given a bottle of antibiotic and is under the impression that once the total contents have been taken no further treatment is necessary.

Repeated attacks of otitis media may be due to sterile pus remaining within the middle ear, but it is essential to look for contributory lesions in the rest of the upper respiratory tract. The adenoids and sinuses are sources of infection which demand investigation and treatment. The "glue ear" is a well-recognized cause of deafness in children, but is overlooked because the drums appear normal. Abnormal physical signs such as a blue or yellow drum may be seen, but in a small child with a narrow canal it may be difficult to be certain of the appearance of the drum.

The operating microscope makes myringotomy a precise operation. The strong light with binocular vision helps the surgeon to see the character of the fluid aspirated and to judge when he has aspirated all the mucus from the middle ear. The fluid may be so tenacious that it takes 20 minutes' continuous suction with several changes of suckers in order to evacuate the middle ear contents completely. Many otologists advocate inserting a grommet to aerate the middle ear and prevent fluid reaccumulating. By doing so the patient is exposed to infection entering the middle ear from the external ear with subsequent otitis media. This risk should be explained to the child's parents.—I am, etc.,

Liverpool.

J. SIEGLER.

Early Mixed Feeding

SIR,—As a clinic doctor and a mother I would disagree emphatically with the view that early mixed feeding is harmful (31 August, p. 541). Many mothers would testify to the relief of their anxiety when the introduction of solids changes their irritable, crying infant to a gurgling, contented one. Not to mention the prevention of anaemia and other deficiency diseases.

It is true that overfeeding is a cause of gastrointestinal upset, but an infective aetiology is far commoner. The only proviso I would make is that mixed feeding should be mixed—that is, a high protein content should be aimed at to forestall the development of carbohydrate-induced obesity so common today. Surely we have progressed past "Nature knows best"? Does your expert desire a thin, anaemic, rickety child proudly fed by a "natural" diet alone?—I am, etc.,

Plymouth.

G. M. WAKLEY.

Suxamethonium Apnoea

SIR,—Dr. A. B. Bray (7 September, p. 620) reported a patient who had been labelled as sensitive to suxamethonium. Both the patient and the general practitioner had been warned of the "danger" following an episode of apnoea after receipt of that drug, but without confirmatory biochemical investigation.

Through the courtesy of Dr. Bray we have examined the serum from this patient. It has a normal cholinesterase activity, and the dibucaine and fluoride numbers indicate a homozygote with two "usual" genes. These results confirm Dr. Bray's finding that under his management the patient reacted normally to suxamethonium,

and that the cause of the previous apnoea must therefore be sought elsewhere.

The Cholinesterase Research Unit was set up to provide a framework which would make a uniform methodology available throughout the country. This unit is willing to examine the serum from any patient who has apnoea after suxamethonium, the only condition being that anaesthetists who send specimens should assist in compiling a family tree and provide some clinical details of the circumstances of the apnoea. In this way it is hoped, in time, to accumulate a register of affected families, and a useful corpus of clinical detail. It is hoped that a greater awareness of the existence of this service will encourage practitioners to have all doubtful cases investigated, and discourage the misleading labelling of patients on inadequate data, of which Dr. Bray so rightly complains.—We are, etc.,

MARY WHITTAKER.
M. D. VICKERS.

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Pyrazinamide and Hyperuricaemia

SIR,—Your Today's Drugs article "Drugs for Tuberculosis" (14 September, p. 664) contains a misleading statement that should be corrected. It concerns the use of aspirin for the treatment of hyperuricaemia and gout resulting from the administration of pyrazinamide. In small doses salicylates impair the renal excretion of uric acid, elevating the serum urate. Only impracticably large doses will produce the required uricosuric effect. If it is required to lower the level of serum urate either probenecid should be used as a uricosuric agent or allopurinol, which inhibits the metabolic pathway by which uric acid is formed from its xanthine precursors.

Phenylbutazone is probably the best drug for the suppression of acute iatrogenic gout.—I am, etc.,

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London S.E.1.

*** What was said in the article was: "Pyrazinamide often causes hyperuricaemia, and gout or generalized pain in the limbs may occur but responds to aspirin or salicylates." This was intended to indicate that pain in the limbs occurring during pyrazinamide therapy usually responds to aspirin or salicylates, *not* that hyperuricaemia was controlled by aspirin or salicylates. Dr. Yates is quite right in pointing out that the usual doses of aspirin may elevate serum urate, and that other drugs may be needed to lower serum urate if the symptoms of pyrazinamide hyperuricaemia fail to respond to aspirin.—Ed., B.M.J.

Herpesvirus hominis Infections

SIR,—In their article on rapid diagnosis of *Herpesvirus hominis* infections in superficial infections by immunofluorescent techniques Dr. P. S. Gardner and others (12 October, p. 89) found that the average time for the appearance of a typical herpesvirus cytopathic effect in tissue cultures of HEp.2, HeLa, and

W.I.38 was 4.3 days for material from skin lesions and 14.5 days from corneal scrapings. These periods are much longer than those we have obtained using primary human amnion cell-cultures. Thus in 51 patients yielding *Herpesvirus hominis* (herpes simplex) from skin or mouth lesions during 1967–8 the mean number of days for productions of a typical cytopathic effect was 1.8 (range 1 to 4); in conjunctival scrapings from nine patients the mean was 2.7 days (range 1 to 5). All these isolations were subsequently confirmed as herpes simplex by neutralization tests. No appreciable difference could be detected in the times required for isolation of virus from patients in whom clinical and/or serological evidence indicated a primary infection from those with recurrent infections. It would therefore appear that *Herpesvirus hominis* may be more rapidly isolated in human amnion cell-cultures than in those used by Dr. Gardner and his colleagues.

The rapid isolation of *Herpesvirus hominis* in human amnion cell-cultures is one good reason why greater attempts have not been made by many laboratories to establish fluorescent antibody techniques for diagnosis of *Herpesvirus hominis* in superficial lesions. Another reason is that there are marked serological cross-reactions between herpes simplex and varicella-zoster viruses. In herpes encephalitis, in which it may be important to reach a diagnosis of infection with a herpes group virus as soon as possible so that chemotherapeutic treatment may be commenced, we have found fluorescent antibody studies of smears disappointingly negative. Thus of direct smears from five brain biopsies examined for herpesvirus by fluorescent antibody studies all were negative, though three of the five yielded herpes simplex virus in tissue culture. It seems possible that antibody present in brain tissue may block attachment of fluorescein-conjugated anti-rabbit globulin. Finally, many laboratories have been discouraged from developing immunofluorescent diagnostic methods by difficulties in obtaining specific, reliable commercial reagents.—We are, etc.,

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Infusion of Liver Tumours

SIR,—Your leading article (10 August, p. 329), the paper of the same date by Drs. J. L. Provan, J. F. Stokes, and D. Edwards, and the letter (30 August, p. 554) by Mr. J. M. Anderson prompt me to comment briefly on my experience, because the above authors have used dosages of fluorouracil which I believe are considerably less than is safely tolerable by the liver.

I have used a similar technique, with a catheter inserted by the diagnostic radiologists into the coeliac axis artery, in 12 cases of primary and secondary liver tumours. Two patients were infused twice. One other case has been infused via a catheter inserted into the hepatic artery at laparotomy. Initial experience suggested that tolerance to fluorouracil was considerably greater in these cases than in carotid, aortic, or pelvic infusions. This has been confirmed. My practice now is to infuse 2 g. daily continuously to a total of 20 g. approximately, terminating the infu-

sions when toxic buccal and gastrointestinal symptoms develop to mild or moderate severity.

One patient received an initial infusion of 11 g. in five days without any clinical benefit or toxic symptoms. Six weeks later infusion was repeated. A total of 31 g. was administered in 14 days. This was excessive, causing severe gastrointestinal and haematological effects, but recovery was rapid. The most recent case, a young British migrant, received 19 g. in nine days into the hepatic artery (not the coeliac axis). This infusion was deliberately terminated early because the patient intended to, and three weeks later did, return to Britain, with a patent catheter in situ.

The clinical course of these cases, and laboratory surveillance by Dr. W. Roman, of the Institute of Medical and Veterinary Science, North Terrace, Adelaide, showed that the dosage used was well tolerated systemically and by the liver parenchyma. Serial serum enzyme estimates by Dr. W. Roman revealed large increases in serum lactic dehydrogenase and very small increases in alanine aminotransferase, but minor changes in other liver-function tests. This was regarded as clear indication of breakdown of tumour cells in preference to parenchymal liver cells. These results have been reported in a paper presented to the Sixth International Congress of Clinical Pathology, with the result of confirmatory hepatic infusion in animals by Dr. S. T. Hopcraft. Full details of this work will be published in due course.—I am, etc.,

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Oestrogens and Thromboembolism

SIR,—I wish to take issue with you over your leading article on oral contraceptives and thromboembolism (27 April, p. 187). This article led recently to a minor panic in the popular press in Australia about the alleged dangers of oestrogens in oral contraceptives, a panic quite unjustified by the scientific evidence you have uncritically quoted.

It is true that the work of Drs. M. P. Vessey and R. Doll (27 April, p. 199) did not incriminate any particular kind of oral contraceptive, and it is also true that there is other evidence that oestrogens may have an effect on blood clotting. But then you go on to say that these findings suggest that it is the oestrogens rather than the progestogens which are responsible for thrombosis. This statement is quite unjustified on the evidence quoted, and so is your next statement that sequential preparations are therefore more dangerous than combined.

The first authority you quote is that of Daniel, Campbell, and Turnbull.¹ These authors used oestrogens in the form of diethylstilboestrol in doses of 30–60 mg. daily for three days and then 20 mg. daily for a final three days, and they reported that this regimen significantly increased the risk of embolism in the puerperium. However, when the doses used are considered, one begins seriously to wonder whether oestrogens, as used in the suppression of ovulation, are necessarily dangerous. Martindale² suggests doses of 5 mg. of diethylstilboestrol three times a day for three days and then 5 mg. daily for six days, for the suppression of lactation (a total of 75 mg. as opposed to the doses used by Daniel *et al.* of 150–240 mg.

given over a shorter period). Martindale quotes 1 mg. of diethylstilboestrol as being equivalent in potency to 0.05 mg. of ethinyloestradiol, so that in effect Daniel *et al.* were using doses, in six days, equivalent to up to 240 by 6 by 0.05 mg. (=72 mg.) of ethinyloestradiol. The dose of this drug for ovulation suppression over the same period would be 0.60 mg. This means that Daniel *et al.* were using doses 120 times higher than those used in ovulation suppression. This casts some doubt on your suggestions about the danger of oestrogens in more physiological doses as used in oral contraception.

The other authority you quote in support of your somewhat shaky arguments is Oliver,³ who found that unstated doses of ethinyloestradiol in men produced more episodes of thrombotic type than occurred in controls. The figures given are not analysed statistically. Oliver also suspects oestrogens and quotes in support of his argument the work of Wynn and Doar⁴ and Wynn, Doar, and Mills.⁵ These authors studied glucose metabolism and other factors of blood chemistry in women who had been on oral contraceptives and compared results with a control group. There were certainly significant changes in the test group, but neither Oliver nor the B.M.J. is entitled to draw any conclusions about the effects of oestrogens from this work, because the oral contraceptives studied, as pointed out by Wynn *et al.*, were almost exclusively of combined type (and in fact most of those used contained 19 nortestosterone derivatives, which are known to have certain androgenic and anabolic properties).

Oral contraceptives are not an entity, but vary widely in their qualities. Conclusions drawn about combined oral contraceptives give information about the effect of combined oral contraceptives—not the relative parts played by different components.—I am, etc.,

A. ARNAUD REID.

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New South Wales, Australia.

REFERENCES

- ¹ Daniel, D. G., Campbell, H., and Turnbull, A. C., *Lancet*, 1967, 2, 287.
- ² *Extra Pharmacopoeia: Martindale*, 25th ed., 1967. London.
- ³ Oliver, M. F., *Lancet*, 1967, 2, 510.
- ⁴ Wynn, V., and Doar, J. W. H., *Lancet*, 1966, 2, 715.
- ⁵ Wynn, V., Doar, J. W. H., and Mills, G. L., *Lancet*, 1966, 2, 720.

Disappearing Drain

SIR,—A recently encountered complication from the use of closed suction drainage may be of interest to your readers.

A 42-year-old man was submitted to a left medial meniscectomy. As he had had previous femoral artery disease which had required surgery a tourniquet was not employed for this procedure. After routine haemostasis had been secured the wound was closed over a perforated plastic closed suction drain. Six hours after the operation the drain was removed, as there had been virtually no return in the suction bottle. The drain came out with some difficulty, and it was therefore strongly suspected that a segment of the drain had in fact broken off within the joint. Multiple x-rays of the joint were taken without revealing any foreign body within the joint. The knee was then x-rayed with the catheter lying on the skin. Under these latter conditions with the catheter filled with air the plastic showed up clearly. The knee was then re-explored through the original operation wound and a 2 cm. segment of plastic drain was removed

which matched exactly to the end of the major fragment, the plastic having broken through one of the perforations. Under the particular circumstances encountered the fragment of drain could not be demonstrated by x-ray examination.

There seems to be a case for having this type of appliance impregnated with radio-opaque material.—I am, etc.,

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Organic Brain Dysfunction

SIR,—The clarification of the questions which Drs. P. Graham and M. Rutter (21 September, p. 695) brought to the combination of organic brain dysfunction and childhood psychiatric disorder was well served by a deliberately restrictive methodology, such as applied in their valuable investigation. They excluded non-current neurological disorder and "minimal brain damage." Important as their findings are for this whole field, they should not, by their acknowledged weight, overshadow the existence of further possibilities and problems which are present in the same field.

This field clearly comprises two sectors: the "coexistence" sector, and the "sequels" sector. They both stand in their own right, but connecting points may be lost to sight if mutual exclusion should become a rule. There is much to be said for the "longitudinal" (or life-developmental) aspect, which brings out further facts relevant to psychiatry. For instance, some children who have suffered from chorea or one of the post-infectious encephalopathies of the encephalitic or meningitic type or even severe concussion (and some like these must have been among the nearly 12,000 Isle of Wight schoolchildren) may in the long run become even more productive of psychiatric symptoms or developments than the children highlighted in the survey.

As one who has applied some endeavour to the investigation of the "sequels" sector,¹ I venture to hope and to plead that research developments may bring about a combination and integration of the two possible aspects.—I am, etc.,

STEPHEN KRAUSS.

Reading.

REFERENCE

- ¹ Krauss, S., in *Proc. 8th Internat. Congr. Neurology, Vienna, 1965*, Vol. 5, p. 145.

"Sniffing" and Addiction

SIR,—The paper by Dr. J. Merry,¹ and your leading article,² on the subject of addiction to "glue sniffing," have prompted me to report another case of addiction to a volatile organic substance.

Not long ago I encountered a young man who had decided to try for fun the effect upon him of inhaling carbon tetrachloride, a liquid much used in industry and to which he had easy access. Liking the feeling of light-headedness (and other sensations) produced when a small quantity of carbon tetrachloride was poured on a handkerchief and inhaled, he could not resist the temptation to repeat the experiment with ever-increasing frequency.