abnormal proportion of time in paradoxical sleep. Other American workers have confirmed this. At first our scepticism was aroused by this 'dream-deprivation' work, so my colleague, Berger, proposed the study of the effects of total sleep deprivation with, *ipso facto*, 'dream-deprivation'. Recordings were first made while six subjects slept normally on four nights each. Then we kept each awake one hundred and eight hours. Then their next four nights' sleep was recorded. On the first of these nights, as expected, paradoxical sleep was greatly reduced, but on the second night, contrary to our prediction, the proportion of the night spent in paradoxical sleep was significantly greater than on the earlier baseline nights, and was again increased on the third and fourth nights. It was as if what they had lost they made up for later (Berger & Oswald 1962). On their first recovery nights these subjects had spent a great part of the time in orthodox deep sleep with high voltage EEG slow waves (the E stage), and it is clear that when we have gone short of sleep it is this old-fashioned kind of deep sleep that takes priority. Such highly sleep-deprived people, when allowed to sleep, take only about twelve to thirteen hours sleep and then feel nearly normal, as if the restitutive properties of the E stage of sleep with its high voltage EEG slow wave picture is greatest.

Three years ago two people in our department lived a forty-eight-hour life, going to bed only every other night and then sleeping as long as they liked. After a month, one was fairly well adapted to it. Both normally slept eight hours each night; on their new routine they both, throughout, took not sixteen hours in each forty-eight, but only eleven and a half hours sleep in each forty-eight. This raises the unanswerable problem, what is the restitutive function of sleep?

Acknowledgments: I should like especially to express my thanks to my colleague, Ralph Berger.

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Meeting May 22 1962

Papers

Magnesium 28 Studies in the Cirrhotic and Alcoholic

by Helen Eastman Martin MD[1] and
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The occurrence of hypomagnesæmia in the alcoholic, with improvement of the symptoms of delirium and tremor following administration of magnesium salts, was first reported by Flink *et al.* (1954). Studies of 42 acute alcoholics in our laboratory (Martin *et al.* 1959) confirmed this finding of hypomagnesæmia, as 52% had low serum magnesium levels. No clear-cut correlation of symptomatology with serum magnesium levels could be established, however.

The studies to be reported were made in an attempt to assess exchangeable magnesium levels in the cirrhotic and alcoholic, as compared with control subjects. Exchangeable magnesium was determined in male subjects: 7 controls, 5 cirrhotics, and 4 acute alcoholics. The cirrhotics entered the hospital because of œdema and ascites. They all received diuretic therapy and two had abdominal paracenteses. At the time of study 2 of the cirrhotics were free of œdema and ascites and 3 had some residual ascitic fluid and œdema. The alcoholics entered the hospital because of acute alcoholism, with the symptoms and findings of this condition, including delirium tremens in 3. They all gave long histories of recurrent bouts of alcoholism, and were considered acute and chronic alcoholics. Three of these patients had enlarged, tender livers, but no ascites, and one patient had pretibial œdema. Two of the alcoholics were considered to have cirrhosis as well as acute alcoholism. While it is obvious that there is some overlap between the cirrhotics and the acute alcoholics, the separation

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into two groups for analysis was made on the basis of a recent bout of prolonged alcoholism, associated with symptoms.

Magnesium 28 with high specific activity, physical half-life 21·3 hours, was obtained from the Brookhaven National Laboratory, New York. Doses of 61 to 91 microcuries of magnesium 28 in a volume of 6–10 ml, pH 4–5, was given to each subject by direct intravenous injection. In the small volume injected there were 2–3 milligrams of stable magnesium. Serum and urine exchangeable magnesium levels were determined at twenty-four and twenty-five hours respectively. Twenty-four-hour exchangeable values were selected, as exchange is slow after this period (Silver *et al.* 1960). Further, with the short half-life of magnesium 28, accuracy in counting radioactivity diminishes rapidly with prolongation of study. In some controls and patients the volume of distribution of the magnesium 28 was determined at intervals from fifteen minutes to twenty-four hours following injection. Stable magnesium was determined by the method of Simonsen *et al.* (1946). The normal range for serum magnesium by this method is 1·5–1·8 mEq/l.

As shown by Silver *et al.* (1960), who used low specific activity magnesium 28, we found that distribution of high specific activity magnesium 28 occurred within one hour into a volume about equal to total body water in both the controls and the patients.

The exchangeable magnesium, determined by serum specific activity at twenty-four hours in the controls and patients, is shown in Fig 1. The total exchangeable magnesium in milliequivalents is correlated with height in centimetres. Height was selected for comparison as there are many problems in determining ideal weight, and because of the presence of œdema and ascites in several patients. The figure shows values of 237 to 360 mEq in the controls, with a straight line correlation with height. Four of the 5 cirrhotics had exchangeable values below the levels obtained in the control subjects of the same height. The range of values was from 195–234 mEq. The 4 patients with acute alcoholism showed an even more striking decrease in exchangeable magnesium levels, with values of 156–189·5 mEq. The mean exchangeable magnesium values calculated for serum and urine were identical in the control subjects, but lower in the urine than in serum in the acute alcoholics and some of the cirrhotics. The levels of urinary stable magnesium were often so low in the alcoholics as to make accuracy of determination difficult. It was felt that this factor was largely responsible for the difference between the serum and urine exchangeable values.

When the exchangeable magnesium was calculated as mEq/kg, the mean figure for the controls was 3·6 mEq/kg (range 3·32–4·03) and for the

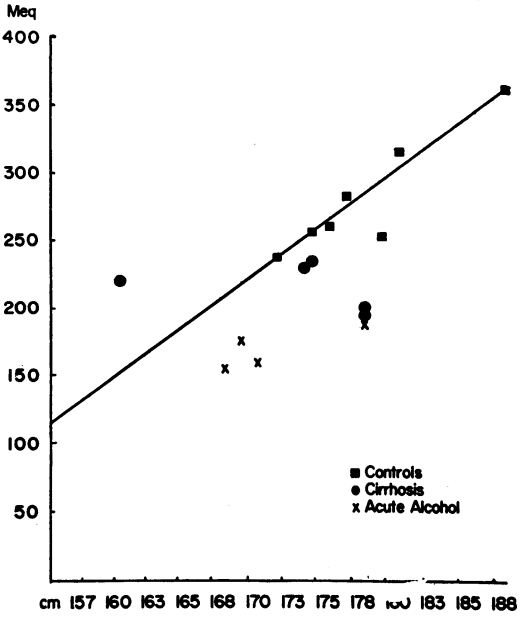

Fig 1 *Exchangeable magnesium at 24 hours*

acute alcoholics 2·55 mEq/kg (range 1·92–2·96). This was a significant difference compared with the controls (t 3·6 with $p<0·01>0·001$). The alcoholic with the value of 1·92 mEq/kg had slight œdema. The exchangeable magnesium values for the cirrhotics were not expressed as mEq/kg due to the difficulty of assessing weight in the presence of ascites and œdema in several of the patients.

Table 1 gives the serum magnesium levels and twenty-four-hour urine excretion of stable and isotopic magnesium in the controls and patients. A striking decrease in the urinary excretion of magnesium is seen in the patients, many of whom also showed hypomagnesæmia. The low output of magnesium in the urine is probably related to several factors – poor food intake, hypomagnesæmia, and depletion of body magnesium.

In 8 additional cirrhotics and 6 acute alcoholics, simultaneous plasma and red-cell magnesium levels were determined. All but one of these

Table 1
Serum and twenty-four-hour urine magnesium levels (mEq/l.)

	Controls (7)	*Cirrhotics* (5)	*Acute alcoholics* (4)
Serum Mg			
Mean	1·64	1·48	1·25
Range	(1·4–1·9	(1·3–1·7)	(1·0–1·7)
Urine ^{24}Mg			
Mean	9·26	4·26	0·73
Range	(4·75–11·7)	(0·92–10)	(0·25● –2·16)
Urine ^{28}Mg			
Mean	5·49	3·28	2
Range	(3·4–7·6)	(1·0–6·4)	(0·3–4)

●or less

patients had hypomagnesæmia, and 8 had lower than normal red-cell magnesium levels. Wallach *et al.* (1962) found low plasma magnesium levels in 4 of 11 cirrhotics, and slightly lower than normal red-cell magnesium levels.

Discussion

No previous studies with magnesium 28 with high specific activity have been made in the cirrhotic or alcoholic to our knowledge. While depletion of body magnesium is shown by our studies it should be stressed that twenty-four-hour exchangeable magnesium measures only a fraction of the 2,100 mEq of magnesium present in the average-size man. Further, our studies do not define the tissues with which the magnesium 28 exchanged. Recent studies with high specific-activity magnesium in the dog by Lazzara *et al.* (1962) demonstrated that equilibrium with skeletal muscle and bone was incomplete at 68 hours. Studies in the rat (MacIntyre & Davidsson 1958) and in man (MacIntyre *et al.* 1961) strongly suggest that the skeleton does not act as a magnesium reservoir, and the depletion seen in magnesium deficiency is in the cells. In man use of low specific-activity magnesium 28 (Silver *et al.* 1960) showed slow exchange with bone, which contains at least 50% of the body magnesium.

Mechanisms which might cause depletion of body magnesium in the cirrhotic and alcoholic include poor dietary intake of magnesium, lack of renal conservation of magnesium, accelerated magnesium loss in the urine due to increase in aldosterone levels, the effect of alcohol on urine magnesium levels, and poor gastrointestinal absorption of dietary magnesium or increased loss of magnesium in the fæces.

McCallister *et al.* (1960) showed a positive magnesium balance in 11 alcoholics when adequate magnesium was supplied in the diet. He felt that poor oral intake was an important factor in the pathogenesis of the magnesium deficiency seen in the alcoholic. Low levels of muscle magnesium have been found in several conditions associated with malnutrition (Metcoff 1960, R R Montgomery 1961, R D Montgomery 1960).

Remarkable renal conservation of magnesium has been demonstrated in the rat on a magnesium-free diet (Martin & Wilson 1960). While it has been shown by Fitzgerald & Fourman (1956) and Barnes *et al.* (1958) that excellent urinary conservation of magnesium occurs in man on diets of 1·1 mEq or less of magnesium a day, small cumulative deficits of magnesium do occur. With a chronically inadequate intake a negative magnesium balance could occur.

Increased aldosterone levels in the œdematous cirrhotic might be a factor in production of magnesium deficiency. This is the reason that cirrhotics with œdema and ascites were studied. Hypomagnesæmia is known to occur in primary aldosteronism (Conn 1955, Mader & Iseri 1955). Administration of aldosterone to both control and adrenalectomized rats has been shown by Hanna & MacIntyre (1960) to cause a magnesium diuresis. All of the cirrhotic patients studied received diuretic therapy. Mercurial diuretics (Martin *et al.* 1952), ammonium chloride (Martin & Jones 1961) and the chlorothiazide group of drugs (Wacker 1961, Glaubitt & Rausch-Strooman 1962) have all been demonstrated to cause a magnesium diuresis. Kalbfleisch *et al.* (1961) have shown that alcohol causes an acute magnesium diuresis in controls and alcoholics, which is independent of water diuresis and more marked in magnesium-deficient subjects. An increased magnesium requirement of the rat when given alcohol has been shown by Gottlieb *et al.* (1959).

Lack of absorption of magnesium from the gastrointestinal tract due to such factors as vitamin deficiencies, changes in pancreatic exocrine function, portal hypertension, and diarrhœa are potentially important. Recent studies by MacIntyre *et al.* (1961) showed low muscle magnesium levels, normal bone magnesium levels, and a low exchangeable magnesium in a patient with steatorrhœa. Alteration of calcium levels in the diet also affects magnesium absorption (Alcock & MacIntyre 1962).

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The following papers were also read:

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Professor Donald W Petit (*Los Angeles*)