coccus faecalis (4). Mixed infections (including *Pseudomonas*, *Staphylococcus aureus*, *Klebsiella*, and *Proteus* spp.) were present in 21 urines from patients with gross urological abnormalities. In 13 instances urine samples were collected following the administration of antibiotics.

All samples were transferred to the laboratory immediately after collection, and bacterial counts carried out by the surface plating method. Part of the sample was immediately refrigerated, while the remainder was incubated at 37° C. overnight. At the end of this period further bacterial counts were carried out, and the creatinine content of both the refrigerated and incubated samples was measured on the Technicon auto-analyser.

In 12 urines which contained 10⁸ organisms/ml., and in nine urines from treated patients, the counts did not rise detectably on incubation. Otherwise, following overnight incubation the bacterial counts rose to 10⁸ or more per ml., representing a rise of more than 1,000-fold in 16 urines, 100-fold in nine, and 10-fold or more in the remainder. Urinary creatinine concentrations ranged from 14 to 236 mg./100 ml. In none of the 90 samples examined was there any change in urine creatinine content outside the analytical error of the method.

The results of these studies thus clearly show that over a wide range of creatinine concentrations bacterial multiplication within the urine over a period of up to 24 hours has no effect on urinary creatinine content. We have therefore concluded that estimations of urinary creatinine for clearance or other purposes are not invalidated by the presence of bacteria in the sample.—We are, etc.,

W. R. CATTELL.
J. M. SARDESON.
E. HUTCHINSON.
F. O'GRADY.

St. Bartholomew's Hospital,
London E.C.1.

REFERENCES

- 1 Healy, J. K., *American Journal of Medicine*, 1968, 44, 348.
- 2 Relman, A. S., and Levinsky, N. G., in *Disease of the Kidney*, edited by M. B. Strauss and L. G. Welt, 1963, p. 80. Boston, Little Brown and Co.

Manson and Malaria

SIR,—The article on Aberdeen Medical School (28 June, p. 816) contains the statement that Sir Patrick Manson discovered the cause of malaria. This distortion of medical history ought not to be allowed to pass.

The malaria parasite was discovered by Alphonse Laveran in 1880 and its transmission by a mosquito by Ronald Ross in 1897. Manson must be given credit for the mosquito-malaria theory, which he formulated and put forward in 1894 and again in 1896, and which guided and stimulated Ross. It remained, however, only a theory until Ross and later workers actually transmitted the malaria parasite by the bite of a mosquito.

The scepticism with which the mosquito-malaria theory was received is illustrated by a story which Sir Patrick's son-in-law, the late Sir Philip Manson-Bahr, used to tell. One day a colleague caught sight of Manson on the other side of the street and remarked to his companion: "Do you know who that is? That's mosquito Manson," and tapped his head significantly.

Conclusive evidence of the part played by the mosquito was given by the experiments

devised by Manson in 1900, when it was shown that it was possible to escape infection in a highly malarious locality in Italy by living in a dwelling protected by wire gauze, and secondly that mosquitoes fed in Rome on patients suffering from malaria infected two persons in London by their bites.

I do not consider it necessary to give any references to the literature as the story is too well known.—I am, etc.,

H. G. CALWELL.

Whitehead,
Co. Antrim.

Paraneoplastic Hypercalcaemia and Renal Malignancy

SIR,—Paraneoplastic hypercalcaemia has been found in association with a wide variety of malignant processes.¹ Cytological specificity appears to exist in certain of the paraneoplastic syndromes.² The present communication considers the possibility of a renal cellular specificity with respect to the syndrome of paraneoplastic hypercalcaemia.

In the 19 cases of renal carcinoma reported in association with "pseudohyperparathyroidism," 11 indicate cell type. Of these, 77% are cells with a clear cytoplasm, and the remainder squamous or transitional cell carcinomas of the renal pelvis. These data suggest the importance of the clear cell in its association with the syndrome, considering that the clear cell renal-cell carcinoma is found in but 40% of renal malignancies.³ The tumour composed of renal cells with clear cytoplasm has already been signalled in association with paraneoplastic erythrocytosis (4 January, p. 51). However, among the 83 cases reporting that syndrome which presented cell type, no tumour of the renal pelvis was noted.

Thus there appears to be a tendency for the clear cell renal-cell carcinoma and the transitional or squamous cell carcinoma of the renal pelvis to be associated with "pseudohyperparathyroidism" more frequently than the cell with granular cytoplasm, Wilms's tumour, or other malignant renal lesion.—I am, etc.,

MICHAEL A. SPERBER.

Harvard Medical School,
Beth Israel Hospital,
Boston, U.S.A.

REFERENCES

- 1 O'Grady, A. S., Morse, L. J., and Lee, J. B., *Annals of Internal Medicine*, 1965, 63, 858.
- 2 *Lancet*, 1964, 1, 317.
- 3 Murphy, G. P., and Mostofi, F. K., *Journal of Urology*, 1965, 94, 48.

Vitamin C and the Elderly

SIR,—We agree with Drs. J. C. Brocklehurst and L. L. Griffiths (28 June, p. 824) that daily doses of ascorbic acid larger than the 40- and 80-mg. doses we chose (17 May, p. 416) would accelerate the rise in leucocyte ascorbic acid concentration and are to be recommended for the correction of gross deficiency. Bowers and Kubik¹ reported in 1965 that a 120-mg. daily supplement of ascorbic acid raised initially low leucocyte concentrations of ascorbic acid to levels above

those of younger, healthy people in four weeks.

Our supplementation doses were chosen to be of the same order but in excess of the B.M.A.'s 30 mg.² and the then United States's 70 mg.³ (now 60 mg. for males and 55 mg. for females⁴) recommended daily dietary allowances. It was therefore surprising that these nutritional levels of supplementation were inadequate to produce a rapid response in our group of elderly subjects. A reduced renal threshold or an increased requirement for ascorbic acid could explain the slow leucocyte response. More investigation is necessary, including more study of the clinical significance of biochemically subnormal levels of ascorbic acid in the elderly, especially as the unsupplemented control group of Drs. Brocklehurst and Griffiths⁵ showed an 87% rise in the mean leucocyte ascorbic acid concentration to a level typical of young, healthy individuals during the first six months of the study.—We are, etc.,

JAMES ANDREWS.

West Middlesex Hospital,
Middx.

M. BROOK,
Manager, Basic Research Department,
Beecham Products U.K.

Brentford,
Middx.

REFERENCES

- 1 Bowers, E. F., and Kubik, M. M., *British Journal of Clinical Practice*, 1965, 19, 141.
- 2 British Medical Association, *Report of the Committee on Nutrition*, 1950. London, British Medical Association.
- 3 National Research Council, *Recommended Dietary Allowances*, 1964, 6th edition, Publication No. 1146. Washington, National Research Council.
- 4 National Research Council, *Recommended Dietary Allowances*, 1968, 7th edition, Publication No. 1694. Washington, National Research Council.
- 5 Brocklehurst, J. C., Griffiths, L. L., Taylor, G. F., Marks, J., Scott, D. L., and Blackley, J., *Gerontologia Clinica*, 1968, 10, 309.

How Many Authors Can Collaborate?

SIR,—The recent paper "Liver Transplantation in Man—III . . ." (5 July, p. 12) appears under the authorship of no fewer than 17 authors—surely a near-record? It is my experience that such therapeutic committees merely provide opportunities for their members to add to the number of their publications.

One man may write a paper; two may, with difficulty, collaborate; three may conceivably achieve something without violence to conscience: but that 17 should agree passes the bounds of credibility or credulity.

As a convinced non-collaborator, my opinion is open to criticism; but 17 . . . —I am, etc.,

J. W. DICKSON.

Ipswich and East Suffolk Hospital,
Ipswich, Suffolk.

Disodium Cromoglycate in Exercise-induced Asthma

SIR,—Various theories have been suggested to explain the bronchoconstriction that follows exercise: (1) a nervous reflex stimulated by hyperventilation and the movement of the bronchial walls; (2) the release of a humoral substance during exercise such

as histamine, SRS-A, or bradykinin; and (3) changes in hydrogen-ion concentration due to lactic acidemia, which stimulates ventilation and results in hypocapnia during the recovery period. Attempts to block the exercise effect by an antihistamine have been unsuccessful,¹ but this does not exclude the possibility of a local release of histamine. Disodium cromoglycate is said to prevent the release of histamine from mast cells following an antigen-antibody reaction, and we thought it was possible that it might also interfere with the local release of histamine on exercise resulting from hyperaemia and the mildly traumatic effect of increased ventilation.

A trial was made on 10 asthmatic subjects who all complained of asthma following exercise. In five of them this was quite troublesome and occurred after fairly ordinary activity such as hurrying after a bus or washing a car. There were nine males and one female with an average age of 28 years (range 17-48 years). Eight had positive skin reactions to one or more antigens and five had an eosinophilia of more than 400/cu. mm.

Experiments were carried out on six occasions at weekly intervals: before cromoglycate, after the inhalation of one Spincap containing 20 mg. cromoglycate without isoprenaline; one and two weeks after three such Spincaps per day; and one and two weeks after stopping cromoglycate. No bronchodilator was allowed within three hours of the test, but otherwise there was no restriction in treatment. During the experiment the F.E.V.₁ was measured at three to five minute intervals for 15 minutes before exercise and up to 45 minutes after exercise. Exercise took the form of running up and down stairs for three to four minutes and was kept as constant as possible for successive studies on each patient. In most patients the maximum fall in F.E.V.₁ occurred within 10 minutes of the cessation of exercise, and the lowest value occurring during this period is used to calculate the exercise effect.

The average fall in F.E.V.₁ after exercise before, during, and after cromoglycate is illustrated in the Figure. The experiments fall naturally into two groups, those carried out during cromoglycate therapy and those carried out before and after. The mean fall in F.E.V.₁ was 0.935 litre during therapy and 1.34 litres without, and an analysis of variance shows that this is a statistically significant difference ($0.01 < P$

<0.05). In all but one patient, in whom the data are incomplete, cromoglycate offered some protection from exercise by inhibiting the fall in F.E.V.₁ by 30% on average.

These results are rather less dramatic, but in accord with those reported by Davies² who

found a marked inhibition of the exercise effect following the inhalation of 1 Spincap of cromoglycate. This rapid effect of cromoglycate, which to some extent we have also found, is analogous to the inhibition of the immediate asthmatic reaction following the inhalation of antigen which has been reported by Pepys *et al.*³ It is interesting that steroids do not protect asthmatics from the effects of exercise, and the partial success of cromoglycate suggests that histamine release may be one of the mechanisms involved.

The question arises as to whether the degree of protection justifies the use of cromoglycate in asthmatics who complain of the adverse effects of exercise. Previous studies have shown the beneficial effect of isoprenaline and other sympathomimetic drugs in this situation⁴ and Crompton⁵ found atropine to be very effective in one subject. We do not therefore feel justified in recommending cromoglycate when exercise-induced asthma is the sole or main complaint.—We are, etc.,

F. G. WARD.

R. GOMES.

R. S. McNEILL.

Department of Therapeutics,
Maryfield Hospital,
Dundee.

REFERENCES

- McNeill, R. S., Nairn, J. R., Millar, J. S., and Ingram, C. G., *Quarterly Journal of Medicine*, 1966, 35, 55.
- Davies, S. E., *British Medical Journal*, 1968, 3, 593.
- Pepys, J., Hargreaves, F. E., Chan, M., and McCarthy, D. S., *Lancet*, 1968, 2, 134.
- Jones, R. S., Wharton, M. J., and Buxton, M. H., *Archives of Disease in Childhood*, 1963, 38, 539.
- Crompton, G. K., *Thorax*, 1968, 23, 165.

SIR,—It may not be generally recognized that, although the airstream sucked from a Spinhaler will deposit agglomerates when directed on to a microscope slide, this technique does not allow collection of the finer particles in the cloud. Provided properly designed apparatus is used this principle can be used to estimate the extent of inhalable particles in a powder cloud.¹ Thus, using an impactor designed² to allow all particles less than 13 μ to pass through a membrane filter gave values of approximately 5 mg. of disodium cromoglycate from a single capsule. Furthermore, laser holography—that is, three-dimensional photography of a portion of the moving Spinhaler cloud—has clearly shown numerous discrete particles less than 5 μ .³ Particle size analysis using a Hexhlet dust sampler⁴ has shown that 1-2 mg. of the drug is likely to penetrate to the alveolar region. In addition to these fine particles the cloud contains larger particles and agglomerates, which are, of course, retained in the upper airways.

The size range ensures that deposition occurs over a wide area of the bronchial tree, and we believe, until more is known about the anatomical location of the allergic reaction, such a distribution is desirable. Preference has been expressed for aqueous sodium cromoglycate solutions (14 June, p. 696), and therefore we feel it is important to record our results with a 5% w/w solution. To achieve a comparable dose to the Spinhaler (1-2 mg. alveolar penetration) would

require approximately 200 actuations of a hand-operated nebulizer.—I am, etc.,

J. S. G. COX,
Director of Research and Development,
Fisons Pharmaceuticals Ltd.
Loughborough, Leics.

REFERENCES

- May, K. R., *Journal of Scientific Instruments and Physics in Industry*, 1945, 22, 187.
- Lundgren, D. A., *Journal of the Air Pollution Control Association*, 1967, 17, 225.
- Investigations into a Holographic Method for a Particle Size Analysis of Powdered Pharmaceutical Products*, Kuhn, Roth, Seger, and Wittig. Battelle-Institute e.V., Frankfurt-am-Main, Germany (available on written request).
- Wright, B. M., *British Journal of Industrial Medicine*, 1954, 11, 284.

Dangers of Certain Appetite Suppressants

SIR,—I read the letter sent by Dr. D. A. Cahal (3 May, p. 316), reporting that certain appetite suppressants "might cause pulmonary hypertension," with some alarm. I have under my care many patients afflicted with chronic chest diseases who are breathless, and among them are some who are grossly overweight.

It has seemed desirable to encourage such patients to lose surplus fat by simple dietary measures, aided in a few instances by the administration of an appetite depressant. The drug used has been fenfluramine. I have also been investigating the effects of prolonged airways obstruction upon cardio-pulmonary function, and by chance have obtained measurements of pulmonary artery pressures at rest and during exercise upon six of them who have been taking fenfluramine. These patients had been on the drug for periods varying from two weeks up to three months before being investigated. On looking through the data collected from these cases to see whether there was any evidence of pulmonary hypertension I was unable to find any such evidence. This failure does not prove conclusively that fenfluramine never causes pulmonary hypertension, particularly as the patients had been taking it for only very short periods of time.

Nevertheless, the available pharmacological evidence¹⁻³ suggests that fenfluramine may not produce pulmonary hypertension in human subjects.—I am, etc.,

F. J. PRIME.

Institute of Diseases of the Chest,
London S.W.3.

REFERENCES

- Coupar, I. M., Hedges, A., Metcalfe, H. L., and Turner, P., *Lancet*, 1969, 1, 925.
- Franko, B. V., Honkomp, L. J., and Ward, J. W., *Journal of Pharmacy and Pharmacology*, 1965, 1, 222.
- Le Douarec, J. C., Schmitt, H., and Laubie, M., *Archives Internationales de Pharmacodynamie et de Thérapie*, 1966, 161, 206.

Management of Unconscious Poisoned Patients

SIR,—In your otherwise excellent and timely leading article on management of unconscious poisoned patients (14 June, p. 647) you refer to "short-" and "medium-acting" barbiturates. The continued use of this traditional classification of barbiturates, based on apparent duration of therapeutic action, still confuses the toxicological situation. "Short-" and "medium-acting" bar-