Part Two

Confidential Filing

Re Cyclotron Trust

NATIONAL HEALTH

Part 1: Jan 1989

Part 2: June 1990

Referred to	Date	Referred to	Date	Referred to	Date	Referred to	Date
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LAWRENCE CRANBERG, PH.D.
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Nov. 7, 1990

Prof. Dr. med. Dr. Klaus-H. Hübener,
Director, Radiation Therapy,
21 Martinistrasse, University Hospital,
Hamburg-Eppendorf
D-2000 Hamburg 20, Germany

Dear Dr. Hübener,

It will be obvious from the copies of correspondence you have received from me since my visit on September 19, how deep an impression was made on me by that visit, and by the too-brief discussions with you and your staff. Please thank Dr. Schmidt for the reprints he sent me under his kind cover letter of October 1. They are particularly valuable, as you can judge from what you already know I am attempting to do. In a word, I hope greatly to strengthen and to diffuse neutron therapy, basically by emulating what you have been doing, but with increased neutron intensity and with other improvements indicated by your experiences both medical and technical.

I have been urging physicians, engineers and scientists in the U. S. and Britain to visit your laboratory and to see for themselves what I had the good fortune to see: an in-house neutron-treatment facility of very modest cost compared to the cyclotron alternative, which continues to be useful for cancer treatment after 15 years of use, and which yet has ample room for improvement despite the recent innovations which have markedly increased target life. The latter will be particularly interesting to those who have been skeptical about target lifetime, and to those hopeful and trusting individuals who have long had a stake in its improvement.

You will probably be particularly pleased to know how favorable a report on my visit I gave to Prof. Robert L. Goodman, Chairman of the Department of Radiation Oncology of the University Hospital of the University of Pennsylvania in Philadelphia. And Prof. Goodman, because his own efforts in a similar direction have been frustrated by supplier failures, may now be inspired to renew his efforts, based on a new and highly qualified supplier - Applied Materials Inc. The latter is a world-wide concern with 3100 employees and assets of half a billion dollars, with a major technical center in Horsham, West Sussex. Horsham's experience with Cockroft-Walton technology in ion implantation is highly pertinent to the needs of neutron therapy.

In keeping with prior practise, copies of this letter are being marked to what might be called "The C-W Neutron Therapy Network" - consisting of those individuals who are presumed to be interested in cooperating to establish reproducible neutron-treatment facilities based on Cockroft-Walton technology.

Sincerely yours,
Lawrence Cranberg
Lawrence Cranberg

cc: Carroll, Goodman, McClung, McInnes, Turnbull

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Nov. 7, 1990

Dr. Diana McInnes,
Private Secretary to the Chief Medical Officer,
Department of Health,
Richmond Terrace, 79 Whitehall St.,
London SW1A 2NS, U. K.

Dear Dr. McInnes,

In a letter of October 30, Mr.Andrew Turnbull, the Prinicpal Private Secretary to Prime Minister Thatcher, gave me your address and suggested that I communicate with you on the matter of neutron therapy. A previous letter from him indicated that materials on the subject I had sent to Prime Minister Thatcher have been relayed to you. I trust, therefore, that you have copies of my letter of September 24 to the editor of the British Medical Journal, and of my paper at Los Alamos on May 29, 1990. If you do not, I shall send them to you directly.

You doubtless now know that my basic purpose is to implement the conclusions of the 1973 Workshop on Clinical Criteria for a Fast Neutron Generator with respect to construction and installation of Cockroft-Walton (C-W) type neutron generators for therapy. Now that there is an emerging network of persons with the same goal, I propose that we concert our efforts, and proceed with all deliberate speed toward that goal.

One small but helpful way in which we can make up for lost time is to use modern communications. I am therefore supplying my 24-hour fax and telephone numbers at the top of this page, and by copy of this letter I am asking all present parties to the network to send me their fax and telephone numbers for distribution to all parties.

Another, more important way to recover lost time is to work toward concurrent procurements of reproducible installations. You already know from copies already sent to you that I first thought another Conference was necessary - particularly to provide a forum for discussion of choice between C-W machines and cyclotrons - but I now feel that the major cost differences between them means one can proceed with the former without compromising the latter. I propose therefore to advance to the stage of gaining agreement on specifications for what I hope will be concurrent procurements by British, German, and American users of C-W machines.

To start the discussion of specifications, I propose an accelerating potential of 350 kv, and a beam current of 50 ma of deuterium ions impinging on a rotating tritiated target, to produce between 5×10^{12} and 1.0×10^{13} neutrons per second over all solid angle. I leave it to our medical colleagues to suggest the Source to Skin Distance, the dose rate, and other medical parameters that are desired. I look forward to your early reply to the above.

Sincerely yours,
Lawrence Cranberg
Lawrence Cranberg

cc: Carroll, Goodman, Hubener, McClung, Turnbull

AT.

As discussed I enclose copies of the editorials in the British Journal of Hospital Medicine.

With Compliments

Richard Packard

Editorial

Neutron therapy defended

'At every crossways on the road that leads to the future, tradition has placed against each of us 10 000 men to guard the past'. *Maurice Maeterlinck*

Are radiotherapists less bright than most other doctors? They work at the crossroads of medicine and physics yet, while physics has been discovering the unimaginable inside subatomic particles and stretching its mind into the interstices of space, radiotherapy hasn't made a significant scientific advance since the introduction of the linear accelerator 40 years ago. Perhaps now we are again on the threshold of such an advance. Megavoltage photons then faced some of the fierce resistance that confronts particle therapy in the UK now.

In the early 1940s Stone used neutrons, a potentially rich new area of radiobiology, to treat patients with very advanced cancer. Sadly he unknowingly gave an excessive dose and radiotherapy put aside the possibilities for 30 years. However, in the early 1970s the MRC started clinical trials in patients with advanced malignancy at the Hammersmith Hospital using low energy neutrons. Encouraging results (Catterall and Bewley, 1979) led other centres to begin trials, though poorly penetrating beams from their very limited physics-laboratory-based cyclotrons had to stand comparison with the precisely collimated, deeply penetrating, skin-sparing photon beams from modern linear accelerators.

The Hammersmith results led the MRC to fund a superior hospital-based low energy cyclotron in Edinburgh. Unfortunately, the team failed to use the Hammersmith dose schedule, now accepted as optimal, and treated tumours at a depth unsuitable for the poorly penetrating, low energy beam. The result was poor tumour control and unacceptable late morbidity.

In the 1980s, hospital-based high energy cyclotrons producing beams comparable to the linear accelerator were developed and the MRC had the vision to install one at Clatterbridge Hospital. This joined the collaborative randomized prospective trials being sponsored in the main by the Radiation Therapy Oncology Group (RTOG) of the USA. To date more than 10 000 patients worldwide have been treated with neutrons.

The excellent results of treatment for inoperable malignant salivary gland tumours have been consistent, conclusive and as predicted by radiobiology. In a randomized prospective trial low energy neutrons achieved 67% locoregional control at 2 years versus 17% for photons ($P<0.005$) with no difference in complication rates (Griffin et al, 1988). Errington (1986) reported 86% complete regression of inoperable paranasal sinus tumours. Many of the tumours at these sites are adenocarcinomas which leads one to anticipate similarly good results with such carcinomas elsewhere.

It is difficult, therefore, not to be enthusiastic about the 10-year results of an RTOG randomized prospective trial in locally advanced prostatic adenocarcinoma (stage C and D_1) comparing a mixed beam of neutrons and photons with photons alone (Russell et al, 1989). At 10 years, in all major end points (local control, survival and disease-specific survival) the mixed-beam group did statistically better than the photon group, with survival rates of 42% vs 27% ($P=0.05$). Criticisms alleging inadequate patients and unbalanced arms in this trial are not tenable (Laramore, 1990).

Neutrons are believed more effective than photons in hypoxic conditions, e.g. in metastatic squamous carcinoma in lymph nodes of the neck. To date head and neck trials have shown no advantage for neutrons but advantage has been seen repeatedly in patients presenting with positive lymph nodes.

This therapy has a role in the treatment of other radioresistant tumours, particularly inoperable sarcomas. Supported by non-randomized data, several US centres use neutrons rather than photons in combination with chemotherapy and surgery for soft tissue, osteogenic and chondrosarcomas (Griffin, 1990).

Reported excessive tissue damage was in low energy neutron studies and due to beam limitations and inadequate knowledge of dose scheduling. 'Devastating' side effects were usually related to very large tumours previously treated aggressively with surgery and radiotherapy. Recent US studies have established safe dose levels in relation to site treated, size of volume irradiated and neutron energy (Cohen et al, 1989; Schultheiss et al, 1990). We must extend to neutrons the same intellectual tolerance that is shown to all new modalities. The early use of vincristine in childhood acute lymphoblastic leukaemia once filled wards with paralysed children but it is now given to outpatients who go out to play afterwards (Hamblin, 1990).

On *current* evidence radiotherapy can safely accept the potential of neutron therapy. If medical arguments, not political ones, guide its actions radiotherapy could see its second major advance in 40 years.

Thelma Bates
Director, South East London Radiotherapy Centre

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Editorial

Fast neutron therapy damned

Ever since fast neutrons were first used to treat patients with cancer in the late 1930s, neutron therapy has remained controversial. Several thousands of patients later there is no clear evidence that it is superior to conventional X-rays in cancer treatment. The overriding problem, which has been encountered by most investigators, has been unexpectedly severe late normal tissue morbidity.

High levels of normal tissue damage were largely responsible for the abandonment of the first investigation of fast neutrons in the USA in 1943 (Stone 1948). Since then protagonists have argued that much of the morbidity seen in this study was due to the fact that patients had been inadvertently overdosed because the biological mechanisms of interaction of neutrons with tissue were not understood at that time.

In the 1970s, a trial reported from the Hammersmith Hospital (Catterall et al, 1977) showed a highly statistically significant increase in local tumour control (75%) in patients treated with fast neutrons compared with those given X-ray therapy (19%). There were, however, shortcomings in the design of that study, particularly in the control of the irradiation technique and dosage in patients given X-ray therapy. Analysis of these patients shows that many were given what most clinicians would consider to be palliative doses of X-rays.

A recent review of these data carried out by an MRC Working Party (MRC Neutron Therapy Working Group, 1986) showed that when only those patients who were given radical doses of X-ray therapy were compared with those given neutron irradiation, the local tumour control rates were the same. This review also confirmed a statistically significant higher level of complications in patients given neutron therapy. Trials subsequently carried out by the MRC in Edinburgh failed to confirm the promise of neutron therapy suggested by the Hammersmith studies. Again, normal tissue morbidity was shown to be a serious problem. In particular, in a trial of patients with bladder cancer, the severity and number of complications observed in neutron-treated patients led to this trial being abandoned.

Concern about normal tissue morbidity has also been expressed in the USA. Patients treated at the Midwest Institute of Neutron Therapy and the MD Anderson Hospital, Houston (Cohen et al, 1989), showed an apparent increase in the number of complications with time following treatment and overall complication rates far in excess of those which would be considered acceptable with modern megavoltage X-ray therapy.

It has been suggested that neutrons may have particular advantages in the treatment of prostate cancer and salivary gland tumours. The evidence to support an advantage in prostate cancer is very scanty and is based on one flawed trial (Russell et al, 1989). Only 91 patients were included in this investigation which is far too small a number to allow any statistically valid conclusions to be drawn. Much is made in the reports on this trial of the improvement in local control and survival seen in patients given neutron therapy.

However, although a recurrence rate of 8 out of 36 patients treated with X-rays is significantly worse than that of 4 out of 55 patients treated with neutrons from a purely statistical point of view, it does not seem a particularly strong case for neutron therapy given the numbers of patients evaluated. Also, the remarkable difference seen between the crude survival (13% at 8 years) and the cause-specific survival (54% at 8 years) in patients receiving X-ray therapy implies that the majority were in poor general health and likely to do badly whichever way they were treated. In support of this is that patients given conventional radiotherapy in this trial did far worse than would be expected from other studies of radiotherapy in prostate cancer, such as that from the MD Anderson Hospital in Houston, and in the patterns of care study where 10-year survival rates of 47% and 38% respectively were obtained in patients with stage C prostate cancers. These figures are remarkably similar to those obtained in the neutron-treated patients (47%) in this trial.

Similar arguments exist in the case of salivary gland tumours where a well-conducted and structured randomized clinical trial has not been performed.

It has also been argued that many of the problems encountered in the past with neutron therapy have been due to only low energy beams being available for investigation. However, well-conducted studies are now being carried out at the Clatterbridge Hospital using high energy neutrons. There is sadly already a suggestion in these studies that morbidity rates in neutron-treated patients may be significantly greater than those in patients given conventional X-ray therapy.

Considering the thousands of patients who have received fast neutron therapy, the fact that there is no clear advantage from its use together with the consistent finding of excess normal tissue morbidity in virtually every investigation that has been conducted is a damning indictment of this form of treatment.

S J Arnott
Consultant Radiotherapist
St Bartholomew's Hospital, London

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DEPARTMENT OF HEALTH

Richmond House
79 Whitehall
London SW1A 2NS
Telephone 071 210 5155
From the Secretary of State for Health

Andrew Turnbull Esq
10 Downing Street

12 October 1990

Dear Andrew,

CYCLOTRON

As requested, I attach a briefing note for the Prime Minister for her meeting with Mr Moore on Monday. It brings her up-to-date with developments since her meeting with representatives of the Cyclotron Trust on 12 July.

As the Prime Minister will see, the results from the US trials of neutron therapy for prostate cancer are not yet available. A great deal of work has however been going on in this country to assess the practical and service implications of moving the cyclotron from Clatterbridge to St Thomas' Hospital, an option which my Secretary of State favours in principle. Before this can happen the Imperial Cancer Research Fund and the Medical Research Council, who jointly own the Clatterbridge machine, will need to be squared. The note therefore suggests that the Prime Minister might encourage Mr Moore and his officers to pursue this option directly with the Department.

I have not had an opportunity to show my Secretary of State this note but will do so over the weekend. If he has any additional comments, I shall pass these on to you on Monday.

Yours

STEPHEN ALCOCK
Principal Private Secretary

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BRIEF FOR THE PRIME MINISTER

PROTON AND NEUTRON THERAPY - CYCLOTRON TRUST

1. At the meeting with Sir Nicholas Bonsor on 12 July, the Prime Minister indicated that a decision on funding should not be considered in advance of preliminary results from the US trials of neutron therapy for prostate cancer. Entry of patients to the trials is due to close this month and the provisional results are likely to be available early next year. No other new evidence on neutron therapy is available and the Department of Health's view of its limited application remains unchanged. There have, however, been some developments in this country which affect the view of proton therapy.

Developments in the UK

2. There has been a change of mind among some British ophthalmologists within the last two or three months and proton beam radiotherapy for certain types of uveal melanoma (an eye cancer) is now considered to be an accepted treatment by an increasing number of them. As a result:

i. the research bodies have decided, subject to formal confirmation, that it is no longer ethical to pursue the proposed randomised controlled trial of proton therapy versus removing the affected eye which was to have taken place at Clatterbridge; ie because the proton treatment is accepted as better.

ii. there is now a case for providing proton and neutron treatment, with a cyclotron potentially occupied for 11 sessions a week, for NHS patients with some types of uveal melanoma (up to 250 patients a year) and with salivary gland tumours (up to 75 patients a year);

iii. there will be some additional spare capacity (previously intended for the uveal melanoma trial) at the Clatterbridge cyclotron, which is already under-used. Moreover, it is now almost certain that the UK element of the neutron therapy trial for cancer of the head and neck will shortly close due to lack of recruitment. Substantial excess capacity will therefore be available to provide the service mentioned in ii. above and the Department of Health is exploring ways in which this might be provided, at least on a temporary basis, within the next 18 months.

3. Since it has become clear to the research bodies and the staff at Clatterbridge that the remaining research work there is likely to be insufficient to warrant keeping this facility running for that purpose alone, a number of proposals have been put forward for using it to provide a treatment service:

i. The Imperial Cancer Research Fund (ICRF) and the Medical Research Council who jointly own the Clatterbridge machine (the money to buy it was provided by a charity in the North West and it is vested in the research bodies) are now said to favour retaining it at Clatterbridge and have set up a working group with the health authority to consider its future funding. The ICRF may be interested in supporting the unit and generating income by providing a service for NHS patients.

ii. An American company is also said to be interested in running the Clatterbridge facility and selling a service to the NHS at what appears to be a very reasonable price.

iii. The United Kingdom Atomic Energy Authority has recently estimated that, for between £3m and £5m, the Clatterbridge facility could be upgraded to provide high-energy protons. This could provide an additional facility (with a much lower risk of side-effects than neutron therapy) for treating certain rare tumours in the skull and close to the spinal cord.

Location of the Cyclotron

4. As explained in paragraph 2(a)(ii), it is expected that up to 11 sessions a week will be potentially required for the NHS patients for whom treatment now appears to be indicated. In addition, the research bodies are likely to continue to want to use a very small amount of the capacity. This could all be accommodated on one machine, although if the NHS demand approached its possible capacity the scope for private treatment would be limited. The key question is, therefore, whether the research facility and service is best provided from Clatterbridge or whether the cyclotron could be moved to a site at St Thomas' Hospital.

5. Mr Moore saw the Secretary of State on 27 September and made it clear that the Cyclotron Trust was pressing the case for moving the ICRF/MRC cyclotron from Clatterbridge to St Thomas's in 1994, when, if building goes ahead, New Riddell House should be ready to receive it. If this could be arranged, it would provide a facility in London, which is more readily accessible to the majority of the population. It would (if the ICRF/MRC could be persuaded to make little or no charge) also be a cheaper capital option than the Trust's original proposal of a completely new facility. Revenue costs (because of higher salaries and accommodation costs in London) would, however, be higher than if the cyclotron remained in Clatterbridge and an NHS service was provided from there; and there would, of course, still be capital costs of providing the building in London. Because New Riddell House would not be available until 1994, it would be necessary to start a service at Clatterbridge in the near future and move it once the building was ready.

6. The Secretary of State favours the idea of moving the Clatterbridge machine but there is now an increasing number of complicating factors. In particular, a move is subject to:

i. ICRF/MRC being willing to release the machine (at little or no charge) to the Trust or the NHS and there is some indication that the ICRF is likely to oppose the idea of releasing it.

ii. The South East Thames Regional Health Authority agreeing to the erection of New Riddell House, the building in which the Cyclotron Trust's machine would be housed at St Thomas' Hospital. Their decision will be informed by an intensive appraisal, not yet complete, to establish whether a **new** building is necessary in order to provide the other services which were to have been located there or whether they might be provided in redesigned **existing** accommodation on the hospital site. If the main part of the building did not go ahead it would obviously call into question the provision of the basement in which the cyclotron was to be sited. The decision is due on 15 November.

iii. A financial appraisal which is still underway. This includes obtaining a definite cost of moving the cyclotron (which has had to be commissioned externally and will not be available for another two weeks) and further work on relative revenue costs of a service run at Clatterbridge and one run at St Thomas's.

Department of Health officials are endeavouring to obtain information as quickly as possible about the intentions of the various parties involved and the possible costs of different options.

Line to take

7. The Prime Minister may wish to indicate to Mr Moore that she is generally in sympathy with the idea of moving the Clatterbridge cyclotron to London but that there are a number of matters to be settled before it will be clear that this is possible, or it is the most economic solution. She may wish to suggest that the Trust's officers enter into detailed discussions with Department of Health and health authority officials to work out more detailed proposals and try to resolve some of the uncertainties.

Note by Cyclotron Trust

PRINCIPAL CONSIDERATIONS IN THE PROPOSAL TO MOVE THE CYCLOTRON TO LONDON

The cyclotron at Clatterbridge is a valuable national asset which is under used. Moving it to London will:

1. Place the cyclotron where it is accessible to at least a nine times larger referred population.
Referral to radiotherapy in Merseyside is 17%, in SE Thames is 38%. Applying these numbers to the OPCS 1985 figures:

11,249 registrations in Merseyside	∴ referred	17% =	1,912
49,047 registrations in Thames	∴ referred	≈38% =	18,657
14,922 registrations in SE Thames	∴ referred	38% =	5,670

2. Demonstrate support for the treatment.
The current medical climate in Britain (which is not of Clatterbridge's making) is such that:

- 4 of 5 patients referred there for neutron therapy refuse informed consent even though this is the preferred treatment. 12% of the machine capacity is used and only 12.5% of patients whom the CMO (Notes of meeting: 29 May 90) believes could benefit are treated.
- 50 patients per annum are currently referred for proton treatment. This is 5% of capacity and 25% of those identified in the CMO's conclusions.

3. Enable many more patients to live at home during treatment - neutron patients must attend 3 times a week over four weeks which can mean staying in a hostel for a month.
For most people London is more easily reached for the day than Clatterbridge.

4. Yield greater patient numbers which will enable relevant reasearch to progress quickly.

5. Produce much needed academic support for the treatment.
Though it is the centre of an MRC trial the Clatterbridge cyclotron is academically isolated. In London it would be co-located with the United Medical and Dental School of Guy's and St Thomas'. It would be supported by the laboratories of the Dimbleby Department of Cancer Research also on site.
High quality imaging immediately available in London with PET (Positron Emission Tomography) and NMR will enable unique research into particle therapy to be undertaken in the UK. PET will be on site at St Thomas'.

6. Defuse the present funding-inspired acrimony.
Giving £3 million to other cancer treatment would be seen by 'rival' cancer charities as equitable.
The principal benefactor of the Clatterbridge cyclotron, Mr J K Douglas, supports the plan to relocate the machine so that it will be fully utilised.
Because further funds for cyclotron will be generated from private patients, the Trust will be taken out of competition for future charitable cancer funds. This will also relieve some of the motive for adverse publicity.

7. Reduce costs to the NHS, to the MRC and to the Exchequer.
With the machine in London, private patients can be attracted relieving the NHS of a significant proportion of the running costs (See Annex A). The net cost to the exchequer over ten years is forecast at £¾ million.
The comparison of costs between the current plan and the move option are set out in Annex A. These costs are based upon the Treasury case prepared in May 1988 and developed by Coopers & Lybrand. Figures in brackets are **revenue.**
It is possible to supplement income to the cyclotron by the generation of isotopes. This has been excluded from the forecasts since machine standing costs include specialist treatment equipment and staff which should be fully utilised for patients.

Annex A

TABLE 1 FINANCIAL COMPARISON OF OPTIONS

£ millions	New London Cyclotron			Move Clatterbridge Cyclotron		
		Govt	NHS		Govt	NHS
Building costs	3.06			3.06		
Machine purchase	7.70			0.99		
Running costs to year 2000	4.77		3.18	4.77		3.18
MRC running costs (4 years) Clatterbridge	2.00	2.00		1.00	1.00	
Grant		6.00			3.00	
Ten year capital & running costs	**17.54**	**8.00**	**3.18**	**9.83**	**4.00**	**3.18**

Notes:
1 Assumes 5% pa inflation
2 Assumes NHS is responsible for 66.67% of the running costs in London
3 Assumes MRC running costs cease on the move of the Clatterbridge machine
4 Uses recently estimated costs for relocating the Clatterbridge cyclotron which are detailed at Annex B.

TABLE 2 EXCHEQUER COSTS WHEN PRIVATE PATIENT INCOME GENERATED

£ millions	New London Cyclotron		Move Clatterbridge Cyclotron	
		Exchequer		Exchequer
Ten year cost to exchequer		11.18		7.18
Revenue from private patients	(9.66)	(6.44)	(9.66)	(6.44)
Net cost/(revenue) in ten years	**7.88**	**4.74**	**0.17**	**0.74**

Notes: 1 Assumes revenue to NHS is 66.67% of income.

Annex B

TABLE 3 ESTIMATED REMOVAL COSTS FROM CLATTERBRIDGE TO LONDON

a.	Disassembly and removal at Clatterbridge	£100,000
b.	Installation of equipment, including running in and acceptance testing but excluding rigging i.e. costs for moving parts from truck into final position in the building	630,000
c.	Transport from Clatterbridge to St Thomas'	25,000
d.	Transport and installation insurance	7,500
e.	Rigging, moving of equipment from trucks into final position	23,000
		785,500
f.	Spares (may be available from Clatterbridge)	54,000
g.	Annual service contract (per year)	81,000
h.	Training	26,000
		946,500
i.	Contingencies (≃ 5%)	43,500
		£990,000

cc FERGUSON

A: CYCLOTRON

10 DOWNING STREET SUBJECT & MASTER

LONDON SW1A 2AA

From the Principal Private Secretary

13 July 1990

CYCLOTRON

The Prime Minister saw Sir Nicholas Bonsor yesterday about the Cyclotron. Your Secretary of State was also present but Mr. Moore did not attend. The Prime Minister began by inviting your Secretary of State to set out his position.

He said that as a non-expert, he had to act on the professional advice available to him. This was firmly that there was not a medical consensus on the value of neutron therapy and there was a clear consensus against expanding capacity in this country by building a second cyclotron before the trials now under way showed clearer benefits from this form of treatment. The Government would be subject to criticism if it committed several £ million to creating a facility which was subsequently under-used. In particular, it would be wrong to start work on the accommodation for the cyclotron at St. Thomas's merely in the hope that current trials would prove to be successful.

The Prime Minister said she deplored the criticism of neutron therapy, much of which was based on ignorance, prejudice and rivalry from other cancer charities. She herself believed that medical opinion in this country would be shown to have been wrong. Nevertheless, she recognised that it was difficult to prevail publicly with the arguments for a second cyclotron while referrals to the first (about 60 a year) were still below capacity (about 300 a year). It was necessary to persuade more doctors to refer their patients for this form of treatment. She asked Sir Nicholas why referrals at Clatterbridge were so low.

Sir Nicholas gave several reasons. First, there was the location. This was not simply a matter of difficult access but also the fact that Clatterbridge was separated from a research base. Secondly, there was the prejudicial reporting the Prime Minister had referred to. Thirdly, it was difficult to find patients for trials as one had to find two patients whose conditions were equally advanced. He was convinced that neutron therapy was beneficial and that this had been confirmed by experience in the United States. There were 28 cyclotrons around the world and more were being developed. It would be a tragedy if a form of treatment originally developed in this country

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lapsed, as would be the case if the second cyclotron were not built. The small team of experts in this field would then disperse.

Sir Nicholas said the Trust believed there were enough cases in this country to justify a second cyclotron but if agreement to the latter could not be achieved it would be better, at least, to ensure that the present cyclotron was fully utilised where it would have better access to patients and better support facilities. He was confident that referrals would be higher. The accommodation could be built, as currently proposed, at St. Thomas's, and the existing machine then moved to London. This might cost around £6½ million, against £11-12 million for installing a second cyclotron. The Trust would be prepared to contribute half towards this smaller figure. If moving the existing cyclotron meant that there was a period in which neutron therapy would be unavailable in this country, the Trust would be prepared to finance treatment abroad in the interim. Your Secretary of State resisted this proposal as even this would require a commitment of £3-4 million before the scientific evidence justified it. He pointed out that a decision could not be delayed indefinitely as the St. Thomas's redevelopment was part of a wider plan which involved a contract to release a site to developers by 1995.

There followed an extended exchange between your Secretary of State and Sir Nicholas on the various scientific sources and on the conclusions which could be drawn about the likely number of cases from the CMO's report. Despite a mutual quoting of experts, no agreement was reached.

Summing up the discussion, the Prime Minister said it was not possible to authorise release of the money while scientific opinion was so divided. The matter should be looked at again in October when the preliminary results of the neutron beam trial on prostate cancer became available. Sir Nicholas said that the Trust would be investigating the technical implications for and the costs of moving the existing cyclotron to London. It was agreed that the Prime Minister should not write to the Trust to record the position reached, as the last letter had clearly found its way into the public domain.

ANDREW TURNBULL

Andy McKeon, Esq.,
Department of Health.

CYCLOTRON TREATMENT

The case for a second cyclotron in the UK was made on the basis of the figures in the first column. More recent information - particularly data from the USA on prostate - has caused the Trust to revise its forecast of eligible patients (second column). The CMO, adopting the most cautious figures, has agreed to those in the final column (reflected in his report which accompanied the PM's letter and the draft notes of the meeting on 29 May).

	Original Case	**Revised Case**	**CMO**
Salivary gland	330	200	150
Uveal melanoma	200	300	200
Para nasal sinus	494	200	50
Soft tissue sarcomas	200)		
Bone sarcomas	)	360	200
Prostate	2000	3860	-
	3224	4920	600
Capacity of one machine	400	400	280

This does not include any figures for:

Palliative use
Research

USA	-	University of Washington, Seattle	1972
	-	University of California, Los Angeles	
	-	Fermi Lab (GLANTA)	1973
	-	M D Anderson (Houston)	1980
	-	Cleveland Clinic (Physics m/c no patients for 2/3 years)	
	-	Harvard (proton only)	
	-	Detroit (new, superconducting)	1991
	-	Berkeley, California (Hydrogen ions)	
	-	California Loma Linda (High proton)	1991
BELGIUM	-	Louvain la Neuve	1980
	-	Bruges	
CANADA	-	Vancouver: Pi-mesons (particles)	
GERMANY	-	Hamburg	1975
	-	Heidelberg	1977
	-	Essen	1975
	-	Munster	1983
	-	East Berlin (Buch)	
JAPAN	-	Chiba University	1980
	-	Tokyo	1980
FRANCE	-	Orleans	1982
	-	Nice	1990
SWITZERLAND	-	Geneva (Paul Sheera Inst) (proton only)	
SOUTH AFRICA	-	Cape Town (Grootschur Hospital)	1989
	-	Johannesburg	1988
SOUTH KOREA	-	Seoul	1988
UK	-	Clatterbridge	
USSR	-		
POLAND	-	Krakow	
INDIA	-	Calcutta (being converted for treatment)	1990

PATIENT NUMBERS

It is very difficult to say how many patients have been treated with Neutrons worldwide.

Griffin estimates in excess of 10,000

Since numbers are not available from several centres and since the literature records patients in trials rather than on routine treatment,

best estimates are nearer 14,000

Defunct

USA	-	George Washington (Manta) (ceased 1978)	1975
	-	Fox Chase, Philadelphia (ceased 1987 unreliable machine)	
HOLLAND	-	Amsterdam	
UK	-	Hammersmith (ceased 1984)	1970
	-	Edinburgh (ceased 1982)	1977

NOTE FOR SIR NICHOLAS BONSOR FOR MEETING WITH THE PRIME MINISTER ON 12th JULY 1990.

Option: Move the Clatterbridge cyclotron to St Thomas'

1. The overall likely costs of this option are in the order of £6.5 million, if we assume no payment is made to the current owners of the Clatterbridge machine. This is at least £4 million less than the current planned cost.

2. If the grant needs to be reduced, notionally to "pay" the NHS/MRC for the machine, there will be a finance gap between grant and cost. This must be such that it can be financed from traditional sources of capital. This scheme is not judged capable of attracting charitable funds.

3. This option is likely to be acceptable to the medical side of the DH. It offers cyclotron treatment a reasonable future in the UK whilst it is numerically supported by the meanest reading of the CMO's report and it does not appear to be expensive.

4. Politically it is sustainable with both the PM and the DH being successful. The "White paper thinking" should be attractive to Kenneth Clarke.

5. This cyclotron is owned by the MRC. It costs them some £0.5 million a year in running costs but is written off as a capital asset. This option would relieve the MRC of about £2 million of running costs. The proton (eye) trial which is funded by the ICRF, who also paid for the proton beam and associated equipment, obliges the MRC to keep the unit running for a further four years. Some 50 patients a year are currently treated. This trial would be interrupted by moving the cyclotron, though the effect could be minimised by the Trust offering to finance patients attending an overseas proton facility during the period of shutdown.

6. The Clatterbridge cyclotron is both geographically and academically isolated, which is accepted by the CMO in the revised notes of the May 29th meeting. The neutron trial is suffering from the adverse publicity (4 of 5 patients now being recruited refuse neutron treatment).

7. Under this option it would be possible to retain radiotherapists with particle treatment interest/experience in the UK. Delay will certainly mean that Sealy returns to South Africa, Bates retires before the project starts and Errington goes to the US.

DJG
11 July 1990

THE CYCLOTRON TRUST FOR CANCER TREATMENT
at The Department of Radiotherapy and Oncology,
St. Thomas' Hospital, Lambeth Palace Road, London SE1 7EH
Telephone: 071-922 8031 Fax: 071-928 9968

DJG/FK/355

Andrew Turnbull Esq
Principal Private Secretary
Prime Minister's Office
10 Downing Street
London SW1W OAA

10th July, 1990

Dear Mr Turnbull

I fear yet more paper from the Cyclotron Trust. I don't think you need to read it in detail but I felt you should see the latest "version" of the notes of our meeting with the CMO on the 29th May. These have been produced by the Department and reflect the adoption of our draft notes almost in their entirety. I append a single sheet of our proposed revisions to the latest draft which points up the relatively small area of disagreement now existing between us.

Please do not hesitate to contact me if you would like any more information in preparation for Thursday's meeting.

Yours aye

Don Grocott

D J Grocott
Director

encs

SENT BY FAX: 10/7/90. (10.45 a.m.)

THE CYCLOTRON TRUST FOR CANCER TREATMENT

at The Department of Radiotherapy and Oncology,
St. Thomas' Hospital, Lambeth Palace Road, London SE1 7EH
Telephone: 071-922 8031 Fax: 071-928 9968

DJG/FK/357

Dr Diana McInnes
Private Secretary to the
Chief Medical Officer
Department of Health
Richmond House
79 Whitehall
London SW1A 2NS

9th July, 1990

Dear Dr McInnes

Thank you for your fax of the 5th July enclosing a revised version of the note of the meeting held between the Trust and the Department on the 29th May.

As I indicated to you on the telephone, there are some minor changes and limited redrafting intended to clarify. I have noted these on the enclosed and look forward to your comments in due course.

Yours aye

Dan Grocott

D J Grocott
Director

enc

Comments on the Department of Health's revised draft note of the meeting held on 29 May 1990. This revision was covered by a letter dated 5 July 1990

Para 3.5.3 The trials referred to in this paragraph as "mentioned in paragraph 3.5.2" might be thought to be the "large randomised controlled trials...comparing neutrons and photons...comparing surgical removal...photon therapy" etc. The agreement between Professor Laramore and Dr Porter relative to routine clinical practice concerned the prostate trial referred to in Griffin's letter dated 22 May 1990 and tabled at the meeting. We suggest, therefore, that this paragraph should read:-

> "Professor Laramore and Dr Porter agreed that neutron therapy remains a research procedure in the management of locally advanced prostate cancer. Its role in routine clinical practice of such a common cancer could await the results of the trials which include neutrons."

Para 3.6 In line 5 we propose the removal of the words "of the trunk".

Para 4.1 The Trust accepts that "assuming that half the estimated number of eligible patients in the UK with inoperable salivary gland and paranasal sinus tumours are referred for neutron therapy" Clatterbridge could cope. However, the Trust does not accept this as a valid assumption, nor do we recollect such an assumption being made. We propose, therefore, that this sentence is rewritten as follows:-

> "If all the eligible patients in the UK, accepted in the CMO's document, with inoperable salivary gland, paranasal sinus tumours or uveal melanoma were referred for neutron/proton therapy, the Clatterbridge cyclotron could not cope."

We suggest that the next sentence should be expanded as follows:-

> "The estimate in the CMO's paper did not include any patients with soft tissue sarcoma or prostate cancer, nor did it allow for any capacity for research."

Para 5. The Trust does not feel that the current wording achieves the sense of the agreement and proposes the following:-

> "There is a narrow therapeutic 'window' when treating with high energy, as well as when treating with low energy, neutrons between benefit to the patient and harm. This has been identified in clinical trials (eg inoperable salivary gland tumours and some inoperable paranasal sinus tumours) and by clinical observation where trials are not possible (eg soft tissue sarcomas). Even with low energy neutrons in some sites better local control has been obtained without an unacceptable rate of serious toxic effects compared with photon therapy. Until the present trials using high energy neutrons are completed one cannot say for certain that a dose of these neutrons would produce better local control than photons. However, low energy neutron experience and levels of toxicity found to date with high energy neutrons indicate that this may well be so. Further work to identify the therapeutic window for other tumours (eg lymph nodes in the neck) needs to be done."

9 July 1990

Richmond House
79 Whitehall
London SW1A 2NS
Telephone 071 210 5150
From the Chief Medical Officer
Sir Donald Acheson
KBE DM MD DSc LLD FRCP FRCS FFPHM FFOM

Mr D Grocott
The Cyclotron Trust
Department of Radiotherapy and Oncology
St Thomas's Hospital
Lambeth Palace Road
London SE1 7EH

5 July 1990

Dear Mr Grocott

Further to your letter of 5 June I am pleased to enclose a revised version of the Note of the Meeting held between the Trust and the Department on 29 May. I am very sorry for the delay in our returning it to you, but this was unfortunately due to absence out of the Country of certain key people who had attended the meeting. I do hope that agreement can now be reached on this version.

Yours sincerely

Dr D McInnes
Private Secretary to The Chief Medical Officer

NOTE OF A MEETING BETWEEN THE CYCLOTRON TRUST AND THE DEPARTMENT OF HEALTH TO DISCUSS THE CHIEF MEDICAL OFFICER'S DOCUMENT ENTITLED "THE PRESENT STATUS OF NEUTRON AND PROTON THERAPY" - 29 MAY 1990 AT RICHMOND HOUSE

Present:

Sir Donald Acheson	-	Chief Medical Officer Department of Health
Dr M Abrams	-	Deputy Chief Medical Officer Department of Health
Dr T Bates	-	Consultant Radiotherapist St Thomas' Hospital, London (Cyclotron Trust)
Dr P Bourdillon	-	Senior Medical Officer Department of Health
Mr D Grocott	-	Cyclotron Trust
Mr J Hungerford	-	Consultant Ophthalmologist St Bartholomew's Hospital
Mr S Heppell	-	Deputy Secretary Department of Health
Professor C Joslin	-	Professor of Radiotherapy Leeds
Professor G Laramore	-	Professor of Radiotherapy and Oncology, Seattle
Mr R Packard	-	Consultant Ophthalmologist Windsor (Cyclotron Trust)
Dr A Porter	-	Radiotherapist - Ontario
Mr A Turnbull	-	Prime Minister's Office

Introduction

1. Sir Donald Acheson explained that the meeting had been arranged to enable the Cyclotron Trust to comment on his document "The Present Status of Neutron and Proton Therapy". In discussion, the following topics were addressed: proton therapy and uveal melanoma, neutron therapy and, in particular, prostate cancer, the workload at Clatterbridge and the toxicity of neutron therapy.

Uveal Melanoma

2.1 Mr Hungerford agreed with Mr Packard's assertion that:

i. There was approximately 95% local control of uveal melanoma with proton beam therapy,

ii. 65% of eyes retained 6/60 vision or better and 35% retained 6/12 or better,

iii. Enucleation studies showed at 5 years that actuarially adjusted mortality from uveal melanoma was 50% for large melanomas and 30% for medium sized melanomas. Actuarially adjusted 5 year survival data are not available stratified for size of tumour following charged particle radiotherapy. Figures have been published for a mixed group comprising of small tumours, medium sized and large tumours. For this series metastasis free survival was 20%.

2.2 Whilst Mr Packard and Mr Hungerford agreed that as yet no randomised controlled trial comparing mortality after enucleation and conservative therapy had been completed,there was no evidence to

suggest that particle therapy was any worse. Mr Packard pointed out that 60% of uveal melanomas were posterior to the equator of the globe and some authorities thought there might be less ocular side effects with particle therapy than plaque therapy. Mr Packard suggested that of 450 uveal melanomas per year 300 could benefit from conservative therapy. The others being those patients with very small tumours exhibiting minor or no growth and patients with very large tumours or having painful blind eye.

2.3 Mr Packard expressed concern that patients' informed consent may pose a problem in the adequate recruitment to the trials for large tumours proposed in CMO's report.

Neutrons

3.1 The value of neutron therapy in inoperable advanced salivary gland tumours was confirmed. Dr Bates pointed out that these included a high proportion of adenocarcinomas and that this might well have significance for adenocarcinomas elsewhere in the body.

3.2 Professor Laramore supported an observation of Professor Wambersie's (Brussels) reported by the CMO that the common histological type of paranasal sinus tumour - the squamous cell carcinoma - responds poorly to neutrons and it is only the rarer types that respond. These rarer types are adenocarcinoma and adenocystic carcinoma, which together have an incidence of 50 cases per annum.

3.3 The value of neutron therapy in advanced head and neck cancer remains uncertain and must await the results of the current American and MRC collaborative trial. Professor Joslin said that further randomised controlled trials would be necessary to confirm the apparent value of neutron therapy in treating inoperable lymph nodes. Dr Bates agreed with this.

3.4 Neutron therapy has not yet been shown to be of value in cancer of the cervix, of the bladder or of the rectum. Dr Bates suggested it may be of value palliatively.

3.5.1 Professor Laramore presented 10 year follow up data of the randomised controlled study comparing mixed beam therapy (neutron and photon) and photon therapy for locally advanced prostate cancer. This showed evidence which was statistically significant in favour of the mixed beam arm having better survival at 10 years. The CMO expressed reservations about using this study alone as a basis for recommending neutron therapy for locally advanced prostate cancer. The CMO's report had stated that the two arms of the mixed beam trial were not balanced. Professor Laramore refuted this and described the raw data and its statistical significance as reported by the RTOG statisticians in confirmation of the opinion expressed by Professor Griffin in his letter of 22 May 1990 tabled at the meeting. Dr Bourdillon queried the consistency of the data in the various publications of the trial, in particular the number of patients with stage D1. Professor Laramore suggested this inconsistency was the result of a typographical error. Some present felt that the outcome of the NCI trial comparing neutrons alone and photons, for which preliminary results would be available in October 1990 and after which no more patients would be entered into the trial, should be awaited before recommending this form of therapy as being superior to photons.

3.5.2 Dr Porter said that neutron therapy was one of the exciting developments meriting study in the management of locally advanced prostate cancer. Others, he cited, were brachytherapy (the

implantation of radioactive sources into the prostate), surgical removal of as much tumour as possible followed by photon therapy, and hormonal treatment with or without photon therapy. Professor Laramore drew the meeting's attention to the high costs of the surgery associated with brachytherapy. Large randomised controlled trials are underway in the United States comparing neutrons and photons, comparing surgical removal of as much tumour as possible followed by photon therapy and photon therapy alone, comparing hormone and photon therapy and photon therapy alone, and comparing short-term and long-term hormone therapy.

3.5.3 Professor Laramore and Dr Porter agreed that neutron therapy remains a research procedure in the management of locally advanced prostate cancer. Its role in routine clinical practice of such a common cancer could await the results of the trials mentioned in paragraph 3.5.2 as well as the results of the neutron therapy trial.

3.6 Professor Laramore said that neutron therapy is used routinely in his and some other centres in the USA in the treatment of soft-tissue sarcomas with or without additional surgery or chemotherapy. Professor Joslin agreed with Dr Bates that neutron therapy may be suitable for some patients with soft-tissue sarcoma of the trunk. It was pointed out that due to the bulk of some of these sarcomas, a large tissue defect may be produced when they are successfully treated. Dr Bates said that in relation to the side-effects of any treatment where no other existed, neutron therapy should be accorded the same intellectual tolerance as other modalities, such as chemotherapy and radical surgery. Dr Bates cited the example of the development of aggressive cytotoxic chemotherapy which led to the improvements in cure of childhood leukaemia which had been included in the reference given in the CMO's paper (Hamblin TJ. Interleukin 2. British Medical Journal 1990; 300: 275-276).

Workload at Clatterbridge

4.1 It was agreed that Clatterbridge could cope with the neutron and proton therapy workload given in the CMO's document, assuming that half the estimated number of eligible patients in the UK with inoperable salivary gland and paranasal sinus tumours are referred for neutron therapy. The estimate in the CMO's paper did not include any patients with soft-tissue sarcoma or prostate cancer. Mr Packard reminded the meeting that the final results of the RTOG prostate trial would be available when the St Thomas' cyclotron would be ready to start treating patients.

4.2 Clatterbridge cyclotron is currently underutilised with an average of approximately 60 patients having been treated with neutrons there per annum over the last 4 years. Regional referral patterns, the continued adverse publicity and personality problems were cited as explanations for this. It was agreed that it was a shame that the Cyclotron had not been placed at a centre where the proportion of patients with cancer referred for radiotherapy was higher.

Toxicity of Neutron Therapy

5. There is a narrow "window" when treating with high-energy, as well as when treating with low-energy, neutrons between benefit to the patient and harm. There remains no evidence as to whether a dose of high-energy neutrons, which can achieve a better local control of tumours than photon therapy, other than in inoperable salivary gland tumours and in some inoperable paranasal sinus tumours, can be obtained without an unacceptable rate of serious toxic effects.

Tabled Papers

6. The Cyclotron Trust tabled papers prepared by the Trust itself and by Professor Laramore and also tabled a letter from Professor T Griffin (Seattle). CMO said that these would be looked at in detail by the Department of Health and the conclusions reflected in the advice promulgated.

Rf:Neutron.g3


10.07.
7110

Please put in the future afternoon reading

THE CYCLOTRON TRUST FOR CANCER TREATMENT

at The Department of Radiotherapy and Oncology,
St. Thomas' Hospital, Lambeth Palace Road, London SE1 7EH
Telephone: 071-922 8031 Fax: 071-928 9968

Andrew Turnbull Esq
Principal Private Secretary
Prime Minister's Office
10 Downing Street
London SW1W OAA

6th July, 1990

Dear Mr Turnbull,

At the request of Mr Richard Packard I enclose herewith a copy of Professor George Laramore's letter which he is proposing to send to the BMJ on Monday next and which he has authorised us to circulate to interested parties.

Yours sincerely,

F. Kacher

pp. D J Grocott
Director

enc.

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Rf:Neutron.g3


10.07.

010

Please put in No 10 for Mrs Thatcher's reading PLS

THE CYCLOTRON TRUST FOR CANCER TREATMENT

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F. Kacher

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enc.

SIR:

In a recent issue of this journal MacDougall and Arnott[1] made numerous erroneous and misleading statements regarding a Radiation Therapy Oncology Group (RTOG) study for locally-advanced prostate cancer. Their remarks were in response to an article in the lay press relating to the installation of a second therapy-dedicated cyclotron unit in Great Britain which in itself is an issue that has polarized the British medical community. In this letter I will not address the political ramifications of the second issue but will simply attempt to answer the concerns put forth by MacDougall and Arnott[1] about the clinical trial.

The RTOG study in question compared the efficacy of fast neutron radiotherapy vs conventional radiotherapy for locally-advanced adenocarcinomas of the prostate gland [2,3]. Given the poorly-penetrating nature of the low-energy neutron beams available at that time the study was initiated, it was elected to use a combination of neutrons and photons (mixed beam) instead of neutrons alone on the experimental arm. Patients with stages C and D_1 tumors were eligible for the study and a total of 91 evaluable patients were randomized between the two arms -- 11 were stage D_1 (positive pelvic nodes) and 80 were stage C. Patients received 50 Gy-equivalent to the pelvis and an additional 20 Gy-equivalent to the prostate bed and other areas of gross disease. Patients were stratified according to histologic grade, prior hormonal therapy status, and pelvic nodal status. Based upon

chi-squared testing, the two patient arms were balanced according to the following major prognostic variables which were prospectively collected: stage (C vs D_1), grade (Mustofi schema), seminal vesicle involvement, serum acid phosphotase levels, prior hormonal therapy status, diagnostic procedure (TURP vs needle biopsy), method of nodal evaluation (lymphangiogram vs laparotomy), patient age distribution, Karnofsky performance status, cardiac status, other intercurrent disease status, race, and presence of benign prostatic hypertrophy. The only variable of marginal significance was the presence of benign prostatic hypertrophy ($p=0.06$) which was higher on the mixed beam arm. Gleason scores were retrospectively evaluated on 73 patients and in this subgroup were balanced between the two arms. Hence, the allegation that the patients treated on the photon arm were in some respect "worse" than those patients treated on the mixed beam arm is simply incorrect!

Ten year results have been presented at the 1990 meeting of the American Radium Society and will be presented at the 15th International Cancer Congress. In regards to all major endpoints the mixed beam group did better than the group treated with photons alone: local control 63% vs 52% ($p=0.05$), survival 42% vs 27% ($p=0.05$), and disease-specific survival 56% vs 42% ($p=0.04$). Whether or not differences between arms in a clinical trial achieve a statistical significances depends both on the number of patients in the trial and the observed endpoint differences. In regards to

the above parameters all differences were statistically-significant based upon a two-sided Mantel-Haenszel log-rank test[4]. Hence, the allegation by MacDougall and Arnott[1] that the patient numbers were too small to draw statistically-valid conclusions is also incorrect. They make comparisons between these results and the results of other trials for stage C tumors. It is important to note that 11 patients with known stage D_1 tumors were included in the RTOG mixed beam study and also that many patients in the study were biopsied even in the presence of clinically-controlled disease. These facts coupled with other patient-related factors make comparisons between studies carried out at other times and places extremely hazardous. This is the main reason why randomized trials are conducted.

Much concern is noted about treatment related morbidity. This is puzzling since this topic was discussed in detail in both the 5-year and the 8-year reports[2,3]. Both acute and late morbidity were evaluated according to the joint RTOG/EORTC scoring schema and were found to be equivalent on the two arms. In toto there were 6 reactions on the mixed beam arm and 5 on the photon arm that were scored as "severe or greater". The only fatal complication occurred on the photon arm -- a patient underwent a diverting colostomy, became septic and subsequently died. To paraphrase MacDougall and Arnott, the "morbidity watchdog did not bark because there was nothing to arouse it".

The study concluded that the mixed beam form of treatment offered improved local control and survival for locally-advanced prostate cancer at no increased morbidity.

The study was stopped when new, high energy cyclotrons having isocentric treatment capability became available in the United States and was replaced with a new study comparing neutrons alone vs. conventional photon irradiation. In the United States alone there are 106,000 new cases of prostate cancer each year[5] and approximately 25,000-30,000 of these fall into the category of locally-advanced disease. This would completely overwhelm the small number of neutron treatment centers that were founded mainly for research purposes. It seemed to the protocol planners that the most important issue was not whether one form of neutron treatment was better than another (as would have been the case if the mixed beam arm would have been the control arm of a new trial) but to ask the question again with larger patient numbers. The new trial has thus far accrued approximately 180 patients. If it confirms the results of the prior study, then we anticipate that neutron radiotherapy will move to the private medical sector in the United States. This is the only way sufficient numbers of machines can be built to accommodate the resulting patient load.

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2. Laramore GE, Krall JM, Thomas FJ, Griffin TW, Maor MH, Hendrickson FR. Fast neutron radiotherapy for locally advance prostate cancer: results of an RTOG randomized study. Int J Radiat Oncol Biol Phys 1985; 11: 1621-1627.

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4. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst. 1974; 22:719-748.

5. Silverberg E, Boring CC, Squires TS. Cancer statistics, 1990. CA-A Cancer Journal for Clinicians 1990; 40: 9-26.

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University of Washington Medical Center
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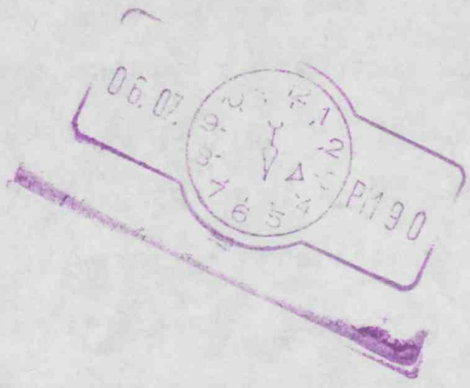
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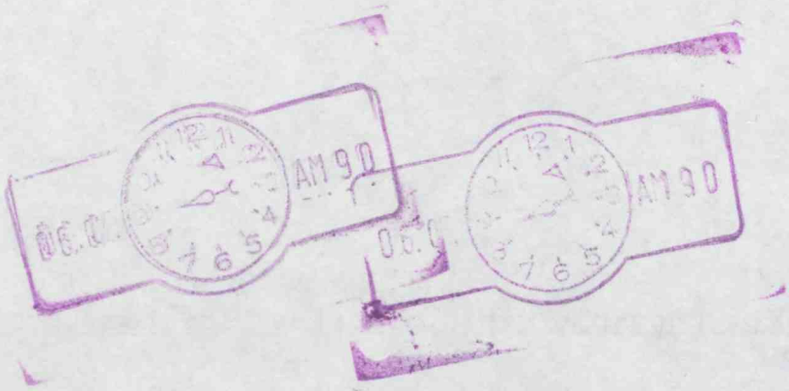
Briefing for possible visit of Prime Minister to Cyclotron Unit in Houston

1. The machine at Houston is a high energy cyclotron (42MeV). (This is similar to the one at Clatterbridge which is a 62MeV machine.) CMO spoke to Dr Lester Peters the Chief of Radiation Therapy at the M D Anderson Hospital, Houston, Texas on two occasions.

2. Dr Peters is participating in the head and neck cancer trial in which Clatterbridge is also engaged. Results will not be available until 1996. (The exact numbers of cases he has treated is not known.) He is no longer recruiting patients into the National Cancer Institute prostate cancer trial because of the frequency of serious toxic effects. In his discussions with CMO Dr Peters reported that he considers that neutron therapy has a small but definite place in the treatment of cancer but does not based on results currently available, regard it as likely to be suitable for treatment of prostate cancer. Dr Peters is concerned about the narrow "margin of safety" between therapeutic benefit and serious toxic effects in relation to neutron therapy. This remains a consideration even in the most skilled hands and with the most up to date equipment.

3. The Prime Minister may wish to speak to Dr Peters about the indications for the use of the cyclotron and the situation with regard to side effects.



PRIME MINISTER

CYCLOTRON

You are meeting Sir Nicholas Bonsor and John Moore to discuss the future of the Cyclotron. The meeting will take place in your room at the House of Commons on Thursday 12 July after your Statement on the Summit. Mr. Clarke will also be present. Although the Government announced earlier that it would contribute £6 million towards the £10 million cost of the project, the Department of Health have had growing doubts about the project. You asked Sir Donald Acheson to review the state of neutron therapy here and abroad. A version of his report was made available to the Cyclotron Trust. They have discussed it with him and subsequently with Mr. Clarke.

No real meeting of minds emerged:

- There were differences about the conditions for which neutron therapy is advised.

- There were differences about the numbers of patients with these conditions who could be treated.

- There were differences about the conclusions to be drawn from existing trials.

As a result, there is a wide gap between DOH's view of possible patients and the Trust's view. One cyclotron can treat 300-400 patients a year. DOH's view of possible patients is slightly greater than that while the Trust believe there could be over 700 patients a year or, if prostate cancer comes to be treated in this way, several thousand. They argue, therefore, that there is a case for building a second cyclotron. DoH, however, take the view that in addition to estimating the potential "market" it is important to estimate what share of that market neutron therapy might capture. Here the evidence is not in the Trust's favour.

28 cyclotrons in world

Only one fully used

in Seattle

—

Lawrence

Berkeley

Berkeley - Stanford

Livingston - U.S.

At present only about 60 cases a year are being referred to the existing cyclotron at Clatterbridge.

In his minute of 20 June, Mr. Clarke concludes that the scientific case for expanding neutron therapy does not command sufficient support in this country, and that the second cyclotron should not be built. At the heart of his case is the view that the supporters of neutron therapy have been unable to convince sufficient of their peers in the medical profession so that consultant radiotherapists around the country and their patients are not opting for this form of treatment. History may show that they are being too cautious, but the CMO's report reflects the low level of support in the medical profession.

The Cyclotron Trust tend to argue in "producer" terms. There is in fact a market as consultants can choose from a range of therapies which they can advise for their patients. Neutron therapy has not managed to secure a large market share. One should base investment decisions on a realistic assessment of the market share that can be achieved, not on the total size of the market.

Mr. Clarke believes that until the proponents of neutron therapy can persuade more of their colleagues to adopt this form of treatment, it would be wrong to expand the capacity.

You have reluctantly accepted this advice, though you did not want the option closed off for all time should evidence emerge over the next few years which was more favourable. You did not want, therefore, to adopt DoH's proposal of reassigning the funds to alternative forms of cancer treatment.

You will need to put these points to Sir Nicholas and get him to accept that campaigns at the political level will not advance the Trust's position. They need to win the argument in the medical journals and in medical symposia. If they succeed, referrals to Clatterbridge will improve and thereby the case for an expansion of capacity.

You can, however, undertake that the position should be reviewed at the end of 1992 when important trials here and in the US will have produced results. (Sir Nicholas may reply that they will miss the opportunity of including space for the cyclotron in a new building at St. Thomas's. He may argue that the go ahead for building the suite in the basement should still be given. I think you ought to say that it would be wrong to commit public money on such an "just in case" basis. We would not dream of doing that anywhere else.)

You can offer to record the outcome of the meeting in a letter.

AT

ANDREW TURNBULL

5 July 1990

c:\pps\cyclotron (kk)

CORRESPONDENCE

- *All letters must be typed with double spacing and signed by all authors.*
- *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.*

The cyclotron saga

SIR,—In the *Sunday Times* of 3 June Dr Thelma Bates, a trustee of the Cyclotron Trust, was quoted as saying that an American study of 91 patients with prostate cancer showed that those given neutron therapy had a 15% better chance of survival after 10 years than those given conventional photon therapy. Although the 10 year follow up data from this study by the Radiation Therapy Oncology Group (originally reported in 1985[1]) have not been published, some further data from the group were published in 1989,[2] and we would like to comment.

This trial is flawed in several major respects. The number of patients is too small to allow any statistically valid conclusions to be drawn. Only 36 patients were treated in the photon therapy (conventional treatment) arm of the study. There is a remarkable difference between crude survival (13% at eight years) and cause specific survival (54% at eight years) in these patients. The implication must be that the patients treated conventionally were in poor general health and therefore likely to fare badly however they were treated. The long term data must be regarded with even greater circumspection: after eight years of follow up there can have been, at most, three patients surviving who had had photon therapy. This is an insufficient number on which to base conclusions that have any pretence to validity.

The survival of the patients treated with photons in this study is significantly worse than would be expected from experience with radiotherapy in the management of localised prostate cancer. Other trials of radiotherapy in patients with stage C prostate cancer have yielded 10 year survival rates of 47% (in 551 patients)[3] and 38%.[4] These figures are remarkably close to the results, quoted approvingly by Dr Bates, for patients treated in the mixed (neutron/photon) beam arm of the Radiation Therapy Oncology Group study—46% survival at 10 years. Viewed in this light the surprise in the Radiation Therapy Oncology Group neutron study is not how good the mixed beam results are (they are simply average) but particularly how poor is the eight year survival rate of 13% seen in the group treated conventionally.

The group of patients treated with *x* rays differs in important respects from the group treated with mixed beam radiation. The patients treated with *x* rays had larger tumours and a higher proportion had been treated previously with hormone therapy. These and other general factors prejudice the survival of the patients treated with *x* rays.

The Radiation Therapy Oncology Group did not adequately examine late radiation induced morbidity in either arm of the study. This is critical as previous clinical studies on neutron therapy have shown that for an equivalent amount of acute damage to normal tissues late effects are more severe in patients treated with neutrons. This is particularly true for the tissues of the pelvis, especially in the rectosigmoid region. Even though the median follow up of the Radiation Therapy Oncology Group study is now 10 years, the late effects of treatment have not been reported. The omission of data is disconcerting and, like the dog that did not bark in the night, provokes speculation as to why these data have not been reported. The lack of information about late rectal morbidity (ulceration, stricture, etc) is of particular concern.

It is noteworthy that these investigators have eschewed the normal practice of using the better arm of a randomised study as the control arm of the subsequent study. They have dropped the mixed beam schedule and their current study, started in April 1986, simply compares *x* rays alone with neutrons alone. This suggests that the investigators may have doubts about the validity of their comparison of *x* rays alone with the mixed beam.

R HUGH MACDOUGALL

Department of Clinical Oncology,
Western General Hospital,
Edinburgh EH4 2XU

SYDNEY J ARNOTT

St Bartholomew's Hospital,
London EC1

1 Laramore GE, Krall JM, Thomas FJ, Griffin TW, Moar MH, Hendrickson FR. Fast neutron radiotherapy for locally advanced prostate cancer: results of an RTOG randomized study. *Int J Radiat Oncol Biol Phys* 1985;11:1621-7.
2 Russell KJ, Laramore GE, Griffin TW, *et al*. Fast neutron radiotherapy in the treatment of locally advanced adenocarcinoma of the prostate. *Am J Clin Oncol* 1989;12:307-10.
3 Zagars GK, von Eschenbach AC, Johnson DE, *et al*. Stage C adenocarcinoma of the prostate. An analysis of 551 patients treated with external beam radiation. *Cancer* 1987;60:1489-99.
4 Hanks GE, Diamond JJ, Krall JM, *et al*. A ten year follow up of 682 patients treated for prostate cancer with radiation therapy in the United States. *Int J Radiat Oncol Biol Phys* 1987;13:499-505.

Human Fertilisation and Embryology Bill

SIR,—On behalf of the medical group of British Agencies for Adoption and Fostering I wish to comment on two points raised by Mr Peter Braude and colleagues in their editorial on the Human Fertilisation and Embryology Bill.[1]

Firstly, with regard to the comparison between children born as a result of donated gametes who, as adults, may seek information about the donor and adopted people who already hold such rights under section 51 of the Adoption Act 1976, the number of inquiries about origins to the general registry office has increased considerably during the 1980s and is now between 4000 and 5000 each year. Moreover, many adopted people already have basic information about their origins, so they seek further information directly from their adoption agency or from various postadoption counselling agencies in the United Kingdom. These agencies are experiencing a steady increase in numbers of inquiries. Although exact figures are not obtainable, a 5% increase can be considered a substantial underestimate. Numbers will probably increase further with the implementation next year of the contact register required by the Children Act 1989.

Adopted people may seek their birth fathers when their names are on the birth certificate or, as is often the case, when information is held by the adoption agency, and many do so. We wish to emphasise, however, that to our knowledge there has been no suggestion that children born by donation should have a statutory right to require a genetic test of a parent. We see no reason why this should not remain subject to free consent or, exceptionally, to order of a court.

Contributory information can be found in the work by Haimes and Timms[2] and other research projects concerning adopted people and those brought up in long term foster homes. It must be stated also that interest in origins has not been found to reflect dissatisfaction with adoptive state.

Secondly, with regard to the recruitment of donors in Sweden, where information about donors is now available by law, it has been assumed that the decrease in donors in Sweden since the law changed in 1985 has been due entirely to withdrawal of donors. In fact, it has been largely due to the closure of three of the 10 Swedish clinics by clinicians after the new legislation, so that recruitment stopped altogether in one large urban area (Professor A McWhinnie, personal communication). Clinics that were already operating in the spirit of the legislation have experienced no diminution, while others have altered their practice and recruitment is improving. Swedish donors are now drawn from a different group: mature men of proved fertility who accept openness as a basic human right. The existence of such donors is borne out by research in Australia.[3]

We wish to emphasise that an initial decrease in the number of donors could be minimised by a well reasoned information service to the professions and the public and contend that the quality of the resulting service, both for children and for their parents, would be much improved.

ANNE JEPSON

British Agencies for Adoption and Fostering,
London SE1 1RQ

1 Braude P, Johnson MH, Aitken RJ. Human Fertilisation and Embryology Bill goes to report stage. *Br Med J* 1990;300:1410-2. (2 June.)
2 Haimes E, Timms N. *Adoption, identity and social policy: the search for distant relatives*. Aldershot, Hampshire: Gower, 1985.
3 Rowland R. The social and psychological consequences of secrecy in artificial insemination by donor (AID). *Soc Sci Med* 1985;21:391-6.

SIR,—As an infertility counsellor for the past 12 years I am pleased that Mr P Braude and colleagues have discussed two important issues—

CONFIDENTIAL

FILE
DA
91/cycl (LI3)
bc PERB
MB

10 DOWNING STREET

LONDON SW1A 2AA

From the Principal Private Secretary

25 June 1990

CYCLOTRON TRUST

The Prime Minister has seen your Secretary of State's minute of 20 June. She has reluctantly concluded that there is not, at present, a sufficient scientific consensus on which to base an expansion of neutron therapy, and that in the meantime the project should not proceed. If, as further information becomes available and the advocates of neutron therapy are successful in convincing medical opinion to make greater use of this treatment, the issue can be reconsidered. In the meantime, the Prime Minister does not wish the funds earmarked for this project to be committed elsewhere.

The next stage is for the Prime Minister to see Sir Nicholas Bonsor and Mr. John Moore to inform them of her conclusions. I will be arranging such a meeting at which she wishes your Secretary of State to be present.

ANDREW TURNBULL

Mrs. Helen Shirley-Quirk,
Department of Health.

CONFIDENTIAL

THE CYCLOTRON PROJECT FOR ST THOMAS' HOSPITAL
BRIEFING NOTE FOR THE SECRETARY OF STATE FOR HEALTH
FOR MEETING 13TH JUNE 1990

Summary of Plans, Justification and Current Status

1. The plan is to install a cyclotron in the basement of a new building on the St Thomas' Hospital site. This will have the following advantages:

   a It will be part of a large radiotherapy centre (4,000 new patients per year) easily accessible from all over the UK and in a region with a high (nearly 40% of all cancer patients) referral rate.

   b It will be linked to Positron Emission Tomography (a new scanning technique).

   c It will be closely associated with the Richard Dimbleby academic department of cancer research.

   d It will be funded from a mixture of private and public sources and run as a business **within** the NHS.

2. The CMO prepared a paper after his recent visit to the United States which, *inter alia*, noted:

TUMOUR	INCIDENCE	DEATH	APPROPRIATE FOR CYCLOTRON
Salivary gland	484	148	150
Uveal melanoma	450		200
Para nasal sinus	494	235	100

In discussion of this paper at the meeting with the CMO on the 29th May the following changes were made:

Soft tissue sarcomas)	782	358	200
Some bone sarcomas)			
Para nasal sinus			-50

On the basis of the Laramore results tabled and discussed

Prostate	19296	3859

The CMO's paper assessed the capacity of a cyclotron treating 2 cohorts of patients concurrently at 280 patients per annum. Professor Sealy at Clatterbridge estimated in his paper for the CMO (25 Oct 1989) that "the maximum number of patients who could be treated on one dedicated cyclotron would approach 400 new patients per annum".

The Cyclotron Trust believes that the figures quoted in the table are conservative and that it will be difficult to leave capacity for research with the anticipated patient load.

Whilst the current adverse publicity is unfortunate and is affecting recruitment at Clatterbridge now, sensible publicity and positive results from other centres will eliminate this problem by the time the St Thomas' machine is treating patients in 1994.

3. The AIP for the project is held up at RHA because of the uncertainty expressed about cyclotron funding. The full design team has been appointed and the project has advanced "at risk".

THE CYCLOTRON TRUST
13 June 1990

THE CYCLOTRON TRUST FOR CANCER TREATMENT

at The Department of Radiotherapy and Oncology,
St. Thomas' Hospital, Lambeth Palace Road, London SE1 7EH
Telephone: 01-922 8031 Fax: 01-928 9968

AS FROM 6th. MAY 1990
PLEASE DIAL 071
INSTEAD OF 01

cc Dr Brian Holmes
P/S Sir Donald Acheson
Dept of Health

FAX TRANSMISSION

You may like to see this. I think Dr Parker is saying that he has not been contacted since Sir Donald wrote his report. AP 22/6

To: Andrew Turnbull Esq
Principal Private Secretary
Prime Minister's office

Date: 22nd June, 1990

Time:

If you have any problems in receipt of this message, please telephone 01-922-8031 and ask for CYCLOTRON.

This is page 1 of ...2. pages transmitted.

At Richard Packard's request enclosed is a copy of the letter received from Dr Robert Parker.

D J Grocott
Director

(2)

UCLA Medical Center

Department of Radiation Oncology
10833 LeConte Avenue
Los Angeles, CA 90024-1714

June 18, 1990

Sir Nicholas Bonsor, Bt., M.P.
House of Commons
London SW1A 0AA

Re: Report of the Chief Medical Officer, Sir Donald Acheson on the Present Status of Neutron and Proton Therapy

Dear Sir Bonsor:

I have not received a copy of the above report and have not been contacted by Sir Donald Acheson.

Sincerely,

Robert G. Parker

Robert G. Parker, M.D.
Professor and Chair

RGP:jyr

10 DOWNING STREET

Prime Minister (1)

You did not manage to read the Clarke minute on FERBs.

Nor did you express a view

AT 21/6

Fil

DEPARTMENT OF HEALTH
EILEEN HOUSE
80-94 NEWINGTON CAUSEWAY
LONDON SE1 6YX
TELEPHONE 01-972 2000

Your reference
Our reference

D J Grocott Esq
Cyclotron Trust for Cancer Treatment
Department of Radiotherapy and Oncology
St Thomas' Hospital
Lambeth Palace Road
London SE1 7EH

21 June 1990

Dear Mr Grocott

Thank you for your letter of the 20th June with ATZ. and for letting me see a copy of Professor Brady's letter of the 1st June to yourself.

For the record, Sir Donald Acheson spoke to both Dr Peters and Dr Parker in March and he visited Dr Suit in Boston.

Yours sincerely

Peter Bourdillon

P J Bourdillon FRCP
Senior Medical Officer
Tel: 071-972-2821 Fax No: 071-972-2844
Radiopager a) phone bureau on 081-884-2844
b) give paging no. DOH 1103040
c) give operator message

cc: A Turnbull Esq ✓
Dr D McInnes

Ref: Grocott.f21

PRIME MINISTER

CYCLOTRON TRUST

Last month, you wrote to Sir Nicholas Bonsor (Flag A) stating that you and Mr. Clarke "have reluctantly concluded that we can no longer justify going ahead on the basis planned"; suggesting alternative uses for the £6 million earmarked for the project; but offering the Trust an opportunity to discuss the CMO's report with him. The Cyclotron Trust took up this offer of a meeting and have also, as you wished, had an opportunity to put their case directly to Mr. Clarke. The note at Flag B provides a good summary of their position.

The latter has now minuted with his conclusions (Flag C). No surprisingly, he repeats his earlier conclusion that the case for a second cyclotron facility has not been made out.

Having attended these meetings, it seems to me that the differences between the Trust and the Department run at several levels:

(i) There are differences about the value of neutron treatment for different conditions. At one extreme, there is almost complete agreement for some tumours that neutron treatment is preferred e.g. of the salivary gland. In the middle are a number of conditions where it is agreed that neutron treatment is beneficial, but the Trust place the case load much higher than the Department, e.g. uveal melanoma and paranasal sinus tumours. At the other extreme, eg prostate cancers, the Trust has concluded that neutron treatment is beneficial but DoH feels a lot more testing is required to draw clear conclusions. The Trust interprets US experience more optimistically than the CMO did after his visit.

(ii) Different tests are being applied. The Trust argue that neutron treatment has to prove that it is superior to conventional photons. DoH say that before

committing money to a major expansion it is necessary to demonstrate not just this but also that neutron treatment is superior to other new treatments currently being developed such as radioactive implants.

(iii) When it comes to numbers, the Trust talk in terms of people with the condition in question, DoH in terms of likely referrals, ie what proportion of those affected will in fact be referred. The gap is huge. It is agreed that a cyclotron has the capacity to treat 300-400 patients. The Trust identifies a "market" around twice that, even before bringing in prostate cancers, and is confident that a cyclotron in London will capture a large share of it. DoH point to the fact that actual referrals number only around 60 a year.

My conclusions are as follows:

(i) There is a genuine scientific controversy about the value of neutron therapy on which it is perfectly reasonable for opinions to differ.

(ii) The supporters of neutron therapy have been unable to convince sufficient of their peers in the medical profession so that consultant radiotherapists around the country and their patients are not opting for this form of treatment. History may show that they are being too cautious but that is the current reality. The CMO's report is a true reflection of the level of support in the medical profession.

(iii) The Cyclotron Trust make the mistake of arguing too much in "producer" terms. There is in fact a market as consultants can chose from a range of therapies which they can advise for their patients. Neutron therapy has not managed to secure a large market share. One should base investment decisions on a realistic assessment of the market share that can be achieved, not on the total size of the market.

(iv) Having failed to win the scientific battle the Trust have transferred it to the political plane, seeking to persuade you and the Secretary of State to give them the backing they have not found from their peers.

(v) Until they manage to persuade more of their colleagues to adopt this form of treatment, it would be wrong to extend capacity.

I think you should accept Mr. Clarke's advice. The point he makes in his penultimate paragraph, which is reinforced in Sir Robin Butler's minute (Flag D), indicates the dangers for the Government of picking and chosing which scientific advice to follow. If the project is forced through, it will not succeed in convincing a wide spectrum of the medical profession. They will not refer patients for a treatment which they believe has been established through political pressure rather than through scientific conviction.

In my view, the right way for the Cyclotron Trust to proceed is to take the battle back where it belongs - into the medical journals and medical symposia - so that they can gradually build up a consensus of opinion in favour of this treatment and thereby establish a case for a expansion of capacity. Then we can reconsider the matter. Should they succeed

- ~~Agree to confirm the earlier conclusion that~~ the project should not be proceeded with, ~~with the funds being devoted to alternative forms of cancer treatment?~~ In the meantime i.e. until further exp. is available.

- Sir Nicholas Bonsor has asked to come and see you. Agree to a meeting? Do you want Mr. Clarke to be present?

NT

Yes

MF

ANDREW TURNBULL

20 June 1990

c:\pps\cyclotron (kk)

KH/6730p

CONFIDENTIAL

Prime Minister

CYCLOTRON TRUST

As you will know from Andrew Turnbull there have been a number of discussions between the Department and the Cyclotron Trust, following the Trust's response to the Chief Medical Officer's paper "The Present Status of Neutron and Proton Therapy". In particular the Chief Medical Officer held a meeting to go through the Trust's comments and further information in detail, and I had a meeting with the Trust so that they could present their case to me personally.

The attached note provides an assessment of all the additional data that the Trust has put to us. In preparing it the Chief Medical Officer has consulted his advisers, particularly those who were at his meeting with the Trust. As the note shows, these advisers are eminent and experienced people in this field who can be relied on to provide an unbiased view of the scientific position.

I was very impressed by the commitment and enthusiasm of the members of the Cyclotron Trust. It was evident that they are all strongly behind the proposals they have put to the Department. I made it clear that I recognised and welcomed their commitment. I went on to reassure them, in the light of concern that they expressed about the media coverage of this issue, that the Department had gone to great lengths to make sure that its assessment of the proposals was fair and even handed. It had deliberately avoided going for advice to those who were known to be against the cyclotron proposals. The Trust could be satisfied therefore that the Department had presented the best available advice to me as Secretary of State.

I had a very thorough discussion with the Trust. They were clearly anxious to know my position. I did not want to raise false hopes so I made it clear at the end of the meeting that notwithstanding the additional data that had been brought forward, it did not seem to me that the Trust had been able to demonstrate that there was a sound scientific case for rejecting the advice of the Chief Medical Officer and the great majority of cancer specialists in this country. Moreover, in spite of the enthusiasm of the Trust, the numbers of referrals for neutron therapy are declining and not increasing.

At the very end of the meeting the Trust asked me to consider a letter that Professor Sealy, at the Clatterbridge Hospital had written to the Chief Medical Officer in October last year, as it had not been mentioned in the Chief Medical Officer's report. This I have done, although in fact it was taken into account by the Chief Medical Officer. It was not included in the reference because it was a confidential letter.

Rupert

700 without mistake

CONFIDENTIAL

I have thought very carefully about the points put to me by the Trust, the additional data and material that they produced before and at the meeting, Professor Sealy's letter and the attached note. My conclusion, which I well recognise will greatly disappoint the Trust, is that there are no grounds for rejecting the advice that has been put to me.

I do not have the scientific knowledge to make an independent judgement of these matters. I am bound to place great weight on the advice I receive. As a Government we rightly lay much emphasis on the importance of taking the best available scientific advice, whether on the environment, public health or medical treatment. It would seriously undermine our general position - for example, in our response on sensitive issues like BSE - if we were seen to reject such scientific advice.

This makes it all the more important that I should be satisfied that the advice I receive is soundly based. I am confident that it is and that the Chief Medical Officer has dealt with this issue with scrupulous fairness. Indeed, I have to say that I have been impressed by the weight of scientific opinion that underpins his advice. The clear direction of that advice is that the cyclotron at Clatterbridge can cope with all the national demand we can currently foresee for neutron and proton therapy. There are therefore no grounds for reversing the decision set out in your letter of 14 May to the Trust.

K C

20 June 1990
Department of Health

CONFIDENTIAL

THE PRESENT STATUS OF NEUTRON AND PROTON THERAPY

These notes respond to the points raised on the paper entitled "The Present Status of Neutron and Proton Therapy" made by Mr Packard to the Prime Minister on 19 May and relayed to Mrs Shirley-Quirk in the letter from Mr Turnbull dated 21 May. They also take account of Dr T W Griffin's draft chapter, of the discussions that representatives of the Cyclotron Trust had with the CMO on 29 May, of the various papers tabled at that meeting, of the discussions that representatives of the Cyclotron Trust had with the Secretary of state on 13 June, of the paper tabled at that meeting and Professor Sealy's letter to the CMO dated 25 October 1989. The paragraphing follows that in Mr Turnbull's letter.

(i) Imbalance in the arms of the study comparing mixed neutron-photon treatment with photon treatment for locally advanced cancer of the prostate

There is inconsistency between the various publications which deal with the trial of mixed neutron-photon treatment versus photon treatment for locally advanced cancer of the prostate on this point. Whilst the 1989 publication (American journal of Clinical Oncology 1989; 12: 307-310) and Dr Griffin's draft chapter which the Cyclotron Trust gave to the Prime Minister, both stated that the two groups were found to be balanced relative to all major prognostic factors, this is not the case in the original 1985 publication (International Journal of Radiation Oncology, Biology and Physics 1985; 11: 1621-1627).

There it is stated:

> "Tumor size based upon the product of the clinically-assessed major diameters was somewhat larger in the photon treatment group ($p<0.05$)."

A further independent statistical analysis of the series of papers concerning this trial was sought on 25 May. The conclusion remains that this study should be regarded as an interesting pilot, that it is subject to a number of potential biases and that it is too small to carry much weight on its own.

(ii) <u>The results of the current National Cancer Institute (NCI) trial comparing neutron and photon therapy for locally advanced prostate cancer</u>

The NCI's view of the status of this trial was stated in a letter of 1 June. A definite conclusion which allows a comparison to be made between benefits and toxic effects of the two treatments will not be available until 1995 although some indicators may be available before that. Although prostate-specific antigen (PSA) levels may prove a useful indicator of control of prostate cancer they have no predictive value in respect of the frequency of serious toxic effects. The CMO is advised that up to the present time 10 Grade IV toxic effects (the most severe grade) have occurred in the neutron-treated patients in this trial (approx 13%) and none in the photon-treated patients. For Grade III toxic effects the figures are 7 (9%) for neutron treatment

and 2 (3%) for photon treatment. In the light of the occurrence of toxic effects the dose of neutrons used in the trial was reduced about 18 months ago. It follows that no information can be available currently or in the near future about the efficacy of local control on the new treatment schedule.

(iii) The capacity of Clatterbridge to handle all the cases for which neutron therapy is the preferred treatment

The expert advice to the CMO is that inoperable salivary adenocarcinomas (estimated at 150 cases per annum) are the only tumours for which neutron therapy is certainly more effective than others. There should also be an option for cancer specialists to refer certain inoperable paranasal sinus cancers although only a proportion of these benefit. Expert advice received by the CMO remains that there is currently no evidence to justify the routine use of neutron therapy for cancers of other sites. The advice is contained in conclusions (ii) and (iii) in the original paper.

Neutron Treatment	Estimated Annual Caseload
Salivary Gland Tumours	75
Paranasal Sinus Tumours	25
Head and Neck Trial	30
Proton Treatment	
Uveal Melanoma Trials	100

	230

The numbers in the Table assume that in the period to 1993 at least, cancer specialists will not wish to refer more than about 50% of the salivary and paranasal sinus tumours potentially suitable. Bearing in mind that in the last 51 months only 250 cases of all types (an average of 59 per annum or an average utilisation rate of 21%) have been treated with neutrons at Clatterbridge, of which 11 and 15 cases were salivary gland and paranasal sinus tumours respectively, this seems a sufficiently generous estimate. In fact, in the three months since the pelvic trial closed only 5 patients have been treated with neutrons. The estimated total of 230 cases, if it were realised, would leave a margin for those cases of uveal melanoma for which there is an absolute indication for proton therapy. If however a throughput of 400, rather than 280, cases per annum is achievable as indicated by the Cyclotron Trust at the meeting with the Secretary of State, then there would be substantially more spare capacity at Clatterbridge.

Prostate cancer cases are not included in the estimates because the evidence is currently insufficient to justify treating patients with this cancer with neutrons other than within a research study. A definite conclusion on this issue will not be possible until 1993 at the earliest and perhaps not until 1995 (see above under ii). Furthermore there are a number of other promising treatments for prostate cancer currently under investigation, any one of which could readily be applied to a much larger proportion of prostate cancer patients than neutron therapy could ever realistically be expected to be applied to.

Soft-tissue sarcoma cases are not included in the estimates because the evidence is currently insufficient to justify treating patients with this cancer with neutrons other than within a research study. An American trial of the value of neutron therapy in soft-tissue sarcoma, and in some other cancers, recently had to close because insufficient numbers of patients volunteered for the trial.

The views expressed about tumours suitable for treatment with neutrons in Professor Sealy's paper of October 1989 were fully considered in "The Present Status of Neutron and Proton Therapy".

(iv) The experts consulted and the breadth of their interest

In view of the public controversy which involved many of the cancer specialists in this country, the CMO visited the United States to seek evidence at first hand. He spoke with a high proportion of all specialists involved in neutron therapy for cancer within the USA, including those in Seattle, Los Angeles, Houston, Batavia Illinois (Fermilab) and Detroit, and an expert in proton therapy at Boston. In retrospect, he considers that there would have been advantage in taking evidence from a number of cancer specialists not involved in neutron therapy so as to avoid bias in favour of this treatment. Subsequently, he has taken advice from a further Canadian expert, Dr Arthur Porter, who has a special interest in prostate cancer and who has been a member of the Ontario Radiation Oncology Commission considering whether or not the Province should invest in neutron therapy. Dr Porter's view is that neutron therapy should not be used in prostate cancer outside a research trial.

Within the UK, the advisors include two distinguished radiotherapists, one of whom is Chairman of the MRC's Heavy Particle Therapy Committee (the Committee which supervises the trials at Clatterbridge) and who is therefore bound to be impartial, a medical oncologist, and two ophthalmic surgeons who together treat at least 80% of all uveal melanomas occurring within the UK.

The implication of a bias against the use of neutron or proton

therapy in the advice received cannot be upheld.

(v) The closure of the Clatterbridge Pelvic Cancer Trial

The failure of this trial to show benefit for neutron therapy is disappointing. It is agreed that too much cannot properly be made of the excess mortality in the neutron arm until a full analysis of the data is available and has been subject to critical review. Nevertheless, the results are likely in the meanwhile to reinforce the current reservations about the safety of neutron therapy held by many British cancer specialists.

Removal of the Clatterbridge Cyclotron to St Thomas's Hospital

Any such proposal would have to be agreed with the Imperial Cancer Research Fund, which provided the greater part of the capital (about £4M), the MRC, which funds a substantial fraction of the running costs and the RHA. In any event, removal at this point in time would have a gravely disruptive effect on the research trials in progress.

Ref. A090/1257

MR TURNBULL

The Cyclotron for St Thomas' Hospital

The Chief Medical Officer, Sir Donald Acheson, has approached me about his concern over his personal position in relation to the Cyclotron for St Thomas's Hospital.

2. The weight put by the Secretary of State on the CMO's advice is stressed in his minute to the Prime Minister and needs no underlining from me. But the sequence of events has caused Sir Donald's advice to become publicly known and I am sure that the Prime Minister will take account of this in the handling of this matter. If she were to modify the earlier decision which was communicated to the Trust, it would be important not to suggest that she was preferring other people's scientific assessment to that of the CMO, not least because the Government has put so much weight on his advice on salmonella, listeria and BSE.

F.E.R.B.

ROBIN BUTLER

20 June 1990

R 20/6

THE CYCLOTRON TRUST FOR CANCER TREATMENT

at The Department of Radiotherapy and Oncology,
St. Thomas' Hospital, Lambeth Palace Road, London SE1 7EH
Telephone: 071-922 8031 Fax: 071-928 9968

Andrew Turnbull Esq
Principal Private Secretary
Prime Minister's Office
10 Downing Street
London SW1

20th June, 1990

Dear Mr Turnbull

Richard Packard asked me to send you a copy of our letter to the Department covering comments received from Professor Brady. These are enclosed.

Richard also asked that I let you see the latest drawings from the architects - the Carnell Green Partnership of Oxford. From these you will see that a considerable amount of design work has been completed.

Yours ever

Dan Grocott

D J Grocott
Director

encs.

THE CYCLOTRON TRUST FOR CANCER TREATMENT
at The Department of Radiotherapy and Oncology,
St. Thomas' Hospital, Lambeth Palace Road, London SE1 7EH
Telephone: 071-922 8031 Fax: 071-928 9968

Dr P J Bourdillon FRCP
Senior Medical Officer
Department of Health
Eileen House
80-94 Newington Causeway
London SE1 6YX

20th June, 1990

Dear Dr Bourdillon

Thank you very much for your letter of 15th June in response to mine of the previous day. You will know that we undertook to let the Department have a copy of the comments from Professor Luther Brady which are now to hand. I am sure you will know Professor Brady and be aware that he has served as President of (*inter alia*):

American Board of Radiology
American Society for Therapeutic Radiology & Oncology
American Radium Society
Inter-Society Council for Radiation Oncology
Radiological Society of North America
Society of Chairmen of Academic Radiology Departments
Society of Chairmen of Academic Radiation Oncology Departments

and has received honours more numerous than can readily be listed. These include 16 medals, many of them gold, and honorary fellowships from the Italian Society of Radiologic Medicine (1983), the Royal College of Radiologists (1985) and the Deutsche Rontgengesellschaft (1985).

The cyclotron issue seems to have been fraught with misunderstanding. You will note from Professor Brady's letter that he had understood from Dr Peters that there had been no contact with the Chief Medical Officer. This would appear from our discussions with Professor Brady simply to have been a matter of timing. It does seem rather odd that Dr Parker has no recollection of such contact though he is listed in the relevant appendix to the CMO's paper.

The important issues, however, are scientific and it was enormously useful to receive from Dr Zink a copy of her letter of the 17th April addressed to Sir Donald. The earlier letter which we used - incidentally with her permission - was written for Third Party Insurers and is not a scientific document. It was good, therefore, to see the more rigorous approach of the April 17 letter and to note the comments on the UCLA experience showing that when the trial was closed due to lack of patient accrual **"physicians referring patients to UCLA demand treatment with fast neutrons"**. Would that that could happen in Clatterbridge! Dr Zink's observations on complication rates from fast neutrons proving to be acceptable and her comments on the currently supported Phase III trials bearing on neutron toxicity are also very relevant. It was not certain from the Secretary of State's remarks relative to the NIH/NCI that he had taken a full brief on the support given by the second letter to the one we had previously tabled.

In response to Dr McInnes' interest in this issue I have copied this letter and its enclosures to her. Please do not hesitate to contact me if you would like to arrange clarification of any of Professor Brady's comments.

Yours ever

Dan Grocott

D J Grocott
Director

enc.

cc: Andrew Turnbull Esq
Dr Diana McInnes, Private Secretary to the Chief Medical Officer.

NBM
PT 18 k R16/6

DEPARTMENT OF HEALTH
EILEEN HOUSE
80-94 NEWINGTON CAUSEWAY
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Your reference
Our reference

Direct Line:071 972 2821

D J Grocott Esq
The Cyclotron Trust for Cancer Treatment
at The Department of Radiotherapy and Oncology
St Thomas' Hospital
Lambeth Palace Road
LONDON SE1 7EH

15 June 1990

Dear Mr Grocott

Thank you for your letter of 14 June.

I can reassure you that there is no confusion here between the two prostate trials in the United States. Although I should add that the Department of Health was unaware of the toxicity in the neutron arm of the current trial when Sir Donald Acheson met representatives of the Cyclotron Trust on 29 May.

I am aware that Dr Bates wrote to Sir Donald Acheson following the meeting on 29 May in which she suggested that Dr Arthur Porter was trying to raise funds to build a cyclotron for neutron therapy in London, Ontario. I think there may be some misunderstanding, as when we clarified the position with Dr Porter he said that he is making no such bid. Rather, he has been a member of the Radiation Oncology Commission for Ontario that has looked at new developments in radiation oncology, and one of the new developments considered has been neutron therapy.

Yours sincerely

Peter Bourdillon

P J BOURDILLON FRCP
Senior Medical Officer

cc: Professor C Joslin
A Turnbull Esq

NAT HOLTON : Cyclotron 62

THE CYCLOTRON TRUST FOR CANCER TREATMENT

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Dr P Bourdillon
Senior Medical Officer
Department of Health
Richmond House
79 Whitehall
London SW1

14th June, 1990

Dear Dr Bourdilla

In the light of the discussions yesterday with the Secretary of State, it appeared to our medical trustees that there may be some misunderstanding or confusion between the two prostate trials which have been conducted in the United States. You will know that the second trial has shown some greater toxicity for patients at one centre (where the collimator is less refined than that used at the other centres or at Clatterbridge) and that this needs to be well understood in the review of the US data. I know that this has been the subject of some conversation between Dr Bates and Professor Joslin.

We are, of course, very anxious to make sure that all the scientific data is available to the Department as it forms its view. Should this matter be of concern there is the opportunity for clarification when Professor Griffin and Professor Laramore are in the United Kingdom on the 26th June. If the Department would like to take advantage of a meeting with them, perhaps you would be kind enough to let me know.

On another matter, Sir Nicholas asked me to draw to the Department's attention that he had omitted one proposed neutron centre from those he mentioned in speaking of progress in other countries. We learned from Dr Arthur Porter, who came to the CMO's meeting on 29th May at the Department's invitation, that he is currently trying to raise funds to build a cyclotron for neutron therapy in London, Ontario. Perhaps you would be kind enough to add this to any note of the meeting that may be produced.

I have taken the liberty of copying this letter to the Secretary of State's private office and to Professor Joslin.

Yours ever

Don Grocott

D J Grocott

cc: The Rt Hon Kenneth Clarke MP
Professor C Joslin
Andrew Turnbull Esq

RHy

THE CYCLOTRON PROJECT FOR ST THOMAS' HOSPITAL
BRIEFING NOTE FOR THE SECRETARY OF STATE FOR HEALTH
FOR MEETING 13TH JUNE 1990

Summary of Plans, Justification and Current Status

1. The plan is to install a cyclotron in the basement of a new building on the St Thomas' Hospital site. This will have the following advantages:

a It will be part of a large radiotherapy centre (4,000 new patients per year) easily accessible from all over the UK and in a region with a high (nearly 40% of all cancer patients) referral rate.

b It will be linked to Positron Emission Tomography (a new scanning technique).

c It will be closely associated with the Richard Dimbleby academic department of cancer research.

d It will be funded from a mixture of private and public sources and run as a business **within** the NHS.

2. The CMO prepared a paper after his recent visit to the United States which, *inter alia*, noted:

TUMOUR	INCIDENCE	DEATH	APPROPRIATE FOR CYCLOTRON
Salivary gland	484	148	150
Uveal melanoma	450		200
Para nasal sinus	494	235	100

In discussion of this paper at the meeting with the CMO on the 29th May the following changes were made:

Soft tissue sarcomas)	782	358	200
Some bone sarcomas)			
Para nasal sinus			-50

On the basis of the Laramore results tabled and discussed

Prostate	19296	3859

The CMO's paper assessed the capacity of a cyclotron treating 2 cohorts of patients concurrently at 280 patients per annum. Professor Sealy at Clatterbridge estimated in his paper for the CMO (25 Oct 1989) that "the maximum number of patients who could be treated on one dedicated cyclotron would approach 400 new patients per annum".

The Cyclotron Trust believes that the figures quoted in the table are conservative and that it will be difficult to leave capacity for research with the anticipated patient load.

Whilst the current adverse publicity is unfortunate and is affecting recruitment at Clatterbridge now, sensible publicity and positive results from other centres will eliminate this problem by the time the St Thomas' machine is treating patients in 1994.

3. The AIP for the project is held up at RHA because of the uncertainty expressed about cyclotron funding. The full design team has been appointed and the project has advanced "at risk".

THE CYCLOTRON TRUST
13 June 1990

PRO

10 DOWNING STREET

Prime Minister

Before minuting you, Mr Clarke has agreed to receive a presentation from the Trust. This is on Wednesday morning. I will be attending.

AT
11/6

This gets more & more worrying. I could visit the Anderson Hospital in Houston. Could we find out who Anderson saw when he was there?

MT

Cyclotron file.

Star Wars killer beam takes on cancer cells

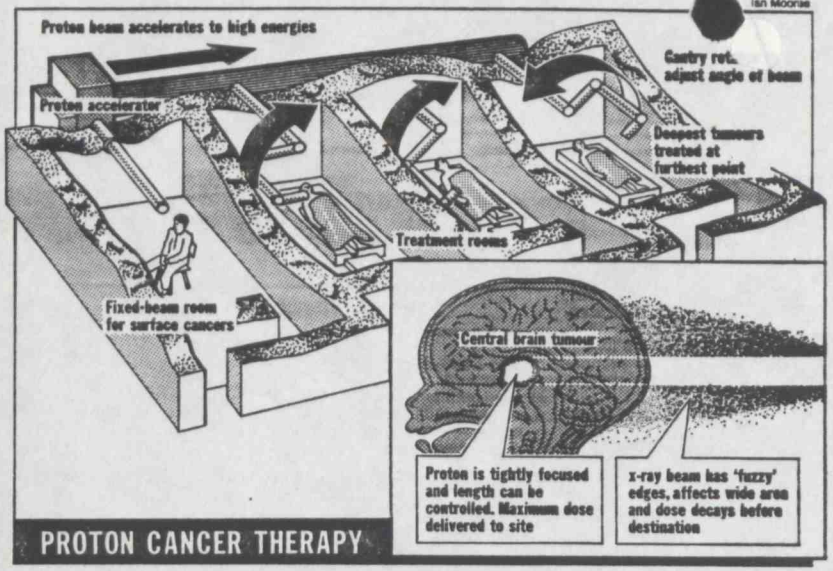
RADIOTHERAPY

Proton radiation, originally developed as a Star Wars space weapon, is being adapted to kill tumours. Experts say that it is more accurate and has fewer side effects than x-rays or neutron therapy. **JANE BIRD** reports

Andy Watts

● Proton type: Griffiths with sub-atomic particle creator

Ian Moores



PROTON CANCER THERAPY

A DEADLY radiation technology developed for Star Wars could provide the most promising treatment yet for cancer by killing tumorous cells.

The technique is being developed at AEA Technology, the newly commercialised arm of the UK Atomic Energy Authority. Originally it was to be used in President Ronald Reagan's Strategic Defence Initiative as a powerful beam to knock out enemy satellites in space.

Now proton therapy, using the positively charged particles in an atom's nucleus, is being adapted for use in hospitals where it could provide significant improvements in radiotherapy.

The results so far look very promising. A cyclotron at Harvard has treated several hundred rare tumours that occur near the brain and spinal cord. It has had a 75% success rate, compared with 30% using x-rays. Data from elsewhere on using protons for eye cancer show a 97% success rate.

Neil Griffiths, medical applications manager at AEA Technology, says: "Protons combine several of the advantages of the conventional treatments with neutrons and x-rays, without the disadvantages."

In the treatment, protons are fired down a pipe where they pick up energy as they are accelerated by surrounding electric fields. When they are at their optimum energy level they are diverted out of the pipe and directed into the patient's tumour.

Beams of radiation have been used for many years to destroy cancerous tumours where surgery was impossible, either because the patient was too old or because the cancer was inaccessible.

The radiation causes ionisation – an effect where electrons are knocked off atoms throughout a cell until its chemical structure is destroyed. The molecules of DNA, which determine the growth of a cell, are broken up so that they can no longer reproduce.

The most popular radiation treatment uses x-rays. But the problem is that the edges of the beam tend to be fuzzy so that treatment always ends up dosing quite a lot of the area around the tumour. This is a severe drawback, especially if the tumour is in a region close to the brain or spinal cord.

Another problem is that an x-ray beam loses energy progressively as it passes through the body, so the maximum dose is at the surface and not at the tumour.

One solution is to fire beams from three different positions so that the highest dose is delivered at the intersection point – the tumour. But side effects can still be unpleasant.

In the past two decades much enthusiasm has centred on an alternative – neutron therapy (neutrons are the electrically neutral components of an atom). It was thought that neutrons would be more effective on tumour tissue than on healthy tissue.

In Britain, cyclotrons to deliver low-energy neutron beams were set up in Edinburgh, Clatterbridge near Liverpool, and Hammersmith Hospital in London. But the results never lived up to expectations, and there have been some cases where the healthy tissue has been damaged more than the tumour. Last month The Sunday Times revealed that more than 30 patients in Britain have died as a result of neutron therapy.

Contrary to the situation with x-rays, the proton beam has a very sharp edge. It travels in very straight lines, can be programmed to stop abruptly at a specific point, and delivers almost all its ionising effect at that point. This means that organs beyond the tumour receive virtually no radiation.

"It reduces the likelihood of side effects, and allows a higher dose of radiation to be given to the cancer. In many cases it could increase the chances of successful treatment," says Griffiths.

Another advantage of protons over x-rays or neutrons is that their electrical charge allows them to be steered by magnetic fields, making them much more precise.

The benefits of protons have been known since the 1940s, but they have not been developed because of the expensive machinery needed to create them. Until now the only proton-beam accelerators have been unsuitable cyclotron machines built about 40 years ago for high-energy physics and adapted for medical use after they had been superseded by more advanced technology in physics.

They are generally some distance from hospitals and the patient often has to be treated in awkward positions because their proton beams are inflexible. Even with protons, there is some dose delivered to the healthy tissue so the beam needs to be fired from three angles.

"If you turn the patient over all the organs flop to one side and the accuracy can be so poor you may even miss the tumour," says Griffiths. "To get good medical effects you need to be able to direct the beam from any angle from a gantry that can be rotated round the patient. Ideally you need a patient to be immobilised in a type of straitjacket, and move the beam around."

Beams of higher energy are also needed so that they can penetrate further into the patient to treat the really deep-seated tumours. Until now the maximum acceleration of protons available has been 180MV which sends them less than 15cm (6in) into the body.

Even so, 8,500 people have received proton cancer treatment in Japan, the Soviet Union, Sweden, Switzerland, and Boston, Massachusetts. Many of the patients were in their thirties and if they had not had this option they would have had little chance of survival.

In Britain there is one small facility at Clatterbridge where the neutron machine has been adapted to produce very-low-energy protons of 60MV which penetrate only a few centimetres and are used to treat eyes. So far it has treated about 30 patients for ocular melanoma where previously the eye would have had to be removed.

Later this month the world's first proton-treatment centre designed specifically for medical use will open at Loma Linda University Medical Centre, near Los Angeles. It creates the beam in a circular accelerator with eight magnets forming a ring about six metres across. These fire the protons round the ring many times, enabling them to pick up energy from the electric fields. When they reach the desired energy level they are directed to the delivery point. It is the first time rotating gantries have been used to deliver charged particles.

But AEA Technology believes it has a more compact design that could undercut the £42m equipment cost of the Loma Linda centre by 10-20%, and be much cheaper to operate.

"The Loma Linda centre is overdesigned. It has taken a standard high-energy physics experiment machine and added all the bits needed for medicine. It is enormous and much more expensive than it would need to be if the design were optimised for the application," says Griffiths.

The particle-beam laboratory at AEA Technology started designing very high intensity beams for heating the plasma inside fusion reactors to millions of degrees. It uses hydrogen atoms that have been stripped of their electrons to leave positively charged protons that can be accelerated by very strong electrical fields the length of the machine.

The design the team came up with for hospitals has a structure like a long corridor alongside four treatment rooms.

It is a linear accelerator, instead of circular or cylindrical like the cyclotrons that are being used in Britain. Different energies of proton beam can be extracted at points along it.

For instance, quite a shallow beam might be needed for the head and neck, and a much deeper one for prostate or abdomen tumours.

The ability to treat four people simultaneously helps to make the facility more economic. Griffiths estimates it could treat 1,000 patients a year at less than £20,000 a patient. "This sounds expensive, but is cheaper than a heart transplant, or equivalent to keeping a kidney patient on dialysis for two years," he says.

Some scientists believe that in the long term protons will be superseded in the treatment of cancer by heavier atomic nuclei of elements such as carbon and oxygen.

These contain neutrons as well as protons and combine the advantages of the two sub-atomic particles. They need to be accelerated to even higher energies than protons. But like neutrons, they are more effective on cancerous tissue.

"We could have gone for the heavier atomic nuclei but this is still regarded as a research field. We felt we should go for something of more practical application that could treat patients immediately," says Griffiths.

Richard Burgess

MR. RICHARD PACKARD

CONSULTING SUITE
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7th June 1990

The Rt Hon. Margaret Thatcher PC MP
10 Downing Street
London, SW1A 2AA

Dear Prime Minister

I am sorry to have to write to you again about the St Thomas' Cyclotron. However after the recent meeting with the CMO and DOH officers to discuss the the CMO's paper, it seems essential. It is now apparent to me that no argument of the Cyclotron Trust or like minded physicians will ever find favour in the DOH. This is borne out by the ridiculously biased and distorted view of the meeting which was issued by the Department. This we have attempted to refute with our own report plus that of Dr Laramore from Seattle who as you know attended also. It is a shame we were not allowed to record the meeting but I am very glad Andrew Turnbull was present.

Although I have no doubt that the Department of Health will say that they are erring on the side of caution in this matter. We believe they are grossly overstating their case. The Seattle Cyclotron already has treated over 1000 patients with high energy neutrons, with negligble side effects.

By the CMO's own admission there are potentially 450 patients a year excluding research and those with prostate cancer, who could benefit from particle therapy. This number includes patients with advanced salivary gland cancer, paránasal sinus tumours and eye melanomas.

Continued/.

B/Forward.
-2-

It was further agreed at the DOH meeting that inoperable soft tissue sarcomas would be best treated this way. As it seems more than likely that prostate cancers will be added to this list by the time St Thomas's begins to treat patients, a fairly substantial body of patients would be likely to benefit. This number would not include those with conditions where essential research would be required but which would in any case be better done at St Thomas's. The reason for this is the presence there of the PET scanner and the academic unit of Radiotherapy as well as the Richard Dimbleby research laboratories.

I enclose with this letter a copy of one just received from Professor Luther Brady which is self explanatory.

I firmly believe that if the DOH have their way the treatment of cancer with particle therapy will be set back at least 5 years in this country.

With kind regards,

Yours sincerely

Richard Packard

R.B.S. Packard MD FRCS.
Consultant Ophthalmic Surgeon

HU
Hahnemann University

Department of
Radiation Oncology and
Nuclear Medicine

215 448 8410

Broad & Vine
Philadelphia, PA
19102-1192

Mail Stop 200

22 May 1990

Mr. R.B.S. Packard, M.D.
Princess Christian's Hospital
12, Clarence Road,
Windsor, Berks, SL4 5AG
England

Dear Richard:

I was very pleased and delighted to have had the opportunity of talking with you with regards to the neutron beam debacle that is currently underway in London. I was absolutely appalled that the political pressure had been so great on Mrs. Thatcher that she temporarily elected to withdraw support for the project but I'm very pleased that she now is more willing to consider the prospects for the reinstitution of the support.

It's interesting in my survey of the institutions in the United States where Acheson was supposed to have visited that he never showed up. These include the Fermi Laboratory in Batavia, Illinois, the University of California in Los Angeles, and the M.D. Anderson Hospital, Houston. I have a strict suspicion that the best thing that he might have done was to have called these areas and not ever visited them.

Without question, there is demonstrated evidences to support the fact that neutron beam therapy is of great advantage in salivary gland tumors, non-oat cell carcinomas of the lung, malignant melanomas, carcinomas of the prostate, and soft tissue sarcomas. Even with that rather limited list, the impact of this treatment program would be of major and significant importance to the care of the cancer patient wherever they may be located in Britain or the United States.

As soon as I've received the information from Mr. Grocott, I shall reply to you directly.

I'm greatly distressed that I shall not be able to be with you in London on Tuesday afternoon, 29 May 1990, at 4:30 in the afternoon. I am in the process of moving from a 1760 house into a 1790 house and I am sure that I will not be able to get everything accomplished to allow me to go to London. However, I shall be in London arriving on the evening of Friday, 8 June 1990, and departing on Sunday afternoon, 10 June 1990, for Lisbon. If I can be of any help during that time frame, I would be pleased and delighted to do so.

As soon as I've received the material from Mr. Grocott, I shall reply to you. I would suggest that an individual from the United States would be most appropriate to speak on Tuesday afternoon, 29 May, and I would suggest either Dr. Thomas Griffin at the University of Washington in Seattle, Dr. Herman Suit at MGH, Boston, Dr. William Powers at Wayne State University. I think that anyone of them would be an excellent spokesman for the validity of the neutron beam treatment program.

I shall be talking with you in the very near future. I hope all goes well next Tuesday.

With very best personal regards.

Yours sincerely,

Luther

Luther W. Brady, M.D.
Professor and Chairman

LWB:mlc

FCy

THE CYCLOTRON TRUST FOR CANCER TREATMENT

at The Department of Radiotherapy and Oncology,
St. Thomas' Hospital, Lambeth Palace Road, London SE1 7EH
Telephone: 071-922 8031 Fax: 071-928 9968

DJG/FK/312

Dr Diana McInnes
Private Secretary to the
Chief Medical officer
Department of Health
Richmond House
79 Whitehall
London SW1A 2NS

5th June, 1990

Dear Dr McInnes

I am sorry to have had to delay our response to the draft note. I hope that the enclosed is agreeable to the Department.

The meeting held on Tuesday, 29th May was, as stated by the Chief Medical Officer, to enable the Cyclotron Trust to comment on the CMO's document "The present status of neutron and proton therapy". The paper tabled by the Trust at the meeting did this and the note accepts this. It was not a meeting to agree views though, happily, there were several areas in which such agreement was reached. Our revision to the draft note prepared by the Department is written to reflect this.

I am also enclosing Professor Laramore's response to the draft which I have elected not to incorporate directly into our revision.

Yours sincerely

Dan Grocott

D J Grocott
Director

enc.

NOTES OF A MEETING BETWEEN THE CYCLOTRON TRUST AND THE DEPARTMENT OF HEALTH TO DISCUSS THE CHIEF MEDICAL OFFICER'S DOCUMENT ENTITLED "THE PRESENT STATUS OF NEUTRON AND PROTON THERAPY" - 29 MAY 1990 AT RICHMOND HOUSE

Present:

Sir Donald Acheson	- Chief Medical Officer Department of Health
Dr M Abrams	- Deputy Chief Medical Officer Department of Health
Dr T Bates	- Consultant Radiotherapist St Thomas' Hospital, London (Cyclotron Trust)
Dr P Bourdillon	- Senior Medical Officer Department of Health
Mr D Grocott	- Cyclotron Trust
Mr J Hungerford	- Consultant Ophthalmologist St Bartholomew's Hospital
Mr S Heppell	- Deputy Secretary Department of Health
Professor C Joslin	- Professor of Radiotherapy, Leeds
Professor G Laramore	- Professor of Radiotherapy Oncology, Seattle
Mr R Packard	- Consultant Ophthalmologist Windsor (Cyclotron Trust)
Dr A Porter	- Radiotherapist - Ontario
Mr A Turnbull	- Prime Minister's Office

Introduction

1. Sir Donald Acheson explained that the meeting had been arranged to enable the Cyclotron Trust to comment on his document "The Present Status of Neutron and Proton Therapy". In discussion, the following topics were addressed: proton therapy and uveal melanoma, neutron therapy and prostatic cancer, the workload at Clatterbridge and the toxicity of neutron therapy.

Uveal melanoma

2.1 Mr Hungerford agreed with Mr Packard's assertion that:
i. There was approximately 95% local control of uveal melanoma with proton beam therapy,
ii. 65% of eyes retained 6/60 vision or better and 35% retained 6/12 or better,
iii. Enucleation studies showed at 5 years that actuarial mortality from death due to uveal melanoma was 50% for large melanomas and 30% for medium sized melanomas. Although not completely comparable, to date particle therapy studies (helium ion or proton) have shown mortality of 20%.

2.2 Whilst Mr Packard and Mr Hungerford agreed that as yet no randomised controlled trial comparing mortality after enucleation and conservative therapy had been completed, there was no evidence to suggest that particle therapy was any worse. Mr Packard pointed out that 60% of uveal melanomas were posterior to the equator of the globe and some authorities thought there might be less ocular side effects with particle beam therapy than plaque therapy. Mr Packard suggested that of 450 new uveal melanomas per year 300 could benefit from conservative therapy. The others being those patients with very small tumours exhibiting minor or no growth and patients with very large tumours or having blind painful eye.

2.3 Mr Packard expressed concern that patients' informed consent may pose a problem in the adequate recruitment to the trials for large tumours proposed in the CMO's report.

Neutrons

3.1 The value of neutron therapy in inoperable advanced salivary gland tumours was confirmed. Dr Bates pointed out that these included a high proportion of adenocarinomas and that this might well have significance for adenocarcinomas elsewhere in the body.

3.2 Professor Laramore supported an observation of Professor Wambersie's (Brussels) reported by the CMO that the common histological type of paranasal sinus tumour - the squamous cell carcinoma - responds poorly to neutrons and it is only the rarer types that respond. These rarer types are adenocarcinoma and adenocystic carcinoma, which together have an incidence of 50 cases per annum.

3.3 The value of neutron therapy in advanced head and neck cancer remains uncertain and must await the results of the current American and MRC collaborative trial. Professor Joslin said that further randomised controlled trials would be necessary to confirm the apparent value of neutron therapy in treating inoperable lymph nodes. Dr Bates agreed with this.

3.4 Neutron therapy has not yet been shown to be of value in cancer of the cervix, of the bladder or of the rectum. It may be of value palliatively.

3.5.1 Professor Laramore presented 10 year follow up data of the randomised controlled study for mixed beam therapy (neutron and photon). This showed strong evidence which was statistically significant in favour of the mixed beam arm having better survival at 10 years. The CMO expressed reservations about using this study alone as a basis for recommending neutron therapy for locally advanced prostate cancer. Some present felt that the result of the NCI trial comparing neutrons alone and photons, for which preliminary results would be available when it is completed in October 1990, should be awaited before recommending this form of therapy as superior to photons.

3.5.2 The CMO's report had stated that the 2 arms of the mixed beam trial were not balanced. Professor Laramore refuted this and described the raw data, its statistical significance as reported by the RTOG statisticians in confirmation of the opinion expressed by Professor Griffin in his letter of 22 May 1990 tabled at the meeting.
Dr Porter said that the neutron therapy results are exciting and merit further study in the management of locally advanced prostate cancer. Other studies he cited, were brachytherapy (the implantation of radioactive sources into the prostate) with which he is involved himself, surgical removal of as much tumour as possible followed by photon therapy, and hormonal treatment with or without photon therapy. Professor Laramore drew the meeting's attention to the high costs of the surgery associated with brachytherapy. Large randomised controlled trials are underway in the United States comparing neutrons and photons, comparing surgical removal of as much tumour as possible followed by photon therapy and photon therapy alone, comparing hormone and photon therapy and photon therapy alone, and comparing short-term and long-term hormone therapy.

3.5.3 Professor Laramore and Dr Porter agreed that neutron therapy remains an important research procedure in the management of locally advanced prostate cancer. Its role in routine clinical practice of such a common cancer could await the results of the trial mentioned in 3.5.2. This trial is closing in October 1990 and the preliminary results look, as reported by Professor Griffin in his tabled letter, favourable and should be available shortly after that time.

3.6 Neutron therapy in the USA is used routinely in centres with a cyclotron in the treatment of soft tissue sarcomas with or without additional surgery or chemotherapy. Professor Joslin and Dr Bates agreed that these are suitable patients for treatment. It was pointed out that unfortunately due to the bulk of some of these sarcomas, a large tissue defect may be produced when they are successfully treated. Dr Bates said that in relation to the side effects of any treatment where no other existed, neutron therapy should be accorded the same intellectual tolerance as other modalities, such as chemo-therapy and radical surgery. Dr Bates cited the example of the development of aggressive cytotoxic chemotherapy which led to the improvements in cure of childhood leukemia which had been included in the reference given in the CMO's paper (Hamblin T J. Interleukin 2. British Medical Journal 1990; 300 275-276).

<u>Workload at Clatterbridge</u>

4.1 The workload of potential patients identified in the CMO's document (which did not include inoperable sarcomas and prostate cancer) was 450 without including research. This is considerably more than could be treated with one Cyclotron. Professor Laramore pointed out that even if only a proportion of these patients were referred the machine time would all be occupied and no research could be done. Professor Joslin stated that recruitment was very difficult at Clatterbridge.

It was agreed by Dr Bates and Professor Joslin that it was a shame that the Cyclotron had not been placed in London where there is access to a larger pool of patients.
The exciting developments in neutron therapy for prostate cancer alone merit a review of its value.
Mr Packard reminded the meeting that the **final** results of the RTOG prostate trial would be available when the St Thomas' cyclotron is ready to start treating patients.

4.2 Clatterbridge cyclotron is currently underutilised with an average of approximately 60 patients having been treated with neutrons there per annum over the last 4 years. Regional referral patterns, the continued adverse publicity and personality problems were cited as explanations for this.

Toxicity of Neutron Therapy

5. In certain sites (see paragraphs 3.1, 3.2 and 3.5) there is now evidence that a dose of high energy neutrons can achieve a better local control of tumours compared with photon therapy without an unacceptable rate of serious toxic effects. Further work (e.g for lymph nodes in neck as cited in paragraph 3.3) needs to be done.

Tabled Papers

6. The Cyclotron Trust tabled papers prepared by the Trust itself and by Professor Laramore and also tabled a letter from Dr T Griffin (Seattle). CMO said that these would be looked at in detail by the Department of Health and the conclusions reflected in the advice promulgated.

4th June 1990
Cyclotron Trust

UNIVERSITY OF WASHINGTON
MEDICAL CENTER

CANCER CENTER

June 4, 1990

Mr. D.J. Grocott
Director, The Cyclotron Trust for Cancer Treatment
Department of Radiotherapy and Oncology
St. Thomas' Hospital
Lambeth Palace Road
London SE1 7EH

Dear Don:

Thank you very much for faxing me the "draft note" from the Chief Medical Officer's secretary. In several respects the note seems to present a somewhat distorted view of what actually transpired at the conference. Comments by item:

2.1 There are three major subtypes of ocular melanomas: spindle cell, mixed cell and epithelioid. For a given cell type, it would seem that the larger tumors would have the worse prognosis.

2.2 Posteriorly located ocular melanomas constitute 50-60% of all ocular melanomas. I thought it was agreed by both Drs. Packard and Hungerford that they would treat such patients with a proton beam if it were available.

3.5.3 In the United States neutron facilities, patients with prostate cancer who are not protocol eligible are routinely given neutron radiotherapy for their disease. When the current study closes, all patients with localized prostate cancer will be offered routine neutron radiotherapy for their tumors as cyclotron time permits. At the University of Washington, the side effects of neutron radiotherapy for prostate cancer have been about the same as for photon treated patients.

3.6 "Large holes" have not been a problem in patients with soft tissue sarcomas treated with the modern high energy neutron facilities. In many cases, patients have been spared amputative procedures by using neutron treatments.

4.1 The meeting participants were polarized on the matter. The salivary gland, ocular melanoma, and adenocarcinomas/adenoidcystic paranasal sinus tumors would completely saturate the Clatterbridge machine even if it were to work multiple shifts. This would leave no time for clinical research.

4.2 Current referral patterns may be hard to reverse at Clatterbridge. A case can certainly be made for a second machine in London, a more medically sophisticated area.

DEPARTMENT OF RADIATION ONCOLOGY, RC-08
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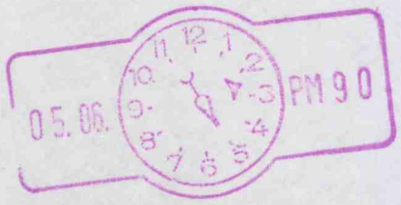
5.0 While narrow, the therapeutic windows for high energy neutron radiotherapy are well known and patients can safely be treated with this modality.

Unfortunately, strong personality issues rather than a cold appraisal of the scientific data seems to be dominating the decision making process. I hope that this will change in the future.

Yours truly,

George E. Laramore, Ph.D., M.D.
Professor of Radiation Oncology
Clinical Director
University of Washington Fast Neutron Radiotherapy Project

GEL/mlb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PRIME MINISTER

This is a very sad saga.

CYCLOTRON

I attended a meeting chaired by Sir Donald Acheson last Tuesday at which the Cyclotron Trust were given an opportunity to comment on his paper. Those attending for the Cyclotron Trust were Mr Packard, Dr Bates, Mr Grocott and Dr Larramore, the latter having come from Seattle. Also attending were the various experts who had advised Sir Donald Acheson. The full list is at Flag A.

The differences can be summarised under two headings, those relating to the science and those to likely utilisation of Cyclotron.

Science

I have attempted in Table A attached to summarise the different ways in which the parties see the application of neutron/proton therapy to different kinds of tumour. There is agreement in some areas, but elsewhere the Cyclotron Trust people are readier to draw favourable conclusions, while the Department of Health feel existing trials need to be completed before clear conclusions can be drawn.

Utilisation

From the differing scientific perceptions one can draw up estimates of the size of the potential usage of Cyclotron. In Table B I have sought to set out the views of Dr Bates of the Cyclotron Trust, Professor Sealy who works at Clatterbridge, and the Department of Health.

The Cyclotron Trust draw the conclusion that the number of patients who could benefit from neutron/proton treatment is substantially in excess of the capacity of one Cyclotron, which is about 300 patients a year. DoH approach the matter

differently. They argue that the number of potential patients is only a step in the calculation: what matters is actual usage. There is no point in expanding capacity if doctors are not referring their patients to the existing facilities. The fact that there are two million cars a year sold in Britain does not justify Rover expanding its capacity to two million. What the DoH observe is that doctors are very reluctant to refer patients for this kind of treatment; indeed, only 60 patients are currently being treated at Clatterbridge. They would not want to expand capacity until they saw this form of treatment being more enthusiastically embraced by doctors up and down the country.

The Cyclotron Trust argue that the present machine is under-utilised in part because of its geographical location, and in part because there has been such a steady stream of negative publicity.

An example of this is the article which appeared in the Sunday Times last week - Flag B. What is happening is that the adverse results which arose from early versions of the Cyclotron at Hammersmith and Edinburgh are being quoted in evidence. It is as if heart transplants were now being opposed on the grounds that Louis Blaiberg did not survive very long. An article making this point appeared in The Times on Thursday - Flag C. The Cyclotron Trust need to make progress in this battle of hearts and minds.

Sir Donald Acheson is putting a submission to his Secretary of State this evening, who in turn will minute you early next week. My expectation is that there has been little movement in either camp.

I will report further when we have Mr Clarke's advice.

AT

ANDREW TURNBULL

1 June 1990

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TABLE A

VIEWS ON NEUTRON/PROTON THERAPY

Cancer Type	Cyclotron Trust	DoH
Salivary gland	Clearly beneficial	Clearly beneficial
Paranasal sinus	Clearly beneficial	Clearly beneficial
Uveal melanoma	Clearly beneficial	Beneficial, though needs to be compared with other treatments.
Tumours of head and neck	Beneficial for some tumours	Possibly beneficial but present trials should be completed
Soft tissue sarcoma and melanomas	Beneficial for some tumours	Possibly beneficial
Prostate	Beneficial. Mixed beam therapy now shown to be better than conventional therapy.	Promising results but too early to draw definitive conclusions. More trials needed.
Pelvic area	Worse than conventional	Worse than conventional

TABLE B

POSSIBLE CASES FOR NEUTRON/PROTON TREATMENT

Cancer Type	Cyclotron Trust	Professor Sealy	DoH
Salivary gland	200	155	150
Uveal melanoma	300	-	200
Paranasal sinus	200	95	100
Soft tissue sarcoma/ melanoma	550	300	-
Prostate	700	150	-
Total	1950	700	450

Dr M Abrams	-	Deputy Chief Medical Officer Department of Health
Dr T Bates	-	Cyclotron Trust Consultant Radiotherapist St Thomas' Hospital, London
Dr P Bourdillon	-	Senior Medical Officer Department of Health
Mr D Grocott	-	Cyclotron Trust
Mr J Hungerford	-	Consultant Ophthalmologist St Bartholomews Hospital
Mr S Heppell	-	Deputy Secretary Department of Health
Professor C Joslin	-	Professor of Radiotherapy Leeds
Dr Larramore	-	Radiotherapist - Seattle (Cyclotron Trust)
Mr R Packard	-	Consultant Ophthalmologist Windsor (Cyclotron Trust)
Dr Porter	-	Radiotherapist - Ontario
Mr A Turnbull	-	Prime Minister's Office

'Life-saving' cancer machine killed 33

Thatcher backed cyclotron experiment with £6m

by Aileen Ballantyne, Medical Correspondent

SENIOR cancer specialists believe that more than 30 patients have died as a result of an experimental form of radiation neutron therapy, a version of which won the personal backing of the prime minister and a £6m government grant.

The Sunday Times has discovered that details of most of the deaths, which occurred among cancer patients at London's Hammersmith hospital and at the Western General hospital in Edinburgh, have been known to the government since the early 1980s.

Sixteen patients, who were all treated for cancer using a cyclotron machine, have died at Edinburgh and 10 at Hammersmith. All 26 deaths, which occurred in the late 1970s and early 1980s, were reported to government medical advisers.

A further seven deaths in the mid-1980s, several years after treatment was given in Edinburgh, have been disclosed to The Sunday Times.

The future of the controversial cyclotron programme is in doubt following serious misgivings among some medical experts.

One of the government's leading advisers on cancer, Sir Raymond Hoffenberg, said he had advised against the project from the start.

"There was always considerable evidence to suggest that neutron therapy was more harmful than conventional radiation therapy," he said yesterday.

In spite of advice by Hoffenberg, and other leading cancer experts, that further cancer treatment with cyclotron should not go ahead until it was proved safe, the prime minister offered an extra £6m funding for a new cyclotron at London's St Thomas's hospital 18 months ago.

That amount is almost as much as the government's total annual spending on cancer research. It is under renewed consideration by the government and is expected to be withdrawn.

Both the Hammersmith and Edinburgh trials used a low-energy form of neutron therapy which is no longer used in Britain. However, a high-energy form has received support from Thatcher. A version of this is being tested as part of a £10m study at Clatterbridge hospital, Merseyside. The effects on individual patients have remained secret and part of the study has now been suspended.

According to some experts, the high-energy form is also likely to cause complications.

"A lot of problems may well be – and I think are – inherent to the way neutrons interact with tissue," said Dr Sidney Arnott, a consultant radiotherapist, who used the cyclotron at the Western General in Edinburgh.

Arnott abandoned his cyclotron trial because of serious fears over patient safety. The cyclotron at Clatterbridge hospital is the only one still in use in Britain and is being used for patients with head and neck cancer.

Arnott, now at St Bartholomew's hospital, London, said 16 patients treated for bladder cancer at Edinburgh in the early 1980s died as a direct result of complications following neutron treatment.

Only two in a comparable group died as a result of conventional therapy.

Yesterday he said: "Some people have undoubtedly died as a result of complications with this treatment, whereas they may not have died if they had been treated with conventional radiotherapy.

"There is no doubt that all of these 33 deaths occurred as a direct result of treatment."

Dr Hugh MacDougall, consultant cancer specialist at the Western General in Edinburgh, who also treated patients with a low-energy cyclotron, said seven patients suffering from head and neck cancer had died as "a direct result" of neutron therapy.

His findings are about to be published and he has since ceased using the treatment.

An earlier published review by the Medical Research Council showed that 10 out of 51 head and neck patients treated with neutron therapy at Hammersmith had died from the treatment.

The therapy, by Dr Mary Catterall, a recently retired consultant radiotherapist at

Continued on page 3

the Hammersmith, was part of a research project which leading doctors believe to be seriously flawed. It is alleged that Catterall failed properly to compare her results with similar patients who were given conventional treatment.

Yesterday, colleagues were highly critical of her methods of assessing the safety and value of the treatment.

Dai Davies, a consultant plastic surgeon at Hammersmith who is treating 35 patients suffering severe complications as a result of neutron therapy at the hospital, said: "Catterall did not run a proper comparative trial on this form of therapy which compared it with the conventional form. Because of that she had no way of knowing whether it was successful or not."

Arnott said: "It was difficult to find anybody apart from Mary Catterall who was actually in favour of this government cyclotron grant, yet it was the evidence from that trial that she herself conducted that swayed Thatcher."

Catterall, a member of the Cyclotron Trust which was offered the £6m grant, last night refused to comment on allegations about the conduct of the Hammersmith hospital trials, or the future of the cyclotron programme.

"The matter is still under discussion, they can all say what they like," she said.

Another member of the trust is Richard Packard, an eye surgeon who carried out the successful operation for the prime minister's detached retina in 1983.

Sir Nicholas Bonsor, chairman of the Cyclotron Trust and Conservative MP for Upminster, yesterday denied claims by cancer experts that funding, and the prime minister's support, was about to be withdrawn. The claims are based on a letter which Thatcher has recently sent to the trust.

"I am hoping to find that we can go ahead, although we may have to renegotiate," said Bonsor. "This has happened because of a pressure campaign mounted by certain ignorant people who don't know what they are talking about."

MEDICAL BRIEFING

DR THOMAS STUTTAFORD

FRANCIS MOSLEY

Time for truce in the cyclotron war

In recent times, one of the most bitter medical wars has been fought over the cyclotron, a machine for producing high-energy neutron beams which can be used to irradiate inoperable tumours. Advocates of this form of treatment claim that press reports over the weekend of 33 deaths had been stimulated by deliberate leaks of the continuing discussions, and are no more than the recycling of old statistics derived from a time when earlier machines were in use, and before new technology made it possible to minimize tissue damage around the tumour being treated. It is suggested that these reports were designed to bolster lingering fears and made little mention of the hundreds of British people, and more than 10,000 worldwide, who have had otherwise inoperable cancers of the salivary glands, post-nasal spaces and melanomata of the eye treated without catastrophe. By its very nature, the treatment was given to patients whose outlook would otherwise have been bleak, so that the battle does not so much rage over its efficacy in saving a life, but more around the tissue damage which, when the old technology was used, sometimes only saved or prolonged the life at unacceptable cost – for some survivors their remaining years or months became a nightmare.

The supporters of the therapy claim that to compare the damage wrought by the older machines in a minority of patients with the results achieved with a new cyclotron – which produces a narrow beam, shaped to the tumour, so that surrounding tissue is spared – is as intellectually dishonest as it would be to threaten patients in a modern X-ray department with the horrendous complications of radiation that were prevalent in the Madame Curie era.

Certainly at the moment it seems unfortunate that the existing centre at Clatterbridge Hospital in Wirral, near Liverpool, is under-utilized. This may be partly because doctors in the area are reluctant to recommend radiation therapy – in the north-west of England, only 17 per cent of patients with malignancies are referred for radiation therapy, compared to 40 per cent in the south-east – but also because of the fear engendered in patients by the controversy.

Dr George Laramore, an American radiation oncologist who is in Britain lecturing on the use of the cyclotron, has no doubt that when the data from the American trials are analysed, which will take a year or two, the cyclotron will be vindicated and become an established tool in cancer treatment.

Dr Laramore said: "It is unfortunate in Britain that the fire of the battle is in danger of obscuring scientific evidence. Many British physicians would agree that the time has now come to devise a peace formula which will allow both sides to settle their differences without loss of face."

Hahnemann University

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1 June 1990 FAX: 01-44-71-928-9968

Mr. Donald J. Groott, Director
The Cyclotron Trust for Cancer Treatment
Radiotherapy and Oncology Department
St. Thomas' Hospital
London SE1 7EH, England

Dear Don:

I have had the opportunity of reviewing the statement made by Professor Donald Acheson relative to his recent visit to the United States to investigate the potentials and benefits that would accrue from neutron beam projects being carried out in the United States. It is my understanding that he visited with the group at the National Cancer Institute including Dr. Samuel Broder who is Director, Dr. Bruce Chabner who is Director of the Division of Cancer Treatment of the National Cancer Institute, Dr. Eli Glatstein who is Chief of Radiation Oncology at the National Cancer Institute, and Dr. Sandra Zink who is the Officer in charge of the Extramural Neutron Therapy Programs.

It is also my understanding that he visited Dr. Herman Suit at the Department of Radiation Therapy in Boston, Dr. Lester Peters at the M.D. Anderson Hospital in Houston, Dr. Thomas Griffin at the University of Washington in Seattle, Dr. Robert Parker at the University of California in Los Angeles, Dr. William Powers at Wayne State University in Detroit, and Dr. Lanek and Dr. Saroja who are at the Fermi Lab and Presbyterian Hospital in Chicago. I learned subsequently that he actually did not visit any of those individuals where the neutron beam projects are currently being pursued but only talked with Dr. Suit on the telephone, Dr. Griffin on the telephone, Dr. Powers on the telephone, and Dr. Lanek and Dr. Saroja on the telephone. I did subsequently talk to Dr. Lester Peters who said that he never spoke with Sir Donald Acheson nor visited with him and the same is true with Dr. Robert Parker in Los Angeles.

Recently at the examinations for certification by the American Board of Radiology, I had the opportunity to speak more in detail with Drs. Peters, Parker and Powers all of whom have read the report submitted by Sir Donald Acheson and disagreeing with the general tenor left by the report.

Certainly, the projects in the United States relative to the identification of neutron beam therapy is a high priority item for clinical investigation by the National Cancer Institute some years ago, there have been a number of problems in actually implementing the randomized clinical trials. These have related to the time for the development and installation of the machines that were committed to the Cyclotron Corporation but ultimately necessitating installation by local staffs at the University of California-Los Angeles, and the M.D. Anderson Hospital in Houston. This was dictated by the fact that the Cyclotron Corporation became bankrupt and thereby delayed considerably the time for installation. The machine at the University of Washington was developed by Scanditronix in Sweden, went on line expeditiously and on schedule, and has been treating patients without difficulty. The Fermi Laboratory facility has been a cooperative venture with the group at the Presbyterian Hospital in Chicago as well as through the initial aegis of the Illinois Cancer Council but more recently with Dr. Hendrickson's program at Rush-Presbyterian Hospital and Medical Center.

Because of the delays, there were a number of problems in finally evolving the randomized control trial protocols and their implementation. However, the University of Washington, the University of California-Los Angeles, M.D. Anderson-Houston, Fermi Laboratory are on line and participating in the clinical trials. The Fermi Laboratory has been on line for some time and has accession to a large proportion of the patients in the randomized clinical trials. The Harvard Cyclotron has been using the protons for treatment of small tumors in critical areas as well as uveal melanomas. The University of California, Berkeley-San Francisco, unit has been used in treatment of small tumors as well as uveal melanomas using the helium ion.

In general, the data that have been accrued from various clinical trials clearly substantiate the benefit that comes from the utilization of neutrons in the treatment of patients with soft tissue sarcomas, prostate cancer, melanomas, head and neck tumors particularly salivary gland tumors and paranasal sinus tumors, with also demonstrated efficacy in the treatment of chordomas and other tumors in sites that are immediately adjacent to vital and critical structures.

In the beginning there was some difficulty in identifying the appropriate fractionation protraction scheme for prostate cancer but that now has been addressed and patients are being treated using the neutron beam or mixed beam with definite positive benefit being accrued to the patients being treated.

Without question, the entire medical opinion has moved to the point where uveal melanomas can be treated successfully by protons, helium ions or various plaques (Iodine-125, Iridium-192, Ruthenium-109, and Cobalt-60) with results that are equivalent to if not better than those that can be achieved by enucleation. In the collaborative ocular melanoma project, there are major problems with regards to accrual of patients to the project primarily because of the demonstrated positive benefits that have resulted from the conservation

treatment programs preserving the eye intact using helium ions, protons and plaque therapy as has been pointed out by the multiple publications from the University of California-San Francisco, the MGH-Boston, and the Wills Eye/Hahnemann University program in Philadelphia. As a matter of actual fact in the collaborative ocular melanoma project, thus far only 300 patients have been randomized between enucleation and Iodine-125 plaque treatment even though there have been somewhat more than 1200 patients registered in the program. There are many ophthalmologists and radiation oncologists in the United States who believe that it's unethical to offer enucleation in the circumstance where conservation programs of management using radiation therapy are clearly equal to if not better than those that have been achieved in the past by enucleation. The anticipation of 10 years to accrue enough patients in the collaborative ocular melanoma program is clearly unacceptable not only from a medical point of view but an ethical point of view as well as the statistical point of view. It is my belief that the collaborative ocular melanoma program even though it may at one point in past been a good idea is certainly at this point in time a failure in view of the fact that it does not have the demonstrated supported from the ophthalmologists as a whole in the United States. There is at the moment a randomized control trial at the University of California-San Francisco between Iodine-125 plaque therapy and helium ion therapy in both instances the eye being preserved intact. The data thus far from that project clearly indicates that the two treatment regimens are equivalent in terms of tumor control.

The data that have thus far been accrued in a number of series worldwide using high energy neutrons indicate the advantage that clearly relates to the neutron therapy trials being superior to the photon trials. Without question, all investigators who had practical direct experience in the utilization of high energy neutrons indicate that it is the choice for advanced inoperable malignant salivary gland tumors.

The same can be said for treatment of those patients with paranasal sinus tumors. These data are comparable to those that have been published by Errington but also, too, studies from the other control trials.

The data that have been accrued relative to advanced tumors of the head and neck are beginning to show significant advantage to the utilization of high energy neutron in treatment of patients with advanced tumors of the head and neck other than those involving the salivary glands and paranasal sinuses.

The numbers of patients that have been entered into randomized trials with regards to cervix, bladder and rectum are limited in character and because of the demographics of patients available for such treatment regimens was closed in 1988. This represents the demographics of patient populations available for randomized clinical trials in the United States, a very desperate and major problem.

With regards to randomized trials in the United States, it's obvious that there have been major changes dictated by pressures relative to the growth and development of multiple cancer centers in the United States for patient material but also, too, the fact that there has been a major reduction in patients available for randomized clinical trials in the United States. Some 10 years ago there were more than 35,000 patients entered into randomized clinical trials in the United States counting only one patient even though a single patient may have been entered into four trials. Therefore, the 35,000 number represents the actual number of patients even though they may have been involved in more than one trial. This is particularly true in medical oncology trials where a patient may cascade through multiple protocols but still represents the same patient. In 1990 it's estimated that somewhat less than 15,000 patients are being randomized to clinical trials in the United States. This is a major and desperate problem which has significant impact upon the potential completion of any randomized clinical trial--a problem that is not nearly so pressing in Britain.

Therefore, the benefit that might accrue in the treatment of patients with cervix, bladder and rectum which had been the initial phase I/II results indicating the positive benefit that might be expected in mixed beam treatment for these tumor sites from the data from the University of Washington and from the M.D. Anderson-Houston is not being explored at this point in terms of its potential benefit.

From the standpoint of carcinoma of the prostate, it must be recognized that 67% to 75% of all patients with cancer of the prostate in the United States receive no treatment beyond the establishment of the diagnosis. This would include the potential venues for treatment such as estrogen therapy, orchiectomy, radical surgery, definitive radiation therapy-external beam, or definitve radiation by interstitial implant. This obviously had significant impact on the availability of patients for any kind of randomized clinical trial. The urologists in the United States at the moment do not pursue active treatment programs in prostate cancer management. However, the benefits that accrue from external beam radiation therapy in cancer of the prostate remain unassailed and represents a comparable equal treatment regimen in terms of end results to radical surgery and the data thus far accrued now that the proper fractionation protraction schemes have been achieved with high energy neutrons indicate a similar expectation if not perhaps better expectation and end results from the mixed beam therapy.

There are a number of other tumors that have on the basis of phase I/phase II clinical trials potential benefits that might accrue in terms of treatment. These include soft tissue sarcomas, osteogenic sarcomas, chondrosarcomas, malignant melanomas, renal cell carcinomas and anaplastic thyroid cancers particularly those that are medullary in basic cell type. The data not only from Catterall and Bewley with low energy neutrons but also the data that have come from the studies in the United States using high energy neutron therapy and photon therapy show significant advantages

but because of the demographics of patient availability and accrual, this program was closed. This does not mean that in any of those instances where the protocols were closed that no benefit was showned but more importantly that the demographics of patient referrals for randomized clinical trials remains the culprit causing the closure of not only many randomized clinical trials in neutron beam therapy but also in randomized clinical trials in many other treatment modalities and many other national cooperative clinical trial study groups funded and supported by the National Cancer Institute. Making comparisons between high energy neutron beam therapy with combination chemotherapy and surgery is in some sense like comparing apples to oranges since the end results at the moment seem to be similar but certainly the complications from combined multidrug chemotherapy regimens may in the end be more drastic and dramatic than the potential for side effects from the high energy neutron therapy. Data thus far do suggest that better local control of tumors can be achieved with high energy neutrons as opposed to photon beam therapy. In spite of the comments made by Sir Donald Acheson relative to the benefits that might accrue from chemotherapy, I believe that the final result from those trials are far from being completed and even though there has been a flush of enthusiasm in the beginning relative to chemotherapy and surgery with regards to the management of radio-resistant soft tissue sarcomas and bone sarcomas, longer follow-up needs to be collected.

It is still too early to make any definitive comment with regards to the randomized control trial of high energy neutrons versus photons in small cell carcinoma of the lung. At this point in time any preliminary conclusion would be inappropriate and capricious in character.

In cancer of the pancreas there seems to be significant benefit that would accrue from better local control as well as improved survival in the use of high energy neutrons along or in combination with photon irradiation in this particular group of tumors.

Certainly, some of the toxicities that have been reported in previous studies relates to the lack of precise knowledge relative to fractionation and protraction as well as fraction size in terms of the use of high energy neutrons in treatment. Most of the side effects that were considered to be "devastating" in character related to the very far advanced character of the tumors being treated where there was a great deal of tumor necrosis and destruction already in existence at the time the patient was treated as well as the fact that low energy neutrons were used and the lack of really precise biologic data indicate fractionation, protraction and fraction size in terms of management. To use data from the past with regards to this situation is inappropriate but also, too, it must be recognized that in all of the studies that had been reported thus far and even in the randomized clinical trials, there has been a major zealous attention to details of reactions to the neutron beam therapy. Therefore, ther probably has been more precise definition of side effects relative to treatment in this group of patients being treated than probably in any other group of patients currently being treated in randomized clinical trials. One has to keep this in mind when looking at the data from any of the publications relative to neutron beam trials.

If one begins to add the number of cases that are potential benefits from high energy neutron beam therapy alone or mixed with photons, it is clear that even in Britain there would be a large patient population that would benefit from the use of this treatment modality. Certainly, a unit located in London would be far more accessible to the population in Britain than one located at Clatterbridge and Liverpool. It would therefore open up a major new treatment facility for a larger proportion of the population in Britain than is currently available or accessible to patients at Clatterbridge.

With a better understanding of the clinical data necessary to treat appropriately, namely fraction size, fractionation, protraction, etc., it would be possible to utilize such a unit on a 6 day a week schedule which would allow two complete sets of patients being treated each week. This more efficient utilization of the facility with its more easy accessibility would clearly be an advantage with the unit located in London.

It is my firm belief that the data clearly substantiates the value of high energy neutron beams in the treatment of patients with cancer and gives results that are clearly better than the results achieved by photon beams.

It is, indeed unfortunate, that the entire situation has taken on such a major public display of inaccuracies, fiction, and downright hysteria in a program that should clearly be underway and contributing to the management of the cancer patient in Britain.

If I can be of any help in any other way, please do let me know.

Again, I was disappointed I could not be at the meeting in London on Tuesday, 29 May 1990, but if I can be of any help in the future, I would be pleased and delighted to help.

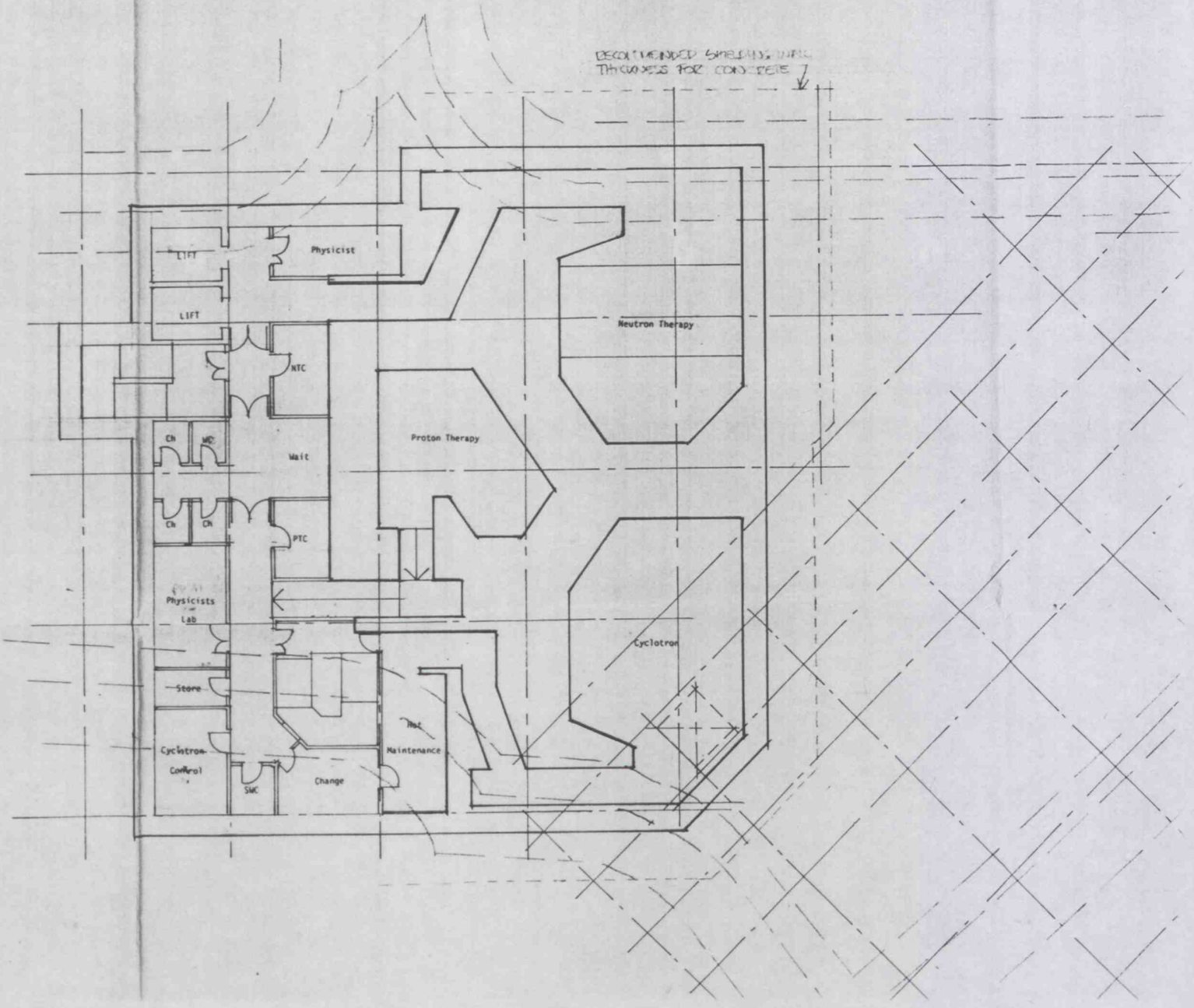
With best personal regards.

Yours sincerely,

Luther W. Brady, M.D.
Professor and Chairman

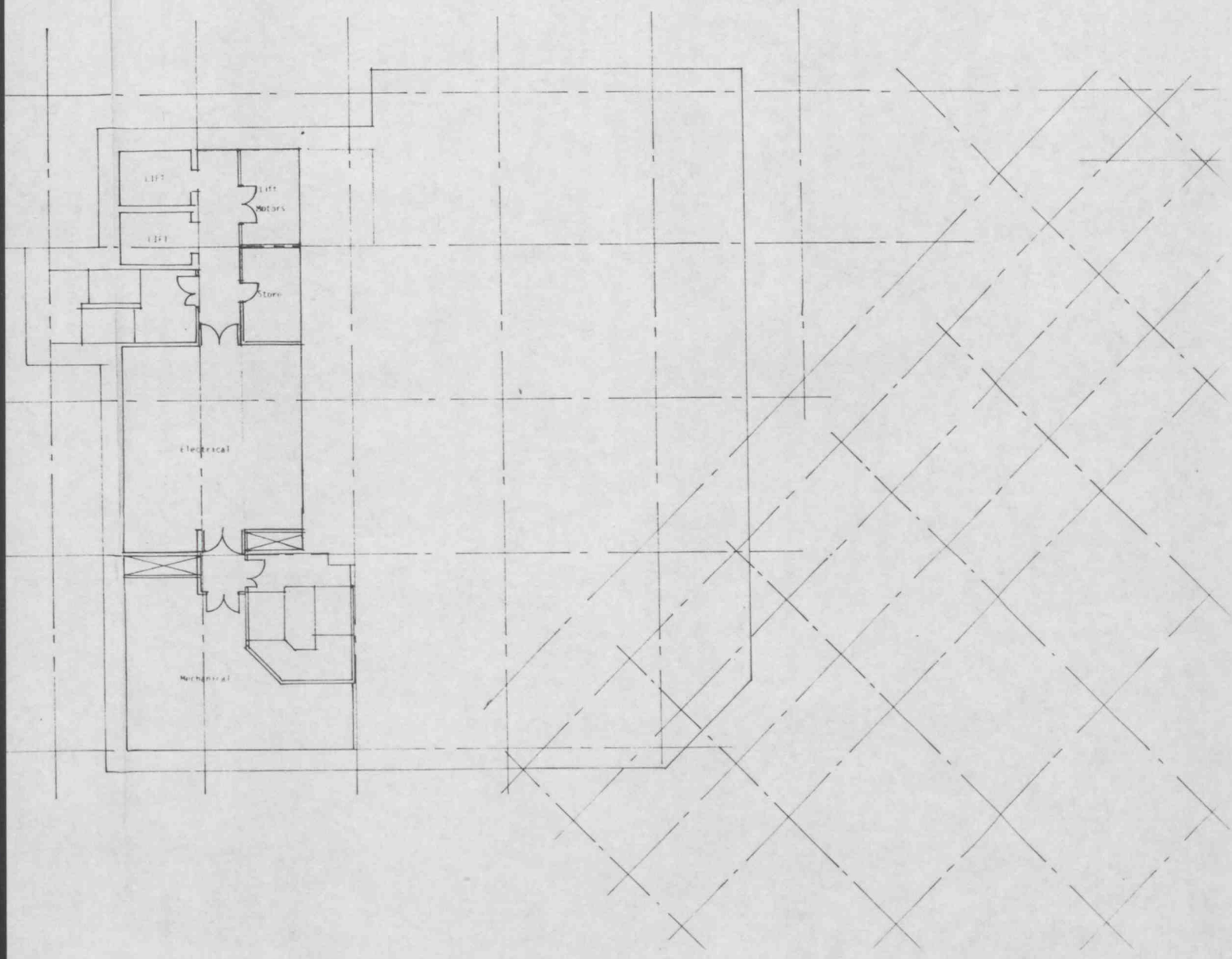
LWB:mlc

cc: R.B.S. Packard, M.D.
Thelma Bates, M.D.



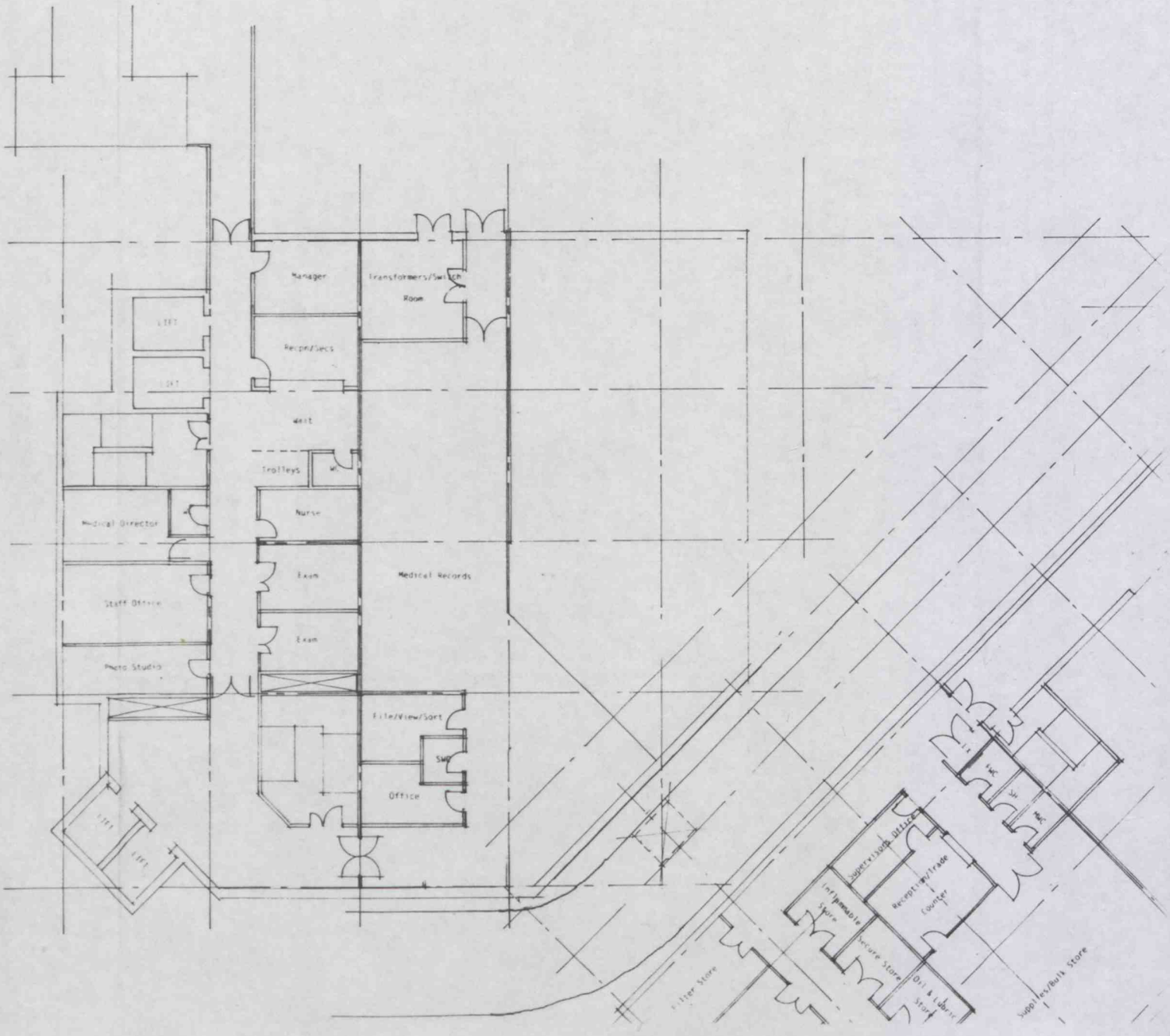
St Thomas' Hospital
New Riddell House

Sub Basement Plan



ST THOMAS' HOSPITAL
NEW RIDDELL HOUSE

Sub Basement Mezzanine



ST THOMAS' HOSPITAL
NEW RIDDELL HOUSE

Basement Plan

THE CYCLOTRON TRUST FOR CANCER TREATMENT

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St. Thomas' Hospital, Lambeth Palace Road, London SE1 7EH
Telephone: 071-922 8031 Fax: 071 928 9968

DJG/FK/310

cc Dr Abrams
Mr Hoppell
Dr Bowdillon.

By Facsimile.

Dr Diana McInnes
Private Secretary to the
Chief Medical Officer
Department of Health

1st June, 1990

Dear Dr McInnes

The Present Status of Neutron and Proton Therapy

Thank you for the draft note of the meeting prepared by the Department and received by facsimile yesterday.

It was anticipated that the notes would attempt to produce a balanced report of the discussions as they took place. This draft will need considerable amendment to achieve this. We shall submit our detailed comments by facsimile on the 4th June.

It is a pity that the Department refused to allow a recording and transcript to be made since this would have made reconciliation of differing recollections easier. Perhaps this is unnecessarily pessimistic.

I look forward to agreeing a note in the early part of next week.

Yours ever

Dan Grocott

D J Grocott
Director

CONFIRMING FAX.

cc Dr Abrams
Mr Hoppell
Dr Bond. Ilm

DEPARTMENT OF HEALTH

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From the Chief Medical Officer
Sir Donald Acheson
KBE DM MD DSc LLD FRCP FRCS FFPHM FFOM

D J Grocott
Director
The Cyclotron Trust for Cancer Treatment
Department of Radiotherapy and Oncology
St Thomas' Hospital
Lambeth Palace Road
LONDON
SE1 7EH

Your ref: DJG/FK/306

31 May 1990

Dear Mr Grocott,

THE PRESENT STATUS OF NEUTRON AND PROTON THERAPY

It was very helpful of you to send us so quickly yesterday the further notes following Tuesday's meeting.

I now attach a draft note of the meeting which has been prepared by the Department. It has been kept deliberately short and focuses on the main points established at the meeting. Perhaps you would be kind enough to let me have any comments that the Trust have on the draft note.

I ought to take the opportunity of making one point on the notes prepared by Dr Laramore. This is that I understand that it was not generally agreed by all those present that the proton beam would be the "treatment of choice" for "posteriorly-located occular melanomas".

DIANA McINNES
Private Secretary to the
Chief Medical Officer

Miscl/7

NOTE OF A MEETING BETWEEN THE CYCLOTRON TRUST AND THE DEPARTMENT OF HEALTH TO DISCUSS THE CHIEF MEDICAL OFFICER'S DOCUMENT ENTITLED "THE PRESENT STATUS OF NEUTRON AND PROTON THERAPY" - 29 MAY 1990 AT RICHMOND HOUSE

Present:

Sir Donald Acheson	-	Chief Medical Officer Department of Health
Dr M Abrams	-	Deputy Chief Medical Officer Department of Health
Dr T Bates	-	Cyclotron Trust Consultant Radiotherapist St Thomas' Hospital, London
Dr P Bourdillon	-	Senior Medical Officer Department of Health
Mr D Grocott	-	Cyclotron Trust
Mr J Hungerford	-	Consultant Ophthalmologist St Bartholomew's Hospital
Mr S Heppell	-	Deputy Secretary Department of Health
Professor C Joslin	-	Professor of Radiotherapy Leeds
Dr G Laramore	-	Radiotherapist - Seattle (Cyclotron Trust)
Mr R Packard	-	Consultant Ophthalmologist Windsor (Cyclotron Trust)
Dr A Porter	-	Radiotherapist - Ontario
Mr A Turnbull	-	Prime Minister's Office

Introduction

1. Sir Donald Acheson explained that the meeting had been arranged to enable the Cyclotron Trust to comment on his document "The Present Status of Neutron and Proton Therapy". In discussion, the following topics were addressed: proton therapy and uveal melanoma, neutron therapy, the workload at Clatterbridge and the toxicity of neutron therapy.

Uveal Melanoma

2.1 The five-year survival of large uveal melanomas is 50% and that of medium-sized uveal melanomas 30%.

2.2 Mr Hungerford and Mr Packard confirmed that no randomised controlled trials have been completed comparing mortality following surgical removal of the eye with that following eye-conserving therapy or comparing mortality in those treated by scleral plaque therapy with those treated by proton therapy. Nevertheless, Mr Packard felt that there was a case for treating virtually all patients by proton therapy, apart from those whose tumours were so large that they had to be removed and apart from those whose tumours were so small that they could be followed up without treatment.

Neutrons

3.1 The value of neutron therapy in inoperable advanced salivary gland tumours was confirmed.

3.2 Dr Laramore supported an observation of Professor Wambersie's (Brussels) that the common histological type of paranasal sinus tumour - the squamous cell carcinoma - responds poorly to neutrons and it is only the rarer types that respond. These rarer types are adenocarcinoma and adenocystic carcinoma, which together have an incidence of 50 cases per annum.

3.3 The value of neutron therapy in advanced head and neck cancer remains uncertain and must await the results of the current American and MRC collaborative trial. Professor Joslin said that further randomised controlled trials would be necessary to confirm the apparent value of neutron therapy in treating inoperable lymph nodes.

3.4 Neutron therapy is not of value in cancer of the cervix, of the bladder or of the rectum.

3.5.1 Dr Laramore tabled some further analyses of the study comparing mixed-beam therapy and photon therapy for locally advanced prostate cancer, which he considered showed strong evidence in favour of mixed-beam therapy. However, there were reservations about using this study alone as a basis for recommending neutron therapy for locally advanced prostate cancer.

3.5.2 Dr Porter said that neutron therapy was one of the exciting developments meriting study in the management of locally advanced prostate cancer. Others, he cited, were brachytherapy (the implantation of radioactive sources into the prostate), surgical removal of as much tumour as possible followed by photon therapy, and hormonal treatment with or without photon therapy. Large randomised controlled trials are underway in the United States comparing neutrons and photons, comparing surgical removal of as much tumour as possible followed by photon therapy and photon therapy alone, comparing hormone and photon therapy and photon therapy alone, and comparing short-term and long-term hormone therapy.

3.5.3 Dr Laramore and Dr Porter agreed that neutron therapy remains a research procedure in the management of locally advanced prostate cancer. Its role in clinical practice must await the results of the trials mentioned in paragraph 2.5.2.

3.6 Some clinicians in the United States are treating patients with chemotherapy-resistant inoperable soft-tissue sarcomas of the trunk with neutron therapy. Many of these patients develop a "large hole" following treatment. Dr Bates suggested that the medical profession shows "intellectual intolerance" to such side-effects.

Workload at Clatterbridge

4.1 It was agreed that Clatterbridge could cope with the neutron and proton therapy workload given in the CMO's document. Were it to be demonstrated that neutron therapy is of value in the management of locally-advanced prostate cancer, the situation would need to be reviewed.

4.2 Clatterbridge cyclotron is currently underutilised with an average of approximately 60 patients having been treated with neutrons there per annum over the last 4 years.

Toxicity of Neutron Therapy

5. There is a narrow "window" when treating with high-energy, as well as when treating with low-energy, neutrons between benefit to the patient and harm. There remains no evidence as to whether a dose of high-energy neutrons, which can achieve a better local control of tumours than photon therapy, can be obtained without an unacceptable rate of serious toxic effects.

Tabled Papers

6. The Cyclotron Trust tabled papers prepared by the Trust itself and by Dr Laramore and also tabled a letter from Dr T Griffin (Seattle). CMO said that these would be looked at in detail by the Department of Health and the conclusions reflected in the advice promulgated.

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PROFILE OF CMO'S EXPERTS AT THE MEETING WITH THE CYCLOTRON TRUST ON 29 MAY 1990

Dr Arthur T Porter

Dr Porter is Head of the Division of Radiation Oncology at the Regional Cancer Centre in London, Ontario. He trained in England before taking up posts in Canada. He has an international reputation for his work on brachytherapy of locally advanced prostate cancer and recently was invited to give a lecture on radiotherapy for prostate cancer by the Royal College of Radiologists.

Professor Charles A F Joslin

Professor Joslin is Professor of Radiotherapy and Oncology at the University of Leeds. He is Chairman of MRC's Heavy Particle Therapy Group which oversees the MRC trials at Clatterbridge. He was a member of the Thwaites team investigating the radiation incident in the Exeter radiotherapy Department in 1988 and Professor Joslin performed the clinical assessment of the patients affected. He is President-Elect of the British Institute of Radiology. He is CMO's former consultant adviser in radiotherapy and oncology.

Mr John Hungerford

Mr Hungerford is a Consultant Ophthalmologist at St Bartholomew's Hospital and Moorfields Eye Hospital. He sees roughly 40 per cent of all patients in the UK with uveal melanoma. He is responsible for the trials of proton therapy being conducted at Clatterbridge and supported by the MRC and the Imperial Cancer Research Fund. A further 40 per cent of these tumours are treated by Professor W Foulds of Glasgow whose expert views were also taken into account in the papers submitted to the Cyclotron Trust.

PART 1 ends:-

Baker to CMO

PART 2 begins:-

Guscott to PS/CMO

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