sterilize cells, and the contents of an ampoule after dilution with 20 ml. normal saline was injected subcutaneously beneath wide areas of skin of both flanks, without prior addition of adjuvant. Inoculations were repeated fortnightly in each patient for 2–4 successive treatments.

Effect of Inoculation of Heavily Irradiated Autologous Tumour Cells on Survival in Ten Patients with Malignant Melanoma

Case No., Sex, Age (Site of Primary)	Survival in Months (a) Pre-inoculation* (b) Post-inoculation
1 Male 39 Ear	(a) 36 (b) 2 (dead)
2 Male 42 Leg	(a) 30 (b) 24 (alive with metastases)
3 Male 58 Shoulder	(a) 17 (b) 11 (dead)
4 Male 32 Chest	(a) 9 (b) 6 (dead)
5 Male 30 Chest	(a) 7 (b) 5 (alive with metastases)
6 Male 53 Choroid	(a) 24 (b) 10 (alive with metastases)
7 Male 50 Arm	(a) 4 (b) 24 (alive with metastases)
8 Male 63 Abdomen	(a) 60 (b) 2 (dead)
9 Female 46 Leg	(a) 5 (b) 2 (dead)
10 Female 35 Chest	(a) 18 (b) 4 (dead

* From time of treatment of primary melanoma till inoculation.

The Table shows survival times for the 10 patients, both before and after inoculation, and the results obtained are summarized as follows:

(1) Inoculations caused no systemic reactions nor local complications from infection or growth of the injected tumour.

(2) Metastases present at time of inoculation did not disappear nor decrease significantly in size. Progress of the disease did not appear altered and further metastases developed, requiring irradiation and chemotherapy to be used to attempt palliative growth control.

(3) Six patients died within six months from the disease, and four were alive at 5–24 months after inoculation, but these four all had metastases and died within a few months after the results in the Table were compiled.

In a concurrent series, 12 patients with similarly recurrent advanced malignant melanoma (six with blood-borne metastases) received treatment by radical irradiation with 4 meV x-rays in high-pressure oxygen for inoperable and recurrent lymph-node metastases, no autoimmunization being given. Six patients died within six months from their disease, four died from metastases 12, 16, 20, and 20 months after irradiation, and two were alive 24 months after irradiation (one with a local recurrence developing at 20 months, the other apparently clear of disease).

It seems doubtful if the two procedures differed in their influence on the natural history of the disease in respect to spread of metastases and probably survival. If irradiation does in any way increase survival by augmentation of an autoimmune process, it would appear that this effect was facilitated as readily by local irradiation in vivo (a practice often regarded as undesirable because depression of immunity is said to result) as by autoimmunization with tumour cells irradiated in vitro. One wonders, therefore, if irradiation of malignant melanoma in vivo was used to treat any of the patients reported on by Dr. Lewis and his colleagues, and if so whether this also causes cytotoxic antibody to appear.

It is of some interest to record that in case 3 (Table) 10^6 unirradiated viable tumour cells were inoculated subcutaneously in this patient on two different occasions at times after autoimmunization when the disease was progressing, but no "take" of tumour resulted. Aliquots of the suspension from which these inocula were taken grew rapidly in tissue culture and formed typical "heaped up" pigmented clones on subsequent passage in vitro. The patient was inoculated on a third occasion with a further 10^7 cells harvested from non-confluent growths of these cells cultured in vitro, but again the inoculum failed to grow. However, relentless progress of the disease with appearance of further metastases was taking place at the times of challenge with living tumour. One might postulate that cytotoxic antibodies become more freely available to cells injected artificially into "virgin territory" than to those distributed spontaneously by blood and lymph, but this explanation seems somewhat unsatisfactory.

These results have been essentially negative in respect to therapeutic value, and the wide variation in natural history of this disease needs to be taken into account in planning trials designed to determine the therapeutic benefits from autoimmunization in malignant melanoma.—I am, etc.,

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Rat and Human Chromosome Studies after Promazine Medication

SIR,—A number of workers have focused attention on the induction of chromosomal aberrations in vivo[1 2] and in vitro[3–6] by a hallucinogen lysergic acid amide (L.S.D.). This effect has, however, been contested by some authors.[7 8] Yet they draw attention to the possibility of some psychotropic drugs in current use inducing chromosomal aberrations.

Two recent studies[9 10] have reported the absence of a noxious effect of phenothiazines on chromosomes.

My own investigations carried out on laevomepromazine have demonstrated complete lack of abnormalities in rat and human chromosomes. The action of laevomepromazine on the chromosomes of white rats from a non-inbred batch was tested. The animals were furnished by the Cantacuzino Institute, Bucharest. A first batch of 25 animals was acutely intoxicated with a 400–600 mg./kg. body weight. A second batch of 25 animals, which served as a chronic experiment, received 50 mg./kg. body weight by mouth for 30 days. A third batch, consisting of 20 rats, served in a 30 days' chronic experiment in which laevomepromazine was used in association with Librium (chlordiazepoxide). In each case 30 metaphases, obtained from bone marrow by standard methods, were examined. In none of the cases was any change observed, neither in the number nor in the structure of chromosomes. The same negative effect was obtained by cultures of the peripheral blood from 12 schizophrenic patients who had previously had one to four years' treatment with chlorpromazine or laevomepromazine.

The negative results obtained do not exclude the possibility of actions at the molecular level. To elucidate this, more thorough and systematic investigations need to be made.—I am, etc.,

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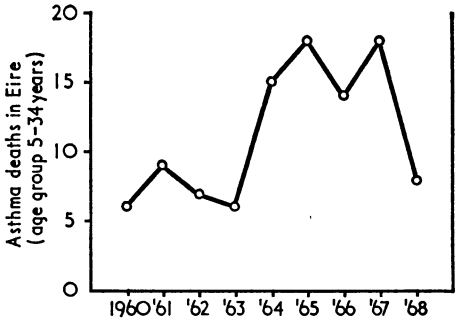
Asthma Deaths in Eire

SIR,—There has been increasing circumstantial evidence that bronchodilator aerosols used in excess have been a factor in the increase of asthma deaths in many countries.[1 2] Further evidence is presented in the graph which shows the number of asthma deaths in Eire during 1960–8 in the age group 5–34 years. This is accepted as being the most representative and suitable age group to demonstrate such an increase, which is also evident in all age groups above five years. Though the numbers are small, the increase, plateau, and decline are similar to that noted in England and Wales. The percentage increase has been smaller, 130% in Eire against about 250% in England and Wales.



1960–3=28 deaths; 1964–7=65 deaths. Increase=132%.

The important difference, however, is that the increase in the number of deaths occurred three years later in Eire. This corresponds to an approximate three-year delay in marketing bronchodilator aerosols in Eire. While they were available here in 1960, it was only in 1963 that they were prescribed in bulk. The indications are that the total sales were relatively less in Eire. In addition, sales fell in 1968 following the pamphlet issued by the Committee on Safety of Drugs in 1967, notices from drug firms, and a statement from

the National Drugs Advisory Board in Dublin in March, 1968. A full report is being prepared.

While the association of bulk sales of these aerosols to occasional asthma deaths appears established, the exact nature of causation is not known. There is a need for more basic research on the effect of isoprenaline in man. It may well be that certain asthmatics develop an idiosyncrasy to it rather than a dose-dependent effect on a hypoxic myocardium in severe airways obstruction. This thought has occurred because of the beneficial use of intravenous isoprenaline in some low output states not always with a healthy myocardium or fully oxygenated arterial blood, and because of the apparently innocuous or moderate airways-obstruction present in many asthmatics shortly before an unexpected death.—I am, etc.,

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Manipulation for Lumbar Disc Prolapse

SIR,—The patients of Britain will have reason to welcome Drs. J. A. Mathews and D. A. H. Yates's pioneer paper (20 September, p. 697), offering visible proof by contrast radiography of the reduction by manipulation of the disc protrusion in lumbago. The hitherto unconvinced medical man need doubt no longer.

Early this century, lumbago was regarded as a disorder of muscle,[1] hence the question of manipulation did not arise. This idea held sway for 41 years, when a body of clinical evidence was put forward[2] that the entity responsible was a displaced fragment of disc. This concept has now gained all but universal acceptance. But the next step in logic—to reconsider treatment—has lagged behind. Even today the standard attitude towards an attack of lumbago, reducible perhaps in one session of manipulation, is rest in bed, supplemented by heat (to the unaffected muscles), massage (ditto), and exercises (ditto), exactly as in the old days of "fibrositis." Such temporizing usually works in the end, of course, but why should physiotherapists' time be wasted on treating the tissue not at fault when a direct approach to the lesion is so feasible and so rewarding? Surely they should no longer be asked to employ their skill in measures that lost their theoretical justification 24 years ago. Otherwise our neglect forces patients with a simple disorder into the hands of lay manipulators. I have in my day trained one thousand physiotherapy students in spinal manipulation and other manual techniques. Let them be sought out and asked to give logically defensible treatment in this type of case.

Quite apart from the question of the relief of avoidable pain and disablement, if the medical profession as a whole now takes note of, and acts upon, this important research, the gain to industry and to the finances of the N.H.S. would be considerable.—I am, etc.,

London W.1. JAMES CYRIAX.

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Subnormal Hospitals

SIR,—Sir Hugh Rose (13 September, p. 652) appears to blame the Mental Health Act, 1959, and the resulting abolition of the Board of Control for the ills of our hospitals for the mentally ill and subnormal. The facts do not support this argument.

The origins of many of our present troubles can be traced to the period when the Board of Control was functioning. Hospitals were starved of money by mean vote-anxious local authorities, ultra-authoritarian administrative structures were established and maintained, staff selection was unsatisfactory, training inadequate, and a therapeutic milieu tolerated that was destructive of the patients' personality. The majority of hospitals were poorly maintained and inadequately supplied with furniture, equipment, and even food. By 1951 the total cost per patient per week in one hospital was still only £3 4s. and many others were similarly or more deprived.

The Mental Health Act, 1959, in fact, made easier the changes that were necessary to improve these neglected prison-like establishments masquerading as hospitals. The changes in admission procedure and the decrease in legal restriction made a freer atmosphere possible in which more emphasis could be placed on treatment than custodial care. Unfortunately, passing a law does not necessarily change people's attitudes, and the most important change that should take place in any backward hospital is a change in attitude of the staff. This can be achieved by better and more careful staff selection, ongoing educational programmes for all grades and types of staff, and the establishment of non-authoritarian therapeutic community-type regimens. The resurrection of the Board of Control would not help bring about these changes.

The proposed Hospital Advisory Service (*Supplement*, 5 July, p. 5) could play an important part in improving hospital care, provided its personnel were appropriately qualified, had persuasive personalities, and were allowed freedom of action. The effective development of such an advisory service, backed by a hospital commissioner with the twin functions of ombudsman and patients' guardian, more democratic hospital management, and a fairer share of available money, could rescue our psychiatric and subnormality hospitals, together with the geriatric and chronic sick services, from their present ditch of despair,—I am, etc.,

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SIR,—In your leading article (23 August, p. 426) you say that the sorrows which have befallen the mental hospitals all began in 1967 with the publication of *Sans Everything*. What *Sans Everything* did was to focus not only public attention but also official attention on a situation which should have been seen and attended to years before by those responsible for the management of these hospitals. It revealed a state of affairs that ought never to have been allowed to develop. The general attitude to these hospitals—apathy on the part of the public who could not visualize any personal need of them; disdain on the part of all other doctors who regarded anything "mental" as beneath their dignity; calculated indifference on the part of hospital management committees whose members served as part of a public service chore; neglect by regional hospital boards whose main concern was with general hospitals—all combined to make the present state of affairs nothing but a logical outcome. Add to that the suppression of disturbing indications of trouble on the grounds of being against the public interest by managements afraid to face the facts and there is the background for what is now coming into the open: the desperate reactions of people overburdened and underestimated.

The seeds of trouble were sown in 1948 and were soon to come into growth. The politicians, to their own satisfaction, had organized these hospitals so that lay managers overruled the former medical direction, with business-efficiency offices taking precedence over remedial departments. While offices and the paper-chase expanded, the caring and rehabilitation and training departments contracted. Clerical staff proliferated while nursing and occupational staff were kept below the official establishment level. Typewriters were more readily come by than teaching material for staff or patients. Despite these conditions much good work was done. The tragedy of it to me was that the public were denied the knowledge of the work being done, particularly in the mental deficiency hospitals.

I have always regarded mental deficiency as a field in which education and medicine collaborate. I know the author of the remark which is described in your leader as bitter cynicism. In its original form it was "Psychiatry is the Cinderella of medicine, but mental deficiency is its illegitimate child."—I am, etc.,

Poole, Dorset. DONALD MAGRATH.

Extra-articular Manifestations of Rheumatoid Arthritis

SIR,—I wish to draw attention to the rarely occurring meningitis that may complicate rheumatoid arthritis. After an admittedly not completely exhaustive search, I have been able to find only one reference in the literature.[1]

I have had the opportunity to study two cases which came to necropsy recently. Both were colliers, aged 60 years and 73 years respectively. Neither case had been recently investigated in hospital. The former, who also suffered from Caplan's syndrome, presented with what appeared to be generalized purulent meningitis. This showed no definite evidence of a microbial aetiology, and active collagen necrosis with a typical cellular reaction was present histologically. The second case presented with focal thickening of the right half of the tentorium cerebelli. Sections of this showed fibrous replacement of areas which strongly suggested that they had previously been the seat of collagen necrosis. The kidneys showed evidence of necrotizing papillitis.

These cases appear to represent each end of the pathological spectrum, the former the phase of activity, the other the repair phase.—I am, etc.,

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