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MAGNESIUM
ITS FUNCTION AND USE IN THERAPY

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Submitted in Partial Fulfillment for the Degree of
Doctor of Medicine

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April 1, 1955

Omaha, Nebraska

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Magnesium, an alkaline earth metal, is one of the basic elements of the body. About three-fourths of body magnesium is found in the skeletal system. Most of the remainder is found in muscle. Magnesium is largely an intracellular ion and, excluding potassium, it is the major intracellular cation.

The primary source of magnesium is cereals, fruit and vegetables. Since magnesium is present in organic combination with chlorophyl, green vegetables provide a good source. Some magnesium is also found in meat and milk.

Many forms of magnesium have been used in therapeutics. Some of the compounds, not, however, used specifically for the magnesium ion effect, are: magnesium carbonate which is used internally against gastric hyperacidity and as a mild laxative; magnesium citrate, a mild saline laxative; magnesium hydroxide, gastric antacid and mild alkaline laxative; magnesium oxide, also antacid and laxative; magnesium trisilicate, perhaps the most useful of this group for relief of gastric hyperacidity and pain in gastric and duodenal ulcer. Basic magnesium salts are all effective antacids.

Magnesium chloride and magnesium sulfate are the two compounds used for the physiologic effect of the ion. Magnesium sulfate is one of the most useful of the saline

cathartics. For the pharmacologic and physiologic action of the magnesium ion, the parenteral route is the avenue for most significant effect, and the compound of choice has always been magnesium sulfate.

For parenteral administration magnesium sulfate is always the compound used for pharmacologic or physiologic effect of magnesium ion.

The significance of magnesium for the organism has been incompletely studied as yet and there is much theory and supposition as regards its biochemical and cell level activity. Magnesium in the disease state has had even less study.

Magnesium requirement is not known for the adult but the growing child requires from 200 to 400 mg. daily to remain in positive magnesium balance. Of ingested magnesium, Martin, Mehl and Wertman(1) say that 60 per cent is excreted by stool and 40 per cent by the urine. They also state that forces governing passage across the cell membrane is unknown, but that rapid changes in serum magnesium suggests shifts in fluid volume. According to Goodman and Gillman(2) about 80 per cent of body magnesium is ionized and diffusible. And, for comparison of some of the cell magnesium values with serum magnesium (which is the only value that can be practically determined clinically), the following values are given: muscle magnesium 21 mgm per cent, erythrocyte

magnesium 4 mgm per cent, and serum magnesium concentration 2 to 3 mgm per cent. Dahl(3), in his studies, observed a slight increase in the magnesium concentration of the erythrocyte with a rising reticulocytosis, that is, in an anemia responding to treatment.

Determination of serum magnesium levels has been done by several techniques. Terkildsen(4) has developed an accurate quantitative method which involves electro-deposition of magnesium (presumably in the form of magnesium hydroxide) on a platinum electrode placed in a volume of serum after which the precipitated magnesium is brought into solution by an excess of acid and the amount determined by acid-base titration. He makes the comment that reliable flame photometers are not yet available. The normal values found by Terkildsen in his group ranged from 1.30 meq. per liter to 2.25 meq. per liter with a mean of 1.7 to 1.8 meq. per liter of magnesium. These values were independent of sex or age.

In the laboratories of Martin, Mehl and Wertman(1) the range of normal for serum magnesium is 1.50 meq. per liter to 1.83 meq. per liter. They determined the magnesium values for the average normal man as to plasma, interstitial and intracellular content qualitatively and quantitatively and obtained a total magnesium content for average normal man of 19 grams. For breakdown of

values see Chart I.

Distribution of Magnesium and Total Body
Magnesium in Average Normal Man

	Volume	Magnesium meq/L	Total Magnesium meq/L
Plasma	3.5 L	1.83	6.4
Interstitial	10.5 L	1.83	19.2
Intracellular	35 L	45.00	1575
Total			1600.6 meq. (19 gm)

Chart I.

Serum magnesium normals by Dahl(3) agree quite
closely with the above, agreeing most exactly with
Terkildsen's. Dahl expressed his values in mgm. per
100 ml. He did determinations on 37 normal men and on
35 normal women obtaining essentially the same average
value of 2.43 mgm. per 100 ml. He did determinations
on 8 boys and 8 girls (before menarche) and obtained
similar average values of 2.24 mgm. per 100 ml. Dahl's
technique made use of hydrochinone method, colorimetric
assays being made with solutions of known concentration.
Age, sex, height and weight were of no significance and
no definite relationship was found with hemaglobin,
hemacrit, nor mean corpuscular hemaglobin. He made
determinations on mothers' milk through period of

lactation and found it contained a fairly high amount
of magnesium.

The only site at which magnesium is known to be
osmotically active to a significant degree is in the
gastrointestinal tract which will be considered later.

Cosgrave and Perry(5) in 1949, after having observed
patients with thyroid disorders, concluded that thyroid
disorders do not effect plasma magnesium. In their
publication of 1952, Martin, Mehl and Wertman(1) say
that parathormone is known to give an increase in serum
magnesium, and that hyperthyroidism gives an increase in
protein bound fraction of magnesium, and myxedema gives an
opposite condition.

Martin, Mehl and Wertman studied four patients in
their laboratory who at one time or other exhibited
diabetic coma. The serum magnesium was found elevated
prior to institution of therapy. Some of the factors
which could not be ruled out were the possible effect
of dehydration, possible decrease in renal clearance and
possible accelerated tissue breakdown. During intensive
insulin and fluid therapy they demonstrated a fall in
18 to 24 hours of the serum magnesium to levels often
below normal. This was often concomitant with the fall in
serum potassium, inorganic phosphates and blood glucose.
They found that as moderate acidosis and ketosis develops

following insulin withdrawal in diabetics the urine
shows an increase in magnesium excretion. It will be
noted that each of the elements and compounds just
mentioned have in common a relationship to carbohydrate
metabolism. Some of the authors to be referred to
consider that magnesium very definitely stands in this
category and that its serum level may well be effected
by carbohydrate metabolism and vice versa.

Three of the patients(above) in diabetic coma had
had very high serum magnesium levels on entry associated
with normal or low potassium level and died despite
heroic therapy. The question of possible shift of
magnesium into cells in carbohydrate metabolism was
raised. At this point one could perhaps compare the
observations of Smith(6) who, in her work with dogs,
injected magnesium sulfate and obtained a 34 to 53
per cent decrease of serum potassium.

Magnesium is vital in intermediate metabolism which
requires magnesium for function of coenzyme and cozymase
(coenzyme I and coenzyme II) which are active in
carbohydrate and protein metabolism. Magnesium ions
greatly increase the activity of the phosphotases which
belong to the enzymes involved in metabolism of carbo-
hydrate, protein and lipids, therefore magnesium is
essential to every cell in the body. Magnesium is of

significance in resorption because it is necessary for
a series of phosphorylation processes. Dahl(7) says
magnesium in cooperation with insulin has an effect
on deposition of glycogen.

Emmel(8) demonstrated the effectiveness of
magnesium sulfate as an activator of alkaline phosphatase
by showing the increased sensitivity of both renal and
intestinal alkaline phosphatase to acid inactivation.

Magnesium is of some benefit in rickets(Dahl 3)
probably by its effect on phosphatase and thereby
ossification.

Goodman and Gilman(2) make a reference to the
importance of magnesium in dephosphorylation process
in muscle. Stoner(9) has conducted experiments on the
effect of magnesium ion on the distribution of phosphate
in the muscle of rat. This study made use of both
chemical and isotopic methods with particular reference
to ATP. Magnesium ion administered parenterally caused an
increase in ATP content of muscle. The animals were
killed when limp, which would make for increased ATP
content, so ether anesthetized animals were killed and
it was still found that the animals treated with magnesium
ion had a slightly higher ATP content in muscle. This
is supposedly due to magnesium inhibition of adenosine-
triphosphatase.

Another effect of parenteral magnesium was demon-
strated by Smith[6]. She considered an across-the-
membrane electrolyte shift when she noted a 35 to 53
per cent decrease of serum potassium with alteration in
respiration and flaccid paralysis. The respiratory changes
could be prevented by simultaneous administration of
potassium. One patient who had familial periodic
paralysis during an attack period of paralysis had a
serum potassium of 1.62 meq. per liter and serum
magnesium of 1.92 meq. per liter. Nine days later when
completely recovered the respective levels were 4.23
meq. per liter and 1.25 meq. per liter. It was question-
ed whether this represented a reciprocal shift of
potassium and magnesium into and out of cells.

The following material on electrolytes and inter-
relationship with magnesium, and particularly in diseased
states, is taken predominantly from the work of Martin,
Mehl and Wertman[1].

Magnesium is absorbed with difficulty from the
gastrointestinal tract and is excreted rapidly by way of
the glomeruli and in the process stimulates excretion of
calcium.

In five patients with chronic renal disease it was
noted that there was no correlation between non-protein-
nitrogen or creatinine and serum magnesium. Also there

was no definite relationship with calcium or sodium but there was a general correlation with potassium. With marked oliguria the serum magnesium was usually elevated. To date no definite evidence has been found of tubular secretion of magnesium, such as is the case with potassium.

In seven patients with acute type renal failure or nephron nephrosis associated with acute anuria or oliguria and azotemia (elevated non-protein-nitrogen), the serum magnesium was elevated above the normal for the Martin, Mehl, Wertman laboratory. Their values ranged from 1.84 to 2.70 meq. per liter. These results suggest a relationship of serum magnesium level to renal clearance.

Ten patients were seen who were receiving ammonium chloride and "mercuhydrin" therapy for congestive heart failure. Marked falls in serum magnesium was noted during periods of diuresis. The mechanism of the fall in serum magnesium was being studied at the time the authors published their paper.

Nine patients were seen who were receiving ACTH therapy both intramuscularly and intravenously. Five had normal serum magnesium levels and two had only slightly reduced levels.

The effect of constant intravenous magnesium sulfate

on renal function and the handling of other electrolytes
by the kidney was tested by Heller, Hammarsten and
Stutzman(10) using six normal young men. Over a
period of several hours a slight but constant drop in
renal plasma flow and glomerular filtration rate was
noted but considered to be of doubtful physiological
significance. There was an increase in urinary excretion
of sodium and chloride and a drop in potassium excretion,
however, over this period of time the serum concentration
of these electrolytes did not change. The mean renal
clearance of magnesium in the basal state was 5.37 cc
per minute. This was increased to 26.3 cc per minute.
following the injection of magnesium sulfate. There is
no definite evidence that the renal tubules are involved
in magnesium excretion.

Dahl(3) mentions a specific kind of renal calculi
which he theorizes may be prevented by administration of
magnesium. He points out that a decrease in magnesium
intake gives rise to production of oxalic acid in the
organism which causes an increase in calcium oxalate.
Magnesium forms magnesium calcium oxalate which is a
readily soluble complex. This mechanism, with admin-
istration of magnesium, may prevent calcium oxalate
renal calculi.

Experiments by Maltaner(11) show that magnesium ion

possesses an enhancing effect upon the clotting activity
of calcium ion. The lower the calcium ion concentration
the greater the effect of magnesium in enhancing coagu-
lation.

In an experiment on effects of magnesium and calcium
ions perfused through the lateral ventricle and also
through the carotid sinus, Leusen(12) used anesthetized
dogs with vagi severed. The carotid sinus was tied off
and perfused separately. A needle for intraventricular
magnesium sulfate was placed in the lateral ventricle
with a needle in the cisterna magna for completion of
the intraventricular perfusion circuit. The detected
systemic effects with intraventricular perfusion using
a solution containing excess magnesium were that the
blood pressure fell to some degree and the same solution
perfused through the carotid sinus depressed the carotid
sinus reflex. Perfusion fluid with calcium in excess
had the same effect, and perfusion fluids with magnesium
deficiency had a pressor effect.

Further metabolic features of magnesium will be
considered under therapeutic applications when the chief
site of action of the magnesium ion, as regards it function
and usefulness in the particular disease state, will be
under consideration.

Magnesium sulfate U.S.P. (epsom salts) is used in
medicine chiefly for two effects according to Stevens

and Wolff(13). When given parenterally in small doses
it is an effective cerebral depressant, and therefore
useful in the control of convulsions. This, according
to the authors of many journal articles, is an incomplete
statement. See other parenteral uses below. Orally in
hypertonic solution it is considered to be poorly ab-
sorbed and therefore useful for its osmotic effect.
Drawing water from the body results in dehydration,
and because of the volume within the gut, diarrhea or
catharsis results. The usual cathartic dose is 15 to
20 grams by mouth.

Hirschfelder(14) found that 40 per cent of mag-
nesium sulfate administered orally was excreted by the
kidneys in 24 hours. In therapeutic dose no increase in
serum magnesium level is noted unless impaired kidney
function is present. Terkildsen(15) found that there was
no difference in serum values after oral administration
of either magnesium sulfate of magnesium chloride. A
15 gram dose of the salt gave a slight increase in serum
level of magnesium. Two groups of healthy young men were
tested using 15 grams of the sulfate salt containing
seven molecules of water of crystalization and 12 grams
of the chloride salt containing six molecules of water
of crystalization. This gave same amount of magnesium in
both series. The slight increase of serum magnesium came

during the second hour after ingestion. Using rabbits Terkildsen was able to demonstrate a large increase in serum magnesium the second hour after ingestion of a large, toxic amount of magnesium salt, after which it tapered off.

Magnesium absorption takes place from rectal instillation for enema purposes if the enema is retained overlong. The common enema used is composed of magnesium sulfate, glycerine and water. See below for cases of magnesium intoxication.

Parenteral magnesium is excreted almost entirely and very rapidly by the normal kidney.

Magnesium deficiencies are denied by many, yet there are a very few reports of cases. Martin, Mehl and Wertman(1) have not been impressed with symptoms and signs of hypomagnesemia; they attribute no electrocardiographic changes to this condition. They hold that some of the reports of magnesium tetany did not rule out hypocalcemia nor alkalosis. This group reports seeing 12 patients with serum magnesium less than 1 meq. per liter and four with less than 0.6 meq. per liter none of whom had tetany. Studies of chronaxie and tetanus ratio in four muscle groups in the forearm and hand of a patient with small bowel resection and hypomagnesemia showed no significant variation in the response between this patient with serum magnesium value of 0.4 meq. per liter and a person with a 1.4 meq. per liter value.

Some of the mechanisms of production of magnesium
deficiency include deficient intake, which would be very
unusual except in case of malnutrition. Mellinghoff(16)
reports that in malnutrition states the balance of
magnesium and calcium metabolism is negative even though
the intake may be greater than normal. Calcium given
intravenously evidently promoted the retention of
magnesium. In malnutrition the fixation of magnesium
in the tissues seems to be disturbed.

Very little work has been done on magnesium loss
from the gastrointestinal tract. Holt, Courtney and
Fales(17) did determinations on normal and diarrheal
stools of infants in 1913 and found that normal stools
contained 4.8 meq. magnesium and diarrheal stools
contained 6 meq. Apparently no serum magnesium levels
have been reported in severe diarrhea.

Renal loss of magnesium has also had only slight
work done on it. Determinations are complicated by the
amount of magnesium bound to protein. Martin, Mehl and
Wertman(1) have gained the impression that magnesium
free urine does not occur and that deficits may occur
due to continued urinary loss with deficient intake.
Accelerated loss in urine may occur under certain cir-
cumstances as shown by findings in diabetic coma and
following diuretic therapy.

Link, Stutzman, Anderson, Konig and Fraser(18) report
two patients who were on prolonged parenteral fluid
therapy and had serum magnesium values of 1.35 and 1.37
meq. per liter as compared to a normal in that laboratory
of 1.91 .2 meq. per liter. The symptoms were mild
confusion and gross tremor, the course of which was
followed with handwriting samples, and which was relieved
by magnesium sulfate therapy.

The above group also had a number of patients who
were in states of chronic alcoholism and chronic alcoholic
delirium, usually with tremor. All had drunk excessively
and eaten poorly for some time. These patients were
treated by a regime of two grams magnesium sulfate
intramuscularly four times a day. Patients had moderate
improvement of tremor and marked improvement of mental
state. It was found difficult to get the magnesium to
stay up as high as 1.6 meq. per liter in these type
patients. In several of the patients relapses occurred
with failure to continue the treatment. These patients
were cleared again with reinstitution of treatment.
The response was found to be quicker in the patients
treated with magnesium sulfate than in those treated
with only vitamins, adrenal cortex extract, paraldehyde
and/or barbiturates. The chronic alcoholics with organic
brain damage, of course, were limited in improvement.

The usual symptoms found in these patients included emotional instability, irritability, restlessness, tremor and insomnia.   The one most usual symptom is tremor.

Miller(19) reported a six year old boy with muscle twitching interfering with finer movements such as writing which was releived by oral administration of magnesium sulfate.   The lowest serum magnesium level found was 0.5 meq. per liter.

Low serum magnesium has been found with tetany (hypocalcemic), chronic renal disease, epilepsy, parathyroid deficiency, toxemia of pregnancy and pancreatitis.

No pathological changes secondary to hypomagnesemia in man have been reported but striking changes in animals suggests potential importance to man.   Some of the changes in animals, as found in Martin, Mehl and Wertman (1), include increased vascular permeability with hemorrhage, fibrosis of myocardium and endocardium, degenerative changes in the nervous system, alterations in nutrition, and changes in renal tubules and glomeruli with development of nephrotic syndrome.   Physiological changes have been increased neuromuscular irritability, tetany, cerebellar tremor, tachycardia and arrhythmias. It may be that hypomagnesemia in man must be severe and chronic to give definite signs and symptoms.   It may also be that serum magnesium level does not reflect

cellular magnesium level.

Elevation of extracellular magnesium levels can be caused by injection of magnesium salts (rarely by ingestion), by renal retention, by hemoconcentration and by accelerated tissue breakdown when associated with renal disease. Martin, Mehl and Wertman(1) say it is not known whether intracellular magnesium excess can occur or not. Clinically hypermagnesemia is usually due to renal failure and dehydration. The above named workers have determined that the critical level for symptoms of hypermagnesemia is 6 meq. per liter at which level pro- gressive depression of cardiac, neuromuscular, and central nervous system function occurs.

Hypermagnesemia may also occur in oxalic acid poison- ing, and in such cases as use of large amounts of magnesium sulfate by slow drip per rectum to induce dehydration in the management of increased intracranial pressure and cerebral edema. Collins and Russell(20) reported a case in 1949 of a four year old boy with megacolon who failed to expel on enema of 30 grams of magnesium sulfate in 12 ounces of glycerine and water mixture. In one hour the boy had flaccid paralysis, respiratory depression, somnolence and coma. Intravenous calcium gluconate failed to rally him. At autopsy six hours later the blood level of magnesium was 30 mgm per

100 ml. Therefore magnesium sulfate catharsis is contraindicated in any condition associated with loss of intestinal motility and increased absorption.

In the literature from 1841 to 1909, Fraser(21) found evidence of poisoning from epsom salts in seven cases with five fatalities. All had taken it by mouth and depression of the central nervous system was the most serious toxic effect.

See chart II for an outline of the pharmacological actions of magnesium and the serum concentrations at which they are usually manifest.

Effects of Parenteral Magnesium, and the Concentrations of Magnesium in Serum at Which They are Usually Manifest	
Action	Magnesium of serum, meq. per liter
No apparent effects	2
Initial tachycardia (dogs).	2-5
Initial bradycardia (man)	2-5
Initial fall in blood pressure (dogs) .	2-5
Flushing, sweating, sensation of heat .	2-5
Vomiting	2-10
Progressive fall in blood pressure . .	5+
Beginning auriculo-ventricular block .	10+
Failure of tendon reflexes	10+
Beginning intraventricular block . . .	12+
Failure of respiration	15+
Failure of corneal reflex	30+
Cardiac arrest	30+

Chart II.

The treatment of hypomagnesemia according to Martin, Mehl and Wertman(1) is parenteral magnesium in

a concentration of 5 meq. per liter in the multiple
electrolyte solutions. Use of this solution is
recommended in diabetic acidosis, diarrhea, burns,
the alkalosis of vomiting and post-operative dehyd-
ration, also in those unable to eat for a period of
time and who have an accelerated loss of magnesium.

The correction for hypermagnesemia is hydration,
use of calcium salts or physostigmine as antagonist,
and improvement of renal function.

The gastrointestinal use of magnesium involves
its use as an antacid. All of its basic salts possess
this function. The first page lists a few of the
compounds used. Magnesium trisilicate, previously
mentioned, is a buffer which is very effective. It is
also emulsant, forms a gel, is well tolerated, and gives
no systemic disturbance such as causing acid base im-
balance.

Magnesium compounds have been very popular saline
cathartics. Magnesium sulfate is also known as a dehyd-
rating agent. At New York Hospital, at least as recently
as 1950, a routine often given patients with increased
intracranial pressure is 300 cc of one-half saturated
magnesium sulfate.

The usual cathartic dose of magnesium sulfate
U.S.P. and B.P. ($MgSO_4:7H_2O$) is 15 grams. A preparation

often more easily taken is "Effervescent salt of
magnesium sulfate" N.F. which is 50 per cent sodium
bicarbonate, tartaric and citric acids. The usual
dose is 16 grams.

Along with the use of magnesium sulfate as a ca-
thartic goes its use in cases of poisoning. It is
used in case of morphine or barbiturate poisoning and
also in cases of would-be poisoning such as occurs in
use of aspidium and similar compounds used to poison
intestinal parasi es. The dosage placed in the stomach
is usually 30 grams. This flushes out whatever poison
has not been removed by aspiration. Terkildsen(22)
noted that in barbituric acid poisoning there is often
marked decrease in peristalsis. His usual treatment is
carbo medicinalis and magnesium sulfate (15 grams)
dissolved in a few hundred milliliters of water. It
was demonstrated that this medication at times lay in
the gastrointestinal tract for several days; also these
patients frequently have impaired kidney functions.
There was the consequent possibility of magnesium toxicity.
Terkildson treated 15 patients in his usual manner and
20 did not receive this treatment. Serum magnesium
determinations were not significant in that four of the
treated ones had elevated serum magnesium levels and they
expired, but so did some of the treated and non-treated

ones who had normal serum magnesium.

Goodman and Gilman(2) make the statement that hypertonic magnesium sulfate introduced into the duodenum gives temporary increased flow of bile which is probably due to relaxation of the sphincter of Oddi. This chologogic action of magnesium sulfate on the sphincter of Oddi is made use of in post-cholecystectomy syndrome in which anti-spasmodic treatment, as with nitroglycerine, has failed. McGowan and Sarkisian(23) have outlined a course of treatment to meet this situation. In following their sequence of treatment, one should institute repeated duodenal drainage using magnesium sulfate in the following manner: After the duodenal tube has been passed into the duodenum, it is irrigated repeatedly with warm tap water. Then 60 cc saturated solution of magnesium sulfate is injected into the duodenum and left there thirty minutes. The magnesium sulfate is then washed out and the patient is given repeated inhalations of amylnitrite. These physicians say that they have obtained considerable benefit with this regimen in intractible cases and have noted considerable amounts of pus in the first few drainages, following which the pus usually disappears.

Experiments on man prove that magnesium in fairly high concentrations is a central nervous system depres-

sant. Peck and Meltzer(24) observed that magnesium sulfate injected intravenously into patients reduced sensitivity to pain and dulled consciousness so that at slightly higher concentrations the patients became so completely unconscious that major surgical operations could be carried out. On recovery there was no memory of what had occurred during the period of apparent unconsciousness. This would appear to be unequivocal evidence that it is a cerebral effect, and not purely and only a neuromuscular effect, which is observed. However, the ratio of lethal to effective dose, or therapeutic ratio, is only a little above one for magnesium so it is impracticable to use magnesium as a general anesthetic unless artificial respiration is supplied as well. The central nervous system is depressed enough by the higher therapeutic levels of serum magnesium so that there is a mild cerebral depressive effect which is of benefit in convulsive syndromes. But it is often maintained that the effectiveness of magnesium sulfate in this type syndrome is due to its dehydrating powers.

Magnesium, when absorbed or administered parenterally, is probably best known for its peripheral neuromuscular effect which is often called curare-like because of the clinical resemblance. Naess(25) has shown some of the differences, for instance, magnesium blocks the stimu-

lative effect of potassium, and curare does not. Also
facilatatory phenomena are more readily produced after
magnesium. He performed myographic examinations on a
preparation of rabbit hind leg muscle stimulated supra-
maximally by way of the sciatic nerve. Solutions of
d-tubocurarine and magnesium chloride were injected by
way of a cannulated jugular vein. Under magnesium a
high frequency stimulus(20 per sec.) was necessary to
elicit a small amplitude contraction and under d-tubo-
curarine it was response to high frequencies which was
the more completely suppressed and any contraction would
drop off very rapidly during the period of stimulation.
No significant potentiation of the combined effects could
be elicited. Using intravenous injection on mice, Naess
(25) determined the LD50 of d-tubocurarine to be
0.133 mgm per Kg., and of magnesium to be 17.6 mgm per Kg.

Hutter and Kostial(26), working on cats, found the
same distribution of failure of response to stimulus
as related above. The preparation used was the cat
superior cervical ganglion which was used for perfusion
with magnesium and d-tubocurarine solutions and arti-
ficial stimulation. The solutions used were magnesium
chloride in a 15 to 20 mM solution and d-tubocurarine
in a 1:160,000 concentration. Regular impulses were
produced for five minute periods with five minute periods

of rest. In this experiment acetylcholine output into
the surrounding fluid was assayed by blood pressure
pressor effect of the perfusate on prepared anesthe-
tized cats. The results found were that failure of
ganglionic transmission produced by magnesium ions
is accompanied by a decrease in the amount of acetyl-
choline liberated as a result of preganglionic stimu-
lation which would suggest that neuromuscular block by
magnesium ion is at least partially block of pre-
ganglionic nerve endings. Addition of the 15 mM
magnesium chloride solution just about halved the out-
put of acetylcholine. The blocking action of magnesium
was relieved by calcium ion and Hutter and Kostial found
that these two ions have opposite effects on the out-
put of transmitter acetylcholine) from the preganglionic
nerve endings and that calcium actually augments the
output of acetylcholine.

The work of Del Castillo and Katz(27) was on the
motor end plate and they say that the effects of calcium
and magnesium are mutually antagonistic at the neuro-
muscular junction. They say that the end plate potential
can be decreased and transmission blocked by either
decreasing the calcium or increasing the magnesium
concentration and magnesium block can be cancelled by
raising calcium above its normal level. They determined

that the normal continuous spontaneous miniature end
plate potentials were decreased 30 to 40 per cent by a
16 mM solution of magnesium.

Del Castillo and Engbaek(28) repeated some of the
work just referred to in the two articles above and
conclude that the magnesium caused reduction in acetyl-
choline release by the motor nerve endings was the
major effect by which transmission was blocked. But
they determined that magnesium ion also affects some
blockage of transmission by raising the electrical
threshold of muscle membrane so that a large end plate
potential is needed to produce a spike, and furthermore
that magnesium has a small depressive effect on the
acetylcholine sens tivity of the motor end plate.
These same authors in a later publication(29) defined
magnesium ion as "a physiologically occurring cation
which blocks neuromuscular transmission in concentrations
which do not prevent either nerve conduction or the
muscle response to direct stimulation".

One of the authors above(27,28,29) had a part in
all of the three publications and in summary of the work
of these related publications they have, 1. determined
that the calcium ion is a striking antagonist to the
effects of magnesium ion in each phase of the latter's
neuromuscular effects thus making it evident that

acetylcholine liberation is a function of the relative
amounts of calcium and magnesium ions present. 2. They
have determined that magnesium has at least the following
three distinct effects on the neuromuscular junction:
a. decreasing the amount of transmitter liberated at
the motor nerve terminals, b. diminishing the depolarizing
action of acetylcholine at the end plate(may be primarily
through magnesium ion activation of cholinesterase
which would effectively depress the sensitivity of the
end plate region), c. depressing the excitability of the
muscle fibre membrane. These three functions of
magnesium ion result in a drastic reduction in end
plate potential.

Terkildsen(30) did some work on antidotes for mag-
nesium toxicity other than calcium. He used rabbits and
showed that lethal amounts of magnesium were not lethal
if 0.3 to 1 mgm physostigmine was given intravenously at
the same time. Neostigmine was also effective. Both
of these drugs inhibit enzymatic hydrolysis of acetyl-
choline which may explain their effectiveness because the
serum magnesium calcium ratios during these experiments
give no indication as to why the lethal dose is not
lethal in presence of physostigmine.

Magnesium sulfate is a logical symptomatic treatment
for tetanus. Goodman and Gilman(2) give as dosage for

tetanus 2 cc of 25 per cent magnesium sulfate for each
20 pounds body weight to be administered subcutaneously
or intramuscularly. This dosage may give relief for
several hours. For immediate results a 6 per cent
solution may be given intravenously at the rate of 3 cc
per minute until relaxation is affected.

Magnesium sulfate has had its greatest usefulness in
the field of abnormal renal function usually in association
with hypertension and hypertonicity or actual convulsions.
Of the many drugs reported to lower or control the
hypertension associated with acute glomerulonephritis,
magnesium sulfate has apparently been the most widely
used agent since its introduction by Blackfan(31) in
1925. The mechanism of its action has been the subject
of much discussion. At first dehydration was considered
its principle mode of therapeutic action. More uni-
versally accepted now is that the principle effect is
to dilate vessels and so counteract vasospasm. Harris
and DeMaria(32) conducted an experiment with 13 normal
fasting dogs under quite rigid conditions including
light sodium pentobarbital anesthesia and maintenance
of serum magnesium levels intravenously. An equilibrating
initial infusion of 50 cc of four per cent solution was
given followed by the fixed dosage of 1 cc per minute of
three per cent solution. Regular blood determinations

and constant intrafemoral blood pressures were recorded.
The inulin and paraminohippuric acid clearances were
measured. The blood pressure recordings showed an average
fall in mean pressure of 30 per cent. No significant
changes were observed in glomerular filtration rate
nor in effective renal plasma flow. The serum magnesium
level was maintained at an average level of 7.5 mgm per
100 ml. It is obvious that the kidney participates in
the general vasodilatation because in spite of the
fall in blood pressure there was no fall in the renal
plasma flow. Failure of any change in the glomerular
filtration rate indicates that the site of decreased
resistance must be in the afferent arteriole.

Harris and DeMaria(32) tested some of the more modern
drugs in the same manner. One of the modern drugs used
was "Priscoline" which was discounted because it reduced
effective renal plasma flow, apparently by producing
afferent vessel spasm. "Apresoline" is occasionally
toxic causing depression of renal function.

Etteldorf, Clayton, Tuttle and Houck(33) did renal
function studies with magnesium on 15 children ages 5
to 11 without renal disease. The dosage used on the
children was 100 mgm(0.2 cc of a 50 per cent solution)
magnesium sulfate per Kg. of body weight given every
four hours for three or four doses. Under conditions of

this study no consistent relationship was observed between serum magnesium level and any of the measured functions.

In the few months after the above studies on normal children, Etteldorf and Tuttle(34) completed studies on six children ages 5 to 9 who had a diagnosis of acute hemorrhagic glomerulonephritis. The history indicated that these children had been ill for two to six days before hospitalization. All six children had findings of gross hematuria, albuminuria, oliguria, varying degrees of edema, systolic blood pressure ranging from 92 to 125 to 169 mm mercury and diastolic pressures ranging from 92 to 110 mm mercury. These children were given intramuscular magnesium sulfate in doses of 100 mgm per Kg body weight every four hours for periods of 18 to 24 hours. Initially before treatment the serum magnesium ranged from 1.1 to 2.2 meq. per liter. Several hours after treatment initiated the serum magnesium levels ranged from 2.9 to 4.4 meq. per liter. The second renal clearance studies were done at this time.

The results of therapy showed a reduction of systolic blood pressure ranging from 10 to 30 mm mercury and a reduction in diastolic pressure ranging from 2 to 36 mm mercury. There was no definite correlation between serum magnesium levels and the reduction of blood pressure

and also the duration of action was unpredictable. The glomerular filtration rate before and during therapy showed no significant shift from a mean 88.8 cc per minute(58 to 115 cc per minute) which is considerably below the mean value for the normal children of 131 cc per minute. Before therapy the mean effective renal plasma flow was 527 cc per minute(range 390 to 747 cc per minute). During therapy the mean effective renal plasma flow was 635 cc per minute(range 462 to 891 cc per minute) which very closely approaches normal. Insofar as renal hemodynamics are concerned the increase in plasma and blood flow has no appreciable effect on the filtration rate and therefore the authors conclude that the only beneficial effect on the kidney is better nutrition.

Harris and DeMaria(35) had a series of patients which they treated in various stages of acute nephritis. A breakdown of these cases with renal function values both before and during magnesium sulfate therapy is given in Chart III. The method of administration used in these cases was intravenous. An initial equilibrating dosage was given and then the rate dropped back to 1 to 2 cc per minute of a 3 per cent solution of magnesium sulfate when the blood pressure began to drop or when a cutaneous vasodilatation and an uncomfortable sense of warmth

The Effect of Magnesium Sulfate on Renal Function of Normal Children
and Children in Various Stages of Acute Nephritis

	Glomerular Filtration Rate	Effective Renal Plasma Flow	Effective Renal Blood Flow	Filtration Fraction
1. Control Children (4)				
Before MgSO$_4$	148 cc/min. (16)*	709 cc/min.(114)	1220 cc/min.(241)	0.21 (.018)
During MgSO$_4$	137 (11)	681 (111)	1154 (231)	.21 (.017)
2. Acute nephritis (9)				
Early stage	82 (45)	445 (117)	655 (157)	.175 (.052)
Later stage (convalescent)	108 (30)	641 (157)	1018 (231)	.168 (.024)
3. Hypertensive acute (7) nephritis				
Before MgSO$_4$	59 (20)	397 (85)	596 (129)	.147 (.031)
During MgSO$_4$	71 (21)	561 (132)	839 (194)	.127 (.071)
4. Subsiding Acute (4) nephritis				
Before MgSO$_4$	112 (16)	661 (77)	1047 (102)	.171 (.026)
During MgSO$_4$	116 (25)	859 (80)	1340 (233)	.137 (.025)

*Plus-minus values of standard deviations

Chart III.

occurred. The total dosage varied according to size and condition of the child ranging from 1.2 to 5.3 grams of the hydrated salt.

In the seven patients in the hypertensive phase of acute nephritis, treatment increased the glomerular filtration rate an average of 24 per cent and the renal plasma flow increased an average of 42 per cent.

In the four cases of subsiding acute nephritis the blood pressure was within normal limits and the patients were markedly improved. On treatment the glomerular filtration rate was increased an average of only 2.5 per cent, but the effective renal plasma flow was still substantially increased averaging 30 per cent. The response to magnesium sulfate was noted to be most marked at initial administration corresponding with the cutaneous flush, warmth and vasodilatation.

In summary of the effect of magnesium sulfate on renal mechanisms, it is apparently very effective only during the acute phase of the disease; at other times the only measureable response in function is slight increase in effective renal plasma flow. The opinion prevalent today is that most of the benefit in these cases is just generalized vasodilatation throughout the body.

Some of the clinical observations made include an appreciable diuresis often maintained on intramuscular dosages. In this regard Blackfan and McKhann(31) say that

improvement is seldom obtained without loss of body
weight.

Etteldorf and his group(33) make the statement that
the complications of acute hemorrhagic nephritis such
as "hypertension, cardiac failure, encephalopathy,
oliguria and anuria can usually be traced directly or
indirectly to generalized arteriolar spasm." Several
workers(33,36) conclude that the beneficial effects of
magnesium on the conditions mentioned above are probably
attributable to generalized relaxation of arterioles
due to direct action on smooth muscle. He considers
reduction of edema in the brain as inconsequential.

If the action of magnesium sulfate is primarily
that of abolishing vascular spasm of acute nephritis and
if the symptoms of hypertensive encepholopathy are a
result of this spasm then one of the first actions of
the drug must be on cerebral vessels. And Marris and
DeMaria(35) report that they have repeatedly noted stupor,
convulsion and headache to be relieved by intravenous
magnesium sulfate before blood pressure had dropped and
occasionally when the dosage was insufficient for
depression of blood pressure. Also the cerebral effect
is apparently more prolonged. Furthermore, these
authors report observing retinal vessels dilate to a
normal calibre during infusion of magnesium sulfate.

The minimal effective serum magnesium level was found to be 5 mgm per 100 cc and some patients required a level of 7 to 8 mgm per cent for effective therapy. The total single dosage suggested by the studies of Harris and DeMaria(35) is 150 to 200 mgm hydrated magnesium sulfate per kilogram body weight given as a 3 per cent solution(5 to 7 cc per Kg.) in the course of one hour. The only symptoms noted were those subjective ones accompanying the cutaneous vasodilatation. Signs of central nervous system depression did not appear. However, a syringe of calcium gluconate was always available.

In attempting to understand the dynamics of the effect of magnesium, it must be remembered that magnesium is an intracellular cation and it apparently equilibrates very rapidly because an excessive plasma level is seldom seen. Also the extracellular spaces in edema will take up magnesium. In early hypertensive acute nephritis 5 per cent of the administered magnesium is excreted during the infusion. During convalescence the percentage rises to 10. In normal children the excretion is 23 per cent as an average.

Butler and Reyerebach(37) reported a case of acute hemorrhagic nephritis in a 4 year old boy with hypertension and secondary congestive failure. The treatment

given was rapid digitalization with cedilanid and he was
also given phenobarbital. After digitalization the boy
received 3 grams of magnesium sulfate in 150 cc 5 per
cent dextrose in water over a 40 minute period. Calcium
gluconate was kept at hand in case of respiratory
depression. The blood pressure was taken every 5 minutes
and was lowered from 150/90 mm mercury to 130/50 mm
mercury. At the end of the procedure the serum mag-
nesium concentration was 6.5 meq. per liter. Combined
oral and intramuscular therapy were not satisfactory on
this patient, giving a concentration of only 3.6 meq.
per liter.

Winkler, Smith and Hoff(38) used magnesium sulfate
2 per cent intravenously in 500 cc units on adults with
nephritic convulsions. The results were neither certain
nor dramatic but the first or sometimes the second
infusion did always control the convulsions.in chronic
nephritis.

As might be expected from the foregoing magnesium
sulfate is useful in puerperal eclampsia and toxemia.
Lazard(39) was one of the early contributors in this
field. Probably the most logical treatment of convulsive
eclampsia makes use of several anti-convulsant drugs
because toxic doses of single drugs would be required.
Eliminative measures should be in constant practice

of course, and for direct treatment of the convulsions magnesium sulfate in 10 per cent solution may be given intravenously in 20 cc amounts every hour in severe cases until controlled. If not having active convulsions, one may give 8 to 12 cc of a 50 per cent solution and inject it deep in the buttocks. This may be followed by 5 cc of a 25 per cent solution in alternate buttocks every four hours. When giving intravenous magnesium one should check the knee jerk reflex frequently and discontinue this treatment at once or give calcium gluconate if the reflex is found to become depressed or absent.

The other sedative anticonvulsant drugs of choice would be a barbiturate and paraldehyde. It is of interest that chloral hydrate has some degree of antagonistic action with magnesium sulfate as determined by Dybing(40) using respiratory paralysis in mice as the criterion.

Magnesium has also a use which is more strictly referable to the uterus. Abarbanel(41) considered that magnesium had promise of being an ideal myometrial spasmolysant. In 1929 Wodon(41) was the first to demonstrate spasmolytic action of magnesium on a uterus rendered tetanic by pitocin. Abarbanel had over 60 patients with abnormally painful tetanic contractions (all of which were induced by various oxytocic drugs) which were releived completely within 30 to 90 seconds

of injection of intravenous magnesium ion. Not only
was spasm abolished but regular rhythmic contractions
appeared. There was only one effect of questionable
value on normal labor and that was mild pain relief.
Abarbanel(41) also told of one case of incarcerated
but separated placenta in the third stage of labor.
Injection of 2 cc of intravenous 50 per cent magnesium
sulfate abolished the tetany and the placenta was easily
expelled by the Crede method. If it is necessary to
minimize the bleeding, calcium gluconate may be given
to control the degree of relaxation.

Use of magnesium sulfate in cardiac conditions has
been overlooked it appears, but it does have some
advantages such as in intravenous use it is safer than
quinine or quinidine.

Stanbury and Farah(42) have shown on cat heart-
lung preparations that the magnesium ion slows the heart
by blocking the sympathetic ganglion transmission at
the stellate ganglion and by depressing the sinoatrial
node independent of nervous influences. They also
demonstrated the sinoatrial node depression in acutely
denervated dog heart at various concentrations of
magnesium. A two to one flutter initiated in the dog
heart by auricular crushing was slowed and eventually,
with increasing magnesium concentration, the block

disappeared.

The effect of magnesium ion on the dynamics of the heart was studied on 14 dogs and it was shown that the bradycardia gave rise to an increased stroke volume and a striking rise in coronary flow as measured by a Morowitz cannula introduced in the coronary sinus. The same 14 dogs were later studied for effect of cardiac glycosides and magnesium. It was determined that there is no effect obtained except by intravenous dosage and administration in which case it is probable that the transiently high magnesium level in the coronary circulation is sufficient to combat hetero-tropic foci in hearts poisoned by cardic glycosides.

Harris, Estandia, Smith, Olsen, Ford and Tillotson (43) ligated the anterior descending coronary artery thereby producing acute myocardial infarction and ventricular ectopic rate. Magnesium sulfate in doses of 1 meq per kilogram body weight hourly reduced the ectopic beats by about 50 per cent.

The increased concentration of magnesium was deter-mined to progressively and linearly elevate the rheobase (the mechanism thought to be magnesium inhibition of adenosinetriphosphatase).

Craver, Yonkman, and Rennick(44) found that it took a high dosage of magnesium to give minimal protection

against ventricular fibrillation induced by mercurial diuretics.

Szekely(45) demonstrated that magnesium gives only minor electrocardiogram changes in the normal heart, that it depresses heterotropic centers preferentially over the normal conduction system, and that intravenous magnesium ion is safe but only temporary. In his publication Szekely justifies the use of magnesium sulfate in paroxysmal tachycardia by the fact that he altered and improved 9 of 13 patients with paroxysmal tachycardia. The remaining 4 had advanced heart disease. Four of the ones improved had normal sinus rhythms restored. From the several cases of extrasystole which he studied he found that only the extrasystoles of digitalization were effected by magnesium sulfate treatment. The usual dose was 20 cc of 20 per cent solution.

Szekely and Wymene(45) pointed out that one of the most frequent, early, well recognized signs of digitalis toxicity and increased irritability of heart muscle is alternating bigeminy alone or with other types arrhythmia. They believe that in cases in which it is advisable to quickly abolish the heterotropic foci intravenous magnesium sulfate is indicated plus slower acting oral quinidine. They reiterate that the chief usefulness for

magnesium is in the abolishing of extrasystole and
tachycardia due specifically to digitalis. Enselberg,
Simmons and Mintz(47) are in agreement in their work
and results with the above. Armbrust and Levine(48)
report that in 107 cases of paroxysmal ventricular
tachycardia magnesium sulfate was only occasionally
useful.

Magnesium sulfate in moderate concentration is an
anesthetic agent on contact with nerve tissue. This
was the basis of its use as a spinal anesthetic but it
has long since been replaced by safer barbiturates.
This drug has been used as a general anesthetic intra-
venously but it is not safe at all without a breathing
bag because of its therapeutic ratio of about unity.

The only application of magnesium sulfate for what
might be termed anesthetic action is its topical use in
packs on a condition such as erysipelas where it is
considered good symptomatic treatment in that it, by
osmotic action, will relieve the tension of blebs
and by topical contact anesthetic action, help relieve
pain.

Svendsen(49) reports using magnesium with success
in cases of threatened gangrene of foot and in one
case of raynauds disease. Previously acetylcholine and
other vasodilators had been used without effect. With 2 to

5 ml intramuscular injections of 50 per cent solution continued for five days there was resultant clinical improvement.

SUMMARY

In summarizing this review of literature on magnesium, an attempt is made to bring out points of clinical interest. Clinical application and an understanding of the use of magnesium ion was the original reason for the research for this thesis.

Many points referred to in the body of the thesis are relatively isolated and unsupported observations undeserving of further serious consideration until such time as more controlled studies have been made and reported.

Use of the basic magnesium salts as antacids needs little comment. Magnesium trisilicate is perhaps the most advantageous to use. The cathartic action of these salts is due to the osmotic effect of drawing water into the gut. The magnesium ion tends to remain in the gut rather than be rapidly absorbed. Only 40% of magnesium in the bowel will be absorbed normally and excreted in urine. The large amount of magnesium not resorbed will osmotically withdraw water causing dehydration.

Endocrine factors have little effect on serum

magnesium. Thyroid may cause some increase in magnesium
in hyperthyroid conditions.

Magnesium is considered essential for proper
function of coenzyme I, coenzyme II, phosphorylation
processes for resorption, dephosphorylation for energy
production and work; and for glycogen deposition.

The evidence that serum magnesium will not be
elevated to a therapeutic level by oral medication is
well grounded and yet is evidently not always true.
Pediatricians say the gut of the young child will
absorb magnesium sufficiently for therapeutic effect.
This is, I believe, often not true. Combined oral and
intramuscular magnesium will barely give therapeutic
levels in some cases. On the other hand, absorption
of magnesium and serious toxicity can result from
presence of magnesium sulfate in a thoroughly atonic
bowel.

Hypomagnesemia occurs in several conditions where
it would be clinically advisable to treat specifically
with magnesium sulfate. Two such conditions are
marked malnutrition and chronic alcoholism. Occasionally
one with high output chronic renal disease becomes
seriously depleted of magnesium. There is apparently
no resorption mechanism and urine is never magnesium
free. The chief symptoms are mental confusion and

tremor.

Hypermagnesemia most commonly occurs after parenteral administration in presence of renal insufficiency and in cases of renal failure(poor excretion) and dehydration.

Magnesium sulfate is useful, after aspiration, in osmotically retaining poison and water in the bowel and flushing it out before serious absorption can occur. It is used in barbiturate poisoning, after aspidium and other toxic medications used to poison gastrointestinal parasites. It is used most effectively in 15 gram dosage mixed with activated charcoal and a few hundred milliliter of water.

In the duodenum magnesium sulfate will relax the sphincter of Oddi, thereby acting as a cholegogue. This action is also useful in allowing passage of stones. The usual procedure is to institute duodenal drainage and irrigate repeatedly with warm water; then place 60 cc saturated magnesium sulfate in the duodenum and leave for thirty minutes. The treatment is usually combined with oral nitroglycerine.

The neuromuscular junction is blocked by magnesium. Acetycholine release is prevented. Thus, magnesium sulfate is a logical treatment for tetanus.

The greatest field of usefulness is in children who have acute glomerulonephritis. The mechanism of

of action is primarily release of vasospasm. This can be observed by funduscopic examination during therapy.

The effective renal plasma flow is increased as is also the glomerular filtration rate. Blood pressure is lowered. These effects often cannot be attained without intravenous administration.

The foremost indication for intravenous magnesium sulfate today is convulsions. The fact that true anesthesia can be attained with magnesium sulfate(at nearly the same concentration as that necessary to stop respiration) is evidence for a cerebral depressant action. Relief of mental symptoms(encephalopathy) has been observed even before the usual flush and general body vasodilatation was observed. All mechanisms producing clinical improvement are not certainly known.

A related condition, puerperal eclampsia, is greatly benefitted by magnesium sulfate and its combined action of cerebral depression, neuromuscular block and release of vasospasm.

The tetanically contracted uterus is seen occasionally at term after the use of oxytocics. Magnesium sulfate is a very effective myometrial spasmolysant when used intravenously in this condition. Regular intermittent contractions usually follow its use.

Intravenous magnesium sulfate is useful in sup-

pressing heterotropic foci of irritable heart muscle
due to digitalis. This procedure is very useful when it
is advisable to quickly abolish ectopic impulses.
Quinidine may be given orally and when effective mag-
nesium may be stopped.

Magnesium sulfate packs reduce painful swelling of
infections like erysipelas and also exert a topical
anesthetic action.

Convulsions are probably at present the chief
indication for the use of magnesium intravenously.
For this indication it is more difficult to maintain an
effective yet safe concentration of circulating mag-
nesium if the intramuscular route is used. Also it is
easier to control the rate of injection of a dilute
 solution and the degree of fall in blood pressure is
more readily controlled. A 2 per cent(approximately
isotonic) solution or one somewhat more concentrated
may be used. About 500 cc of this solution may be in-
jected intravenously in thirty to sixty minutes. The
blood pressure is followed at frequent intervals as is
also the knee jerk and respiratory rate. Disappearance
of the tendon reflex precedes any serious respiratory
depression and so is a good guide in determining the
rate of injection.(50)

In patients with normal kidney function one may

consider that the excess magnesium has been largely
cleared from the body in about six hours and may freely
give more. However, in patients with definite depression
of renal function, clearing may require several days
in which case it would be well to limit the administration
of magnesium solution to a liter or so in 24 hours.

Calcium chloride is the antidote for respiratory
depression due to magnesium. It should be remembered
that rapid intravenous injection of calcium carries
the danger of sudden ventricular fibrillation.

CONCLUSION

Magnesium sulfate is a clinically useful drug by
reason of application of the following physiologic
effects:

1. Osmotic properties

2. Topical anesthetic

3. Relaxation of sphincter of Oddi

4. Neuromuscular block by means of decreasing
   transmitter(acetylcholine) release, by de-
   creasing the depolarizing action at the end-
   plate(activation of cholinesterase), and by
   decreasing the excitability of muscle fiber
   membrane.

5. Generalized vascular dilatation and release
   of vascular spasm, especially in acute
   glomerulonephritis. The initial site of
   spasmolysis is in the cerebral vessels.
   Increased renal clearances are part of the
   general response(vasodilatation of afferent
   vessels).

6. Cerebral depressant function(still not well explained)

7. Myometrial spasmolysis

8. By intravenous concentration only, find increase in stroke volume giving marked increase in coronary flow. Sinoatrial nodes are depressed. Heterotropic foci are depressed preferentially over the normal conduction system specifically in hearts poisoned by digitalis. The rheobase is elevated progressively with increasing magnesium (magnesium inhibition of adenosinetriphosphatase).

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