the rat, but diazepam will cause an increase in contraction height by a direct effect upon the muscle.—We are, etc.,

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REFERENCE

- ¹ Hunter, A. R. *British Journal of Anaesthesia*, 1967, **39**, 633.

Early Breast Cancer

SIR,—In his article on the treatment of early breast cancer Mr. J. I. Burn (23 May, p. 467) comments on the administrative disadvantages of "multicentre" clinical trials, quotes Handley¹ as saying that a controlled trial should be carried out in a single unit by a single team, and suggests that if Deeley's system² of paired randomization is adopted "large numbers of patients may not be necessary." We feel that these remarks, with their implied discouragement of multicentre participation in clinical trials, are unfortunate at a time when the idea of widespread collaboration is at last gaining ground. It may also mislead people into embarking again on trials where the likely rate of patient intake will make the effort of very doubtful value.

Too few patients in a trial are a disadvantage for two reasons. Firstly, the randomization procedure, although eliminating obvious bias, may not result in the final treatment groups consisting of closely comparable clinical material. It may not therefore be possible to draw any valid conclusions from the trial. This is the problem dealt with by Deeley,² and his system of paired randomization is designed to give comparable groups even with small numbers in a trial.

The second disadvantage of small numbers, which is not overcome by Deeley's procedure, arises from the fact that if the difference we are looking for between two treatments is small (and it seems likely that this will be so in the cancer field), then it is not possible to demonstrate such a difference convincingly with small numbers. To give a simple example: if 100 patients are treated in each of two treatment groups and 60 survive in one compared with 50 surviving in the other then this difference is not statistically significant at the usually accepted 5% level, however carefully we may have designed our trial. But if there are 1,000 patients in each group, and 600 are cured by one treatment while only 500 are cured by the other, then a highly significant difference between the two treatments will have been demonstrated, although the percentages cured are still the same as in the smaller trial.

Collaboration between a number of centres therefore appears to us to be the only way of obtaining in a reasonably short time the numbers of patients required to make useful comparisons of cancer treatments possible. We have found great enthusiasm for this collaboration among surgeons working away from the major centres, and this enthusiasm, the surgeons' skill, and the numbers that they treat must not be lightly abandoned. The administrative difficulties of a multicentre trial are not insurmountable, and Burn's apparent prefer-

ence for the small trial in a single centre is, in our view, misguided. To be fair to the authors he quotes in his support it should also be noted that Deeley² makes no claim that pairing will reduce the numbers required for statistical significance, and Handley¹ advocated a trial "in the same unit by the same team" as being preferable to uncontrolled comparisons between different series each treated in different centres. He did not discuss at all the relative merits of single centre as compared with multicentre trials.—We are, etc.,

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REFERENCES

- ¹ Handley, R. S., *Cancer*, 1969, **24**, 1270.
² Deeley, T. J., *Methods of Information in Medicine*, 1966, **5**, 100.

Purification of Ampicillin

SIR,—According to a recent article concerning the incidence of rash and the purification of ampicillin (Penbritin), Dr. E. T. Knudsen and others (21 February, p. 469) isolated protein from their ampicillin preparations and found it to be immunogenic. We have examined eight different lots of ampicillin produced by Bristol Laboratories U.S.A. (Polycillin) for protein, and found none to be present.

Dr. Knudsen and colleagues cite no procedure used for the isolation of protein impurity and no procedure for identifying their contaminant as protein. We isolated macromolecular material by a preliminary sterile molecular sieving of 300-g. batches of ampicillin through Sephadex G25. The macromolecular fractions were then subjected to dialysis through cellophane dialysis tubing against a constant flow of water. The retentate obtained was hydrolyzed with hydrochloric acid in a sealed tube and analyzed with a Technicon Autoanalyzer for lysine, proline, and histidine as indicators of protein content. With this technique an amidase enzyme, when introduced as a contaminant in ampicillin, would be detected at a concentration of one $\mu\text{g./g.}$ of ampicillin. The eight lots of Bristol ampicillin tested showed no evidence of protein content. Traditionally ampicillin has been produced by utilizing 6-aminopenicillanic acid obtained by cleavage of penicillin G with a bacterial enzyme, thus potentially introducing a source of protein contamination. We wish to report that presently all of our 6-aminopenicillanic acid is obtained through a completely chemical process of splitting a natural penicillin to yield 6-aminopenicillanic acid,¹ thus completely eliminating any possibility of bacterial enzyme as a source of protein contamination of the final product.

Immunogenic response to sensitizing protein has been considered to be a more critical test than chemical analysis. The immunogenic liability of non-protein macromolecular material isolated from our ampicillin was tested following procedures similar to those described by Dr. Knudsen and others. We found no evidence of an immune response (penicilloyl specific antibody production) using either complete

or incomplete Freund's adjuvant. Interpretation of the results presented by Dr. Knudsen and others in Table I is open to some question in view of the report of Batchelor and Dewdney² describing the rapid penicilloylation of the mycobacteria of Freund's adjuvant. Complete details of our work will be reported elsewhere (O. B. Fardig, *et al.*, in press).—We are, etc.,

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REFERENCES

- ¹ Weissenburger, H. W. O., and van der Hoven, M. R., U.S. Patent 3,499,909, 1970. Washington, U.S. Patent Office.
² Batchelor, F. R., and Dewdney, J. M., *Proceedings of the Royal Society of Medicine*, 1968, **61**, 897.

Pancreatic Enzyme Therapy

SIR,—We have read with interest the Today's Drugs article on pancreatic extracts (18 April, p. 161), and although we agree with several points made in the article, such as the erratic nature of the release of the drug from enteric coated tablets and the advisability of administering pancreatic extracts together with food, there are several points on which our opinions diverge.

Figure illustrates the treatment of a patient with pancreatic enzyme deficiency with pancreatic replacement.

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Such points include the frequently unimpressive nature of the results of pancreatic enzyme therapy; also the suggestion that treatment with pancreatic extracts is not essential, as fat absorption can proceed without lipase and can be enhanced by increasing the dietary intake of fat. Though this indeed can occur, it is usually

accompanied by diarrhoea and gross steatorrhoea, loss of weight, and the feeling of ill health.

In this unit we have handled a number of adult patients suffering from various forms of pancreatic insufficiency, until last year under the direction of the late Dr. A. C. Frazer, one-time professor of medical biochemistry and pharmacology at the University of Birmingham. According to Frazer's teaching, patients with a pancreatic enzyme deficiency usually improve with replacement treatment and sometimes results were most impressive. Frazer stressed the importance of using pancreatin itself and not one of the other preparations. He advised sprinkling the pancreatin from a pepper pot on to the food immediately before eating it and using an amount of 10 g. or more daily as required. The Figure illustrates the response of one of our patients to such pancreatic enzyme replacement treatment.—We are, etc.,

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Oral Ergotamine

SIR,—I would like to make some comments on the trial of ergotamine described by Dr. W. E. Waters (9 May, p. 325).

In any migraine trial an essential criterion is the severity of the headache. The trial described by Dr. Waters has omitted this fundamental fact. If these headaches were as severe as one knows they can be in migraine surely some patients would have attended a doctor, and the best method of treatment for these vascular headaches would have been ergotamine in a suitable form for the patient. If, on the other hand, the headaches were not severe and the patient did not attend a doctor, then obviously these headaches would have been treated with some other medicament, and because they were not severe vascular headaches of the migraine type ergotamine would have been of little help.

Because Dr. Waters treated all patients with ergotamine one assumed that every headache was due to a type of migraine. Is it not possible that some of these headaches were non-vascular? Lance notes¹ that 10% of patients with tension headache are also subject to migraine, and it should not be forgotten that a headache may have several components and a tension headache may be the precipitating factor in migraine.

The conclusion must be that these 88 women have had headaches not severe enough to send them to their doctor, yet they have been given ergotamine tartrate for headaches of extremely variable quality and doubtful aetiology. In fact, there is no justification for administering a potent drug in random order in this community survey.

The author commences by describing headache with the features of migraine, yet ends up with migraine. It would have been advisable to talk of vascular headache of the migraine type, and classify the patients into classical and common migraine, migrainous neuralgia, and the other conditions that are accepted by clinicians.

It is a well known fact that ergotamine

causes nausea. Ryan² mentions 15% of patients. This would certainly put patients off a tablet when they only had a headache which would have responded to a simple analgesic. If there had been a clear indication in this trial for ergotamine, the following criteria should have been adhered to:

(1) the dose of ergotamine should be tailored to the individual.

(2) The formulation should be acceptable to the patient. (Inhalations and suppositories have been shown to be the best methods of administration.³)

(3) Ergotamine should be given as early as possible in the attack, and this means with the aura and not the headache. This is not clear in the paper.

There are other points for criticism, and Dr. Waters knows my views. Dr. Waters is to be congratulated on the hard work that he has put into this trial but the results are meaningless if the wrong drug is given in the wrong dosage to the wrong patient.—I am, etc.,

WILLIAM P. MACLAY.

Farnborough, Hants.

REFERENCES

- 1 Lance, J. W., *Mechanisms and Management of Headache*, London, Butterworths, 1969.
- 2 Ryan, R. E., *Headache*, 1970, 9, 212.
- 3 *British Medical Journal*, 1963, 1, 661

Campbell de Morgan Spots

SIR,—The Campbell de Morgan spot is a small angle of capillary blood vessels under the epithelium of the skin. A similar lesion is sometimes found in pregnancy in the mucosa of the mouth, where it may bleed and cause annoyance. Perhaps this observation might help those who are looking for a dietetic factor in an outbreak of such spots. Do any foods contain a quantity of luteal hormone?—I am, etc.,

HELEN RUSSELL.

Edinburgh.

Resistance to Change

SIR,—For one who with advancing years finds it increasingly hard to retain his youthful optimism about the medical future in this country your account of the recent Special Representative Meeting (*Supplement*, 16 May, p. 111, and 23 May, p. 129) provided a ray or two of comfort. For instance, there was Dr. Ronald Gibson's *bon mot* about "little elephants," and the evidently widespread acceptance of this as "a true word spoken in jest" about one of the Green Paper proposals. The Canadian Prime Minister has recently observed that "if you share a bed with an elephant you have to watch out which way it turns." Though Mr. Trudeau was speaking in another political context, his observation is nonetheless true in ours.

What I find less encouraging is that many, perhaps most, of our present generation of medical politicians do not seem to perceive that there is a profound and important difference between these two situations. In the first place, for the Canadians the arrangement, however uncomfortable, has (presumably) some compensating economic advantages for both them and their elephant. But this is not the case either for us or for our elephant. Again, the Canadians probably have little choice in

the matter, whereas we do. The assumption that our present political predicament is ineluctable often derives more, I suspect, from mental laziness than from hard-headed political realism, as those who make it would have us believe. I do not, of course, have in mind those who genuinely believe that the presently existing relationship between the Government and the doctors of this country is both necessary and desirable, but rather those who devote much of their public utterance to criticizing its consequences ("knocking the Health Service" in Kenneth Robinson's phrase), yet are foremost in opposing any attempt even to begin considering the possibility of change. One almost wonders if they actually enjoy watching and dodging the elephant.

Hitherto doctors have had the reputation of being individualistic and conservative in their outlook; indeed have sometimes been charged with being excessively so. Perhaps they have changed, but if not then it is surely something of a paradox that their professional Association is now spending much of its time and most of its money in bolstering up what is and must continue to be an essentially socialist system of providing medical care for the people of this country. If the current crisis over remuneration were to lead to a serious reappraisal of this policy it could turn out to be a blessing in disguise.—I am, etc.,

E. R. C. WALKER.

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Retired

SIR,—Retired does not mean no longer interested, and many retired consultants act as locums or do honorary work in postgraduate and other fields. Even so their names are often removed from mailing lists so that they no longer receive many valuable hand-outs.

The award of an honorary appointment does not cancel out this result of being retired, for the names of consultants so honoured are not included on the strength and so are missed if the *Medical Directory* is used to make mailing lists.

Some may prefer to be left off all lists when they retire, but could not they be asked first and retained if (even "blotting paper") medicine remains of interest.—I am, etc.,

C. ALLAN BIRCH.

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Sussex.

Consultancy in Radiology

SIR,—Good luck to the East Anglian Regional Hospital Board in its search for a consultant radiologist (hospital appointments, 25 April, p. xxxii). But why is it obligatory for candidates to have a higher degree in radiology? The Board is surely preventing from applying many senior registrars and other consultants who do not possess the F.F.R.

This cannot be the policy of the Faculty of Radiologists; if it is, it is a deplorable situation. Perhaps the Regional Hospital Board or the Faculty could enlighten me on this.—I am, etc.,

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