PANEL SESSION: "ACCELERATORS FOR HOSPITALS"

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WIDEROE

The title of this session is "Accelerators for Hospitals". The theme is difficult: three different fields come together and even a whole week would be too short for discussing the problems. Here we only have 55 minutes and must restrict ourselves to some essential questions about radiotherapy. We start with J. P. Blaser, perhaps the physicist here being least impeded by medicine; he will say some words about present and future accelerators. Next, I will talk about radiobiological aspects. G. Burton will mention neutrons, high-LET radiation, and B. Larsson the low-LET prospect: protons. Finally, K. E. Scheer will help us with the cardinal question: "What sort of accelerators should the hospital have?".

The physicists today ask this question of the doctors, but we all know that so far, history has run other ways. In most cases, the physicists built their toys for various reasons and then asked the doctors to try them out on patients. Today, the situation might be slightly different. Perhaps we can say what we need, but perhaps it is still too early. Time will show.

BLASER

I may just say a few words to outline the problem as we have seen it from the standpoint of the Conference. We thought it useful to have some discussions to try to bring into contact the needs of medicine, the present and the future ones mainly, with the capabilities of accelerator builders. We thought that some of the best accelerator builders are assembled here. It could be useful to convey to them the immediate needs of the medical community. There is a difficulty in this task - mentioned already by R. Wideröe - that we have at present a whole spectrum of problems, a whole range between small and very large facilities. For instance, pion therpay should and will be tried out at Los Alamos, TRIUMF and SIN. Then there is the multipurpose facility in South Africa, where physicists and medical people work together (about 50 % each on the same machine). The very specialized machine for hospitals, which R. Wideröe has already mentioned, is probably a thing of the future, with the exception of the presently already working compact cyclotron.

There is no hope at the moment to build an accelerator which you could put into a hospital and fulfill all the needs. For example, pion and neutron therapy has to be tested at the large facilities for a long time. There, the initiative will remain with the physicists. It is hopeless to ask our medical people to tell us what we should build; so the physicists should be interested in providing beams and beam time to their medical colleagues, and in this way new methods will be developed! On the other side of the spectrum, with very specialized machines, there are quite different boundary conditions and two of the most important are the operational and financial conditions. It must be realized that any routine in medicine has to be financially reasonable, what ever that means, and that, operationally, a machine has to fulfill very different conditions than the physicists are used to. For these specialized machines, I think the medical community should really tell the accelerator specialists what they need and I hope that from some problems raised in this panel we may have some advice from specialists. It is clear that in hospitals there are a variety of needs. We have heard about isotope production. Some isotopes ought to have a routine service, with things like purity of nuclides, availability of the cyclotron at any time, and, again production cost being very important. I would like to mention that in planning isotope facilities, one should not forget that the chemical facilities needed to really produce the isotopes may be much larger than the irradiating cyclotron itself. Then, for isotope production, we have to distinguish between on-line machines and larger ones which may be needed for economical production of specialized isotopes, like I^{123}. Now, in therapy it gets even more complicated. I think we should not talk about X-rays and gammas and electrons: these are well provided for already by industry. The main particles to be discussed are neutrons and protons, both for therapy and radiography. Then, for the very far future, which has not to do at the moment with accelerators for hospitals, we can discuss how to produce pi-mesons economically. In producing pi-mesons, it is clear that the machines will remain extremely costly, so that one should not start now already to make cost effectiveness calculations. If one would do that, one probably would stop working with them, which would be a pity. That is all I wanted to say as an introduction for the panel.

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WIDEROE

I would like to talk now about radiobiological aspects of tumour inactivation: tumour treatment with ionizing radiation is based on destruction and sterilizing of the tumour cells. When the number of tumour cells is reduced below a certain value (n_a), the tumour will disappear and not resurrect. With n tumour cells surviving, the probability for control is

$$\exp(-n/n_a).$$

A total dose of D will create

$$n = n_o \exp(-D/D_o^*)$$

surviving cells and the probability for tumour control will thus be

$$\exp(-n_o \exp(-D/D_o^*)/n_a.$$

The decay factor D_o^* depends on the single doses given, the sensitivity of the tumour cells and also on the quality of radiation. Clinical experience has shown that average tumour cell sensitivity is similar to values measured in vitro and decay factors can often be calculated fairly well. There is a great difference between oxygenated and anoxic cells, the latter might be 1.5 to 3 times less sensitive to radiation, depending on the type of radiation used. The anoxic tumour cells represent a great problem to radiotherapy: very often they might decide between success and failure.

Reoxygenation which can be influenced by the treatment program might be of great help in overcoming the problem, but today, the process is not well known and it may fail, so that tumours will resurrect and grow out of control.

There are two other ways to deal with this problem:

1) The use of certain drugs such as Metronidacole and Ro07 - 0582 to sensitize the anoxic tumour cells, and

2) the use of types of radiation for which the sensitivity of the anoxic cells is greater (i.e., the radiations with a lower OER), such as high-energy neutrons and negative pions.

The first way has been studied for many years but promising results have been achieved only quite recently. The solution would be a very elegant one and perhaps will eliminate all use of high-LET radiation, but the investigations might still need 5 to 10 years.

The second way is represented by neutron and pion irradiation. The neutrons have the disadvantage that the depth doses are too low (about 48 % at 10 cm depth for 16 MeV neutrons) and, consequently, most clinical trials have been made with head and neck lesions, i.e. not very deep-seated tumours. The clinical results so far might perhaps show some improvements over low-LET radiation (especially Co 60 gamma rays), but they are very questionable and do not at all indicate any break-through. The negative pions produce much better depth dose curves and they give a substantial advantage over the neutrons. The drawback is, of course, the great cost of their production. For the next years to come, they will surely be used for investigations and for research mainly.

In conclusion, I would like to say that all three possible ways to solve the anoxic cell problem, improved re-oxygenation, drug sensitizers and high-LET radiations, need more investigation and clinical research before an evaluation might seem possible. Clinical work always needs time and ten years are not too much if you want to get a good convincing statistic. So far, the long term side effects of high-LET radiations and also some nasty effects, such as the induction of malignant tumours, have not been sufficiently studied.

BURTON

At Hammersmith, we have been working with neutrons for quite some time and the results, up to the end of last year, have been published in the British Medical Journal and in the Medical Research Council Annual Report. They show that neutron therapy gives a striking advantage to patients in terms of the regression of the primary tumour. As a result of all this, in the United Kingdom they are in the process of installing a second cyclotron at Edinburgh for the sole purpose of treating patients with neutrons in conjunction with the VEC group at Harwell and the Radiobiological Unit at Harwell. We are planning to do clinical trials on the VEC at 42 MeV. So, I think, there is the beginning of considerable evidence that neutrons have advantages in radiation therapy.

SCHEER

We see, indeed, an increasing interest in the use of neutrons for radiotherapy. As a consequence, I think, mainly initiated and stimulated by G.W. Barendsen, a group in the EDRTC has been formed in order to try to make some recommendations to introduce some uniformity in the conditions, some standardization, so that it will be possible at a later date to compare these results with have been obtained with neutron therapies at different places. I would say there is much evidence, on the basis of results obtained at Hammersmith, that neutrons have a real benefit, at least in some kinds of tumours. There is, however, no definite proof of that, and the proof will take many, many years to come through. But we feel that it is justified, on the basis of the encouraging observations at Hammersmith, to recommend that, at different European centers, clinical trials with fast neutron beams should be carried out. That is what the EDRTC is doing.

BARENDSEN

The EDRTC has, as K.E. Scheer mentioned, formed a Task Group on Neutron Clinical Radiotherapy and any center which plans to start clinical applications of fast neutrons, pions or heavy ions, could join this effort by writing to me as secretary of the Task Group.

WIDEROE

The great difficulty with neutrons are quite truly their late effects, as observed after the first experiments at Berkeley. There are also quite nasty effects which you can get with neutrons: I think, for instance, of the inducement of cancer.

BURTON

I can say categorically that at Hammersmith, we spent something like 10 years on animal experiments, and I am quite sure that the clinical treatment would not have been started if there was any danger of the later effects that were observed after the Berkeley trials in the 1940's. But it is perfectly true that the survival rate of patients is very low at Hammersmith because of the fact that, so far, we still treat cases with very low prognosis. Nevertheless, we have had some extremely good results in terms of enhancement of the survival rate and the improvement of the patient comfort. M. Catterall - and I know that I would be expressing her views here - regrets the fact that at the moment she is unable to progress to patients with a much better prognosis for survival. Until this happens, the true effect of neutrons is really not likely to be seen. The sooner we can move to that position the better; but this seems to be more of a political problem within the medical field rather than a practical problem.

WIDEROE

Do you think that there are advantages with high-energy neutrons?

BURTON

Yes, our present energies are certainly too low, as has been stated this morning. We accept this at Hammersmith - there is no doubt about it - and this is the reason why we are collaborating with the VEC in order to use the higher deuteron energies which are available there. The main thing, of course, is the increased depth dose. I do not think that there is anything else to say. I personally believe we accelerator engineers, and I class myself as that because that is what I do at Hammersmith, should really look at this question of the design of accelerators and find out what the medical field is likely to require. We should not necessarily accept that what is good for the physics establishment is really wanted for the hospital establishment. I personally do not accept that a 40 MeV deuteron machine is an expensive machine. I think that it could be designed economically and design studies should be done. In fact, in one or two cases they have been done; certainly I have done some of my own studies at Hammersmith, based on ring machines. I think that the same approach has been made in the proton field, the pion field and the high-energy heavy ion field. I do not think that anyone can expect that machines like the Los Alamos linear accelerator or the S.I.N. cyclotron would fit into a hospital; they just will not. Therefore, one has to look for a new way of tackling this problem, and I am certainly looking at it from an outside point of view. I think that much more serious studies should be made on synchrotrons. (I think you will chase me out of the hall at the end of this meeting, for saying this!) You do not need high intensities when you are using the primary particles, such as protons and high-energy heavy ions for treatment. Therefore, you can get away with much less complicated and cheaper machines.

WIDEROE

About how much would such a big accelerator for protons cost?

LARSSON

We have published a fairly extensive report on a model project for 200 MeV protons at Uppsala. We calculate on the basis of 200 treatment sittings per day. For these 200 patients, we need five treatment rooms and we have carefully considered the installations in these treatment rooms. With all this system, we had economical similarity with a system of betatrons or linear accelerators; this means about 20 million Sw. Fr. for the machines, magnet and so on.

I am convinced that a cyclotron or a synchrotron for 200 MeV protons will fit into a hospital. This is what we are going to have, and it keeps us conveniently supplied with treatment rooms. But let me make now some general statements about tumour treatment.

I think that you have heard that there are about 100 types of tumours in terms of cellular origin and degree of malignancy. It is very difficult to draw conclusions from clinical trials, even if the first trials have to be performed in order to create a certain confidence for radiobiology among the clinical people. It is also necessary to realize that it is impossible to rely, in radiotherapy, on the principles of physics and radiobiology alone. Look, for example, at the scattered points on G.W. Barendsen's diagram today, where he showed that the tumours with fast growth should conveniently be treated by low-LET particles and the tumours with slow growth by . radiation with high-LET. This is, of course, not the proof that the same thing is valid in man; it is not the proof at all, but it is an indication that there might be a place for both high-LET and low-LET in tomorrow's radiotherapy. We have to be prepared to live with this question for years to come: we do not know whether high energy or low energy radiations will do. Probably both will do and they will do it in common. Therefore, I think that if anyone is considering a big machine for a hospital, he should be prepared to be able to use this machine both for the production of high energy and low energy radiation. Say, for example, 200 MeV protons and 50, 60, 70 MeV deuterons, and use some originality, perhaps mix the radiations in one single patient. I think that it is very important that we keep the versatility of our machines, even when they are going into the hospitals. The situation is not going to be broken. Somebody, here or there, will show anything about high energy radiation and its advantages over the lower energy radiation. The next week somebody else will propose that, for 95 % of the tumours, low energy radiation is much better than high energy radiation.

SCHEER

I fully agree that versatility is a very important thing. About three years ago, the IAEA was considering recommendations on cyclotrons for medical use and came to the conclusion that one should not limit oneself too strongly on the maximum available energy, since higher energy gives more possibilities.

On the other hand, we should perhaps not neglect to consider a possible neutron production facility as the other end of the scale, in terms of price and economics. Neutron generators have not yet been successful in medical use due to two main disadvantages: the one is the very limited lifetime of the targets, the other is the rather low (not to say insufficient, but a little lower than we would need it) dose rate. But it seems that, with some newer technical development, these disadvantages have been overcome. A machine like that, due to its size as well as its operational tasks, fits much better into a hospital than one of the big cyclotrons. I feel that, if the interest on the application of neutrons for radiotherapy grows, most hospitals, in a few years, will be in a position to produce these neutrons on the basis of the low energy deuteron-triton reaction.

WIDEROE

While we are still discussing the deuterons, I would only like to stress a point which I forgot to mention. For neutrons, the reoxygenation is also important and in order to get 90 % tumour control, we need about 3000 rad. The so-called tolerance dose, however, is only about 2000 rad. How is it then possible that these neutrons can be used and give such good results? First of all, I have to mention that the radiosensitivity of the tumour cells is not the same in all cases, of course. Next, I have to say that the size of the tumour is very, very important. If you have a small tumour, the tolerance doses will be higher. This might be the explanation why M.M. Kligerman got so good results with his very small tumours using pions. So, when you are making comparisons, do not forget the size of the tumours.

Going back to protons: There is some interest in proton therapy in Russia. Have you heard anything special about that, Mr. Larsson ?

LARSSON

The proton treatments in Moscow and Dubna are indeed very interesting. We have a collaboration with these groups, and I am very happy to say that these are very interesting projects. At present, the Russians are at the same level as we are in Sweden, the number of patients being about 100. These patients are scattered in various categories, and, having listened to my lecture before, you will understand that I am not willing to make any conclusions on the basis of such a small number of patients. But what they have shown is that they could work with those patients and that the technology of proton radiotherapy is very worthwhile studying. I also think that the reason why they are interested in our activities might be that they feel there is an economical way of treating patients with protons, which could perhaps be worthwhile testing. Moscow would certainly be a good place for doing that.

WIDEROE

Do you know about other places where there is some interest in proton therapy ?

LARSSON

Yes, of course. I refer to Harvard and Berkeley and there are also some considerations about using the 200 MeV injectors at Brookhaven and at the Fermi Laboratory. I think that the Harwell synchrocyclotron has been suggested, too, for these types of activities.

SCHEER

I think that there is a definite interest in utilizing protons for radiotherapy purely because it is a physically very appropriate radiation, not considering any RBE at all at the moment. You have advantages if you can shape clearly a uniform dose distribution within the field, provided you know where the tumour is and what the extension of the tumour is. In order to take a profit of these physical advantages of proton beam irradiation, you must have much improved diagnostic procedures. With somewhat complicated systems and a computerized program, protons can offer a great help in providing much more details based on smaller differences of density inside the body than is currently the case with X-rays.

WIDEROE

Is there any question from the audience ?

ALBERT

I would like to point out that between the two extreme cases of a compact cyclotron in a hospital and the hospital around a big accelerator, we have in Orléans, France an intermediate stage. Our C. G. R. - MeV cyclotron, e. g. 50 MeV α, is about 2 km away from a big hospital. A special section of this hospital was built around the target room of the cyclotron for the routine use of short lived isotopes in medical diagnostic.

BURTON

I would never be able to speak to D. Silvester again, if I did not mention the use of accelerators for isotope production in hospitals. As an example I would like to illustrate the type of work that is done at Hammersmith with a cyclotron and use it to comment on some of the problems that have to be solved by an accelerator in a hospital. This year we could no longer leave the machine just "free for everybody" during running time. Occasionally things go wrong; the machine does not start up first thing in the morning. Something is not O. K. and you do have to spend a few minutes getting the cyclotron on the air. But our schedule is so tight with patients being transported to the hospital, that we have to do technical maintenance on the cyclotron between clinical uses. Furthermore we had to choose a priority system with the following order of priority:

A on-line patient work with direct neutron irradiation or whole body activation analysis.

B production of isotopes for a hospital somewhere in the United Kingdom. Fixed train or airplane schedules have to be met.

C non patient irradiation. This can be clinically oriented like in beta analysis.

D experimental work, usually physical or experimental engineering developments.

Another feature I would like to draw your attention to is that we have got A/A and A/A/A which indicates that during this particular period of time, top priority is going to two or three clinics. In July of this year, we tried for the first time to keep three clinics going with neutron therapy, use of ^{13}N and use of ^{15}O all piped to different places within the hospital complex. This has been so successful that we have extended this scheme. On Mondays and Fridays, the machine is totally given over to clinical work, and virtually every day of the week we have on-line work.

Let me close by listing the main requirements for neutron therapy, as quoted by M. Catterall:

1) reliability - if treatment is delayed it could be too late.
2) output intensity - treatment times should be comparable to ^{60}Co irradiations.
3) vertical and horizontal beams are needed.
4) adjustable or interchangeable collimators are essential.
5) accurate monitoring - dose should be repeatable to $\pm$ 2 %.
6) initial deuteron energy need not be greater than 40 MeV.
7) the accelerator should be sited in a hospital.

BLASER

I will try to sum up the consequences of this talk and to give to our accelerator specialists assembled here some work to take home. We have found that, for our medical community, there is still a need for versatile and sometimes very large and complex installations. So, very different machines are needed, not a single type. For neutrons, which are very well introduced, we note that higher energies are desirable and that the intensity problem should also be worked on in order to get sufficient doses. A very important conclusion for accelerator specialists is, I think, that protons probably have a very interesting future both for tumour treatment and for radiography. If, for example, radiography is successful, we would not need a high intensity. Now, such an accelerator does not exist yet and I would suggest that some people present here try to think a little bit on how to make such machines. For the two others, more future applications, pi-mesons and heavy ions: I agree with G. Burton that machines thinkeable in that field do not fit into hospitals. I know that E. Knapp of Los Alamos does not agree with me. He quoted that, for 5 million dollars, he could build a 500 MeV proton linac, fitting under a parking lot and operated by a nurse. Well, we all know that they have indeed large parking lots in the United States, but concerning this super nurse, we would like to hire her on the spot! - Jokes aside, for acceleration of intense proton beams, one can use linacs or cyclotrons. Linacs are very expensive machines in terms of power consumption. But for both machines, I would like to stress the importance of radioactivity problems. One should, therefore, concentrate on catching all pions produced by protons at the target. - For radiotherapy with heavy ions, the intensities at high energies are still low.