than two weeks to over 40 weeks (the maximum time of complete remission may be longer by now). These remission times are not as long as those which have been reported by M. Boiron and colleagues[4] with the use of daunorubicin alone; some patients in their series remained in complete remission for up to two years.

In a recent communication C. Bernard and his colleagues[7] describe some cases of acute myeloblastic leukaemia with survival beyond five years. The remission followed treatment with prednisone alone or in combination with 6-mercaptopurine. This is unusual, but it does seem that a few patients may have surprisingly long remissions and that these may show no particular features at the onset of the disease to distinguish them from the majority of patients in whom therapy is either ineffective or beneficial for only short periods.

The combination of daunorubicin and cytosine arabinoside used by Crowther and his colleagues was easy to use and serious side effects were few. While severe depression of bone marrow developed in all their patients it was temporary and is probably an inevitable consequence of effective treatment. The resultant severe neutropenia and thrombocytopenia lays the patient open to fulminant septicaemia and serious haemorrhage, so that prompt supportive therapy with appropriate antibiotics and blood transfusions is essential to tide the patient over this critical period of marrow aplasia until repopulation of the marrow with normal haemopoietic cells. Infection was a cause of death in seven of the eight patients who died during treatment, and the causative organism was considered to be endogenous. The patient's bowel is probably the main source of these organisms,[2] and sterilization of the bowel may be important in preventing such infections. Crowther and colleagues treated their patients in a general ward, and they consider that the advantages of treatment in special units under strict asepsis remain to be established. If endogenous organisms are the cause of the septicaemic complications, bowel sterilization may be more important than nursing the patient in a sterile unit.

The breakdown of a large mass of leukaemic tissue during treatment would be expected to produce hyperuricaemia, which might produce acute obstructive nephropathy, but in only one patient was death attributed to uraemia. Renal failure, even in the patients with high circulating blast cell counts, did not complicate the course perhaps because the regimen did include allopurinal. This drug does not interfere with the metabolism of either daunorubicin or cytosine arabinoside, unlike its effect on 6-mercaptopurine.

The failure of L-asparaginase to improve the results of treatment when added to the combination of daunorubicin and cytosine arabinoside is somewhat disappointing, for it seemed promising when first introduced. The finding is of particular interest because a multicentre controlled trial under the auspices of the Medical Research Council is in progress to determine the value of L-asparaginase in an intermittent regimen which includes daunorubicin and cytosine arabinoside. The value of non-specific immunotherapy with B.C.G. vaccine remains to be established, but it is interesting that Crowther and colleagues found no significant difference between the patients maintained with chemotherapy and those maintained with B.C.G.

Though the treatment of acute myeloblastic leukaemia in adults is now becoming more effective, at least in terms of obtaining a complete remission initially, there still remain the important problems of maintaining the remission once achieved and the treatment of relapses, whose frequency is still very high. This is bound up with the problem of how leukaemic cells become resistant to drugs and how the disease recurs. Almost all the antileukaemic agents are effective only in the D.N.A. synthetic phase (S phase) of the cell cycle, and in any one case there may be a substantial number of leukaemic cells which are not in the S phase and therefore not susceptible to the chemotherapeutic action of most of the drugs now in use. The problem of the resting cell and its reactivation into the proliferative phase of the cell cycle is one of the outstanding problems in the treatment and control of neoplastic diseases. Since daunorubicin acts by forming complexes with preformed D.N.A., it may be effective against cells in the resting phase as well. Cytosine arabinoside is a pyramidine antagonist and would be active only against cells in the synthetic phase.

The recently developed regimens for the treatment of acute myeloblastic leukaemia give ground for cautious optimism. Better forms of treatment will probably follow, but the road ahead is still long and difficult.

Another Drug Interaction

Though many doctors regard the tetracyclines as relatively non-toxic, they do have some serious adverse effects. Fungal or bacterial superinfections,[1] usually of the gut, are not uncommon complications of both oral and parenteral treatment, especially when prolonged. Toxic effects on the liver[2-4] and kidneys[3-5] may arise, more frequently after parenteral therapy but also after ordinary dosage by mouth in patients either with renal insufficiency[6] or using expired degraded tetracyclines.[7 8] Because of serious effects on tooth development tetracyclines are absolutely contraindicated for children aged under 8 and for pregnant or lactating women.[9] Patients must be carefully selected, reviewed during treatment, and warned not to keep unused drugs for another occasion.

Again, though these antibiotics are usually absorbed adequately, if incompletely, in the upper gastrointestinal tract, they may be bound by a variety of divalent and trivalent cations.[1] Thus antacids and milk or milk products reduce absorption of tetracycline. As the plasma level obtained from the usual dosage by mouth is not much above the minimum required to inhibit the infecting organisms, this type of interaction may cause the treatment to fail. The antibiotic should be taken between meals, and the patient should not receive antacids during treatment.

In the *B.M.J.* this week Dr. P. J. Neuvonen and his colleagues draw attention at page 532 to an interaction between tetracyclines and ferrous sulphate. They showed that when ferrous sulphate and the recommended dose of various tetra-

[1] Weinstein, L., in *The Pharmacological Basis of Therapeutics*, ed. L. S. Goodman and A. Gilman, 3rd edn., p. 1242. New York, Macmillan, 1965.
[2] Miller, S. E. P., MacSween, R. N. M., Glen, A. C. A., Tribedi, K., and Moore, F. M. L., *British Journal of Experimental Pathology*, 1967, **48**, 51.
[3] Davis, J. S., and Kaufman, R. H., *American Journal of Obstetrics and Gynecology*, 1966, **95**, 523.
[4] Schiffer, M. A., *American Journal of Obstetrics and Gynecology*, 1966, **96**, 326.
[5] Castell, D. O., and Sparks, H. A., *Journal of the American Medical Association*, 1965, **193**, 237.
[6] Shils, M. E., *New England Journal of Medicine*, 1966, **275**, 113.
[7] Mavromatis, F., *Journal of the American Medical Association*, 1965, **193**, 191.
[8] Lindquist, R. R., and Fellers, F. X., *Laboratory Investigation*, 1966, **15**, 864.
[9] Manten, A., in *Side Effects of Drugs*, ed. L. Meyler and A. Herxheimer, vol. 6, p. 283. Amsterdam, Excerpta Medica, 1968.

cyclines were given orally the plasma levels of antibiotic reached only 10–50% of the level expected. Because iron and tetracyclines bind in equimolecular ratios, the reduction in the amount of tetracycline absorbed was relatively greater for those with a low recommended dose than for those with a high one. From this work it can be predicted that only insignificant amounts of antibiotic would be absorbed if 200 mg. of ferrous sulphate and 250 mg. of any tetracycline were given simultaneously by mouth.

Patients requiring both iron and tetracyclines for their treatment are commonly seen. Moreover, iron is a constituent of popular tonics and beverages freely available to the public. Thus the interaction between iron and tetracycline, as a result of which neither is absorbed, is likely to be common and could lead to failure of antibiotic therapy. Clearly iron by mouth must not be prescribed while a patient is receiving a tetracycline.

Flashes in Astronauts' Eyes

Travellers to and from the moon on Apollos 11, 12, and 13 have reported seeing flashes of light at average rates varying from several times a minute to once every two minutes during the time their eyes were dark-adapted. Yet similar phenomena have never been reported by either American or Russian astronauts while orbiting the earth nor by any Apollo men while in orbit round the moon.

Charles A. Berry, director of medical research at the National Aeronautics and Space Administration (N.A.S.A.) base at Houston, Texas, disclosed this news at the recent International Astronautical Congress at Konstanz, Germany. It appears that most of the observers reported plain flashes, but one, Fred Halse, said that many of them reminded him of "Roman candles". Now an astrophysicist from Harvard, U.S.A., and two nuclear physicists from Harwell, England, have offered a physical explanation of this phenomenon in a joint paper published only a week after the congress.[1]

The authors suggest two possible mechanisms to account for the flashes, basing their calculations on the known physical properties of both the eye and cosmic radiation. Firstly, there is the so-called Cherenkov radiation, caused by interaction between a primary cosmic ray particle and a medium through which it passes, such as the vitreous humour of the eye, resulting in flashes of light being produced. Their calculations show that flashes of about the observed frequency should be expected, and they remark that even such tiny particles as pi-mesons have been known to produce Cherenkov radiation in the vitreous at sea level. The alternative suggestion is that the flashes are caused by direct impact of cosmic particles on the receptors in the retina, and the authors state that heavy particles such as the nuclei of iron could cause shapes like the heads of comets or even Rugby footballs to be seen. They believe this explanation to be far less likely though nevertheless possible.

Their explanations of why no such flashes have been seen when orbiting the earth are far more tentative. They do not discuss the fact that orbiting astronauts keep well below the Van Allen radiation belt, but suggest that while the earth is in view the crews are kept busy with matters which would distract their attention from any light flashes. Dark adaptation would occur chiefly during sleep, and one of the moon travellers, Fred Halse, once counted ten flashes during the five minutes it took him to get to sleep. Experiments designed to solve the mystery will be carried out during the next moon shot. For example, astronauts will see whether or not more flashes appear when they face away from the moon, which acts as a shield against cosmic radiation.

[1]Fazio, G. G., Jelley, J. V., and Chapman, W. N., *Nature*, 1970, **228**, 260.

"Tropical Doctor"

All who have the well-being of the developing countries at heart will welcome the appearance this month of *Tropical Doctor*,[1] a new quarterly published by the Royal Society of Medicine with financial support from the Commonwealth Foundation. It is a journal of modern medical practice—not just of tropical medicine, and is intended primarily for the isolated medical worker in the developing countries of the tropics and subtropics. It aims to provide him, wherever he may be stationed, with a continuous, practical, postgraduate course in clinical medicine, surgery, obstetrics and gynaecology, and preventive medicine, and to counter his sense of isolation by publishing newsletters from colleagues in similar parts of the world. Its initial distribution is to 1,800 hospitals, mostly up country, in the Commonwealth, and also, principally through subscriptions of missionary societies, to doctors in developing countries outside the Commonwealth.

In the hands of an editor as experienced as Dr. Hugh Clegg, supported by an editorial committee under the chairmanship of Professor A. W. Woodruff and a distinguished advisory board, *Tropical Doctor* is well manned to achieve its aims. All the contributors to its first issue have first-hand experience of medicine in the tropics, indeed for most of them the tropics is where they have spent much of their working lives; so they are writing of that with which they are familiar. Topically, in view of the East Pakistan flood disaster, the first article of the first issue deals with the treatment of cholera. The need for down-to-earth postgraduate education of this sort is undoubted. *Tropical Doctor* is a brave enterprise that deserves success.

[1] Annual subscription £3 ($8), post free anywhere, from the International Relations Office, Royal Society of Medicine, Chandos House, 2 Queen Anne Street, London W1R 0BR, England.

Controlling Gastric Acid

The normal stomach has a robust and highly efficient mechanism for producing a potent solution of hydrochloric acid.[1] The parietal cell is the factory for this process. It is a complicated cell containing intracellular channels, into which, it is believed, the acid solution is pumped before passing to the stomach. Parietal cells have been isolated and found to be one of the most active cells in the body in terms of oxygen content. They also have an unusually alkaline intracellular pH and high sodium content.[2] The amount of acid they produce is influenced by the secretion of gastrin from the mucosa of the antrum of the stomach and by the activity of the vagus nerve. How in clinical practice can the acidity of gastric secretions be controlled?