Holmberg, C. G. & Laurell, C.-B. (1948). *Acta chem. scand.* **2**, 550.
Lahey, M. E., Gubler, C. J., Chase, M. S., Cartwright, G. E. & Wintrobe, M. M. (1952). *Blood*, **7**, 1053.
Marston, H. R. (1952). *Physiol. Rev.* **32**, 66.
Pálsson, P. A. & Grímsson, H. (1953). *Proc. Soc. exp. Biol., N.Y.*, **83**, 518.
Percival, T. (1785). *Med. Trans. Coll. Phys.* **3**, 80.
Playoust, M. R. & Dale, N. E. (1961). *Metabolism*, **10**, 304.
Popper, H. (1961). In *Wilson's Disease: Some Current Concepts*, p. 192. [J. M. Walshe and J. N. Cumings, editors.] Oxford: Blackwell Scientific Publications.
Richterich, R. (1961). In *Wilson's Disease: Some Current Concepts*, p. 81. [J. M. Walshe and J. N. Cumings, editors.] Oxford: Blackwell Scientific Publications.
Rosenoer, V. M. & Michell, R. C. (1959). *Brit. J. Radiol.* **32**, 805.
Ryś, R. (1959). *Nature, Lond.*, **183**, 1596.
Uriel, J., Götz, H. & Grabar, P. (1957). *Schweiz. med. Wschr.* Suppl. **14**, 431.
Van Wyk, J. J., Baxter, J. H., Akeroyd, J. H. & Motulsky, A. G. (1953). *Johns Hopk. Hosp. Bull.* **93**, 41.
Walshe, J. M. (1956). *Lancet*, **270**, 25.
Wilson, J. F. & Lahey, M. E. (1960). *Pediatrics, Springfield*, **25**, 40.
Wintrobe, M. M., Cartwright, G. E., Hodges, R. E., Gubler, C. J., Mahoney, J. P., Daum, K. & Bean, W. B. (1954). *Trans. Ass. Amer. Phycns*, **67**, 232.
Zimdahl, W. T., Hyman, I. & Cook, E. D. (1953). *Neurology*, **3**, 569.

Chronic magnesium deficiency

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Magnesium deficiency has only rarely been recognized in man and the criteria for its diagnosis are not established (Anonymous, 1960). Most reports so far have been based on the finding of a low serum Mg content. The patients fall in three groups:

(1) The first includes patients with a low serum Mg content for which no satisfactory explanation can be produced. Miller (1944) described tetany in a child with a low plasma Mg content. Flink, Stutzman, Anderson, Konig & Fraser (1954) claimed that Mg deficiency could complicate chronic alcoholism and even explain delirium tremens. These observations were not satisfactorily controlled (Clough, 1960) but recent reports from the same laboratory show that patients with alcoholism, cirrhosis and malnutrition may have a Mg deficiency (McCollister, Flink & Doe, 1960). There is, however, no satisfactory evidence to show that this deficiency produced delirium tremens. Other authors have described patients with an unexplained low serum Mg content (Hirschfelder & Haury, 1934; Suter & Klingman, 1955; Randall, Rossmeisl & Bleifer, 1959). More recently it has become obvious that an excessive secretion of aldosterone (Hanna & MacIntyre, 1960) should be considered as a possible factor.

(2) The second group comprises patients who had been losing intestinal fluids while maintained with fluids given parenterally which did not contain Mg. The intestinal secretions normally contain less than 3 m-equiv. Mg/l. (Nicolaysen, 1936), therefore losses must continue for several weeks before a serious deficit can arise (Flink, McCollister, Prasad, Melby & Doe, 1957; Hammarsten & Smith, 1957; Card & Marks, 1958; Randall *et al.* 1959; Vallee, Wacker & Ulmer, 1960; Baron, 1960; Cope & Barnes, 1960).

(3) The third group consists of patients with intestinal malabsorption. Calcium deficiency has long been recognized in steatorrhoea and since the chemical properties of Mg are very close to those of calcium, steatorrhoea might be expected to produce

deficiencies of Mg too. Tibbetts & Aub (1937), however, in a classic work found that their patient absorbed Mg normally, and perhaps because of this observation little interest was shown in the problem in the intervening years. Quite recently Fletcher, Henly, Sammons & Squire (1960) and Hanna, Harrison, MacIntyre & Fraser (1960) have described Mg deficiency complicating steatorrhoea. The two patients both had a low plasma Mg content. They had few symptoms other than weakness and our present concept of the clinical syndrome of Mg deficiency is based on patients in the second group. Apart from weakness the main symptoms are nervous and may be classed as cortical, extrapyramidal and peripheral. The cortical symptoms are those of an organic dementia; several authors have emphasized irritability and aggressiveness. The extrapyramidal symptoms consist of involuntary athetoid movements and tremors. The peripheral nerves are abnormally excitable and there may be tetany (Vallee *et al.* 1960). Certain observations, however, lead one to doubt whether tetany can be the result of uncomplicated deficiency of Mg. Thus, when Mg is withdrawn from the extracellular fluid of dogs by extracorporeal dialysis the animals do not have tetany (Grantham, Tu & Schloerb, 1960). Vallee *et al.* (1960) emphasized that tetany in their patients could be abolished with Mg alone, but this does not in any way settle the problem since Mg has the pharmacological effect of diminishing neuromuscular irritability (Frankenhaeuser & Meves, 1958) and tetany from calcium deficiency can be abolished with Mg (Eliel, Smith & Thomsen, 1960).

The total deficit of Mg has been assessed only once by Card & Marks (1958). Their patient became extremely ill after losing daily 5 l. of intestinal fluids for over a month. The patient, a woman, was small and the calculated deficit, 340 m-equiv., must have represented about a quarter of her normal Mg store.

The investigation

Our own observations concern four patients with steatorrhoea, who had a normal plasma Mg content and no symptoms of Mg deficiency. We studied the effect of giving them Mg parenterally, which normally is fairly rapidly excreted in the urine but not in the faeces (Table 1).

Table 1. *Urinary and faecal excretion of injected magnesium by different species*

Reference	Species	No. examined	Mg injected (m-equiv.)	Salt	Route	Period	Urinary Mg (as percentage of dose injected)	Faecal Mg
Mendel & Benedict (1909)	Dog	13	14	Sulphate	SC	48 h	62–72	No increase
Nicolaysen (1936)	Dog	2	12	Sulphate	SC	72 h	74, 82	No increase
Smith, Winkler & Schwartz (1939)	Dog	5	50–77	Sulphate	IV	24 h	50–88	No increase
McCance & Widdowson (1939)	Man	6	255	Gluconate	IV	14 days	100	No increase
Pritchard (1955)	Man	2	33	Sulphate	IV	24 h	99	
FitzGerald & Fourman (1956)	Man	2	49, 82	Sulphate	IV	3 days	94, 100	
Womersley (1958)	Man	2	70	Lactate	IV	24 h	100	
Smith (1959*a*,*b*)	Ox (calf)	2	83	Sulphate	SC			No increase
McCollister *et al.* (1960)	Man	2	48, 96	Sulphate	IM	6 days	92, 90	

SC, subcutaneous; IV, intravenous; IM, intramuscular.

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Procedures

Intravenous infusions. The urinary excretion of Mg was measured during and after the infusion of 84 m-equiv. Mg as the sulphate and as the chloride. The infusions were given at a constant rate of 1 l. isotonic dextrose solution, and lasted 6 h. Control observations were made on two medical students and on one woman aged 34 with asthma.

Repeated intravenous injections. The urinary excretion of Mg was measured daily while the patients received injections of 42 m-equiv. $MgSO_4$ daily or on alternate days, for a number of weeks (see Fig. 3). We were thus able to estimate the total amount of Mg retained.

Methods

The methods used for the determination of Mg, calcium and creatinine were: Mg in urine, Garner (1946); in plasma, Wilkinson (1960); Ca, Fales & Paubionsky (1958); creatinine, Kingsley, Schaffert & Reiner (1953).

Patients

Patient no. 1 (J.R.), a man born in 1902, had attacks of abdominal pain and fatty diarrhoea since 1959. He complained of weakness which was at first attributed to anaemia, and subsequently of failing vision caused by cataracts. Early in 1960 he began to have tetany. At this time his plasma Ca was 8·5 mg/100 ml; plasma proteins, total, were 5·8 g/100 ml and albumin was 3·4 g/100 ml. There was no Ca in the urine by the Sulkowitch test (Barney & Sulkowitch, 1937). The bones of the spine and pelvis were radiologically less dense than normal but there were no pseudo-fractures and a biopsy of the costochondral junction showed no evidence of osteomalacia. Between January 1960 and his admission to hospital in December 1960, his plasma Ca fell from 8·5 to 4·0 mg/100 ml and then fluctuated between 4·0 and 5·5 mg/100 ml. Parathyroid extract (Eli Lilly & Co.), 5 ml daily for 7 days, did not increase the plasma Ca content. Vitamin D, 10 000 units parenterally (two doses), also had no effect. During his admission he had many attacks of carpopedal spasm which were always relieved by the injections of Mg. In December 1960 the plasma Mg was 2·0 mg/100 ml.

Patient no. 2 (R.B.) a man born in 1920, began to have fatty diarrhoea in 1955, with occasional abdominal colic. In 1959 he began to have tetany and later in the same year he had pain low in the back. His plasma Ca was then 7·8 mg/100 ml, his plasma inorganic P 2·2 mg/100 ml and the serum alkaline phosphatase was 25·4 King–Armstrong units (King & Armstrong, 1934) per 100 ml. The total serum proteins were 7·1 g/100 ml and the serum albumin was 5·3 g/100 ml. The bones were radiologically less dense than normal, but there were no pseudo-fractures and a bone biopsy from the iliac crest did not reveal osteoid tissue. With a gluten-free diet and calcium citrate, 20 g/day (equivalent to 4 g Ca/day), the tetany ceased and the diarrhoea improved. During the 9 weeks of his stay in hospital, March to May 1961, the plasma Ca varied between 7·7 and 9·2 mg/100 ml. When we began our investigations the plasma Mg was 1·9 mg/100 ml.

Patient no. 3 (A.P.) a man born in 1904, had in 1959 an extensive intestinal infarction from an embolism of the superior mesenteric artery. At operation all the small intestine was resected apart from 12 in. of jejunum and 4 in. of ileum. He became very weak and had fatty diarrhoea. Three months after the operation he complained of pins and needles and cramps in the legs, but these symptoms lasted only a month. The bones were radiologically normal. When we began our investigations the plasma Ca was 9·0 mg/100 ml and the plasma Mg 1·65 mg/100 ml.

Patient no. 4 (G.S.), a woman born in 1941, first had fatty diarrhoea in 1957. In 1959 she complained of severe weakness and tiredness. Her haemoglobin was 8 g/100 ml and she improved after a blood transfusion. There were no symptoms of tetany and her plasma Ca was 9·5 mg/100 ml, and the inorganic P 4·9 mg/100 ml. With a gluten-free diet the diarrhoea improved, but she failed to adhere to the diet. By February 1961 she was again very weak. The bones of the pelvis and spine were radiologically less dense than normal; there were no pseudo-fractures. A biopsy from the iliac crest did not reveal osteoid tissue. During the 11 weeks of investigation the plasma Ca varied between 6·9 and 8·8 mg/100 ml. Her plasma Mg on admission was 2·0 mg/100 ml.

Four weeks after admission she had tetany; her plasma Ca was then 7·9 mg/100 ml. The tetany responded to injections of Mg.

Results

Intravenous infusions. Table 2 shows the urinary excretion of Mg in three normal persons, 24 and 48 h after an infusion of Mg, and Table 3 shows the corresponding values for patients with steatorrhoea.

Table 2. *Urinary excretion of magnesium by three normal persons in the 24 and 48 h after an infusion of 84 m-equiv. Mg as $MgSO_4$ or $MgCl_2$*

		Mg excreted				
		m-equiv.			As percentage of dose	
Subject no.	Infusion	24 h before	24 h after	48 h after	24 h after	48 h after
1	$MgSO_4$	11·4	58·6	69·4	70·0	82·5
	$MgCl_2$	10·1	67·5	79·6	80·5	94·7
2	$MgSO_4$	7·0	—	99·8	—	118
	$MgCl_2$	5·1	62·2	72·6	74·0	86·5
3	$MgSO_4$	—	60·5	75·2	72·0	89·5

Table 3. *Urinary excretion of magnesium by patients with steatorrhoea in the 24 h and 48 h after an infusion of 84 m-equiv. Mg as $MgSO_4$ or $MgCl_2$*

		Mg excreted				
		m-equiv.			As percentage of dose	
Patient	Infusion	24 h before	24 h after	48 h after	24 h after	48 h after
1 (J.R.)	$MgSO_4$	0	17·87	18·47	21·2	22·0
2 (R.B.)	$MgSO_4$	1·5	31·4	33·6	37·4	40·0
	$MgCl_2$	2·2	29·4	38·8	35·0	46·2
3 (A.P.)	$MgSO_4$	0·65	17·28	20·48	20·6	24·4
	$MgCl_2$	0·82	2·0	2·9	2·38	3·46
4 (G.S.)	$MgSO_4$	10·5	52·9	62·8	63·0	74·8
	$MgCl_2$	4·0	23·8	32·6	27·4	38·8

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The normal persons excreted more than 80% of the injected Mg in 48 h. The patients with steatorrhoea all excreted much less than that.

Fig. 1 shows the rate of excretion of Mg on the day of the intravenous infusions in the normal persons. The cumulative percentage of the total daily excretion of creatinine excreted with successive urine collections is shown on the abscissa and serves as a measure of time. The percentage of the infused Mg excreted is shown on the ordinate. The excretion of Mg increased rapidly in the first quarter of the day and then rose slowly to its value at the end of the 24 h period.

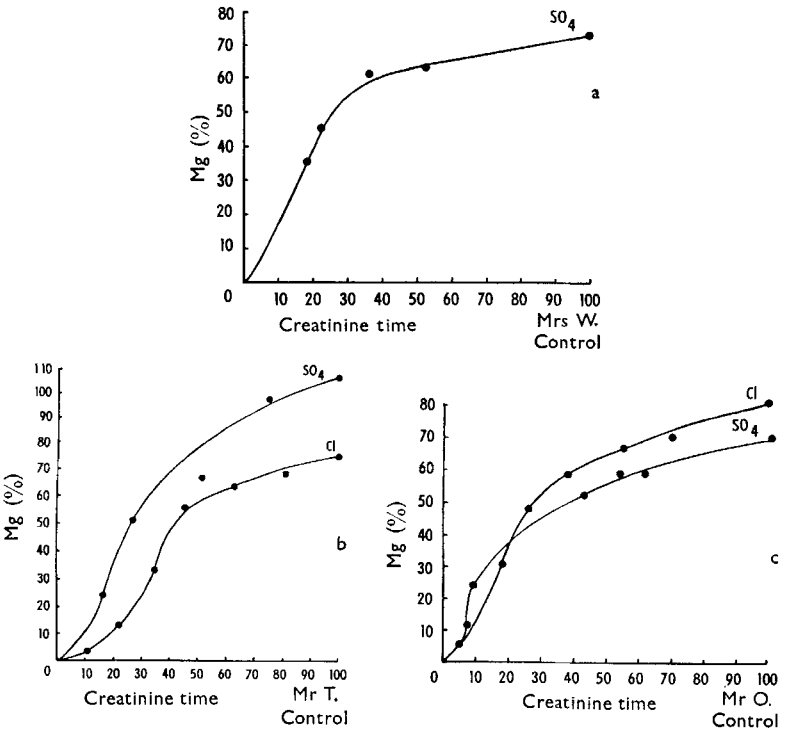

Fig. 1. Rate of excretion of magnesium on the day of its intravenous infusion into normal persons. The cumulative percentage of the total creatinine excreted in successive urine specimens during the day is shown on the abscissa, and serves as a measure of time. The percentage of the injected Mg excreted is shown on the ordinate. SO_4, Mg infused as $MgSO_4$; Cl, Mg infused as $MgCl_2$.

Fig. 2 shows the rate of Mg excretion in the four patients. It will be seen that the excretion of Mg increased less rapidly in the patients than in the normal persons.

Patient no. 1 was studied three times (Fig. 2a). He increased his excretion of Mg more quickly after he had retained 132 m-equiv. Mg.

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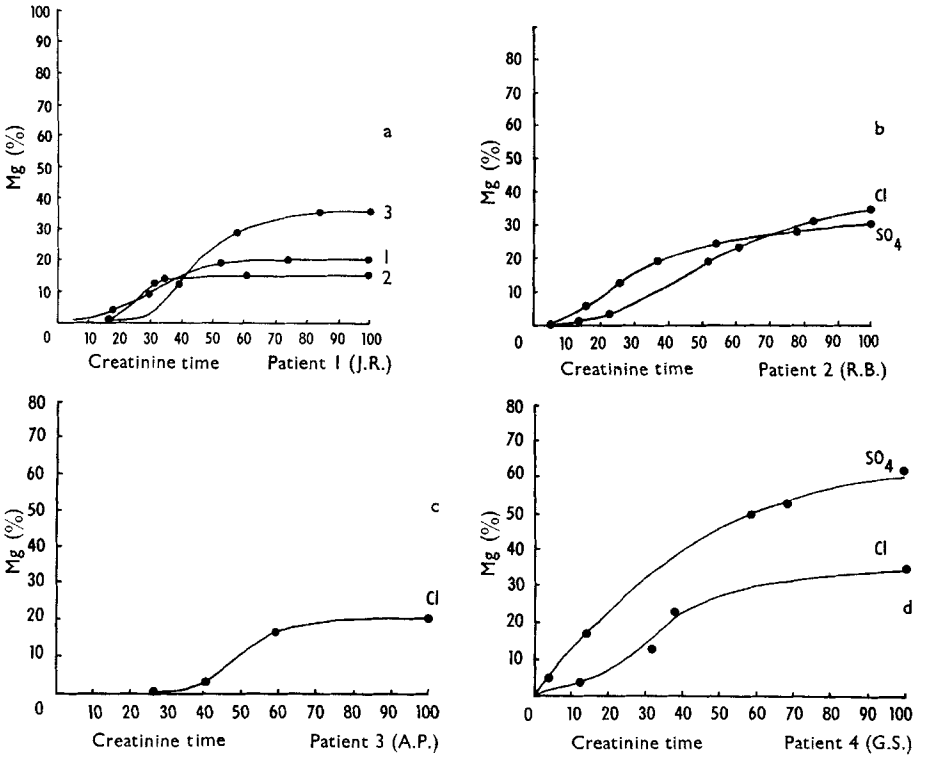

Fig. 2. Rate of excretion of magnesium on the day of its infusion in four patients with steatorrhoea. For explanation see Fig. 1. With patient J.R. the excretion was studied three times after infusions of $MgSO_4$.

Repeated injections of Mg. The second part of the investigation was designed to measure the total Mg deficit. Fig. 3a shows the urinary excretion of Mg in patient no. 1 during 83 days when he had thirty-one injections and a total of 1428 m-equiv. Mg. During this period he excreted only 970 m-equiv. Mg in the urine, apparently retaining 460 m-equiv. The cumulative retention of Mg is shown in the upper half of Fig. 3a. The lower half of the figure shows the Mg excretion from day to day. The amount retained after each injection decreased progressively over the period of 80 days.

The calculated deficit of 460 m-equiv. in patient no. 1 involves the assumption that Mg given parenterally is excreted only through the kidneys (see Table 2) and that the small amount of Mg absorbed from the diet can be neglected. It can be seen from Fig. 3a that the urinary excretion of Mg was very small on days when the patient was not given an injection. Fig. 3b,c,d shows the successive changes in Mg excretion after its injection in patients nos. 2, 3 and 4. Fig. 3b,c also shows the accumulated retention of Mg in patients nos. 2 and 3. They retained 460 and 440 m-equiv. in 60 and 40 days. The values for patient 4 were incomplete.

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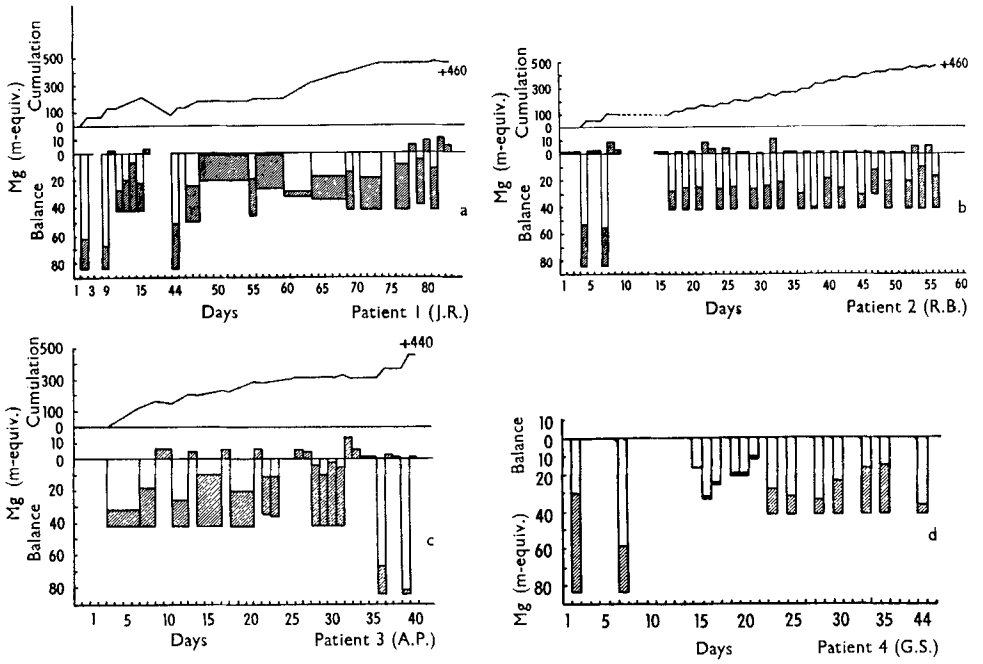

Fig. 3. The lower part of each chart shows the urinary excretion of magnesium from day to day in four patients with steatorrhoea while they were receiving injections of Mg as the sulphate. The amount of Mg injected is plotted downwards from the zero line. The excretion of Mg is plotted upwards from the apparent intake, assumed to be zero on the days when the patient had no injection. The difference between the amount injected and the amount excreted, shown as a clear area on the chart, represents Mg retained. The amount retained after each injection fell steadily. The upper part of the charts for patients J.R., R.B. and A.P. shows the calculated cumulative gain of Mg. Information about patient G.S. is incomplete.

Discussion

The large deficits of Mg in these patients were entirely unexpected. They were not associated with the recognized symptoms of Mg deficiency or with a low plasma Mg, but two of the patients felt a considerable gain of muscular strength when their deficit was corrected. One of the patients (J.R.) had a persistently low plasma Ca content and intractable tetany. His plasma Ca content rose and his tetany remitted.

The problem of the fate of the injected Mg has not been investigated. Mg depletion in growing animals affects entirely the fraction in bone (Cunningham, 1933; Orent, Kruse & McCollum, 1934; Tufts & Greenberg, 1937–8; Watchorn & McCance, 1937; Duckworth, Godden & Warnock, 1940; Blaxter, Rook & McDonald, 1954; Smith, 1959*a*,*b*), but in older animals and in man Mg deficiency may affect also the soft tissues, and in particular the muscle (MacIntyre & Davidsson, 1958; McAleese & Forbes, 1961; MacIntyre, Hanna, Booth & Read, 1961). The problem can only be

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investigated by the analysis of samples of muscle and bone, but it is worth while at this stage to draw attention to a possible difference between the composition of bone in steatorrhoea and bone in rickets or osteomalacia caused by simple deficiency of vitamin D. In classical rickets the Mg content of bone increases, partly replacing the deficit of calcium. Our results suggest that in osteomalacia caused by steatorrhoea Mg may not be available to replace calcium in bone.

REFERENCES

Anonymous. (1960). *Nutr. Rev.* **18**, 72.
Barney, J. D. & Sulkowitch, H. W. (1937). *J. Urol.* **37**, 746.
Baron, D. N. (1960). *Brit. J. Surg.* **48**, 344.
Blaxter, K. L., Rook, J. A. F. & McDonald, A. M. (1954). *J. comp. Path.* **64**, 157.
Card, W. I. & Marks, I. N. (1958). *Ciba Fdn Colloquia on Ageing*, **4**, 301.
Clough, P. W. (1960). *Ann. intern. Med.* **53**, 615.
Cope, M. & Barnes, B. (1960). *Ann. Surg.* **152**, 518.
Cunningham, I. J. (1933). *N.Z. J. Sci. Tech.* **15**, 191.
Duckworth, J., Godden, W. & Warnock, G. M. (1940). *Biochem. J.* **34**, 97.
Eliel, L. P., Smith, W. O. & Thomsen, C. (1960). *J. Okla. med. Ass.* **53**, 359.
Fales, F. W. & Paubionsky, P. (1958). In *Standard Methods of Clinical Chemistry*, Vol. 2, p. 1. [D. Seligson, editor.] New York: Academic Press Inc.
FitzGerald, M. G. & Fourman, P. (1956). *Clin. Sci.* **15**, 635.
Fletcher, R. F., Henly, H. A., Sammons, H. G. & Squire, J. R. (1960). *Lancet*, i, 522.
Flink, E. B., McCollister, R., Prasad, A. S., Melby, J. C. & Doe, R. P. (1957). *Ann. intern. Med.* **47**, 956.
Flink, E. B., Stutzman, F. L., Anderson, A. R., Konig, T. & Fraser, R. (1954). *J. Lab. clin. Med.* **43**, 169.
Frankenhaeuser, B. & Meves, H. (1958). *J. Physiol.* **142**, 360.
Garner, R. J. (1946). *Biochem. J.* **40**, 828.
Grantham, J. J., Tu, W. H. & Schloerb, P. R. (1960). *Amer. J. Physiol.* **198**, 1211.
Hammarsten, J. F. & Smith, W. O. (1957). *New Engl. J. Med.* **256**, 897.
Hanna, S., Harrison, M., MacIntyre, I. & Fraser, R. (1960). *Lancet*, ii, 172.
Hanna, S. & MacIntyre, I. (1960). *Lancet*, ii, 348.
Hirschfelder, A. D. & Haury, V. G. (1934). *J. Amer. med. Ass.* **102**, 1138.
King, E. J. & Armstrong, A. R. (1934). *Canad. med. Ass. J.* **31**, 376.
Kingsley, G. R., Schaffert, R. R. & Reiner, M. (1953). In *Standard Methods of Clinical Chemistry*, Vol. 1, p. 55. [M. Reiner, editor.] New York: Academic Press Inc.
McAleese, D. M. & Forbes, R. M. (1961). *J. Nutr.* **73**, 94.
McCance, R. A. & Widdowson, E. M. (1939). *Biochem. J.* **33**, 523.
McCollister, R. J., Flink, E. B. & Doe, R. P. (1960). *J. Lab. clin. Med.* **55**, 98.
MacIntyre, I. & Davidsson, D. (1958). *Biochem. J.* **70**, 456.
MacIntyre, I., Hanna, S., Booth, C. C. & Read, A. E. (1961). *Clin. Sci.* **20**, 297.
Mendel, L. B. & Benedict, S. R. (1909). *Amer. J. Physiol.* **25**, 1.
Miller, J. F. (1944). *Amer. J. Dis. Child.* **67**, 117.
Nicolaysen, R. (1936). *Skand. Arch. Physiol.* **73**, 75.
Orent, E. R., Kruse, H. D. & McCollum, E. V. (1934). *J. biol. Chem.* **106**, 573.
Pritchard, J. A. (1955). *Surg. Gynec. Obstet.* **100**, 131.
Randall, R. E., Rossmeisl, E. C. & Bleifer, K. H. (1959). *Ann. intern. Med.* **50**, 257.
Smith, P. K., Winkler, A. W. & Schwartz, B. M. (1939). *J. biol. Chem.* **129**, 51.
Smith, R. H. (1959*a*). *Biochem. J.* **71**, 306.
Smith, R. H. (1959*b*). *Biochem. J.* **71**, 609.
Suter, C. & Klingman, W. D. (1955). *Neurology*, **10**, 691.
Tibbetts, D. M. & Aub, J. C. (1937). *J. clin. Invest.* **16**, 511.
Tufts, E. V. & Greenberg, D. M. (1937–8). *J. biol. Chem.* **122**, 693.
Vallee, B. C., Wacker, W. E. C. & Ulmer, D. D. (1960). *New Engl. J. Med.* **262**, 155.
Watchorn, E. & McCance, R. A. (1937). *Biochem. J.* **31**, 1379.
Wilkinson, R. H. (1960). *Chemical Micromethods in Clinical Medicine*, p. 88. Oxford: Blackwell Scientific Publications.
Womersley, R. A. (1958). *J. Physiol.* **143**, 300.