effective than single-agent therapy; well, it all depends what you mean by "more effective." It is true that the aggressive combined regimens applied in advanced breast cancer produce more immediate objective responses; but, as has recently been pointed out, this has not been reflected in any overall improvement in survival.[7] Furthermore, a recent paper has shown that a sequence of single agents used in advanced breast cancer will eventually produce the same result as combining all agents together at the first injection.[8] Next, a consensus of opinion broadcast from the National Institutes of Health by a group of distinguished and committed medical oncologists, does not make me tremble at the knees as if a pronouncement has come down from Mount Olympus. Medical oncologists in America are notorious for their tunnel vision and have to continue struggling to justify their very existence as a specialty. Furthermore, as already pointed out, practice in the United States can never be transplanted to the United Kingdom or the developing world without an enormous investment in capital and recurrent expenditure.

Finally, let us remember that only 8% of patients with breast cancer are being entered into prospective trials in the United Kingdom each year.[9] This may be due to inertia on the part of clinicians, but it is more likely that the prospective trials so far offered to busy clinicians are very demanding in unrewarded effort and often unrealistic in their proposals. There are plenty of patients available to answer all the questions applying to the management of early breast cancer; there is certainly room for groups investigating Dr Price's approach as well as for groups of clinicians who are interested in the modest benefits that might accrue as a result of applying the soft option.

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## Statistics and ethics in medical research

SIR,—I was disappointed to read Mr Douglas Altman's article (8 November, p 1267), suggesting that the use of placebos in trials was excessive. More detail should have been provided. Certainly the absence of a placebo group in trials of psychotropic drugs has led to the prescribing of numerous compounds of highly doubtful value.

A particular example is the proliferation of so-called antidepressants, where in a "piggy-back" fashion newer antidepressants have been compared with older forms so that these in turn become regarded as established treatments and provide the reference for yet newer drugs. Unfortunately, even the most established antidepressant drugs have been shown in many trials to be little or not at all superior to placebo, and the nature of the sample of patients and the design of the trial have obviously been critical. This means that later comparisons of newer drugs with these, without a placebo group, have been almost meaningless.

A further serious problem has been the total neglect of the role of type II error and the $\beta$ probability associated with this. This is the probability that when trying to *sustain* the null hypothesis, which is that two drugs are equally potent, this could have arisen purely by chance. Unlike the $\alpha$ probability for type I error, which is required when attempting to *reject* the null hypothesis, as is the case in placebo comparisons, the $\beta$ probability is usually very substantial unless one has quite large numbers, five or 10 times the number used in placebo trials. The glib statement that, for instance, 15 patients on an established drug and 15 patients on a new drug showed no difference significant at the 5% level (where this is always given as the $\alpha$ probability) has led to the use of what are in fact virtually untried compounds.

Of course it is of practical significance to compare truly established methods of treatment with newer therapy, but this is only realistic and of value where the methodological considerations for that comparison are such that they do not lead to this common form of mathematical nonsense.

It is to be hoped that, in psychiatry at least, the placebo will be encouraged rather than the reverse in future research.

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## What is a nuclear shelter?

SIR,—Since there are no licensing or approval procedures in this country, and most others, the entrepreneurs have entered this field; it seems that just about anybody can market a "nuclear shelter." As an independent, objective, and knowledgeable nuclear physician who really does understand what the effects of a nuclear explosion are, I am alarmed to find a lamentable lack of information in the "nuclear shelter" brochures about the radiation protection factors.

Outside the zone of the physical effects of a nuclear explosion the problem is one of protection from the immediate gamma rays and the substantial aerial and deposited radioactive debris and dust. As ground zero is approached these radiation hazards increase about logarithmically. Quite near the bomb the radiation hazards mount steeply with the superimposition of more instantaneous gamma rays on neutron-induced radioactivity in the air and earth and more continuing gamma rays from relatively more terrestrial fallout (coarse debris).

Neutrons, especially those arising from a bomb of high rating or an enhanced radiation weapon (ERW), are 10 times more lethal than gamma rays. Shielding against neutrons poses very special problems because the best materials are either very weak structurally, scarce, or very expensive.

I am sure that nobody would wish to purchase an expensive "nuclear shelter" which would protect his family from the physical effects of a nuclear bomb yet leave him to watch them dying of an overdose of radiations. Much more specific data should be given by suppliers of nuclear shelters. Errors of omission are as important as errors of commission. We are after all dealing with a matter of life and death.

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## Pancreatic transplantation

SIR,—Your leading article "Pancreatic transplantation" (25 October, p 1091) failed to distinguish between the transplantation of isolated pancreatic islets and islet tissue. Current methods of isolating and purifying rat islets have failed to produce substantial numbers of islets when applied to the human pancreas. Hence Mirkovitch[1] and later Najarian[2] abandoned attempts to separate islet and exocrine tissue and instead produced a crude pancreatic digest using collagenase—the "dispersed pancreas." It is this islet tissue which has proved so disappointing in human pancreatic transplantation.

Furthermore, I challenge the statement in the article that "patients treated in this way have not been harmed." Intraportal autotransplantation of this digested pancreas regularly produces an elevation of portal pressure and in one patient produced acute disseminated intravascular coagulation.[3] Finally, prolongation of rat islet allograft survival by tissue culture prior to transplantation can only be achieved using purified islets. Survival is not prolonged if non-islet pancreatic tissue contaminates the culture and transplantation of these islets.[4]

It is my opinion that safe and effective pancreatic transplantation in the young diabetic patient will only be achieved using purified isolated islets combined with more effective methods of immunosuppression.

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## Transplants—are the donors really dead?

SIR,—Having resisted for a month the temptation to re-enter the columns of either the medical or public press, I feel I cannot let pass the allegation by Mr Deehan (15 November, p 1332) that I have passed off conjecture as fact. He refutes as incorrect my statement that ". . . the previous day I had been offered five minutes to reply to *Panorama* on a serious programme and the Director-General vetoed it within half an hour." That such a minor scene in this important drama should be replayed so long after it happened suggests that the BBC is anxious to cast doubts on my veracity as a witness, in view of the threatened retrial by television of the technicalities of diagnosing brain death.

My version of the incident is simple and clear. Arrangements had already been made to record my interview, when the producer rang to cancel it. The explanation given to me was that the Director-General had insisted on the inclusion of one of the *Panorama* team, and that none of them could (? would) participate. Given only that information I consider that my comment was fair. My relations with Mr Deehan's department have always been

excellent, and I am sure that they acted with perfect propriety in what must have been an embarrassing situation for them. When journalists asked me to identify the programme involved I refused to do so, because I wished to protect Mr Deehan's staff. He has had no such qualms about trying to discredit me.

Attention must now be focused on the second *Panorama* programme. This has been hailed as a concession to the doctors ("*Panorama* critics win rehearing"; "BBC backs down over transplants"; "As Mr Jenkins told the Commons this would give the medical profession a chance to refute effectively the charges made in the original programme.") It was even reported that the *Panorama* team would this time consult fully with the (British) medical profession. In preparation for this a number of experts have been discussing how best to explain to a television audience what brain death is, how it is diagnosed, and why there seems to be such controversy about the role of the EEG.

It now appears, however, that the BBC sees this programme in quite a different light. Replying to a letter from a prominent lay person, who expressed satisfaction that there was to be another programme to put the record straight, the editor of *Panorama* wrote (6 November): "I don't believe that our record is in any need of the correction you suggest. We are doing a second programme not because we thought the first one wrong, but because of the immense interest in this subject both by doctors and by the general public." In view of this attitude, and of the experience of the first programme, the experts in the field are unwilling to appear on the second programme unless the BBC agrees to certain conditions about the format and content, which have been formulated by the royal colleges and the BMA. Should the BBC not agree to these conditions but none the less transmits a second programme, it should be recognised that this will not include the representative views from British experts.

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## Diagnosis of brain death

SIR,—I wish to address myself to the problem of the diagnosis of brain death. These comments are specifically directed to the British code on brain death, the BBC television programme presented on 13 October ("Transplants: Are the Donors Really Dead?"), and the variety of responses from the British medical community.

I believe that the diagnosis of brain death could be made with a high degree of certainty if the British code was followed exactly to the letter, with absolutely no error in clinical judgment. But to quote Hippocrates, "Life is short, the art is long, the occasion fleeting, experience fallacious, and judgment difficult." We are dealing with a situation where it is medically acceptable to diagnose a dead brain as alive, but it is never justified to diagnose a live brain as dead. Therefore we are committed to use a set of criteria that should not permit even minuscule uncertainty in the diagnosis of brain death. There should be no uncertainty in the minds of the physicians pronouncing brain death, or of those involved in the transplant procedure, and no uncertainty in the public domain—including potential donors. It should be made unmistakably clear that the classical criteria of death (irreversible absence of heart beat, respiration, and movement) and the criteria for brain death in situations where the patient is being artificially maintained by life support systems represent different criteria for the pronouncement of death. We are not dealing with two different kinds of death but different criteria for diagnosis.

Since there are inherent errors in all scientific observations, it is incumbent upon us to use all those measures that are practically available. The British code demands that the diagnosis should not be in doubt and there should be no evidence of drug intoxication, and indicates that repeated examinations may be performed for periods as long as 24 hours. There are situations in which the primary diagnosis may not seem to be in doubt, but if one is dealing with multiple aetiologies, such as drug intoxication and intracranial haemorrhage, for example, it may be difficult if not impossible to absolutely rule out the contribution of the drug to the patient's condition. In other words, there is a possibility of error.

Since intoxicants can mimic the clinical findings of "brain stem death" for prolonged periods, the additional ancillary tests for electroencephalographic activity and cerebral blood flow are required to decrease the possibility of a misdiagnosis. Therefore, depending on the circumstances, the more stringent the criteria the less probable the error in diagnosis.

Although repetition of the evaluation might be as long as 24 hours according to the British code and the major purpose in the diagnosis of brain death is transplantation, examinations could be made less frequently. This also leads to a potential error. In our part of the "collaborative study," criteria for brain death were primarily studied independently of transplant requirements. I mentioned 14 patients who on initial examination were comatose, apnoeic, and cerebrally unresponsive, with absent cephalic reflexes, who subsequently survived. In 12 drug intoxication was the aetiology. In the remaining two patients the aetiology was not intoxication but transient cardiac arrest in one, and probable brain stem vascular insufficiency in the other. Both these patients had electroencephalographic (EEG) activity at the time of examination and when re-examined within 12 hours showed return of cephalic reflexes and respiratory activity. They were discharged subsequently in a neurologically normal state. Strict adherence to the British code in conjunction with appropriate clinical judgment might not result in diagnosing these patients as brain dead, but what if they were examined less frequently or if their condition had persisted for over 24 hours?

I believe that the criteria for diagnosis of brain death should be considered as an issue independent of the problems related to organ transplantation. The British code, however, links the diagnosis of brain death irretrievably with transplantation. If this position is maintained, should not the criteria be as strict as Dr Nesbakken suggests and include not only EEG but even studies of cerebral blood flow? This would obviate any questions of uncertainty and be applicable to the problem of brain death and transplantation in children and infants as well. It is in this group, especially in younger children, that the diagnostic criteria have been found to be less reliable.[1 2]

Our ability to deal with the enormous complexities of the process of the death of an individual is essential given the ever-increasing requirements for organ transplants.[3]

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SIR,—The article by Dr P W de Leeuw and Professor W H Birkenhäger (1 November, p 1181) describing hypothermia occurring in an inpatient treated with prazosin highlights yet again the problems which may occur with a variety of drugs. In the home environment the elderly may easily become hypothermic when subjected to relatively small temperature drops, while an increasing problem is the younger sportsman—canoeist, sailor, potholer, mountaineer—subjected in an emergency to sudden temperature drops—for example, in the Fastnet disaster. I can record from personal experience frostbite affecting two toes together with symptoms of generalised hypothermia, under conditions where this would not normally be expected, in an individual taking propranolol. I would be most interested to hear from any practitioner who has similar data occurring in any situation.

I also read with interest the letter from Mr Robert Sells (1 November, p 1212) in which he notes that—for donor purposes—"re-examination of the corpse at a temperature of more than 35°C was, of course, mandatory." At a recent symposium at Yosemite, California, Dr Cameron Bangs was emphasising (with reference to accidental hypothermia) that "they are not dead until they are *warm* and dead." Surely *all* victims found apparently cold and dead, whether prospective donors or not, should be given the "mandatory" rewarming to 35°C before the all-important "final" decision is made? This is certainly not being done at present, so how many lives are lost?

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## Millions of mild hypertensives

SIR,—Your leading article "Millions of mild hypertensives" (18 October, p 1024) encourages general practitioners to treat middle-aged persons in Britain with diastolic pressures over 100 mm Hg. The article goes further and points out that it may prove necessary to treat diastolic pressures over 90 mm Hg. We agree that this advice may prove correct but question whether there are actually four million such persons in Britain. The high prevalence figures are presumably derived from surveys of *casual* blood pressure, and, although casual blood pressure is important in predicting subsequent mortality, the general practitioner can be expected to treat hypertension only when it is sustained. When a patient's blood pressure falls to "normal" levels owing to familiarisation with the measurement or the surroundings or to natural fluctuation of the condition, the general practitioner will not start treatment. There are 15 million persons aged 40-64 in Britain and it would appear unlikely that four million of these have a sustained diastolic pressure equal to or over 90 mm Hg. The proportion with sustained