff, tail deviates to right side, seems weak, not as belligerent as formerly. May 4, 11 A.M. (91 hours after injection), found dead; arms, legs, fingers, etc., flexed and rigid. Was seen alive by the attendant one hour before.

Monkey B, female, 1698 grams. April 30. Soon after the injection of the tetanus toxin 0.4 c.c. of a 25 per cent. magnesium sulphate, = 0.06 per kilo, was injected through the fourth (?) lumbar space. Spinal fluid obtained. No recognizable effect. May 1, 11 A.M. Injected into fourth space 0.45 c.c. 25 per cent. magnesium sulphate. Spinal fluid obtained(?). Shortly after hind legs completely paralyzed; 9.55, P.M., completely recovered from paralysis. May 2, animal normal; no injection given. May 3, 2 P. M. (70 hours after toxin injection), right hind leg used less than other, seems somewhat rigid, tail deviates to right. Injected into fourth lumbar space 0.2 c.c. 25 per cent. magnesium sulphate. No marked effect. May 4, 11 A.M. (91 hours after injection of toxin), animal lying on side, right hind leg rigid, left leg less so, jaws closed, cannot be opened passively; arms moderately stiff, but can grasp things. 11.10 A.M., injected 0.25 c.c. magnesium sulphate into fourth (?) lumbar space.

---

<sup>2</sup> For the tetanus toxin used in these experiments we are indebted chiefly to Dr. J. J. Kinyoun who supplied us with a dry toxin.

no fluid obtained. 12 M., no definite change, perhaps jaw less locked. 2.10 P.M., injected 0.25 c.c., spinal fluid obtained. 2.15, considerable relaxation of hind legs, almost perfectly flaccid. 4.30 P.M., lies on side, moves arms occasionally, neck relaxed but unable to open jaws. May 5, 10 A.M. (114 hours after toxin injection), very rigid, arms and legs contracted, head retracted. 12.15 P.M., injected 0.25 c.c. 25 per cent. magnesium sulphate into fourth space; spinal fluid obtained. 1.05 P.M., hind legs completely relaxed, head only slightly retracted, respiration slow. Jaws still locked. May 6, 1 A.M., found dead by watchman. Animal lived at least 126 hours after injection of tetanus toxin.

Monkey C, 2178 grams. April 30, soon after the injection of the tetanus toxin 0.45 c.c. 25 per cent. magnesium sulphate injected through fourth space; no spinal fluid obtained, no recognizable effect. May 1, 11 A.M., animal normal. Injected through fourth space 0.55 c. c. 25 per cent. magnesium sulphate (0.063 per kilo); spinal fluid obtained. Hind legs paralyzed within a few minutes. 11.20, unable to move, respiration slow, lid reflex active, pupils small. 11.30, respiration getting slower. 11.40, no lid reflex, no respiration, heart-beat cannot be felt. Tracheotomy made and artificial respiration started. 11.50, corneal reflex present again; heart-beat strong again. Artificial respiration continued. 3 P.M., able to breathe spontaneously when artificial respiration is stopped. Artificial respiration continued till 6 P.M., then wound sutured but tracheal canula allowed to remain in place. Animal breathes well. Left without attendance. 9.55 P.M., found dead but still warm.

Monkey D, 1708 grams, female. April 30. Soon after the injection of the toxin 0.4 c.c. of 25 per cent. magnesium sulphate injected through fourth lumbar space; spinal fluid obtained. 20 minutes later animal lying on floor of cage, moves head occasionally; respiration good. May 1, animal normal; no magnesium sulphate given. May 2, animal lively, normal. 12 M., injected 0.3 c.c. of 25 per cent. magnesium sulphate into fourth space; spinal fluid obtained. Almost immediately hind legs relaxed. 1.50 P.M., animal lying flat on belly, head resting on floor, breathing very slowly but deeply, moves head slightly but apparently unable to move arms or legs. May 3, normal and fairly active. 2 P.M. (70 hours after injection of toxin), right hind leg moderately stiff, tail deviates to right side. May 4, 11 A.M. (91 hours after injection of toxin), hind legs stiff but not as marked as in "B"; able to open jaws moderately (still able to eat this A.M.). 11.15, injected 0.2 c.c. magnesium sulphate through fourth space; spinal fluid obtained. 11.30, considerable relaxation of hind legs, able to open mouth wide. 3 P.M., hind legs entirely relaxed, grasps with arms. 4.30, hind legs more rigid again, however able to open mouth (eating again) and neck fairly relaxed. May 5, 10 A.M. (114 hours after injection of toxin), lying on side, legs and arms rigid, head retracted. 12.30 P.M., 0.25 c.c. of 25 per cent. magnesium sulphate injected through fourth space; spinal fluid obtained. 1.05, some relaxation of hind legs; arms and head rigid. Injected again 0.15 c.c.; no further change. May 6, 5 A.M., found dead by watchman. Animal "D" lived about 130 hours after the injection of the toxin.

In this series of experiments in which doses of toxin used were double the minimal lethal dose for guinea-pigs, the control animal died in 90 hours and the animals B and D, which

received the magnesium, lived at least 125 hours. Furthermore, 44 hours after the injection the control monkey already showed slight stiffness of the right leg, while the treated animals showed nothing; 70 hours after injection the right leg was definitely stiff in the control while in B the right leg "seemed somewhat rigid" and in D the right hind leg was "moderately stiff."

There were also some noteworthy differences between the monkeys B and D. The first injection of magnesium had no effect at all in B, while it nearly completely paralyzed all the extremities in D. The second injection in B, which was larger and given on the following day, only paralyzed the hind legs, while in D the second dose, which was smaller than the first and repeated after forty-four hours, again paralyzed the entire animal. D was apparently more profoundly affected by magnesium than B. Corresponding with this we find that ninety-one hours after the toxin, when the control animal was already dead, the hind legs of D were stiff "but not as marked as in B" and D was able to open the jaws "moderately" while in B "the jaws were closed and could not be opened passively."

We may therefore say that in this series the intraspinal injection of magnesium salts had, apparently, a retarding effect upon the development of the symptoms as well as upon the fatal action of the tetanus toxin, and the retarding action seemed to be the more pronounced the more the magnesium salts had exercised their paralytic influence.

Series II. The same dried toxin used.

A test on guinea-pigs showed the toxin to be unaltered. July 5, injected into three monkeys 6/100 mgr. tetanus toxin for each 100 grams body weight.

Monkey A, 1935 grams; control. July 5, 4.15 P.M., injected the toxin into the right gluteal region intramuscularly. July 6 and 7 no sign of general or local effect. July 8, 11 A.M. (67 hours after injection), right hind leg stiff, "definitely stiffer than in the other monkeys"; right arm seems stiff; almost unable to open jaws. July 9, 10.30 A.M. (about 90 hours after injection), found dead; "still warm." Head retracted, jaws locked; arms flexed at elbows and wrists, pressed on body.

Monkey B, male, 2000 grams. July 5, 3.15, received toxin into right glutei. 3.25, injected through third space (?) 0.6 c.c. magnesium sulphate; no spinal fluid obtained; no effect. July 6, 2.25 P.M., injected 0.6 c.c. magnesium sulphate through third space; spinal fluid obtained. Within two minutes hind legs completely paralyzed, flaccid, no sensation; within ten minutes front legs weak, falls on side. 3.20 P.M., lid reflex active, pupils small, entire body completely relaxed.

July 7, active, no magnesium given. July 8, 11 A.M. (68 hours after the toxin), right hind leg stiff, "less than control," opens jaws wide, eats, tail slightly deviated to right. 11.20, injected through third space 0.4 c.c. of 25 per cent. magnesium sulphate. 12 M., no distinct paralysis, but lies quietly in cage. Injected again 0.2 c.c. magnesium; spinal fluid obtained. 1 P.M., very quiet, feels no pinch in hind legs but uses them to grasp. July 9, 10.30 A.M., (92 hours after toxin), head retracted, jaws moderately locked, able to open about 0.5 cm.; legs and arms stiff, unable to sit or stand. 10.45, injected 0.5 c.c. 25 per cent. magnesium sulphate between fourth and fifth lumbar vertebræ; no spinal fluid obtained. 11.40, no definite effect. Injected 0.3 c.c. magnesium sulphate between third and fourth lumbar vertebræ; spinal fluid obtained. 12.45, no marked relaxation. Injected 0.3 c.c. magnesium sulphate between third and fourth lumbar vertebræ. 1.10, legs and abdomen much relaxed, respiration slow. 2 P.M. hind legs completely relaxed, arms not so stiff, head moderately retracted. 5 P.M., hind legs flaccid, front legs a bit stiffer now, head more retracted, jaws cannot be opened passively. July 10, animal died at 10.40, A.M., 114 hours after injection of toxin.

Monkey C, female, 2540 grams. July 5, 3.45 P.M., received toxin into right glutei. Injected 0.7 c.c. 25 per cent. magnesium sulphate between third and fourth lumbar vertebræ; spinal fluid obtained. No noticeable effect, later shows marked weakness in hind legs. July 6, 2.30 P.M., monkey normal. Injected between third and fourth lumbar vertebræ 0.6 c.c. 25 per cent. magnesium sulphate; spinal fluid obtained. Hind legs paralyzed almost at once, front legs show weakness, head sinks to floor. Placed inclined, head higher in cage. 4 P.M., upper part of body more relaxed than before; lid reflex active. July 7, very quiet, moderate weakness, eats. No magnesium given. July 8, 11 A.M. (68 hours after toxin), right leg moderately stiff, less than control, eats, opens jaws wide, yawns. 12 M., injected 0.4 c.c. 25 per cent. magnesium sulphate between third and fourth lumbar vertebræ; spinal fluid obtained; shortly after hind legs paralyzed, right hind leg apparently less stiff than before; lies in cage. July 9, 11 A.M. (92 hours after toxin), able to support herself; ate this afternoon; no retraction of head; able to open jaws moderately; front legs held flexed, close to body, but are moved freely; grasps objects. Hind legs held flexed at hip and knees, moderate resistance to extension. Tail practically straight. Animal shaken by spasmodic contractions. 11.20 A.M., injected 0.7 c.c. 25 per cent. magnesium sulphate between third and fourth lumbar vertebræ; spinal fluid obtained. 11.25, no spasmodic movements so far. Suddenly respiration stopped, time lost with compression of chest, traction of tongue, etc. Later tracheotomy made and regular artificial respiration begun. No effect, animal dead.

July 9, a fourth monkey was injected with  $1\frac{1}{2}$  m.l.d. of the toxin used on July 5. Toxin tested on guinea-pigs and proved to have the same strength as on July 5.

Monkey D, female, 2362 grams. July 9, 12.20, P.M. received in the right glutei 1.5 m.l.d. of toxin per 100 grams. 12.26, injected 0.5 c.c. magnesium sulphate between third and fourth lumbar vertebræ; spinal fluid obtained. Some magnesium lost. 1.05, no visible effect. Injected again 0.3 c.c. magnesium sulphate; spinal fluid obtained. 2 P.M., hardly able to use legs, scratches buttocks frequently. 5 P.M., same, except that she does not scratch; does not feel

pressure of foot on tail. July 10, uses legs well. 11.30, injected 0.4 c.c. 25 per cent. magnesium sulphate between fourth and fifth lumbar vertebræ; spinal fluid obtained. In a few minutes unable to use hind legs, scratches buttocks again. 5 P.M., able to sit up but cannot use hind legs. July 11, 2.30 P.M., no sign of stiffness or paralysis. Injected 0.3 c.c. 25 per cent. magnesium sulphate between fifth lumbar and sacrum; no fluid obtained. 3 P.M., unable to use hind legs, otherwise active. 5 P.M., hind legs completely paralyzed, scratches lower parts. July 12, still scratches herself; uses hind legs; right hind leg a little stiff (11 A.M., 71 hours after toxin). 12 M., injected 0.4 c.c. 25 per cent. magnesium sulphate between fourth and fifth lumbar; spinal fluid obtained. 1.30 P.M., hind legs paralyzed and relaxed; scratches herself continually. July 13, 11 A.M. (95 hours after toxin). Right hind leg definitely stiff but can grasp with toes. Able to open jaws but not as widely as yesterday. No scratching. Injected 0.4 c.c. 25 per cent. magnesium sulphate between fourth and fifth lumbar vertebræ; spinal fluid obtained. 11.20, rests head on table, no scratching. 4.15, hind legs flaccid, uses arms freely; scratches lower parts, occasionally even bites skin. 4.20, injected 0.25 c.c. between fourth and fifth lumbar vertebræ; spinal fluid obtained. No notes on effect. July 14, 11 A.M. (119 hours after toxin), lies on left side curled up, legs flexed on hips and knees, body curved, opisthotonus, head moderately retracted, can be moved, able to protrude tongue through jaws; unable to eat. 10.40, injected 0.5 c.c. magnesium sulphate between fourth and fifth lumbar vertebræ; spinal fluid obtained. 11.45, hind legs fully relaxed, flaccid. 12 M., no pain felt in lower two-thirds of body. 1.30, lies on inclined board, head down; looks greatly relieved and improved. July 15, animal died about 6 A.M.—about 138 hours after injection of toxin.

In Series II we again see the control animal dying 90 hours after the injection of toxin, while the animals which received magnesium lived, in case of B 114 hours, and D 138 hours, while C lived only 92 hours. The last animal, however, died not of tetanus but of an overdose of magnesium while she was still in a good condition.

There was, therefore, marked difference in the development of the symptoms between the control and the treated animals. Sixty-seven hours after the injection of the toxin the control was unable to open the jaws, the forearms seemed stiff, and "the right hind leg was definitely stiffer than in the other monkeys." The other three monkeys at this time opened their jaws wide, were able to eat without difficulty, and were using their legs with only little impediment.

To recapitulate briefly, the series of eight monkeys received tetanus toxin in quantities apparently above the minimum lethal dose. Two served as controls and six were treated with magnesium sulphate intraspinal injection in varying doses and at



varying intervals. Two of the latter animals died from overdoses of the magnesium. The two controls died about ninety hours after the injection of the toxin, while four animals which received smaller doses of the magnesium survived the controls, one by twenty-four hours, one by thirty-six hours, one by forty hours, and one by forty-eight hours. In five of the magnesium treated animals the onset and the development of the tetanic symptoms were distinctly retarded in comparison with the controls. Furthermore, the retardation appeared to be more pronounced in those animals in which the injection of magnesium produced the most marked effects.

The completely relaxing effect of the injections of magnesium salts was evident in some of the injections given in these series. For reasons which will be mentioned presently we had to avoid larger doses in these series just at the advanced stage of the tetanic symptoms, and we were, therefore, frequently not in a position to demonstrate, by a single dose of the magnesium salts, the complete overpowering of all tetanic symptoms, especially at their height. But we were able to do this, as stated above, in other experiments in which magnesium was not given from the very beginning and in which the interval between injections was sufficiently long to permit the use of large doses. Here in these cases a single injection of a sufficient dose would cause in a short time absolute relaxation, and suppress completely a condition of violent tetanus.

Repetition of the injections, in the above series, brought to light an instructive fact with regard to the effects of intraspinal injections which compelled us to avoid in serial injections the use of larger doses. While a single dose of 0.06 or 0.07 gram of the salt per kilo animal would in normal monkeys produce hardly more than paralysis of the posterior extremities and pelvic region, and never proved fatal, we saw that in animal C of Series I on the second day a dose of 0.063 gram per kilo abolished the respiration within a short time after the injection; and in animal C of Series II a dose of 0.069 gram per kilo administered on the fifth day killed the animal within a few minutes, while the same dose injected on the first day had only a very

moderate effect. The fatal result was, evidently, caused by cumulative action of the magnesium salt. Some of the injected solution, apparently, remains for a time in the spinal canal or in some part of the central nervous system. At present it cannot be stated how much of the solution and how long it remains there. As the tetanus intoxication progressed we had to grope our way carefully with regard to the dose of magnesium salt to be injected as well as with regard to the intervals which had to pass between the injections. Towards the last, therefore, the doses given were often small and inefficient as we did not care to risk losing the animal through an overdose at this stage of the disease.

It is obvious that in judging the significance of our results the last mentioned fact has to be taken into account. Had we been less bound by economical considerations, and had we risked towards the end of the disease somewhat larger doses at more frequent intervals, we feel confident that we would have been successful in some cases in prolonging the life of the animal by many more days, although we might have killed some monkeys prematurely by an overdose of magnesium. With regard to Monkey D in Series II, for instance, we feel confident that had we given a slightly larger dose on the seventh day and repeated the dose of magnesium also on the evening of that day, the animal would not have died on the eighth day following the injection of toxin. Furthermore, it is possible that in some cases we might even have been successful in tiding over the animal until the newly formed antitoxin could have overtaken the balance of free toxin, and the metabolic processes of the body have mastered the toxin fixed by the nerve cells; or in other words we might have saved the animal's life.

While, therefore, as far as this short series of experiments is concerned we were unsuccessful in saving, by means of intraspinal injections of magnesium, the lives of any of the animals poisoned with tetanus toxin, the results do not justify the conclusion that such intraspinal injections are incapable of saving tetanic animals. On the contrary, the experiments brought out certain rather encouraging facts. It was established that the intraspinal

injections are capable of abolishing completely all tonic and clonic muscular contractions, thus eliminating for many hours at a time one at least of the most dangerous factors in the disease. Moreover, the experiments disclosed the important fact that intraspinal injections of magnesium salts are capable of retarding perceptibly the progress of the disease.

The last fact is a new and, in a certain sense, an unexpected point, inasmuch as the retardation of the progress and development of the tetanic symptoms cannot be considered simply as a consequence of the inhibitory property of the salts or of their ability to relieve the symptoms. This effect was, however, not wholly unexpected by us, since, as we stated above, on the basis of a certain hypothesis which we had formed, we looked for it, and, therefore, in a part of the experiments we began to inject the salts long before there appeared tetanic symptoms to relieve. As regards the hypothesis itself, we believe it would be premature to state it here; we intend, however, to discuss it shortly in connection with another investigation.

We mean to mention in this place some distinctions with reference to our problem between human beings and monkeys which might have theoretical as well as practical significance. There is in the first place a difference in the two species of extension of the spinal cord in the lumbar canal. The autopsies on monkeys taught us that in the species which we employed the cord extends to the sacrum. Any injection made, therefore, in the lumbar region could produce injury of the cord. It is, however, noteworthy that every monkey except one (an animal which had been used previously for other experiments) showed, nevertheless, no effect due to this cause, although in some cases repeated injections were made. Yet it cannot be excluded that in some cases a part of the fluid may have entered and remained in the cord, a possibility which might perhaps account for variation of effect where an identical dose of the salt was employed under apparently the same circumstances. In human beings, on the other hand, the injections are always made below the cord.

Another point of distinction arises from the circumstance that in monkeys only very little spinal fluid can be obtained and none

of the injected fluid could be recovered, even soon, after the injection. When intraspinal injections are made in human beings, spinal fluid equal in amount to the injected quantity of the salt solution can be removed previously. This preliminary lowering of the pressure within the canal aids possibly in a more rapid distribution of the solution through the entire canal, and is perhaps partly responsible for the observed fact that in human beings the effective dose of the magnesium salt (per kilo body weight) is not even one-half that which is required for monkeys. Furthermore, in human beings "washing" of the canal proved to be a helpful procedure. When the respiration became too slow spinal fluid was withdrawn and saline was injected several times and again withdrawn. The patient soon recovered from the effects of the magnesium salts. In monkeys we were deprived of such a help in case of danger and had, therefore, to keep away from the danger line.

Intraspinal injections of magnesium sulphate have already been employed in a small number of cases of human tetanus. We shall append here brief notes, as far as they have come to our notice, concerning these cases.

Case 1, described by Dr. J. A. Blake.<sup>3</sup>—A boy of fifteen had trismus, opisthotonus, etc., and a temperature of 104.4 F. This was on the sixth day after the first tetanic symptoms appeared, which began seven days after injury to the fingers, and he had already received 115 c.c. of tetanus antitoxin and morphine without relief. The boy's weight was about 65 kilos and 4.5 c.c. of a 25 per cent. solution of magnesium sulphate was injected into the spinal canal, that is 0.02 gram per kilo. "Six hours after the injection the jaws could be opened wide; the stiffness of the neck and back had disappeared . . . and the temperature had fallen to 102.6 F, the pulse to 104; the respirations were 14." Thirty-three hours after the injection of magnesium sulphate its effect seemed to have entirely passed off and another injection of the same amount was made. "In two and a half hours he was relaxed and asleep." After twenty-four hours there was a steady increase in the spasmodic contractions and after thirty-seven hours the opisthotonus returned. Another injection was then given of 8 c.c. of 12½ per cent. magnesium sulphate. This injection was again followed by complete relaxation. A similar injection to the last was repeated after twenty-nine hours with a similar result. In the next four days "the symptoms were not severe and the patient was kept comfortable with morphine and chloral." On the sixth day after the last injection "the opisthotonus became more severe

---

<sup>3</sup> J. A. Blake, *Surgery, Gynecology, and Obstetrics*, 1906, v, 541.

and there was considerable rigidity of the jaw muscles and considerable pain," so that a fifth injection of magnesium was given which was followed by marked relief. After this the convulsions were much less frequent and severe, and gradually disappeared, so that after fourteen days the boy was practically well.

In this case with complete recovery five intraspinal injections were given without any injurious effect whatsoever. Each injection produced complete relaxation lasting quite a long time. There was no evidence of a cumulative effect, but, on the contrary, "a certain amount of tolerance seemed to be established for the sensory impulses and the cerebrum . . . the motor symptoms were practically the same after each injection." No rise of fever occurred after the last three injections.

Case 2, boy reported by Dr. Samuel Logan,<sup>4</sup> New Orleans.—Tetanus set in on the ninth day after an injury of the hand inflicted by a toy pistol. On the third day of the disease, after antitoxin and chloral and bromide had been given in full doses with no avail, 4 c.c. of a 25 per cent. solution of magnesium sulphate were injected into the spinal canal—1 c.c. for every 20 pounds of body weight—under anæsthesia. It was noticed "that under complete anæsthesia the abdominal muscles were never relaxed, the abdomen being rigid and hard as a board on palpation." Forty minutes after the injection all the muscles of the body were completely relaxed, the abdomen was soft, and the mouth could be opened readily; the patient was perfectly conscious and said that he felt well. About five hours after injection a profuse bronchorrhœa developed and the breathing grew rapid and shallow. Atropin seemed to have relieved this condition perceptibly. Pulse was 140 and thready. (On the day before the injection the pulse varied between 120 and 140 and the respiration between 24 and 36.) About twelve hours after the injection the tetanic symptoms began to come back, and eleven hours later the muscles of head, neck, and abdomen were rigidly contracted, but the general convulsions did not return. Temperature 102 F., pulse 150 and thready; respiration 30. Under anæsthesia a small dose of magnesium sulphate (50 minims of a 25 per cent. solution) was again injected. Thirty-five minutes after the injection, all the muscles of the body were again completely relaxed. Three hours after injection bronchorrhœa again developed which was again partially relieved by atropin and applications of heat. The general condition of the patient, however, gradually became worse; the pulse rose to 192, the respirations to 50, and the patient died in a state of complete relaxation about sixteen hours after the last injection. No autopsy was made.

In this case too the intraspinal injections of the magnesium abolished promptly and completely all tetanic symptoms. The

<sup>4</sup> Samuel Logan, *Journal Am. Med. Assoc.*, 1906, xlvii, 1502.

bronchorrhoea was probably no after effect of the magnesium injection, but possibly of some complication (pulmonary tetanus?); the high pulse and respiration before the injection of magnesium would seem to indicate this.

Case 3, observed by Dr. Charles D. Peck, at the French Hospital, New York. We are enabled, by the courtesy of Dr. Peck, to give the following notes.—A man thirty-five years old received an insignificant wound in the sole of the foot, which healed rapidly. Four days after the injury a violent tetanus broke out. He received large doses of antitoxin and sedatives but no relief. An intraspinal injection of magnesium sulphate, 1 c.c. of a 25 per cent. solution to every 25 pounds of body weight, had only a moderately relaxing effect. After twenty-four hours the injection was repeated but this time 1 c.c. of the solution was given for every 18 pounds of body weight. The anæsthetizing and relaxing effect was now complete. We had the privilege of seeing the patient about four hours after the second injection was made. He was under perfect general anæsthesia; all parts of the body were completely relaxed, the abdominal muscles being especially soft; no sign of tremor or twitch anywhere except now and then a slight retraction of the right corner of the mouth produced by tickling the nasal mucous membrane. Lid reflex was present, respirations 22 per minute, fairly deep. Pulse 120, of fair quality, and temperature 102 F. The temperature and pulse were the same as before the injection. Three hours later the patient was given an intravenous injection of 60 c.c. antitoxin. The patient died suddenly about two hours later. Dr. Peck informs us that the respiration remained good to the end.

These three cases show that in human beings the intraspinal injection of magnesium sulphate is capable of abolishing completely for quite long periods the severest symptoms of tetanus. In the first case it was apparently the means of saving the patient's life. That the other two patients died while their muscles were in a perfectly relaxed condition may be taken to indicate that tetanus toxin has other poisonous effects besides those which produce the tetanic symptoms. Since, however, other interpretations are possible, we cannot afford to enter here into a discussion of this subject.

#### CONCLUSIONS.

Intraspinal injections of magnesium sulphate, in doses which do not affect the respiratory centre or other vital function, are capable of abolishing completely all clonic convulsions and tonic contractions in cases of human tetanus, and experimental

tetanus in monkeys. The relaxing effects of the injections may last twenty-four hours or longer.

In experimental tetanus in monkeys early intraspinal injections of magnesium salts are capable of retarding the progress and development of the tetanic symptoms.