

PHYSIOLOGICAL AND PHARMACOLOGICAL STUDIES
OF MAGNESIUM SALTS.¹

V. THE INFLUENCE OF NEPHRECTOMY UPON THEIR TOXICITY.

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Introductory.—The narcotic effect as well as the toxicity of magnesium salts, when introduced subcutaneously, depend to a great degree upon the readiness with which they are eliminated from the body. By what path are these salts eliminated? Are they excreted by the intestinal canal or are they eliminated through the kidneys? Meltzer and Auer² state that from their experiments they gained the impression “that animals which urinated frequently had a better chance for recovery. Early urination seemed also to prevent the full development of anesthesia. Furthermore it seems that magnesium sulphate after subcutaneous injection acted as a diuretic.” Such observations seemed to indicate that the kidneys are taking an essential share in the elimination of the magnesium salts. On the other hand J. B. MacCallum³ states that magnesium salts (magnesium chloride) not only do not act as diuretics, but exert directly an inhibitory effect upon the urinary secretion. Furthermore from a remark recently made by Mendel it seems to follow that magnesium as an alkali earth leaves the body by the bowel. Mendel⁴ states that the studies of the paths of excretion for inorganic compounds seem to “indicate a noteworthy difference in the mode of elimination of these alkali metals in contrast with corresponding salts of the alkali earths. The latter have been shown to leave the body in far greater quantity by the bowel than in the urine.”

¹ Studies I-IV were published in the *American Journal of Physiology*.

² Meltzer and Auer, *American Journal of Physiology*, 1905, xiv, 386.

³ MacCallum, “On the Mechanism of the Physiological Action of the Cathartics,” Berkeley, 1906, p. 45.

⁴ Mendel and Closson, *American Jour. of Physiol.*, 1906, xvi, 45.

Of the alkali earths Mendel himself studied the elimination of strontium⁵ and barium salts.⁶ For the paths of elimination of calcium salts Mendel refers to Rey.⁷ For the salts of these three alkali earths it was variously established experimentally, as stated above, that no matter by what path introduced, they leave the body in far greater quantity by the bowel than in the urine. Magnesium like calcium is an alkali earth and from the rule laid down by Mendel for this class of inorganic compounds it seems to follow that the salts of magnesium also leave the body in far greater quantity by the bowel than in the urine. Are there any experimental facts for such an assumption?

Mendel who does not discuss specially the paths of elimination of magnesium, gives only one reference; it is to Lusk.⁸ But here we meet with a statement which is contrary to that assumption. Lusk says that "in carnivorous urine the major part of excreted magnesium is found in the urine, the balance being given off through the intestinal wall to the feces." Lusk mentions no authority for his statement. But the literature on metabolism of inorganic salts contains many studies which bear out this view of Lusk. In the extensive studies of F. Müller,⁹ for instance, we find a statement which is exactly like the one made by Lusk. He says "dass beim Fleischfresser der Kalk zum weitaus grössten Theil durch den Darmkanal aus dem Organismus ausgeschieden wird, während die Magnesia . . . hauptsächlich durch den Harn verlässt." Other writers speak of the fraction of magnesium salts which leaves the body through the kidney as being between thirty and forty per cent. However this may be, there is a unanimity of opinion amongst all the investigators, at least as far as we can see, on one point which is of especial interest to us, namely that there is a striking difference between calcium and magnesium with reference to the path of elimination,

⁵ Mendel and Thatcher, *American Jour. of Physiol.*, 1904, xi, 5.

⁶ Mendel and Sicher, *ibid.*, 1906, xvi, 147.

⁷ Rey, *Archiv f. exp. Path. u. Pharm.*, 1895, xxxv, 295. See Rüdell, *ibid.*, 1893, xxxiii, 79.

⁸ Lusk, "American Text-Book of Physiology," 2d edition, 1900, Vol. i, p. 527.

⁹ Müller, *Zeit für Biol.*, 1884, xx, 334. Heiss, *ibid.*, 1876, xii, 156. Bertram, *ibid.*, 1878, xiv, 335. Renvall, *Skandinavisches Arch. für Physiol.*, 1904, xvi, 94.

the former preferring the alimentary canal, while the latter favors the kidney. In the quoted metabolism experiments the salts of magnesium and calcium were administered by the mouth. As far as we know, there are no experiments on the mode of elimination of magnesium salts when they were given subcutaneously or intravenously. Possibly in the latter cases the elimination through the kidney would prove to be still more favored. At any rate the rule laid down for the elimination of calcium, strontium and barium cannot be applied *a priori* to the elimination of magnesium.

We may therefore claim that there is, to say the least, no experimental evidence based on chemical analysis against the assumption that the kidneys are taking an important share in the elimination of magnesium salts. On the other hand, the above quoted observation of Meltzer and Auer "that animals which urinated frequently had a better chance for recovery" may be taken as an indication in favor of such an assumption. The authors, however, had at that time not made a special study of that question; they speak only of their impressions. Besides, the fact that urination and recovery went hand in hand is not safe evidence that the urination contributed to the recovery. Possibly the recovery takes place through the elimination of magnesium into the intestines and urination occurs on account of the removal of magnesium and in accordance with the above mentioned claim of MacCallum that the presence of magnesium in the blood inhibits urinary secretion; the coincidence of recovery and urination would then mean that recovery is the cause and urination the result and not the contrary.

There is, however, another biological method by which the share of the kidneys in the elimination of the magnesium salts can be systematically studied and which is capable of bringing out reliable results. It is the study of the susceptibility of the animal to the toxic effect of magnesium salts after nephrectomy. Such a series of experiments were carried out by us and the object of this paper is the report of the findings of this research.

THE SUSCEPTIBILITY OF THE ANIMAL TO THE TOXIC EFFECT OF
MAGNESIUM AFTER NEPHRECTOMY.

Method.—The experiments of Meltzer and Auer on the anesthetic effect of subcutaneous injection of magnesium salts were made on seven species of animals and with the sulphates as well as with the chlorides. The present experiments were made on rabbits only, and only magnesium sulphate was employed. Under ether anesthesia double nephrectomy was performed and after recovery from the ether anesthesia variable quantities of magnesium sulphate in molecular solution were injected subcutaneously, using approximately the same region for injection in all animals and observing the same conditions. The results of this research will be presented best by quoting a few abbreviated protocols of experiments.

Fatal Dose.—In the following experiment one gram of the salt per kilo animal was injected shortly after nephrectomy.

Experiment 1.—June 19, 1906. A series of three rabbits was used.

A. White rabbit, 2,480 grams. 3 p. m. Both kidneys exposed by lumbar route, pedicles firmly ligated and the greatest part of each kidney removed.

3.35. Rabbit recovered from ether, appears quiet and normal. Injected magnesium sulphate ($\frac{M}{I}$ solution), one gram per kilo weight.

4.10. Animal drowsy, chin rests on floor, head to one side, respiration shallow.

4.35. Lying on side, completely relaxed.

4.43. No conjunctival reflex; reacts feebly to probe in nose.

5.05. Respiration very shallow, 36 per minute.

5.15. Respiration stopped, heart still continues to beat. Animal died one hour and forty minutes after the injection.

B. (Nephrectomized control.) Black rabbit, 2,340 grams; appears to be less robust than A.

3.20. Nephrectomized as in A.

4.00. Does not recover from the anesthesia as rapidly as A; trembles (carbolic intoxication?).

4.20. Hops around, rises on hind legs and seems normal.

June 20. Eats cabbage, appears normal.

June 21, 10 a. m. Did not eat at morning feeding, drinks a little water.

12 noon, found dead.

This animal died about 45 hours after nephrectomy.

C. (Magnesium control.) White and black rabbit, 1,625 grams, not operated.

3.30. Injected magnesium sulphate ($\frac{M}{I}$ solution) one gram per kilo weight.

At no time was there the slightest sign of a magnesium effect, the rabbit appearing at all times as normal as before the injection.

In this series one gram of magnesium sulphate per kilo animal weight killed the nephrectomized animal one hour and forty minutes after the injection (two hours and fifteen minutes after the operation), whereas the same dose had not the slightest effect upon the normal rabbit and the nephrectomized control animal which received no magnesium, lived forty-three hours and appeared to be normal until a few hours before its death. From the experiments of Meltzer and Auer it appears that a dose less than 1.75 grams per kilo, when given subcutaneously and without massage is not fatal to the rabbit. For the nephrectomized rabbits a dose of only one gram of the salts per kilo animal proved to be fatal; that means an increase of the susceptibility of the animal to the poisonous effect of the magnesium salt nearly equal to fifty per cent.

Experiment 2.—Series of two rabbits. June 25, 1906.

A. Gray rabbit, 2,500 grams.

2.15 p. m. Double nephrectomy.

4.10. Injected one gram magnesium sulphate per kilo animal.

4.30. Animal shows signs of beginning anesthesia and paralysis. All symptoms gradually increased and the animal died at 7 p. m. about three hours after the injection.

B. Control (Rabbit C from former experiment). Not operated.

June 25, 4.10 p. m. Injected 1.6 magnesium sulphate per kilo animal.

5.30. Animal greatly relaxed; lid reflex much retarded. Anesthesia and paralysis were at no time complete; the animal soon began to show recovery, and next morning appeared to be perfectly well again.

In this experiment again in the nephrectomized rabbit one gram per kilo killed the animal in a few hours after the injection, while in the normal animal 1.6 grams per kilo was even insufficient to produce complete temporary anesthesia.

In these and in other similar experiments it was then found that one gram per kilo, injected two or three hours after nephrectomy, proved to be a fatal dose, the animal becoming first anesthetized and paralyzed a few hours after the injection.

Effect of Late Injection.—The result was different, however, when the injection was not administered until about eighteen hours or more after the nephrectomy. The following protocols will illustrate.

Experiment 3.—June 26, 1906. Rabbit A, weighing 1,992 grams, was nephrectomized at 6.30 p. m. Rabbit B, weighing 1,957 grams, was nephrectomized at 6.50 p. m.

A. June 27, 12.35 p. m. (eighteen hours after nephrectomy). Injected magnesium sulphate one gram per kilo in $\frac{M}{I}$ solution; *slight massage*.

2. Chin rests on floor, animal remains lying on side when turned over; recovers posture when tail is pressed.

4.45. Animal lying stretched out, relaxed, conjunctival reflex slight. Reacts to probe in nose and on pressing tail.

June 28, 11.40 a. m. Animal shows some recovery, occasionally makes an effort to rise; lid reflex retarded, but definitely present; on pressing the tail, the animal moves head and feet and cries feebly.

Animal died at 1.30 p. m., twenty-five hours after injection, forty-three hours after operation.

B. June 27, 12.40 p. m. About eighteen hours after nephrectomy injected magnesium sulphate one gram per kilo in $\frac{M}{I}$ solution; massage, stronger than in A.

1.20. Strongly influenced by the salt. Lies flat, head on floor. Raises head when tail is pinched, lid reflex still present.

4.40. Lid reflex completely gone; no reaction to pressure of tail or to probe in nose.

Animal died at 8 p. m., about seven hours after the injection, twenty-five after nephrectomy.

Both animals were injected about eighteen hours after nephrectomy and in both the injected places were massaged, in *B* a good deal more strongly than in *A*. Animal *A* was never completely under anesthesia, had shown later some slight recovery and lived about twenty-five hours after the injection. Animal *B* was completely under anesthesia and died without recovery about seven hours after the injection.

This last rabbit (*B* of Experiment 3) was the only animal which lived so short a time as seven hours after the injection when the latter was given late after nephrectomy. Some animals lived twenty-four hours and more after the injection, and one rabbit lived as long as sixty-three hours after an injection of one gram of the salts per kilo animal, which was given twenty-four hours after the double nephrectomy. The narcotizing effect was in this case fairly outspoken and the recovery was very slight, the animal remaining for about three days in the semi-paralyzed and semi-stuporous state.

In general it may be stated that the later after the nephrectomy one gram salt per kilo was given, the less fatal it proved to be and also, perhaps, the less complete was the state of depression; the recovery, however, was in all cases but slight.

Anesthetic Dose.—In eight experiments the dose of the salt injected into the rabbits amounted only to 0.8 gram per kilo animal. We shall illustrate the results by one abbreviated protocol.

Experiment 4.—June 21, 1906. Gray rabbit, 1,520 grams.

1 p. m. Double nephrectomy.

1.50. Injected magnesium sulphate 0.6 grams per kilo in $\frac{M}{1}$ solution.

3.50. Lying flat, completely relaxed, respiration very slow. Conjunctival reflex present, but diminished.

4.45. Lying completely relaxed on side, conjunctival reflex gone.

6. No change.

June 22, 1.30 p. m. Improved; able to sit up; conjunctival reflex returned.

June 23, 12 noon. Rabbit died, about forty-six hours after injection.

In this experiment with 0.8 grams per kilo, injected very soon after nephrectomy, the animal was completely anesthetized, the depression lasting about twelve hours followed by a moderate degree of recovery. The animal survived the injection by forty-six hours, death apparently being due solely to the nephrectomy. In other experiments with the same dose and under the same conditions the profound anesthesia lasted sometimes more than twenty

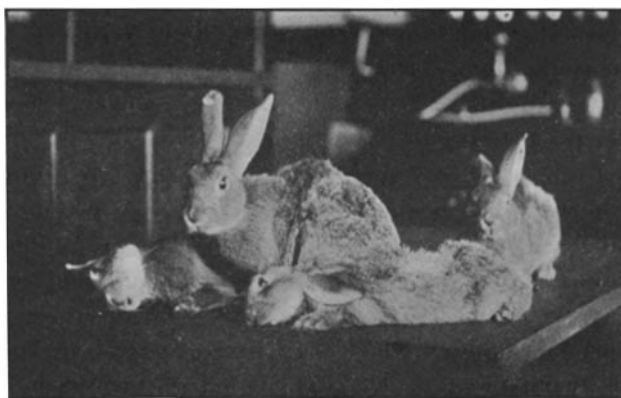


FIG. 1. All four rabbits were nephrectomized about twenty-two hours before the photograph was taken. The two animals lying on the table received two hours after the nephrectomy subcutaneous injections of magnesium sulphate, 0.8 per kilo, and about two hours later were completely under the toxic influence of that salt. They remained for about eighteen hours profoundly anesthetized and paralyzed. At the time when the photograph was taken the rabbit on the right hand side showed a slight recovery. The other two rabbits are (nephrectomized) controls.

hours; in other cases again the anesthesia was sometimes a little less complete and the recovery a trifle better than in the last quoted experiment (see Figure). But in the entire series there was no case without distinct anesthetizing and paralyzing effect and none with a fatal outcome due to the magnesium salts. It is hardly necessary to add that in normal rabbits a dose of 0.8 grams per kilo had not the slightest effect.

In a few experiments a dose of 0.8 grams of the salt per kilo animal was given twenty-four hours after nephrectomy. The following protocol is an illustration.

Experiment 5.—July 2, 1906. Grey rabbit, 1,810 grams, 11.40 a. m. Double nephrectomy, perfect recovery.

July 3, 1.54 p. m., about twenty-six hours after nephrectomy, injected magnesium sulphate 0.8 grams per kilo in $\frac{M}{I}$ -solution.

3.00 p. m. Animal relaxed, lid reflex very slight.

4.00. Lid reflex gone; no spontaneous movements and no reaction to pressing tail, etc.

10.00. Condition unchanged.

July 4, 10 a. m. Slightly improved, moves head when probe is put in nose, but no reaction to pinching of tail and no lid reflex.

July 5, 10 a. m. Considerably improved; can almost sit up; lid reflex retarded, but present; moves away on pressing tail.

3 p. m. Recovery still more pronounced. Head erect; movements irregular and jerky.

July 6, 8.30 a. m. Found in a dyspnoic state; the animal died five minutes later, about sixty-seven hours after the injection and about ninety-three hours after the operation.

This animal, although injected twenty-six hours after the nephrectomy, became influenced by the salt very rapidly; the depression was very profound and lasted over twenty-four hours. It survived the injection, however, longer than any other animal and the final recovery was more advanced.

Here again, as in the experiments in which a dose of 0.8 grams of the salt was given soon after the nephrectomy, the extent of the effect of the injection was somewhat variable, but the effect was on the one hand never missing and on the other hand never fatal.

In general it may be said that for a dose of 0.8 gram per kilo of the salt there was not a marked difference between the effects of the injections whether given soon after nephrectomy or twenty-four hours later, and this difference certainly cannot be compared

with the striking differences observed in the experiments with one gram per kilo animal.

Minimum Dose.—We have made seven experiments in which a dose of only 0.6 gram of the magnesium salt per kilo rabbit was injected. The following few abbreviated protocols will illustrate the corresponding results.

Experiment 6.—June 21, 1906. Gray rabbit, 1,520 grams.

1 p. m. Double nephrectomy. Completely recovered.

3.20. Injected 0.6 gram of magnesium sulphate per kilo animal in $\frac{M}{I}$ solution.

4.45 and 6 p. m. Appears normal in every way. Animal remained normal until its death which occurred June 24, 8 p. m., about seventy-two hours after injection and seventy-four hours after operation.

In this animal 0.6 gram per kilo had apparently no effect whatsoever.

Experiment 7.—July 6. White rabbit, 1,610 grams.

11 a. m. Double nephrectomy; complete recovery.

2 p. m. Injected 0.6 gram magnesium sulphate per kilo in $\frac{M}{I}$ solution.

3.15. Some loss of muscular control, especially of hind legs; reflex much retarded.

5.15. Stretched out, completely relaxed; lid reflex sluggish but present; reacts promptly to pinch of tail.

8.15. Shows some recovery; able to sit up.

July 7, 9.30 a. m. No further recovery. General muscular weakness, especially of the anterior part, reacts sluggishly to stimulation, lid reflex retarded. Animal remained in the same state until it died July 8, 7 p. m. It lived fifty-three hours after the injection and fifty-six hours after the operation.

This animal was moderately but distinctly influenced by a dose of 0.6 gram per kilo. It recovered from a major part of the depressing influence within five hours after the injection, but retained some degree of depression until death which was apparently due solely to the nephrectomy.

These two experiments represent both extremes of the results. Out of seven experiments with 0.6 per kilo three have shown practically no signs of depression. In the other four animals anesthesia and paralysis were present in a variable degree, but were never complete and lasted only a few hours. In two the recovery was not complete.

In two experiments the injection of 0.6 gram per kilo was given about twenty-four hours after the nephrectomy. In one the de-

pression was hardly noticeable and in the other the depression was well marked, but of only short duration with complete recovery.

Apparently in nephrectomized rabbits a dose of 0.6 gram per kilo is bordering on the minimum toxic dose and the various uncontrollable minor factors which frequently influence to a slight extent the degree of absorption cause this dose to be sometimes without any effect and at other times to produce a well defined, though only temporary influence.

Cumulative Effect.—An interesting point is the question of the cumulative effect. In normal animals the effect of several subminimum doses administered at various times is not equal to the effect of the sum of these doses when given in single injection on account of the elimination which takes place during the intervals between the injections. It was different, however, with the behavior of magnesium salts in nephrectomized animals, as can be seen in the following experiment.

Experiment 8.—July 6, 1906. White rabbit, 1,740 grams.

12 noon. Double nephrectomy.

2.15 p. m. Injected magnesium sulphate 0.3 gram per kilo in $\frac{M}{I}$ solution.

3.30 and 4 p. m. Animal normal.

4.15. Injected again, 0.3 gram per kilo of the magnesium salt.

4.30. Animal lying on side, completely under anesthesia; lid reflex gone.

8.15. Seems somewhat improved; moves head.

8.20. Injected again 0.3 gram per kilo.

11 p. m. Animal profoundly under anesthesia.

July 7. 9 a. m. Somewhat improved; moves head and feet, but lid reflex still absent.

9.25. Injected again (fourth time) 0.3 gram per kilo.

12 noon. Profoundly under anesthesia; respiration very shallow.

Animal died at 2 p. m.

In this animal two subminimum doses of 0.3 gram per kilo given two hours apart had after the second dose at least as much effect as 0.6 gram per kilo given in one dose. A similar result was obtained when a dose of 0.2 gram per kilo was given hourly. About half an hour after the third dose the animal became fairly well anesthetized and recovered again after a few hours. In these cases, if the interval between the injections did not exceed two or three hours, the cumulative effect was perfect and in fact the sum of two or more doses seemed to be even more effective than a cor-

responding single dose. Possibly the cumulative effect might have been due to the fact that a single dose was given in only one place, while the several smaller doses were given in several different places, the latter circumstance favoring absorption.¹⁰

Discussion.—The following facts were brought out by the foregoing series of experiments.

A dose of one gram magnesium sulphate per kilo animal, when injected subcutaneously within two or three hours after double nephrectomy proved invariably to cause death a few hours after injection. In normal animals such a constant result could be obtained only with a dose of 2 grams per kilo.

A dose of 0.8 gram per kilo, injected within two or three hours after nephrectomy, was never fatal to the animal, but the animal became invariably more or less completely anesthetized and paralyzed. In normal animals such a constant effect could be attained only with a dose not less than 1.6 gram per kilo.

The susceptibility to the anesthetic and toxic effects of the magnesium salts was therefore in the nephrectomized animals increased with about fifty per cent. This increase of susceptibility is apparently due to the decrease in the facility of elimination of the salts by the urine. These experiments therefore tend to show that normally the kidneys carry off at least fifty per cent. of the injected salts. We should, however, lay little stress upon the exact figures. But we are, we believe, justified in stating that the experiments demonstrate conclusively *that the kidneys play an essential part in the elimination of the magnesium salts.*

In harmony with this conclusion is the observation which was made upon the cumulative action of the magnesium salt in the nephrectomised animals. The effect of the two or three injections of subminimum doses was at least equal to the sum of these quantities given in a single dose; a fact which can only be explained by the assumption that during the intervals none of the salt was eliminated. This observation would seem to contain the suggestion that at least during the first few hours after an injection no elimination takes place except through the kidneys. We shall, however, not dwell too much on this side of the question.

¹⁰ Meltzer, *Jour. of Exper. Med.*, 1901, v, 643.

A further instructive fact is the observation that the profound anesthesia and paralysis produced by an injection of a dose of 0.8 gram per kilo lasted undiminished twelve to twenty hours and sometimes a good deal longer. Furthermore the recovery which finally took place was only moderate, the animal remaining until death in a pronounced state of paresis and stupor in sharp contrast with the nephrectomized control animal. In normal animals the anesthesia which was brought on by an efficient, but not fatal dose lasted at the utmost two hours and then the recovery was complete. This fact again can be best explained by the assumption that in the nephrectomized animal no fraction of the absorbed salts is eliminated for twelve or eighteen hours.

An interesting fact finally is the observation that a dose of one gram per kilo which is invariably fatal when given soon after nephrectomy is no longer fatal when injected eighteen to twenty-four hours after nephrectomy, although it still produces deep anesthesia; in other words eighteen to twenty-four hours after nephrectomy a dose of one gram per kilo acts like a dose of 0.8 per kilo injected soon after nephrectomy. This seems to indicate that some time after nephrectomy vicarious paths of elimination develop which thus assist in converting a fatal dose into only an anesthetic dose. This assumption would also explain the cause of the recovery from deep anesthesia twelve or eighteen hours after an injection of a dose of 0.8 gram per kilo; as at that time some of the salt becomes eliminated.

The degree of this vicarious elimination, however, is apparently very small; it never converted a fatal dose or an anesthetic dose into a harmless one, and the recovery from the anesthesia is only moderate, the animal generally remaining until death under a considerable influence of the salts.

The results which were obtained by us in the study of the effect of nephrectomy upon the toxicity of magnesium salts are in marked contrast to the results obtained by Meltzer and Salant¹¹ in their study of the effect of nephrectomy upon the toxicity of strychnin. Strychnin is generally assumed to be eliminated essentially through the kidney. Meltzer and Salant nevertheless found that the mini-

¹¹ Meltzer and Salant, *Journ. of Exper. Med.*, 1905, vi, 107.

imum toxic dose is for nephrectomized rabbits the same as for normal ones. For magnesium we found that for nephrectomized rabbits the dose is half of that which is toxic for the normal animals. Furthermore, the cumulative effect of strychnin is remarkably small. In intervals of two or three hours subminimum doses can be given, until they equal the sum of two or three times the toxic dose before any toxic symptoms will appear. For magnesium we found that the toxic effect will appear as soon as the sum of the subminimum doses becomes equal to the single minimum dose which is capable of producing an effect. Finally in nephrectomized rabbits no dose of strychnin was ever observed to produce continuous convulsions for any length of time; the animals either succumb soon or the convulsions gradually subside. With magnesium we observed that in nephrectomized rabbits the anesthesia may last uniformly for twenty-four hours and longer. Strychnin apparently finds soon after nephrectomy a satisfactory vicarious path for its elimination from the body, at least in rabbits. It should be mentioned that for guinea pigs Meltzer and Langmann¹² observed that within the first three hours after nephrectomy the toxic dose is indeed smaller than for the normal animal and that at that period in some animals a subminimum dose produced a continuous vibration which the authors termed a *subtetanic reaction*. They explained these observations by the assumption that in guinea pigs during the first few hours after nephrectomy vicarious paths for the elimination of strychnin are not yet developed.

Vicarious paths for elimination of magnesium even in rabbits do not develop until late after the nephrectomy and even then only in an unsatisfactory manner.

Conclusions.—Magnesium salts when introduced subcutaneously are eliminated to a great extent through the kidneys. In nephrectomized rabbits the susceptibility to the toxic effect of magnesium salts is increased by about fifty per cent.

The profound anesthesia which a toxic dose of magnesium produces in nephrectomized rabbits may be continuous for twenty-four hours and longer.

The cumulative effect of magnesium salts in nephrectomized

¹² Meltzer and Langmann, *Journ. of Med. Research*, 1903, ix, 19.

rabbits is very striking. The effect of several subminimum doses is equal to the effect produced by the sum of these doses given in a single injection.

A dose which when given soon after the nephrectomy is fatal, causes only a non-fatal anesthesia when given eighteen hours or later after the nephrectomy. Probably at that period vicarious paths develop sufficient for elimination of a fraction of the salts.

It is, probably for the last mentioned reason, that the profound anesthesia produced by a proper dose of the magnesium salts is partially recovered from about twelve to eighteen hours after nephrectomy.