ence with four other patients was less dramatic. One patient had acute typhoid fever and did not respond to two tablets (6 mg trimethoprim-30 mg sulphamethoxazole per kg body weight) but responded to three tablets. Another patient had paratyphoid A fever and continued to have positive blood cultures up to the 17th day while on the drug; blood was sterilized only when we doubled the dose. Two other salmonella paratyphi A urinary carriers with pretreatment positive blood cultures continued to have positive blood cultures up to the 8th and 21st day while on the drug again at the same low dosage (6 mg trimethoprim, 30 mg sulphamethoxazole per kg body weight). We have increased their dosage.

Based on this experience we recommend that other workers increase the dose according to body weight.—We are, etc.,

SAMIR BASSILY
ZOHEIR FARID
J. S. LEHMAN, jun
KURT SORENSSEN

U.S. Naval Medical Research Unit No. 3,
(Cairo, Egypt),
Fleet Post Office,
New York, U.S.A.

Prolonged Corticosteroid Therapy

SIR,—My pleasure in reading that Dr. L. Westerhof and others (28 November, p. 534) have confirmed our conclusion that "... the therapeutic efficacy of small doses of corticosteroids is due to summation of exogenous and endogenous steroid, since small doses do not suppress secretion of cortisol by the adrenal"¹ was diluted by their dismissal of our work as not having been done on patients who had *prolonged* corticosteroid therapy. It is difficult to understand this misreading of our paper since we went out of our way to point out that the findings had been obtained in patients "... who had been taking corticosteroids for an average of 26 months. This dose was therapeutically adequate in all and had not been altered for an average of 15 months." One of the patients had in fact been taking corticosteroids continuously for 54 months. Our findings are therefore very relevant to the practical problem of prolonged corticosteroid therapy.

The therapeutic efficacy of doses of corticosteroids within the physiological range is still questioned by some, apparently because they believe these small doses will suppress pituitary-adrenal function. The paper by Dr. Westerhof and colleagues is therefore timely in drawing our attention once again to an aspect of applied physiology which has a good deal of therapeutic importance.—I am, etc.,

SAM SHUSTER

Department of Dermatology,
University of Newcastle upon Tyne

¹ Shuster, S., and Williams, I. A., *Lancet*, 1961, 2, 674.

An Unusual Cause of Oesophageal Stricture

SIR,—A lady of 78, who was a mild diabetic, was admitted to hospital in June of this

year having swallowed a Clinitest tablet by mistake. Immediately after she felt a very hot burning sensation in her throat, and she started to sweat profusely and then to vomit. Her doctor correctly gave her the advice to drink large quantities of water, followed if possible by citrus fruit juice and olive oil, as the tablets are clearly marked "caustic" on the bottle. She was unable to drink very much as she was continuously vomiting. The next day the pain was a little better but she had dysphagia which rapidly progressed until she had to be admitted to hospital.

I oesophagoscoped her on three consecutive occasions, but the improvement did not last longer than two weeks before she again needed dilation. I did not think that she was suitable for a major resection which would be required to deal radically with the stricture at this level, so I inserted a Celestin tube. Since then she has remained well, but on one occasion recently, had to be re-admitted as her tube had become obstructed by food debris.

Clinitest tablets contain 38.5% of sodium hydroxide, and when one of these tablets is placed in a test tube of water a very considerable amount of heat is produced. One can well imagine the acute inflammation which occurred when this tablet was temporarily held up at the level of the aortic arch (fig.).—I am, etc.,

MICHAEL BATES

Thoracic Department,
North Middlesex Hospital,
London N.18

Phenytoin Tolerance Tests

SIR,—Dr. A. J. Handley (25 July, p. 203) in following phenytoin concentrations after oral and intravenous administration of phenytoin found a biphasic plasma phenytoin disappearance curve in four patients who had been given 250 mg phenytoin intravenously. After initial high levels plasma phenytoin decreased to values below 3 µg/ml one to two hours after administration, followed by a secondary rise to values between 10 and 17.5 µg/ml.

During the last five years we have determined the phenytoin half-life in blood after

intravenous injection of 100 mg phenytoin to which 20µCi ¹⁴C-phenytoin was added. Thin-layer chromatography was performed on all serum extracts to ensure that all radioactivity was located in the phenytoin spot. The procedure has been described in detail elsewhere.¹ The radiophenytoin determination was usually done on blood samples taken 3 to 12 hours after the injection, because these values give a linear disappearance in a semilogarithmic system.² In 24 patients, however, we also determined the two-hour values and these were in all cases considerably higher than the three- and four-hour values. In the Figure the mean values of ¹⁴C-phenytoin in serum after intravenous injection in 24 patients are shown (A). In an additional four patients the disappearance curve was studied during the first two hours. These patients were given doses between 25 mg and 250 mg phenytoin intravenously. The mean values of these four cases are shown (B).

In no cases have we found biphasic curves as those reported by Dr. A. J. Handley. We have no explanation of this discrepancy.—We are, etc.,

K. SIERSBAEK-NIELSEN
L. SKOVSTED
J. MØLHOLM HANSEN
M. KRISTENSEN

Medical Department F,
Gentofte Hospital,
Copenhagen, Denmark

¹ Hansen, J. M., Kristensen, M., and Skovsted, L., *Epilepsia*, 1968, 9, 17.

² Hansen, J. M., Kristensen, M., Skovsted, L., and Christensen, L. K., *Lancet*, 1966, 2, 265.

Combination Chemotherapy in Acute Myeloblastic Leukaemia

SIR,—We read with great interest the report of Dr. D. Crowther and his colleagues (28 November, p. 513) on their favourable results in the therapy of acute myeloblastic leukaemia using intermittent chemotherapy. They rightly stress the advantages of multiple drug therapy (increased remission rates and drug synergy) and the disadvantages (the dangers of marrow hypoplasia). Hypoplasia occurs commonly in this disease, possibly because all marrow elements are abnormal. To avoid increasing these risks the drugs they use are carefully chosen and used only when bone marrow hypoplasia is not present.

More gentle therapy, designed to achieve more gradual elimination of the tumour

cells, has been tried in our group to minimize the problem of hypoplasia and drug toxicity. The regimen using cytosine arabinoside and 6 thioguanine (Table I) was chosen after personal communications from Dr. Crowther and Dr. E. Freireich (M.D.

It is suggested that because of the nature of the disease, in acute myeloblastic leukaemia it is beneficial to initiate treatment gently in order to avoid the serious complications of aplasia. Indeed the same can be said of the treatment of acute

TABLE I

Day	Drug	Dose	Route
1-5	Cytosine arabinoside	80 mg/m ² daily (200 mg/m ² daily)	Intravenous Subcutaneous (Intravenous eight hourly)
6-7	No treatment		
8-12	6 Thioguanine	70 mg/m ² daily (100 mg/m ² daily)	Oral (Oral)
13-21	No treatment		
22	Restart cycle as at Day 1		

Anderson Hospital, Houston, Texas), who has used a similar programme in the past. This represents an attempt to synchronize the blast cell cycle. Inhibition of DNA synthesis by the cytosine arabinoside leads to partial bone marrow hypoplasia, with a "rebound" of activity following the withdrawal of this drug. Crowther and Freireich suggested that the maximal rebound activity

lymphoblastic leukaemia; if treatment is started with combination chemotherapy of three or four drugs the morbidity is severe, even leading to mortality, whereas the use of two agents only (prednisolone and vincristine) is associated with virtually no toxic side effects. After remission is achieved increased numbers and doses of drugs can be given more safely, and we feel

TABLE II

Case	Age (Years)	Diagnosis	Pretreatment		Result	Length of Remission
			Platelet per mm ³	Blasts per mm ³		
1	12	Acute myeloblastic leukaemia	5,000	10,000	CR	7+ months
2	23	Stem cell leukaemia	5,000	40,000	CR	3 months
3	20	Acute myeloblastic leukaemia	18,000	80,000	F	—
4	50	Acute myeloblastic leukaemia	<10,000	6,000	CR	4+ months
5	19	Stem cell leukaemia	50,000	—	CR	3+ months
6	31	Acute myeloblastic leukaemia	13,000	38,000	CR	5+ months

CR = complete remission. F = failed.

occurs between 24 hours and 72 hours. 6 thioguanine was therefore administered after a gap of 48 hours for 5 days, when it was thought there would be augmented uptake due to increased DNA synthesis.

When remission is achieved the marrow is capable of withstanding larger doses of both these drugs. In our cases the doses were increased to the higher level in four of six patients when in complete remission. A fifth patient achieved a partial remission on the smaller dose and went into complete remission when the dose was increased to the higher levels.

The results are shown in Table II. Six patients with acute myeloblastic leukaemia or stem cell leukaemia have so far been studied. All the patients had received previous antileukaemia therapy or had to be excluded from the current Medical Research Council protocol for other reasons. Of the six patients, five achieved a complete remission and one showed no response. One patient relapsed after three months; the others are still in remission, the longest seven months. These encouraging results were achieved with minimal side effects attributable to drug toxicity and no evidence of marrow aplasia. Platelet counts started to return to normal between 20 and 38 days—that is, after two or three courses. The treatments were continued after remission. The maximum number of courses so far achieved is six. It is intended to carry on with these treatments while remission lasts. In one case the treatment had to be changed after five courses because of drug intolerance; she was in remission at the time and remains so now.

this approach to therapy offers many advantages over previous regimens, with much less morbidity and higher remission rates.—We are, etc.,

R. J. GUYER
D. A. WINFIELD
R. T. SHAHANI
E. K. BLACKBURN

Department of Haematology,
Children's Hospital,
Sheffield, Yorks

Labelled Fibrinogen in Renal Transplantation

SIR,—I would like to reply to the letter of Dr. P. W. Straub (19 December, p. 746), in which he makes certain remarks about the use of radioactive fibrinogen for diagnosing rejection in renal transplants during the early postoperative period (30 May, p. 517).

He found elevated levels of radioactivity over the transplants of two patients in whom there were no other signs of rejection. In one of the patients postoperative bleeding could well have produced the anomalous result. The labelled fibrinogen was given on the second post-transplant day, which is earlier than I would suggest since a certain amount of "oozing" of blood and lymph is to be expected at this time. This would have resulted in a local extrarenal collection of labelled fibrin, which would have caused an increase in the radioactivity of that area. The second patient showed a positive response to the test some 16 days after transplantation, when postoperative bleeding was evidently

not the cause. Dr. Straub has attributed this result to "wound healing" and he may be right. One point to note, however, is that the transplant radioactivity exceeded that of the heart (>120%) only on the sixth day of the test. It is my experience that when rejection is occurring the increased transplant activity becomes evident much earlier, usually within 2-3 days of the time the fibrinogen was injected. All the same a late rise as found by Dr. Straub may not always be a "false-positive," as the accompanying Figure shows.

Male 14 years. Cadaveric renal transplant. ¹²⁵I-Fibrinogen was given on the seventh post-transplant day, when renal function was depressed as a result of ischaemic tubular necrosis. An increase in the percentage radioactivity of the transplant occurred a week before any other signs of rejection.

This patient, who received a cadaveric renal transplant, was given labelled fibrinogen on the seventh post-transplant day, when the effects of ischaemic tubular necrosis were still evident. Renal function improved one week later, but at this time the percentage radioactivity of the transplant began to increase. Unfortunately, he was not treated for rejection at this time and a week elapsed before rejection was evident clinically and appropriate action was taken. This episode was not reversed and the rejected kidney was removed two weeks afterwards.

I accept that occasional false-positives will occur with this technique, as they will with any investigative procedures, but on the whole it has proved reliable in my hands and I believe it to have a definite place in the management of renal transplant patients during the early anuric period.—I am, etc.,

JOHN R. SALAMAN

University Hospital of Wales,
Cardiff

Simple Guide to Prognosis in Hypertension

SIR,—In your leading article (19 December, p. 697) on prognosis in hypertension, you highlight a common practical problem in clinical medicine—namely, how