

FAST NEUTRON THERAPY

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ABSTRACT

This paper discusses the rationale of fast neutron therapy and presents some early results obtained at the Medical Research Council's Cyclotron Unit at Hammer-smith Hospital, London. The importance of the oxygen enhancement ratio for fast neutrons is considered, together with the significance of the small proportion of anoxic cells present in most tumours. The significant features of the preliminary results obtained in patients with malignant disease are presented and the characteristics of fast neutron beams for radiotherapy are discussed.

INTRODUCTION

Neutrons, uncharged particles of unit mass, were discovered by Chadwick in 1932 and a year later Lawrence and Livingstone had developed the cyclotron which was capable of producing fast neutron beams, sufficiently intense for radio-biological experiments. Within three years, Lawrence, Aebersold and Lawrence had carried out the first neutron radiobiological experiments using the cyclotron neutron beam. They found that there were qualitative similarities between the biological effects of neutrons and x- and gamma-rays but that there were quantitative differences. They found that the biological effectiveness of the neutron beam with its more intense specific ionisation was greater than the effectiveness of x- and gamma radiation. This early neutron radiobiology led Robert Stone to start a trial of fast neutron therapy in the treatment of human cancer in 1937 at Berkeley. In 1937 little was known about the radiobiology of x- and gamma rays let alone that of fast neutrons. The oxygen effect had not been discovered and consequently the ability of fast neutrons to deal more effectively with anoxic cells was unknown. It is fitting therefore to pay tribute to the pioneer work of Robert Stone and his collaborators in starting the first trial of fast neutrons in clinical radiotherapy. Full accounts of the work have been published and only the salient features will be reviewed.

FAST NEUTRON THERAPY TRIAL OF 1937 - 1942.

Between 1937 and 1942, Stone treated about 250 patients with the fast neutron beam. Initially his results were very encouraging. Some tumours regressed and disappeared completely and in some cases, no cancer cells could be found in post mortem specimens. No qualitative differences could be found between the tissue damage produced by neutrons and that produced by x-rays. However, many patients suffered from severe late skin and subcutaneous damage especially radio-necrotic ulceration which failed to heal, but these patients had also had severe early reaction. The work had to cease in 1942 because the cyclotron was required for other purposes, but Stone's experience of late skin and subcutaneous damage prevented him from re-starting the work after World War II and delayed further work in the field for twenty years.

SCIENTIFIC RATIONALE FOR FAST NEUTRON THERAPY.

Gray, in 1953, had shown that oxygen concentration had a most important effect on the radio-sensitivity of cells to radiation. In figure 1 is shown the variation of radio-sensitivity against oxygen tension for x-rays and fast neutrons. The thin curve starting from the origin shows the variation of radio-sensitivity against oxygen tension for x-rays and it can be seen that at high oxygen tensions the radio-sensitivity for x-rays has been increased by a factor of between 2.5 and 3. The oxygen enhancement ratio, $m-X$ represents the oxygen enhancement ratio for x-rays. The same curve for fast neutrons is in fact of precisely the same shape but does not reach the same level of increased radio-sensitivity. The neutron curve is represented in figure 1 with a thick curve and has been superimposed on the curve for x-ray. It is seen that $m-N$ represents the oxygen enhancement ratio for fast neutrons and is of the order of 1.6. Gray and Thomlinson in 1955, showed that most tumours over about 1 cm. in diameter contain a proportion of anoxic viable cells and much evidence has been produced since then to suggest that in human tumours the proportion of anoxic viable cells is probably of the order of 1%. These anoxic viable tumour cells present a serious problem in clinical radiotherapy where radiation doses on the borderline of tolerance of the well-oxygenated normal cells are in routine use. The anoxic viable tumour cells represent tumour cells which probably cannot be killed in normal radio-therapeutic practice. They therefore may be responsible for local recurrence, and failure to cure human malignant tumours. These two radiobiological facts, reduced oxygen enhancement ratio for fast neutrons and the presence of anoxic cells in tumours, represent the scientific rationale for the further investigation of fast neutrons for radiotherapy.

Figure 2 represents the results of calculations of the effects of 1% of anoxic cells in determining the single doses of x-rays and fast neutrons required to produce a 90% chance of complete sterilization of tumours of various sizes. It is clear that with radiations of low energy transfer such as x-rays, the effect of even 1% of anoxic cells is of great significance. The x-ray dose required to sterilize a tumour of 75 mm in diameter under oxygenated conditions is around 4,800 Rads, while under anoxic conditions it becomes almost 12,000 Rads. With 1% of anoxic cells present, the radiation dose required is almost 10,000 Rads. With fast neutrons, on the other hand, an equivalent dose of 4,800 Rads would sterilize a 75 mm. tumour, while with 1% of the cells anoxic, the equivalent neutron dose required would be 6,800 Rads. Alternatively, if the normal tissue response limited the radiation dose to, say 6,000 Rads, then, if 1% of the cells were anoxic, such irradiation dose would provide a 90% chance of cure of a tumour just over 2.5 mm in diameter, if the radiation used were x-rays. If fast neutrons were used, on the other hand, the equivalent fast neutron dose would produce a 90% chance of sterilizing a tumour 25 mm in diameter, a tumour volume a thousand times greater. The advantage of using fast neutrons to treat tumours containing anoxic cells is obvious, despite the fact that the oxygen enhancement ratio of fast neutrons is 1.6 - 1.7 and the oxygen effect is therefore not completely eliminated.

It is worth pointing out that an alternative solution to the anoxic problem in radiotherapy is the use of hyperbaric oxygen. Under suitable conditions it is theoretically possible to eliminate completely the anoxic problem. However, to do this it is necessary to completely oxygenate all the anoxic tumour cells. In actual practice, tumour cells are anoxic because the blood supply of these anoxic areas is poor; in effect the tumour has outgrown its blood supply. The success in re-oxygenation of anoxic areas using a hyperbaric technique depends upon an intact blood supply, so that in practice it seems doubtful whether the full oxygen disadvantage can be eliminated by hyperbaric oxygen techniques. Nevertheless, in many parts of the world hyperbaric oxygen has been used and has been shown to be of considerable value in selected tumour sites. This work seems to confirm the importance of oxygen effect in clinical radiotherapy and confirms that in clinical practice anoxic tumour cells are present and provide problems in the treatment of human tumours. Neutron therapy therefore may well be worth pursuing especially when it is considered that the ability of the neutrons to overcome the oxygen effect does not depend upon the integrity of the tumour blood supply.

It has already been pointed out in an earlier paragraph that following the neutron therapy administered by Robert Stone, there had appeared a number of severe late radio-necrotic effects which were at that time difficult to explain. The severity of these late effects had effectively prevented the development of neutron therapy for twenty years. Any further study of the value of fast neutrons for radiotherapy therefore had to begin by investigating the possible causes of the late severe effects noted by Stone. Stone had begun by assessing the relative biological effectiveness of the fast neutron beam as compared with the conventional x-ray radiation which he used at that time. He had determined the erythema dose of fast neutrons necessary to produce a typical skin erythema on patients' skins, and compared this dose with the x-ray dose required to produce the same effect. The doses of x-rays and neutrons which he used for this comparison were, in fact, single doses and were not fractionated courses of radiation. His treatment schedules were based on the relative biological effectiveness which he had found from these single exposures of neutrons and x-rays.

It appeared therefore that it was desirable to start the study of the use of fast neutrons in radiotherapy again by determining the relative biological effectiveness of the neutron beam from the M.R.C Cyclotron at Hammersmith, relative to x-rays.

THE HAMMERSMITH PIG EXPERIMENTS.

The object of the experiment was to try to determine the relative biological effectiveness of the fast neutron beam relative to x-rays using the skin of an experimental animal as the test object. Pigs were chosen simply because pig skin and human skin is much the same in chemical composition, texture and thickness; the subcutaneous tissues are also much the same in chemical composition as those of the human patient. Pigs were therefore given skin doses of fast neutrons and x-rays and the resulting erythema was observed for up to three months following irradiation. Figure 3 illustrates the results obtained. The increase in neutron and x-ray dose of various fractionated regimes is expressed as the ratio of the total fractionated dose to the single dose for equal skin reaction. The much smaller increment of dose required with neutrons is obvious, and attempts were made to establish to what extent this difference was due to a reduction in short-term recovery, or to changes in re-population in pig skin. It was found that the recovery following neutron irradiation was about two thirds that measured after x-ray.

It is clear, therefore, that the relative biological effectiveness of the fast neutron beam increases with the number of fractions given to produce a certain reaction, or the relative biological effectiveness increases with decrease of radiation dose per fraction. Stone's late effects were observed in patients given fractionated courses of fast neutrons, where the dose per fraction was smaller than the single doses he had used to determine his initial relative biological effectiveness. This initial finding suggested that the late tissue damage was a consequence of the increased relative biological effectiveness of the neutron beam with decreasing dose, and also suggested that awareness of this fact might reduce the possibility of late severe tissue damage in any future neutron therapy clinical trial.

It is interesting to speculate on the reason for this increase in relative biological effectiveness with decreasing radiation dose. Figure 4 plots the cell survival curves for x-rays on neutrons and anoxic and well-oxygenated conditions. There are two features which need to be noted in this figure. Both the oxygenated and the anoxic neutron curves have a less well-defined shoulder than the corresponding x-ray curves. Inspection of the figure will show therefore that the relative biological effectiveness of the neutron beam as compared with x-rays, both for the anoxic and the well-oxygenated condition, depends upon the level of damage produced by the given radiation dose. The higher the level of damage, that is, produced by a relatively high radiation dose, the smaller the relative biological effectiveness under both anoxic and well-oxygenated conditions. It appears therefore that the reduction in the shoulder of the neutron curve might be a possible explanation of the late severe damage produced by the fast neutron beam when the increase in relative biological effectiveness with reduction in dose per fraction of radiation is ignored.

It appeared crucial to try to repeat the skin erythema experiment with human patient volunteers and table 1 shows the results of such an experiment. Human volunteers were given doses of 8 MeV x-rays and 7 MeV neutrons to the skin of the thighs and the resulting erythema observed, as had been done previously with pig skin. The relative biological effectiveness increases from 2.9 for single doses of neutrons to 5.3 for twelve fractions in six weeks. It is interesting to note that the relative biological effectiveness obtained as a result of these experiments for human skin was rather higher than the corresponding values obtained for pig skin. The radiation dose per fraction given to the pigs was rather higher than the radiation dose corresponding fraction given to the human patient volunteers; it was thought desirable to do this in order to reduce the possibility of producing severe late skin changes in patient volunteers. The fact that the relative biological effectiveness

for the reduced doses given to human patients tended to be correspondingly higher again confirms the hypothesis that the change in relative biological effectiveness is due to the smaller shoulder on the cell survival curve obtained with fast neutrons.

Figure 5 shows the value of the relative biological effectiveness obtained for both pig skin and human skin, plotted against the radiation dose given per fraction. It can be seen that the results from the pig experiment and the results from the erythema reactions produced on human patients are consistent with the hypothesis that a reduction in radiation dose per fraction is accompanied by an increase in relative biological effectiveness.

THE HAMMERSMITH CLINICAL TRIAL OF FAST NEUTRONS.

The radiobiological investigations as described in the previous paragraphs were complete by the summer of 1966 and in September 1966 the first patient was treated with the neutron beam from the MRC Cyclotron at Hammersmith. At that stage it was considered essential, in view of the previous severe late effects noted by Stone, to ensure that patients did not suffer ill-effects from the neutron treatment. In consequence the first patient was treated with a relatively low dose of neutrons per fraction; in fact a dose of 80 Rads per treatment was given and he had two treatments per week for nine weeks. The skin reaction was minimal and the effect on the tumour was relatively slow in developing. This first patient had a carcinoma of the piriform fossa with chest metastases and by the end of his treatment there had been some regression of his primary tumour but it had not disappeared completely clinically. He survived three months after treatment. It was clear from the initial experience with this patient that the dose per fraction was rather low and patients with advanced tumours were selected for treatment during the next part of the trial in order to try and determine an optimum neutron dose per fraction. From September 1966 to October 1969, forty-five patients were treated. These had tumours in many varied sites, were all well advanced with little hope of cure by conventional means. The neutron dose per fraction was increased until finally an optimum dose of around 125 Rads per fraction, twice weekly for six weeks, was arrived at. During the preliminary three years, one patient in particular had a dose per fraction rather higher than this and developed early on in the course of treatment, a severe reaction which necessitated the postponement of the rest of the treatment schedule. However the radiation reaction healed as one would expect a normal x-ray reaction to heal, in two to three weeks, and she was able to complete her neutron therapy without further mishap.

It is not possible to produce statistical results on the treatment of these forty-five patients. It is only possible to report that tumours responded, that reactions seemed to be qualitatively similar to those obtained with x-rays, these reactions healed satisfactorily, but taking rather longer to heal than the corresponding x-ray reaction. Four patients treated during these early years are still alive, two had had previous irradiation from low LET sources and these have developed necrosis of the skin in the area which had received two separate courses of radiation. One patient who had a liposarcoma of the perineum and was treated with the fast neutron beam has also developed some radio-necrosis in the perineum; this has subsequently healed and there is no evidence of recurrence or residual tumour.

Since October 1969 the clinical work using the neutron beam has expanded greatly; Catterall et al have reported the early observations on a further group of patients treated from October 1969 to June 1970. She has shown that a practical therapeutic regime is 1,440 Rads of fast neutrons given in twelve fractions over twenty-six days and using this regime which implies a dose per fraction of 120 Rads, the relative biological effectiveness is 2.9 - 3.0. During the past two years a further one hundred and thirty-eight patients have been treated. Most of the tumours treated have been tumours of the head and neck regions, but tumours of the stomach and breast and other sites have also been included in this preliminary trial. It is impossible to quote statistical results on the patients already treated because of the different sites included in the preliminary trial and the small number. However, it is true that the results have been encouraging; in all patients who live more than six months, the tumour has shown signs of regression and in very many cases, the tumour has regressed completely, provided an adequate dose of fast neutrons has been given. This is surprising in view of the fact that all the patients treated have been referred for fast neutron therapy because it was thought they had tumours which would not respond well to x- or gamma irradiation. There have been some technical problems in treatment because of the fact that the neutron beam is a fixed horizontal beam. The results of treatment of carcinoma of the stomach and adeno-carcinoma of the large bowel have been most encouraging. A few patients have shown no evidence of viable tumour cells within the treated area at autopsy. However, irradiation of the abdomen has occasionally provided problems due to the irradiation of normal gut.

A control trial of fast neutron therapy in head and neck tumours is in the process of being commenced.

SELECTION OF NEUTRON BEAMS FOR RADIOTHERAPY.

The neutron beam from the Medical Research Council's Cyclotron at Hammersmith has a modal energy of 7 MeV. The depth dose obtained in tissue is slightly better than that from a 250 kV x-ray machine. It is produced by bombarding beryllium with 16.7 MeV deuterons. The target skin distance is 125 cms. The beam is collimated using concrete and borated teak applicators.

Any beam of radiation used for clinical radiation must have a sufficient dose at depth to enable tumours at any site in the human body to be effectively treated. This proviso means that a fast neutron beam of at least a modal energy of 7 MeV is desirable. With the existing Hammersmith beam there is some skin sparing but a higher energy neutron beam would produce more skin sparing and a better depth dose. It is also desirable that the oxygen enhancement ratio should be as low as possible. Information regarding the oxygen enhancement ratio of neutron beams above 14 MeV is not very complete, however there appears to be little difference in the oxygen enhancement ratio for 7 and 14 MeV neutrons. Differences in relative biological effectiveness of various energy neutron beams is, in practice, of little real consequence in the clinical application. Provided experimental radiobiological work is carried out to determine the accurate relative biological efficiency value for the appropriate neutron beam, the clinical dosage used can be modified without difficulty.

It is important also to reduce the radiation dose from the fast neutron beam at points outside the actual field area used. Such scattered radiation is likely to irradiate the whole body and vital structures such as the lens of the eye and the bone marrow can therefore receive some neutron dose. In view of the fact that such neutron dose will inevitably be a small dose, the relative biological effectiveness is likely to rise to quite high values and the problem of cataract formation and marrow depression must be appreciated. It is therefore essential to reduce the neutron dose outside the radiation field to as low a level as possible, this requirement may in fact be far more stringent than the similar requirement for supervoltage x-ray machines in current use.

CONCLUSION

Since the first clinical trial of fast neutron therapy conducted by Stone in Berkeley, a scientific basis for fast neutron therapy has been established as a result of fundamental radiobiological research into the effects of oxygen. The problems of the early neutron therapy trial have been explained and the preliminary work on the present clinical trial has

confirmed that fast neutron therapy can be safe. Both the early trial and the present one have demonstrated that tumours can be controlled by means of fast neutron therapy. The controlled clinical trial is the only means whereby the superiority or otherwise of fast neutrons over low LET radiation can be demonstrated. The fast neutron beam used clinically can also provide means of increasing knowledge into the fundamental action of radiation. Even if the results prove eventually to be disappointing, the study of their effects and comparison with x-ray therapy may well result in a more rational use of radiation in malignant disease.

ACKNOWLEDGEMENTS.

I would like to express my appreciation to Mr. D.D.Vonberg, Director of the Cyclotron Unit at the Medical Research Council, Hammersmith Hospital, members of the Cyclotron staff, in particular Dr. David Bewley, Dr. C.J. Parnell and Mr. G. Burton for providing the neutron beam and to Dr. Robert Morrison, Director of the Radiotherapy Department, Hammersmith Hospital for his help and encouragement.

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Fractionation scheme	Patient	r.b.e values	Mean doses per fraction.	
			8 MeV x-rays (rads)	6 MeV fast neutrons (rads)
Single dose	1	2.99 + 0.5	850	340
	2	2.93 + 0.3	950	345
	3	3.00 + 0.5	1,050	380
	4	2.72 + 0.5	1,050	380
Six fractions in three weeks	5	4.30 + 0.5	425	107
	6	4.17 + 0.4	425	119
Eleven fractions in 5½ weeks	7	4.73 + 0.4	354	71
Twelve fractions in six weeks	8	5.35 + 0.5	333	67
	9	5.28 + 0.5	354	71

TABLE I

Neutron r.b.e. Values Determined from Skin Erythema Reactions on Volunteer Patients.

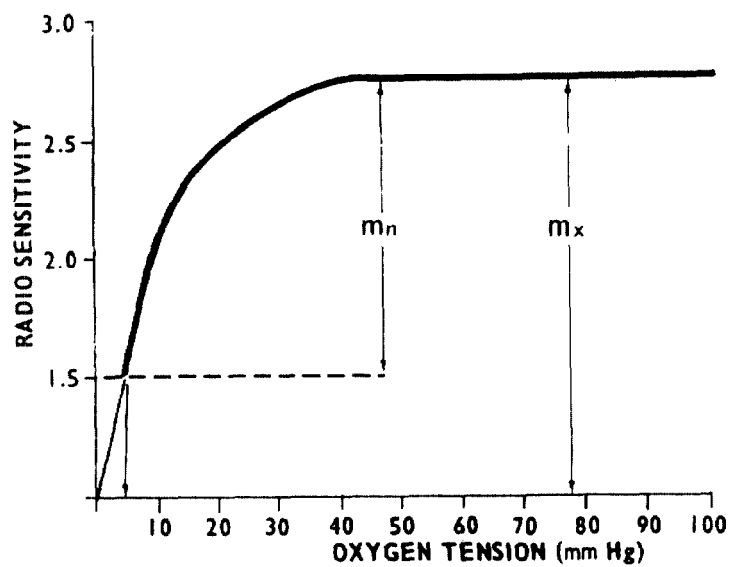


FIGURE 1

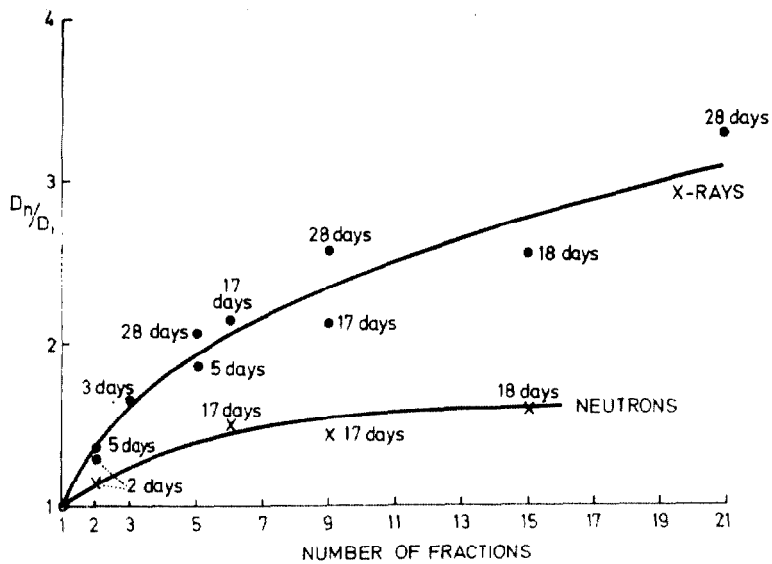


FIGURE 3

FAST NEUTRON THERAPY

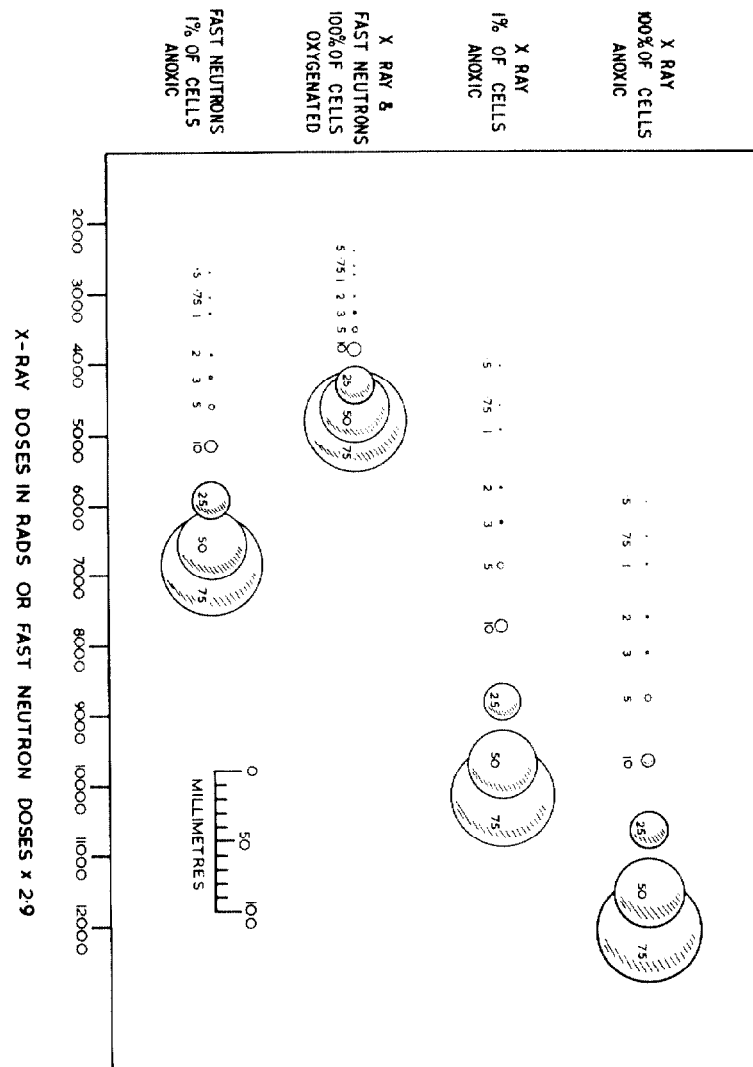


FIGURE 2

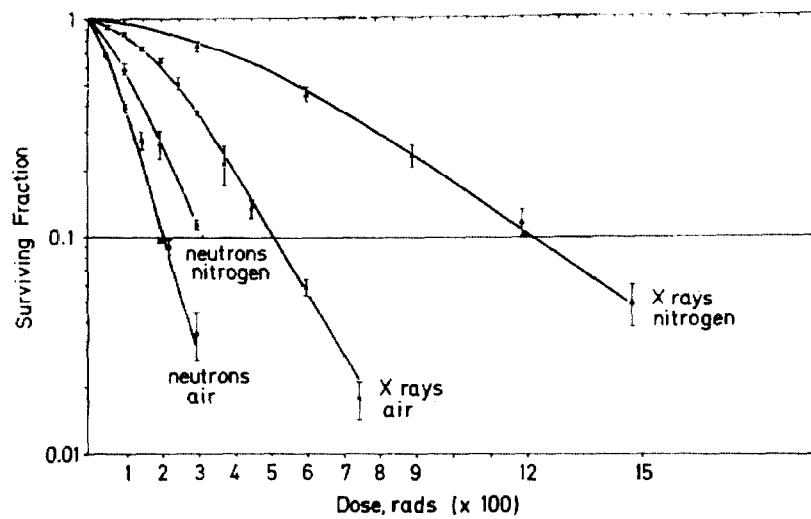


FIGURE 4

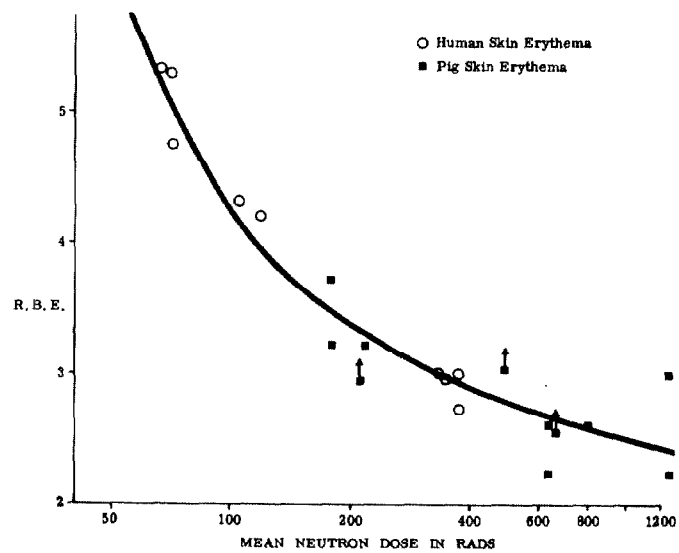


FIGURE 5

DISCUSSION

BLOSSER: I was talking with a radiologist a few months ago who made the statement that for some types of cancer the Hammersmith neutron work had made something like a factor of ten improvement in the survival rate from, I believe, 5% up to about 50%. Could you comment on this?

MORGAN: I think this is a little early to make any statements regarding survival rate improvement. A controlled clinical trial of head and neck tumours has been started, but this is in an early stage and, in fact, the majority of tumours treated in the last few years have been fairly advanced. But it is true to say also that we have seen some quite astonishing long-term survivors. The man I showed you with a liposarcoma, notoriously difficult to treat by conventional means, has in fact survived four years without any sign of recurrence. One wouldn't have expected this; one would have expected something like nine months to a year. A man with a very advanced carcinoma of the tongue which was treated in 1969 is still alive, again without any sign of recurrence. There are cases of this sort showing excellent unexpected responses, but statistical results of significance are not yet available. I cannot honestly say that one could be able to quote figures suggesting a 10 times improvement in the survivor rate yet.

BLOSSER: Is the quotation in agreement with the present state of things?

MORGAN: I think in general it probably is, but I wouldn't have thought that one should quote figures; it is sufficient to say that preliminary results are very encouraging.

HARPER: I wonder if you could comment briefly on the relationship between the neutron energy and the radiobiological effect. At what point do the fast neutrons lose their favourable radiobiological effect?

MORGAN: I can't really answer this because I don't think we have enough evidence at the moment. The best beam that we need for radiotherapy is a beam with as low an oxygen enhancement ratio as you can get compatible with as high a depth dose as you can get. Now when you think of the x-ray analogy, if you consider something like 8 or 10 MeV x-rays producing a 50% depth dose at around about 12, 13 or 14 cm deep to the skin, there isn't a great deal of point, from the point of view of ability to deliver an adequate dose to any tumour anywhere, to having a beam with a higher depth dose than that. By analogy this will take you to a mean neutron energy of around 15 to 25 MeV. The evidence we have is that there is a fall in oxygen enhancement ratio as you go up in energy from 7 MeV; at 14 MeV the reduction in OER is slight. The higher you go I would have thought that you were not going to have a very significant fall in OER, but experimental evidence is lacking.

HARPER: Suppose you go down in energy?

MORGAN: If you go down in energy, you are then limited entirely by depth dose, and I would have thought that the 7 MeV mean neutron energy we have at Hammersmith, with depth doses like 250 kV x-rays, is about as low an energy as one can use. I don't think one can really go lower than this and still be able to treat the tumours one wants to. One cannot deliver the physical dose at depth, and after all is said and done, even with all the advantages of neutrons, in the end one is still dependent on being able to deliver a sufficient dose to produce a biological effect at depth. There isn't any way around this, I think, unless one can implant a neutron source, and that is an entirely different story.

TUNNICLIFFE: There are two arguments I have heard against neutron therapy. Perhaps we could take these one by one. One attacks the oxygen enhancement ratio. The argument goes: if I use γ -rays to treat the tumour and use proper fractionation, as the tumour shrinks the anoxic cells in it regain their blood supply. Is there any validity in that argument?

MORGAN: I am sure there is. This is a very important argument and applies not only to neutrons but also to x-rays. The point that the argument makes is this: after the first fraction of radiation, be it x-ray or neutron, the whole pattern of life inside the tumour has changed. Some cells perhaps have become more anoxic because of the pressures from the irradiation effect on the cells that have been damaged; other cells have become less anoxic. What happens in a particular case is open to a good deal of speculation. We haven't much evidence to suggest what really happens. It is difficult to measure any changes in local oxygen concentration, and there isn't a model that I know of which gives an answer that can be accepted clinically.

Now the argument goes on to suggest that after a few fractions of x-rays the blood supply improves because the tumour tension decreases and allows the oxygen to get in a little more easily. Each fraction after that has a better effect because the number of anoxic cells has gone down. This is almost certainly true. If the anoxic problem were the only factor determining the cure of tumours, it is difficult to see how radiotherapists have cured so many tumours over the past 70 years or so by conventional techniques without exploiting the oxygen effect at all. The whole problem is complex and although it seems likely that after successive fractions of radiation the anoxic areas change, it is difficult to quantitize this change. The argument is perfectly valid, but unfortunately the lack of quantitization makes it impossible to suggest whether x-rays, neutrons or a combination of both should be used. It may be argued that neutrons should be used initially to reduce the number of anoxic cells and again at the end of the course of treatment to destroy the last surviving anoxic cells. The argument is valid but is a little imprecise and cannot at the present time be used as a basis for a rational scheme of radiation therapy.

TUNNICLIFFE: The second point is connected with the use of high and low LET radiation; the neutrons are basically high LET radiation. The argument attacks the use of high LET radiation. The figure you showed where you have a semi-logarithmic decay in the cell population with high LET radiation compared with the x-ray curve--there is a shoulder on the low LET curve, that shoulder is said to be due to a region of sub-lethal damage to cells, and what one really wants to do in the treatment is to take advantage of that sub-lethal damage. Therefore, low LET irradiation like x-rays is the proper radiation to use.

MORGAN: I wouldn't accept this. I would agree that the shoulder represents the sub-lethal effect. I would agree in fact this is a region where cell repair occurs. It may be that the differential effect we see between tumour cells and normal cells is due just to this part of the curve. It may be that we kill the tumours because normal cells can repair much more quickly after radiation damage than tumour cells can. Therefore, each successive fraction gives you a bigger differential between normal cells and tumour cells until eventually you hope there are no tumour cells left. If you think of the lymphomas, where experimental evidence suggests that perhaps there isn't a shoulder, these are tumours that can be destroyed easily. It may be those tumours which are curable by x-rays, with relatively low doses of radiation, those tumours where the tumour cells exhibit a cell survival curve without a shoulder, or at least with a very small one. The point I am making all the time is that these are valid speculations, but we haven't very much in the way of concrete evidence as far as normal human tumours are concerned to be able to use these as a basis for any therapy technique.

URTASUN: Can you make any comments on the repair of hypoxic cells? Is there any repair of hypoxic cells as compared with oxygenated cells?

MORGAN: As compared with what? Under x-ray conditions or neutrons?

URTASUN: Under x-ray conditions and if you have any idea about neutrons. There is some revision of our concepts on repair, whether repair occurs or not under hypoxic conditions.

MORGAN: I suspect it probably does, but to a reduced degree. I think that a lot of the difficulties which radiotherapists are experiencing now are due to the fact that we cannot very easily translate effects that are observed in vitro into the human tumour problem. One of the efforts we ought to be making is to try and design radiotherapy regimes not only to try and cure the patient but to provide some information on what is actually going on radiobiologically in the tumours concerned. This is something we haven't been doing to any great extent yet.