made monthly during the trial but in general they were badly recorded. Complete tablet counts were obtained for all 31 Glasgow patients but for only 6 of the 61 patients attending other centres, and the influence of the regularity of taking medication could not therefore be assessed. Data from Glasgow patients indicate that relapse was more likely in those patients who did not take their medication regularly, but the number of cases from this one centre was too small for any firm conclusion to be drawn. However, it would not be too surprising if patients took medication more regularly when regularly asked to return unused medication at each visit to the clinic.

Dr. Leff bolsters his case by referring to the clinical arrangements made in Glasgow, and this requires some clarification. One of the difficulties in conducting this trial was that a great many patients referred to the psychiatric clinic had already received some antidepressant medication. In order to improve the accuracy of selection and of the initial ratings Glasgow doctors who regularly referred their cases to the clinic were asked to refer patients before prescribing any medication, arrangements having been made to see such referrals at short notice. Dr. Leff suggests that "patients referred in response to this plea would be less seriously depressed" but to my knowledge only four such referrals were made; three were unsuitable for the trial and the remaining patient did not respond to antidepressant medication. Dr. Leff also by suggesting that "nearly all the Glasgow patients were contributed by one psychiatrist" perhaps implies that his criteria for selection must have been liberal. The patients were, in fact, contributed by four psychiatric teams but for administrative convenience and in the interest of consistent rating these patients were transferred to the care of one consultant and his assistant. The patients were therefore always seen by the same doctor whenever they attended the clinic and it is possible that this increased the psychological support they received. Such "non-drug" factors are known to have considerable influence in psychopharmacology and this is difficult to control or assess in large multicentre trials. However, the variation in the ease with which tablet counts were obtained in the several clinics is probably some indication of the differences in the general clinical setting and management of the trial between Glasgow and elsewhere and perhaps tells something about the relationship between the patients and their doctors.

It is my view that the low relapse rates in Glasgow, in patients taking placebo or active drugs, are less likely to be a reflection of case selection than of the differences in residual symptoms, drug defaulting, and perhaps especially the "non-drug" factors.—I am, etc.,

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¹ Mindham, R. H. S., Howland, C., and Shepherd, M., *Lancet*, 1972, 2, 854.

² Mindham, R. H. S., Howland, C., and Shepherd, M., *Psychological Medicine*, 1973, 3, 5.

SIR,—Dr. J. P. Leff's diligence in peeping behind the apparently unequivocal results of three recent clinical trials (20 October, p. 156) has led to some important findings.

After reading his paper it is easy to see how two very similar investigations can yield opposite conclusions because of differences in selection procedure. It is because of this that what may appear to be relatively trivial details should be included in published reports.

Trials are many and journal space is limited, but we are all too often in the dark about such items as source of patient referral, reasons for inclusion and rejection, previous treatment, and the therapeutic expectations of the physician. Dr. Leff has shown us that these are at least as important as descriptions of the experimental design and use of double-blind procedure; they should be given equal prominence if the value of a clinical trial is to be fully assessed.—I am, etc.,

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Influenza Vaccination

SIR,—Once again this winter there will no doubt be panic demand for the latest influenza vaccine and perhaps this is a good time to remind everyone, especially those with jet vaccinators, that Tauraso *et al.*¹ examined the effects of giving influenza vaccine intradermally in a much smaller dose than that usually recommended and reported that the antibody response to the first inoculation given intradermally was higher than that to subcutaneous injection of the standard dose.

It would appear that the current influenza vaccines could be given intradermally in a dosage of 0.1 ml and thus five to 10 times more people could receive protection with the limited amounts of vaccine that are going to be available. Saving of cost to the country could be enormous, and especially in industry, where large amounts of vaccine are used. In the winter of 1971 some £2m worth of vaccine was used and had this been given intradermally, using a vaccinator gun, the saving in the United Kingdom alone could have been £1.8m. Multiply this over the world and there is ample money for vaccination campaigns in underdeveloped countries to be undertaken.—I am, etc.,

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¹ Tauraso, N. M., *et al.*, *Bulletin of the World Health Organization*, 1969, 41, 507.

Diabetic Pregnancy

SIR,—The comprehensive survey of diabetic pregnancy by Dr. N. L. Essex and her colleagues from King's College Hospital (13 October, p. 89) raises some questions. Apparently the number of "gestational" diabetics seen annually is six. As the number of deliveries in the obstetrical unit is not quoted it is not possible to make direct comparisons, but it would appear that the number of latent diabetics detected at the antenatal clinics at K.C.H. is substantially less than elsewhere—for example, in Boston,^{1,2} Belfast,³ and Dublin.^{4,5} If this is in fact so, it would be of interest to know what programme of case detection is applied at the antenatal clinics in K.C.H.

In detailing their method of management the authors discuss their attitude to family planning and to sterilization but do not refer to the use of therapeutic abortion. How many abortions on diabetic patients were performed in the 22-year period under review and what were the indications? This question is not posed in any pejorative sense, but in the conviction that it is not possible to evaluate any system of management without having all the data. It is only then that we can judge whether "we are seeing a real improvement."—I am, etc.,

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¹ Wilkerson, H. L. C., and Remein, Q. R., *Diabetes*, 1957, 6, 324.

² O'Sullivan, J. B., and Mahan, C. M., *Diabetes*, 1964, 13, 278.

³ Hadden, D. R., Harley, J. M. G., Kajter, T. J., and Montgomery, D. A. D., *Diabetologia*, 1971, 7, 87.

⁴ Drury, M. I., and Timoney, F. J., *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1970, 77, 24.

⁵ Drury, M. I., and Timoney, F. J., *Journal of the Irish Medical Association*, 1970, 63, 281.

Crohn's Disease and Intestinal Cancer

SIR,—With reference to your leading article "Does Crohn's Disease Predispose to Intestinal Cancer?" (6 October, p. 3), a statistical assessment of malignancy in Crohn's disease has already been carried out on a relatively large series of patients.^{1,2} The results, from both morbidity and mortality data, demonstrated a significant excess of tumours within the digestive tract which could be attributed specifically to tumours of the small bowel and pancreas. No corresponding excess of tumours in the colon or rectum could be shown. The analytical approach was to compute an expected number of tumours as a basis for comparison with the number of tumours observed in the patients. The cancer incidence rates which were used in the analysis were directly applicable to the series because they related to the region of the country from which the patients were drawn.

The practice, by no means uncommon in the literature, of expressing cancer morbidity rates in terms of a crude percentage of total cases is unacceptable in the context of the quoted analysis.³ The resultant rate will depend on (1) the initial age distribution of the series, (2) the length of time for which the patients were observed, and (3) the pattern of mortality experienced by the series. For these reasons it is invalid to combine or compare individual series in terms of crude percentages. Further, cancer incidence rates based on population figures are readily available,⁴ so that there seems little point in attempting estimations from two sets of data which refer to different populations in different continents.

The final analysis, as quoted in your article, compares annual incidence rates combined with a prevalence rate for Crohn's disease (whether point or period prevalence is not stated) with the crude incidence of the association. Assuming that the prevalence figure does refer to the number of established cases existing during one calendar year, the resultant multiplicative probability would then relate to one calendar year. The crude percentage incidence of the association, on the other hand, is based almost certainly on the number of tumours arising in several

series over many years. The value of such comparisons is therefore extremely doubtful.—I am, etc.,

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Queen Elizabeth Hospital,
Edgbaston, Birmingham

¹ Prior, P., Fielding, J. F., Waterhouse, J. A. H., and Cooke, W. T., *Lancet*, 1970, i, 1135.

² Fielding, J. F., Prior, P., Waterhouse, J. A. H., and Cooke, W. T., *Scandinavian Journal of Gastroenterology*, 1972, 7, 3.

³ Darke, S. G., Parks, A. G., Grogono, J. L., and Pollock, D. J., *British Journal of Surgery*, 1973, 60, 169.

⁴ Doll, R., Muir, C., and Waterhouse, J. A. H., eds. *Cancer Incidence in Five Continents*, vol. 2. Berlin, Springer, 1970.

Mobile Coronary Care Provided by Ambulance Personnel

SIR,—Dr. J. Ross (27 October, p. 234) is quite correct. The Brighton ambulance men carried out the original pilot scheme without any question of remuneration being mentioned. They said they were not interested in anything except the success of the project.

Unknown to them I got in touch with their trade union, the National Union of Public Employees, at the outset, explained our intentions, and asked them to await our findings. This they did for more than a year. By mutual agreement we then met and settled for an extra payment of £2.15 per week, so increasing the wage bill by £1,900 in 1972, which is not unreasonable as the service is available on a shift basis for every hour of every day in the year. Incidentally, this recognizes the place of the well-trained ambulance man as a paramedical technician.

Without the constructive help of their union I could not have safeguarded the interests of our men. It is the other side of the picture from that of the hairy militants.—I am, etc.,

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Non-accidental Injury to Children

SIR,—It must surely be time for society to delete from its vocabulary such euphemistic expressions as, "battered baby (or child) syndrome," "non-accidental injury to children," and "child abuse." The legal expression "grievous bodily harm" is, I suggest, sufficient to express accurately the nature of the injuries in cases of assault and battery upon any individual, be he defenceless or not, child or adult. The acceptance of this fact would help to reduce the public complacency which is becoming more apparent every day. It would also ensure that no one section of the community, by privilege of intellect or position, could continually investigate, diagnose, and treat both parties.

In a democracy it is unwise to usurp either the established pattern of consideration by a professional investigator and the Director of Public Prosecutions or the deliberations of a jury and one of H.M. judges. It is the latter who should, where appropriate, initiate and delegate the supervision of the therapy outlined in the report of the Tunbridge Wells Study Group (13 October, p. 96).—I am, etc.,

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Palmerston on Cholera

SIR,—The present pandemic of cholera has awakened interest in the nineteenth century outbreaks which had such a powerful effect on the course of British public health history. The fear generated by the visitation of 1848 did much to stifle opposition to the Public Health Bill of that year, and the resultant Act of 1848 may fairly be said to have been conceived by cholera. Regrettably, the Act was limited to an experimental period of five years, and when in 1853 cholera struck again the Board of Health, born of fear in 1848, was struck down in revenge in 1854.

The Church of Scotland was convinced of the divine origins of cholera and had succeeded in getting that belief enshrined in an Act of Parliament. It was natural, therefore, that when the terrible outbreak of 1853 and 1854 was seen to be heading in the direction of Edinburgh, the Presbytery should petition the Home Secretary, Lord Palmerston, to advise the young Queen Victoria to declare a day of national prayer against the visitation of the cholera. Palmerston's reply¹ is worth quoting in full.

Whitehall, Oct. 19th, 1853

"Sir,

I am directed by Viscount Palmerston to acknowledge the receipt of your letter of the 15th inst., requesting, on behalf of the Presbytery of Edinburgh, to be informed whether it is proposed to appoint a day of national fast, on account of the visitation of the cholera and to state that there can be no doubt that manifestations of humble resignation to the Divine Will, and sincere acknowledgements of human unworthiness, are never more appropriate than when it has pleased providence to afflict mankind with some serve visitation; but it does not appear to Lord Palmerston that a national fast would be suitable to the circumstances at the present moment.

"The Maker of the Universe has established certain laws of nature for the planet in which we live, and the weal or woe of mankind depends upon the observance or neglect of those laws. One of those laws connects health with the absence of those gaseous exhalations which proceed from overcrowded human beings, or from decomposing substances, whether animal or vegetable; and those same laws render sickness the almost inevitable consequence of exposure to those noxious influences. But it has at the same time pleased Providence to place it within the power of man to make such arrangements as will prevent or disperse such exhalations as to render them harmless, and it is the duty of man to attend to those laws of nature and to exert the faculties which Providence has thus given to man for his own welfare.

"The recent visitation of cholera, which has for the moment been mercifully checked, is an awful warning given to the people of this realm that they have too much neglected their duty in this respect, and that those persons with whom it rested to purify towns and cities, and to prevent or remove the causes of disease, have not been sufficiently active in regard to such matters. Lord Palmerston would, therefore, suggest that the best course which the people of this country can pursue to deserve that the further progress of the cholera should be stayed, will be to employ the interval that will elapse between the present time and the

beginning of next spring in planning and executing measures by which those portions of their towns and cities which are inhabited by the poorest classes, and which, from the nature of things, must most need purification and improvement, may be freed from those causes and sources of contagion which, if allowed to remain, will infallibly breed pestilence, and be fruitful in death, in spite of all the prayers and fastings of a united but inactive nation. When man has done his utmost for his own safety, then is the time to invoke the blessing of Heaven to give effect to his exertions.

"I am, sir, your obedient servant.

"HENRY FITZROY."

It is difficult not to feel some sympathy for the Presbytery. Palmerston was never overawed by the Almighty (or anyone else) and his habit of treating God as an equal had irritated the Church of Scotland on previous occasions and was to do so again. Even on his death bed (when few men are at their best), on being asked by a priest if he believed in the redemption of the world through Jesus Christ he replied, "Oh, surely." Less stern critics than the Church of Scotland might have thought such a reply somewhat lacking in piety.—I am, etc.,

GRAHAM DON

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¹ Ashley, A. E. M., *Life and Correspondence of Henry John Temple, Viscount Palmerston*, vol. 2, p. 265. London, R. Bentley, 1879.

Mode of Action of Polyene Antibiotics

SIR,—We read Professor E. F. Gale's article "Perspectives in Chemotherapy" (6 October, p. 33) with great interest. We have been working with a number of antimicrobial agents, including the polyene antibiotic candidin, and have been studying potassium efflux using specific ion electrodes. Details of our techniques and some of our results are published elsewhere.^{1,2}

Candidin is 30 times more active against *Candida albicans* than either nystatin or amphotericin,³ though all three of these polyenes appear to share the same mode of action. Our work suggests that destruction of selective permeability by polyenes allows cations to leak out of yeast cells and allows the entry of protons to neutralize the charge so created. This causes internal acidification and death, and in this respect our interpretation of the mode of action of polyenes differs from that of Professor Gale. However, we have also observed a nutritional influence on polyene sensitivity of *C. albicans*, and this may have clinical significance.

The interaction between polyene antibiotics and sterols is well established, and recent studies have indicated that resistance of *C. albicans* to polyenes may be related to qualitative and quantitative alterations in sterol patterns.⁴ However, we have shown that the nutritional status of *C. albicans* influences the amount of sterol produced and

Minimum Inhibitory Concentrations (M.I.C.) of Candidin, Ergosterol Content, and Absorbed Candidin values for *Candida albicans*.

	M.I.C. ($\mu\text{g/ml}$)	Ergosterol, (mg/100 mg dry weight of yeast)	Bound ¹⁴ C-candidin ($\mu\text{g}/$ 100 mg dry weight)
Grown on alcohol-containing medium ..	0.2	0.77	8.3
Grown on Sabouraud dextrose broth ..	0.01	1.54	12.1
Grown on corn steep liquor/molasses ..	0.005	1.70	15.9