NEUTRON BRACHYTHERAPY

SIR,—We note with interest the results of Professor Maruyama and colleagues (May 18, p 1120) in advanced carcinoma of the cervix but do not consider that they represent an advance on existing techniques. We have achieved a five-year survival of 38% in stage III carcinoma of the cervix with predominantly external beam radiotherapy.[1] Others have described similar results.[2,3] The 80% local relapse rate in Maruyama's historical controls reflected in their very poor five year survival of only 12% in stage III disease. The dose to the pelvic side-wall was not standardised and additional caesium and californium implants were used, so the data provided do not allow us to compare the two groups. The principal advantage of intracavity treatment is the very rapid fall-off of dose by an inverse square law. The technique makes only a modest contribution to dose at the pelvic side-wall. Since about 38% of patients with stage III carcinoma of the cervix will have spread of disease outside the pelvis at presentation,[4] long-term survival is unlikely to be further improved by alterations in local radiotherapy technique.

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SIR,—The notion that hypoxic but potentially clonogenic cells are a major cause of local treatment failure in radiotherapy has been current for nearly 30 years. However, diligent efforts have failed to reveal significant benefit in advanced cervical cancer from either treatment in hyperbaric oxygen[1] or treatment in the presence of selective hypoxic cell radiosensitisers.[2] Professor Maruyama and colleagues (May 18, p 1120) report yet another strategy designed to overcome the alleged problem of hypoxia in advanced cervical cancer—namely, the use of densely ionising neutron particles derived from the radioisotope californium-252. 5-year survival in stage IIIB carcinoma of the cervix was 54% in patients treated with californium and external pelvic irradiation (in that order), and 12% for patients treated with identical pelvic irradiation and subsequent intracavitary irradiation by caesium-137. The validity of these results is doubtful:

(1) In this trial, which was not a randomised study, the number of patients with stage IIIB disease allocated to early californium brachytherapy or to conventional caesium brachytherapy is small (42).

(2) The 12% 5-year survival for the "control" arm of the trial would be regarded as very poor in most major radiotherapeutic institutions.

(3) 50% of stage IIIB patients had distant metastases, but a 54% 5-year-survival rate is claimed. Are Maruyama et al claiming to cure every case of stage IIIB cervical cancer that has not already undergone distant metastasis?

Most cervical cancers reduce in size during external pelvic irradiation and some degree of re-oxygenation is believed to occur during such irradiation.[3] Consequently, the absolute numbers of hypoxic cells would be expected to be lowest at the conclusion of pelvic irradiation and they would be expected to be concentrated centrally in the pelvis; in this situation they might well prove to be vulnerable to the poorly penetrating 2·3 MEV fast neutrons emitted by californium. The californium appeared to confer benefit only when used before pelvic irradiation and not when used afterwards is an apparent paradox that Maruyama et al make no attempt to explain.

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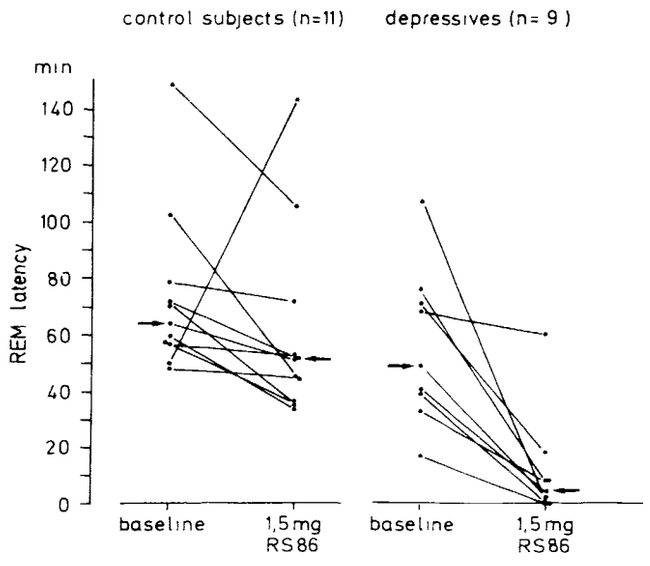
CHOLINOMIMETIC DRUG RS 86, REM SLEEP, AND DEPRESSION

SIR,—Shortening of rapid-eye-movement (REM) sleep latency is often present in patients with major depressive disorders and is regarded as a characteristic biological abnormality. In healthy subjects, infusion of the cholinergic drugs arecholine or physostigmine during the first non-REM period provokes earlier onset of REM sleep, suggesting that the spontaneous shortening of REM latency in depression is a consequence of cholinergic overactivity.[1] This overactivity, or hypersensitivity of the cholinergic receptor, has been further illustrated by the effects of arecholine during the second non-REM period, when the REM-sleep-provoked effect was significantly more pronounced in depressive than in healthy subjects. However, when we gave physostigmine infusions to depressed patients during the first non-REM/REM cycle, REM latency was not shortened; indeed most patients woke up.[2]

In the above studies the drugs were given by infusion because of their short half-lives. Also required, before infusion, was intramuscular methscopolamine, a peripheral antidote. The cholinergic agent RS 86 (Sandoz) offers the opportunity for more convenient investigation of this issue. RS 86 is an orally acting central muscarinic agonist with minor peripheral side effects.[3] It is a spirosuccinimide derivative with a half-life of 6–8 h.

In eleven healthy subjects (six females, five males, aged 18–45) and nine inpatients with a major depressive disorder on Research Diagnostic Criteria (five females, four males, aged 18–59), we studied the effect of an oral dose of 1·5 mg RS 86 on the first REM latency. In a double-blind design healthy volunteers randomly received placebo or 1·5 mg RS 86 for one night. Depressed patients received either placebo or RS 86 for two nights. The drugs and placebos were taken 1 h before going to sleep. 1 night of adaptation preceded the study for both healthy and patient volunteers.

1·5 mg RS 86 shortened REM latency from 73±29 to 61±34 min in healthy subjects (mean×SD; Wilcoxon test, one-tailed, $p<0·05$). This result accords well with Spiegel's study.[3] In depressed patients, the effect of RS 86 was much more pronounced; REM latency fell from 56±28 to 11±19 min ($p<0·005$) (see figure).



REM latency.
Arrows show medians.

The results with RS 86 support the assumption that the shortening of REM latency in depressives is caused by cholinergic overactivity, which may be due to a hypersensitivity of cholinergic receptors.[1] Since RS 86 can be taken by mouth and since there is no need for a peripheral blocker this compound may have advantages for multiple testing of the cholinergic involvement in affective disorders.

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ACUTE POISONING WITH ORPHENADRINE

SIR,—A 40-year-old man with no previous history of epilepsy was found convulsing in bed. He had a cardiorespiratory arrest in the ambulance and on arrival in casualty he had a profound bradycardia (20/min); his blood pressure was unrecordable and he had severe acidosis. Intubation, ventilation, and cardiac massage were started. Asystole supervened and huge doses of adrenaline, dopamine, and dobutamine were needed to achieve a systolic blood pressure of 110 mm Hg. No tablets were seen on gastric lavage. Because a neurological cause for the convulsions could not confidently be excluded, a computerised tomographic head scan and lumbar puncture were done but were normal.

A drug screen revealed orphenadrine at a concentration of 16·2 mg/l in blood taken on admission (therapeutic range below 0·2 mg/l). Treatment with cathartics and activated charcoal was started. Subsequently his wife told us that he was a chronic schizophrenic on regular intramuscular depot phenothiazines and oral orphenadrine. He had gone to bed normally the night before admission and she had woken up to find him convulsing beside her.

24 h later he was alert and without neurological deficit. Inotropic support was gradually withdrawn but acute renal failure ensued. No casts were seen in the urine, and myoglobin was not detected in blood or urine sampled on admission. His total creatine phosphokinase (CPK) rose to 12 400 IU/l (normal 15–125) but with an MB-CPK fraction of less than 6%, indicating that significant myocardial damage had not occurred. Transient hyperphosphataemia and hyperuricaemia were observed, suggesting that rhabdomyolysis might have contributed to the acute renal failure besides the hypotension. His serum creatinine reached a peak of 873 μmol/l (normal below 120 μmol/l) but with conservative measures became normal within 10 days. The patient has since admitted to poisoning himself deliberately but he could not estimate how many tablets he had taken or tell us exactly when he had swallowed them.

Orphenadrine is rapidly absorbed.[1] It is toxic to most organs and is directly cardiotoxic. Toxicity begins at concentrations in the circulation of 2 mg/l, and concentrations of 4–8 mg/l may be fatal.[2] Blood levels up to 33 mg/l were reported in one series of purely orphenadrine-related deaths.[3] Between 1977 and 1980 twelve deaths due to orphenadrine were recorded by the National Poisons Unit at Guy's Hospital (Dr M. Boland, personal communication). In the three cases of pure orphenadrine poisoning where blood levels were measured post mortem they were 7, 9, and 18 mg/l, which suggests that the survival of the patient described here was remarkable.

Many doctors are unaware of the dangers of orphenadrine in overdose.[4] Treatment with orphenadrine may carry a greater risk than the drugs whose side-effects it is deemed to control. Up to 50% of patients on neuroleptic drugs are also given prophylactic anticholinergic agents.[5] Yet in up to 80% of them extrapyramidal symptoms do not recur when anticholinergic drugs are withdrawn.[5] Drugs such as orphenadrine should be prescribed carefully and only in small amounts to patients in whom it is considered that there is a real risk of self-poisoning.

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EPIDEMIOLOGY FOR CLINICIANS

SIR,—Your June 1 editorial (p 1256) states that clinicians can update their knowledge of epidemiology only by attending one-week courses in Southampton and, now, Edinburgh. Besides our longer courses we have three-week intensive summer courses in epidemiology.

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DURATION OF CYTOSTATIC THERAPY

SIR,—Sir Stanley Peart (May 4, p 1045) describes a case of reticulum cell sarcoma in which the cessation of cyclophosphamide after 11 years may have precipitated a fatal relapse. There is no agreement on the length of cytostatic therapy in malignant diseases. In bronchial carcinoma the question does not usually arise because of the brevity of survival in patients with non-operable disease. However, I have seen a case of lung cancer, resembling Peart's case, which has influenced my views on the length of cytostatic therapy.

In July, 1978, a 58-year-old man came to hospital for repair of an inguinal hernia. A preoperative chest X-ray revealed atelectasis of the right upper lobe. Studies of sputum and transthoracic fine needle biopsy specimens revealed microcellular carcinoma. Two cycles of vincristine and cyclophosphamide were followed by radiotherapy. The atelectasis disappeared and a 5×4 cm tumour was then seen in the right hilum on chest X-ray. Because of tumour progression cytostatic therapy was reintroduced in May, 1979, and 37 cycles were given over the next 4½ years, during which the patient's condition and the size of his tumour remained stable.

In August, 1983, cytostatic therapy was stopped because of eczema and the attainment of 5 years' survival. 7 months later progression of the tumour was seen. Cytostatic therapy with vincristine and cyclophosphamide was restarted, but the response was poor. The tumour continued to grow slowly. Palliative radiotherapy had only a limited effect and cisplatin and etoposide were ineffective. Metastasis to the brain was treated with radiotherapy in January, 1985. The patient died in April, almost 7 years after presentation.

As in Peart's case it is difficult to believe that stopping cytostatic therapy did not precipitate the relapse. This case, clinical experience, and the experience of Merlier and Le Brigand[1] that after resection of bronchial carcinoma relapses or new growth are common even after 10 years and that excess mortality due to cancer is significant up to 15 years indicate that cytostatic therapy in cases of complete and partial response or stable disease should be continued for as long as possible and be stopped only because of severe side-effects or when the maximum safe total dose of a drug (eg, doxorubicin) has been reached.

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