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- No letter should be more than 400 words.
- For letters on scientific subjects we normally reserve our correspondence columns for those relating to issues discussed recently (within six weeks) in the *BMJ*.
- We do not routinely acknowledge letters. Please send a stamped addressed envelope if you would like an acknowledgment.
- Because we receive many more letters than we can publish we may shorten those we do print, particularly when we receive several on the same subject.

Extracranial-intracranial bypass, one; clinical trials, nil

SIR,—Many of us outside the specialty of cerebrovascular surgery have nevertheless followed the correspondence relating to the international extracranial-intracranial bypass trial with interest.^{1,2} The interpretation of the trial made by Professor H A F Dudley (13 June, p 1501) raises many questions of concern to all those involved in randomised trials in which one "arm" is a surgical procedure.

Trials of technical innovations in a single centre with interested parties are difficult enough to perform; trials including many centres inevitably encounter problems related to quality control and protocol violations. Once a trial becomes truly multicentre and international, however, gathering accurate data is likely to be fraught with difficulties.

It is intriguing to consider why some eligible patients are selected for randomisation while others who are equally eligible are not. In addition, what reasons are there for a randomised patient not receiving the allocated treatment? Discrepancies of this type obviously throw doubt on the validity of any data obtained. From experience of randomised surgical trials for over 10 years, I would suggest that the two chief reasons for trial idiosyncrasy are, firstly, problems with informed consent and, secondly, a lack of time and commitment on the part of the participating surgeon.

Both these reasons are understandable. It can be extremely difficult (and time consuming) to explain to a patient that he has a potentially crippling or fatal disease that is suitable for randomisation but that whereas one treatment arm

is active, the other consists of a "wait and see" policy. Equally, once a patient is included in a trial entailing long term careful follow up and investigation the extra time needed and resulting paperwork may be considerable.

There is no doubt that surgeons are often willing, for the very best of motives, to participate in therapeutic trials. Such enthusiasm, however, may backfire if the protocol is not scrupulously adhered to. In my view, when a surgeon agrees to participate in a randomised clinical trial he should be made fully aware of all the potential difficulties, ethical considerations, time, and attention to detail that such a commitment entails. Strict adherence to the protocol is essential, and the surgeon must accept that his clinical freedom will be inhibited. If a patient admitted under his care is eligible for randomisation then that patient must be included in the study. If the patient does not give informed consent to randomisation then, whatever treatment is provided, the patient's progress should nevertheless be monitored in exactly the same way as it would have been had he been allocated to the randomised treatment.

Accordingly, if a surgeon is invited to participate in a controlled randomised trial he should consider carefully the overall implications before agreeing. Should he decide to participate in this long term and time consuming exercise, with all its ethical dilemmas and pitfalls, then he immediately forfeits a certain degree of clinical independence. Failure to adhere to the protocol, with non-randomisation of eligible patients or randomisation of ineligible patients, can have serious long term consequences,

as illustrated so dramatically in the extracranial-intracranial study.

The truth, as Popper pointed out, is never manifest, and therefore we must make do with science. It is most important that the scientific status of any therapeutic procedure is established, and in clinical medicine this demands a careful and disciplined approach to clinical trials.

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1 Extracranial-intracranial Bypass Study Group. Failure of extracranial-intracranial bypass to reduce the risk of ischaemic stroke. Results of an international study. *N Engl J Med* 1985;313:1191-200.

2 Sundt T. Was the international randomised trial of extracranial-intracranial arterial bypass representative of population at risk? *N Engl J Med* 1987;316:814-6.

The search for a hormonal switch for obesity

SIR,—We think that there is a good case for adding two regulatory peptides to the already long list cited by Drs C Dieguez and M F Scanlon in their interesting leading article on possible endocrine causes of obesity (30 May, p 1371). These are neuropeptide Y and galanin, both of which have been convincingly shown to be among the most powerful known central stimulants of appetite in rodents.

Neuropeptide Y (the most abundant neuropeptide in the brain) is found in high concentrations in the hypothalamic nuclei,¹ including the para-

ventricular nucleus, which, as pointed out by Drs Dieguez and Scanlon, is increasingly thought to be important in controlling food intake. Injection of neuropeptide Y (and its close analogue, peptide YY) into the paraventricular nucleus stimulates eating, particularly of carbohydrate rich food,^{2,3} and chronic administration may lead to obesity.⁴ Galanin, another hypothalamic regulatory peptide, similarly causes hyperphagia when injected into the paraventricular nucleus.⁵

The increasing length of the list of candidate peptides underlines both the complexity of peptidergic appetite control mechanisms and the difficulty of relating experimental findings to real life. We, however, have recently identified pronounced disturbances in hypothalamic concentrations of both neuropeptide Y and galanin in different rodent models of obesity or diabetes, or both, all of which show hyperphagia. This suggests that these two peptides have a key physiological role in appetite regulation in the intact animal. In the yellow obese KK (KKay) mouse and the diabetic Chinese hamster hyperphagia (with hyperinsulinaemia and insulin resistance) appears early in the evolution of the metabolic syndrome, which is completed by the development of obesity and glucose intolerance.⁶ In both of these spontaneous syndromes whole hypothalamic neuropeptide Y concentrations are significantly reduced compared with those in matched non-diabetic controls.^{7,8} In the KKay mouse hypothalamic galanin concentrations are also significantly reduced, both peptides being decreased in both the hyperphagic pre-diabetic phase and the complete syndrome.⁷

Hypothalamic concentrations of these appetite stimulating peptides may be reduced in an attempt to counter extrahypothalamic causes of obesity, such as defective signalling of satiety from the gut.⁹ In contrast, rats rendered diabetic with the β cell toxin, streptozotocin, show a striking and consistent increase in hypothalamic neuropeptide Y, occurring in both the central hypothalamus (containing virtually all the hypothalamic nuclei, including the paraventricular and ventromedial) and the lateral hypothalamus.¹⁰ The fact that hyperphagia in streptozotocin diabetic rats is preferentially for carbohydrate,¹¹ as is seen after intra-hypothalamic neuropeptide Y administration,³ strengthens the argument that increased concentrations of neuropeptide Y may mediate hyperphagia in this model. Though overall galanin concentrations in both lateral and central hypothalamus were similar to those in controls, immunocytochemical studies have recently identified major morphological changes in galanin containing neurones throughout the hypothalamus in streptozotocin diabetic rats (unpublished findings).

Disturbances in hypothalamic neuropeptide Y and galanin in these quite different models of hyperphagia (both spontaneous and artificially induced) suggest that they are implicated in physiological appetite control in rodents. The relevance of this plethora of peptides to man is, of course, entirely speculative at present. Nevertheless, continuing progress in developing "tailor-made" peptide analogues with specific agonist or antagonist properties may ultimately produce a rational treatment for human obesity.

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cular nucleus injections of peptide TY and neuropeptide Y preferentially enhance carbohydrate ingestion. *Peptides* 1985; 6:1205-11.

- 4 Stanley BG, Kyrkouli SE, Lampert S, Leibowitz SF. Neuropeptide Y chronically injected into the hypothalamus: a powerful neurochemical inducer of hyperphagia and obesity. *Peptides* 1986;7:1181-92.
- 5 Kyrkouli S, Stanley BG, Leibowitz SF. Galanin: stimulation of feeding induced by medial hypothalamic injection of this novel peptide. *Eur J Pharmacol* 1986;122:159-60.
- 6 Herberg L, Coleman DL. Laboratory animals exhibiting obesity and diabetes syndromes. *Metabolism* 1977;26:59-99.
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- 9 Bailey CJ, Flatt PR. Anorectic effect of fenfluramine, cholecystokinin and neurotensin in genetically obese (ob/ob) mice. *Comp Biochem Physiol [A]* 1986;84:451-4.
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- 11 Koopmans HS, Pi-Sunyer FX. Large changes in food intake in diabetic rats fed high-fat and low-fat diets. *Brain Res Bull* 1986;17:861-71.

Cervical smears: new terminology and new demands

SIR,—Professor H Fox (23 May, p 1307) states that all women with mild dyskaryosis or even persistent inflammatory changes should be referred for colposcopy and treatment. Dr M J Campion and colleagues (p 1337) speak of a dramatic increase in deaths from cervical cancer in young women and suggest that the current practice of relying on cytological surveillance is inadequate. These follow other recent reports and statements of increasing stridency by doctors, politicians, and women's rights campaigners on society's failure, incompetence, and indeed criminal negligence.

These allegations are being made in spite of evidence that current measures have already made a significant impact.¹ There can be no question that screening by cervical cytology is both reliable and effective. The latest Scandinavian study relates mortality quite clearly to the level of cytological cover.² This resulted in an 80% fall in mortality between 1963 and 1982 in Iceland, which had the widest population coverage, and in decreases of 50%, 34%, and 25%, respectively, in Finland, Sweden, and Denmark, where cover was less extensive. It is interesting to note, however, that in Norway, where only 5% of the population was screened, mortality still declined by 10%. The extent of cover in the United Kingdom is a matter for argument, but the overall mortality between 1968 and 1984 fell from 12.53/100 000 to 9.10/100 000 and mortality in those under 30 rose from 0.22 to 0.91.³ The increase is fourfold in the young but it still represents only 10% of total mortality. It should also be noted that carcinoma of the cervix is the tenth least common malignancy in women. All this hardly adds up to a monster epidemic.

Our laboratory provides a five year screening service for two districts (Exeter and North Devon) with a combined population of 118 000 women aged 20 to 64 years. Broad data from computerised records are available from 1979 to 1985, mainly for Exeter. Detailed analysis awaits completion of a 10 year period. The yearly number of smears rose from 21 545 to 26 800; the number showing any grade of cervical intraepithelial neoplasia remained static between 1563 and 1638, but the number with grade 3 went up from 52 to 233. Cytology detected 518 potentially lethal lesions (cervical intraepithelial neoplasia grade 3, 499; microinvasive carcinoma, 19). Those below and above the age of 35 were equally affected. Assuming a 40% risk of progression to invasive cancer, 207 cases would have occurred, 145 in Exeter alone, at all ages.

During the same period 152 cases of carcinoma of the cervix were diagnosed by the histopathology service in Exeter. Of these, 10% occurred in women under 35 and 27% in women over 65. Overall, 44% had either never had a smear or had not had one in the preceding five years. Unsatisfactory and negative smears or changes characteristic of cervical intraepithelial neoplasia grade 1-grade 2 had been reported in 14%, and in most repeat smears were recommended but the patients underwent biopsy instead because of clinical symptoms. Clearly, at least as many cases were prevented by cytology as occurred, halving the actual rate, which is a notable achievement with an estimated screening cover of just over half of the population. At most only three cases a year were "missed" because a smear was not fully diagnostic in the first instance. We are yet to see a significant increase of invasive carcinoma in younger women, and the main problem lies in the older women who have not been screened.

Resources remain finite, and carcinoma of the cervix is one of many competing demands, none of which will ever be met fully. We deplore selective reporting and overstatement and we do not see valid reasons for panic. The first priority must be a well implemented five year call/recall system, which the country can afford now, coupled with careful long term surveillance to ensure that a gradual reduction of the disease is achieved. The alternative is chaos. The national press refers to two year waiting lists for colposcopy in some centres; this is not only unnecessary but irresponsible and unforgivable.

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- 2 Laara E, Day NE, Hakama M. Trends in mortality from cervical cancer in the Nordic countries: association with organised screening programmes. *Lancet* 1987;i:1247-9.
- 3 Communicable Disease Surveillance Centre. Sexually transmitted disease surveillance in Britain—1984. *Br Med J* 1986;293:942-7.

SIR,—We welcome Professor H Fox's leading article (23 May, p 1307) and its clear recommendation that, ideally, all women with dyskaryotic cells in their cervical smears and those whose smears show persistent inflammatory changes should be referred for colposcopy. Professor Fox did not, however, mention the possibility of concomitant genital tract infection in women with abnormal cervical cytology and its impact on management.

In a recent study in this clinic 93 women whose smears were reported to show a variety of minor changes not sufficiently pronounced to be termed dyskaryotic underwent colposcopy and biopsy when indicated. In each case a firm clinical diagnosis had not been apparent, and a repeat smear at varying intervals was recommended by the cytologist. Excluded from the study were those patients whose smears had been reported as unsatisfactory for technical reasons or where a specific micro-organism—for example, *Trichomonas vaginalis*—was identified in the smear.

Fifty two of the women had histologically verified abnormal cervical epithelium. Of these, 32 had cervical intraepithelial neoplasia. Twenty three of the smears that were repeated at colposcopy were reported to be normal; eight of these women had cervical intraepithelial neoplasia, giving a false negative cytology rate of 35%.

Cervical intraepithelial neoplasia behaves as a

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