VNIVERSITAT DE VALÈNCIA

Investidura com a Doctor "Honoris Causa" per la Universitat de València a Ugo Amaldi

Discurs d'acceptació

València, 8 novembre de 2000

Valencia, 8 November 2000

PARTICLE ACCELERATORS: FROM FUNDAMENTAL RESEARCH TO CANCER THERAPY

-A study case of spin-offs from science to society-

Ugo Amaldi

University of Milano Bicocca and TERA Foundation, Italy

1. INTRODUCTION

No one of the scientists sitting in this wonderful hall doubts that *basic research* has to be pursued for the only sake of understanding in depth and enjoying the world in which we live. Still, since about twenty years both politicians and the public ask scientists more and more frequently to

(i) better describe what we do, what we learn and
(ii) fully explain what advantages society draws and can expect to obtain in the future from the funds – often large funds – allocated to fundamental research.

In this address I want to discuss the second request, which can be summarised in a direct question addressed to any scientist: "*what are the benefits of what you do for our society?*".

It is common experience in physics that only a fraction of the accumulated scientific knowledge produces almost directly spin-offs. I call it "*usable knowledge*". But since there are more pathways by which a scientific activity can influence society, I shall discuss the case of particle accelerators considering four output streams:

usable knowledge,
people,
methods,
technologies.

I have chosen this study case mainly because I know it well – since I have devoted my professional life to it – but also because it displays at best, I think, the many facets of such a complicated issue.

2. 'USABLE' KNOWLEDGE

The history of our field opens with a wonderful example of usable knowledge. In 1895, within days from the discovery of X-rays, Röngten took the famous radiography of the hand of his wife. Within months the first irradiation of a superficial cancer took place. Without any doubt the 'pure' scientific knowledge acquired with the best electron accelerator of the time – a Crookes tube - was also 'immediately useful' knowledge.

X-rays are an exceptional case since detailed studies show that twenty-five years are needed, on average, for a fundamental discovery to find its application. However the scientific activity that at the beginning of last century was called '*nuclear physics*' and now we call '*subatomic physics*', '*particle physics*' or '*high-energy physics*', has seen other examples of rapid applications. For instance nuclear fission was discovered at the end of 1938 and the first nuclear reactor was running in 1942, after exactly four years.

Opposite examples can be given. For instance, the antiproton was discovered in 1954 at the Berkeley Bevatron. For this discovery in 1959 Owen Chamberlain and Emilio Segrè were awarded the Nobel Prize in physics, but often-mentioned applications were never realised. However, after more than 50 years, in May 1999, the NASA Marshall Space Flight Center in Huntsville announced to the press that "*we are experimenting with laser propulsion and antimatter as viable options for space travels*" [1].

There are also very long ranging misses. In 1956 using muons produced by a Berkeley accelerator, it was discovered that the capture of a muon catalyses the fusion of a proton with a deuteron to form a tritium nucleus and a neutron with the liberation of energy. As Louis Alvarez declared some time later, together with the other authors of the discovery "*for a few days we thought to have solved all the fuel problems of mankind for the rest of time*" [2]. In fact a so-called *muon-fusion reaction* is very interesting, because – after catalysing the fusion of two nuclei with the liberation of energy – the same muon is free to catalyse the fusion of other pairs of nuclei creating a sort of chain reaction. Unfortunately it was later shown that (even for other more energetically favourable fusion reactions) the probability for a muon to stick to one of the produced nuclei is large and a muon cannot catalyse on an average more than twenty fusion reactions. It is a pity that some not so fundamental nuclear properties have not allowed to engineer *muon-fusion reactors* in which a powerful proton accelerator would easily produce an intense proton beam of a few GeV, which hitting a target creates pions that in turn decay in muons. Otherwise today the price of oil would not worry all of us so much.

The question now is: can some 'usable knowledge' also come from discoveries that could still be made around the accelerators running at present? To answer this question one has to shortly review the present landscape of subatomic physics and its frontiers.

* * *

The largest accelerator in the world is LEP, the Larg*e Electron-Positron collider* running at CERN since 1989. Twenty years ago to exploit it, with the Valencia physics group lead by Professor Antonio Ferrer and other groups coming from twenty Nations, from Russia to Brazil, we have created an International Collaboration called DELPHI. Our research facility, which is known with the same name, is an ensemble of fifteen sophisticated detectors occupying a volume of 12 x 12 x 10 cubic metres. In LEP electrons and positrons move in opposite direction on a circular orbit that has a diameter of about 8 km. DELPHI is located 100 metres underground and fully surrounds one of the four points in which every few seconds an electron annihilates with a positron moving in opposite direction. Since the electron and the positron have up to 103 GeV of kinetic energy, in the point of the annihilation an energy at maximum equal to 206 GeV is liberated in the form of a microscopic Big Bang. This concentration of energy immediately transforms in twenty newly created particles that fly away almost with the speed of light.

It has to be underlined that the energy of one of the electrons, circulating for hours in the 27 km long evacuated beam pipe, is ten millions times larger than the energy of one of the electrons accelerated by Roengten in his '*tube*'. Indeed the energy unit used in particle physics, the GeV, equals one billion electronvolts while Roengten energies were expressed in keV, that is in thousands of electronvolts.

LEP belongs to the family of accelerators called '*colliders*', since the circulating particles collide in four points around the circumference, where are located the facilities detecting the flying away particles created in each annihilation. The first circular accelerator, the so-called '*cyclotron*' invented in the thirties by Lawrence at Berkeley in California, could instead stay in one hand. Cyclotrons do not accelerate electrons but are ideal to produce beams of heavier particles, such as protons and all the atomic nuclei up to the heaviest Uranium isotopes. They are still much in use today for nuclear physics research and medical applications.

In a cyclotron the particles move in an evacuated chamber having the shape of a tobacco box placed horizontally on a table. Starting from the centre of the box, they follow a helical trajectory till they reach the periphery of the evacuated chamber where they - moving in straight line - bombard an external target. A strong vertical magnetic field bends the path of the particles obliging them to follow the wanted helical trajectory and at each turn an oscillating electric field adds some energy to the circulating protons or ions.

The magnet of a cyclotron has to cover the whole trajectory, from its central starting point to its most external turns. When higher energies are requested the magnet becomes very large and very expensive so that, to accelerate to energies larger than one GeV, '*synchrotrons*' are used. During the acceleration time in such a machine the particles (either electrons or protons or nuclei or their antiparticles) follow the same circular trajectory along which they are bent by many relatively small magnets forming a circle. The bending magnetic field increases synchronously with the increasing energy and the particles circulate in a vacuum chamber that has the shape of an evacuated doughnut with a diameter of kilometres and a cross section of 10 centimetres.

Since the war synchrotrons of larger and larger diameters have been built so to reach at CERN for electrons and positrons the 100 GeV of LEP and in the Unites States for protons and antiprotons the 1000 GeV of the Fermilab *Tevatron*. Both these machines are special synchrotrons working as colliders in which particles of opposite charge move for hours inside the same circular doughnut. They circulate in opposite directions and collide in a few predetermined points where energy transforms in mass with the creation of tens of new particles, reproducing the subatomic reactions that were happening during the first second of life of our Universe. Most of these particles live less than a millionth of a second and thus have disappeared from the Universe since long, but we can create and detect them with particle accelerators.

The experiments performed in the second half of last century have allowed particle physicists to construct a very satisfactory and elegant theory of these fundamental particles and of their interactions that goes under the too modest name of '*Standard Model*'.

The building blocks of this theory are *twelve particles* that are grouped in *three families* and, being the constituents of all known matter, can be called the '*matter-particles*'. The first family comprises the lightest four of all the matter-particles: *two leptons* (the usual charged electron and the neutral electron called 'neutrino') and *two quarks* (called quark-u and quark-d). These four matter-particles are sufficient to explain all matter *around* us and *in* us, since each proton and each neutron is essentially a bound state of three quarks of the first family. Thus also all nuclei, being composed of protons and neutrons, are compound systems made of quarks. For instance a Carbon ion stripped of all its electrons is made of six neutrons and six protons and thus it contains 12 x 3 = 36 quarks. Particle physicists have given the name of '*hadron*' to every particle made of quarks, so that protons, neutrons and nuclei are all hadrons made of three quarks. Their antiparticles are made of three antiquarks. There are also unstable hadrons made of a quark and an antiquark, the most known being the 'pion'.

In the Standard Model the second and third family of matter-particles have the same structure of the first one, but the two leptons and two quarks are heavier and decay very rapidly in the lighter particles. For instance the heaviest quark, called quark-t for 'top', has a mass 500 times larger than the ones of the quarks u and d.

Two forces act among the twelve matter-particles and fully explain both the way in which they bind to form hadrons and atoms and the paths by which they decay one in the others. These *electro-weak* force and the *strong* force acting between two matter-particles are nothing else that a manifestation of the exchange of force-particles called *intermediate bosons* and *gluons* respectively Since their exchanged produces itself as a force, these other *twelve* particles deserve the name of '*force-particles'*. The hundreds of different measurements performed by DELPHI and the other LEP experiments have confirmed in a spectacular way all the predictions of the Standard Model but one. Let us now discuss this missing piece.

The unifying power and elegance of the Standard Model is based on the fact that the existence of these particular force-particles can be deduced by applying a *very general* invariance principle to the known matter-particles. In a sense the known forces with their precise laws of action are a consequence of the fact that matter-particle exists. The weakness of the Standard Model is that this is naturally true only if the matter-particles and the force-particles have all mass rigorously equal to zero. How can then be explained that they have mass and they bind together in nuclei, atoms, molecules and finally objects that all carry mass? This is the question at which us, particle physicists, are trying to answer since about twenty-five years.

The most intellectually satisfactory possibility is that space is filled, since the beginning of the Universe, of a distributed entity, a sort of modern ether called '*scalar field*' or, more frequently, '*Higgs field*'. Immersed in this field all particles would interact differently with it and, slown down in their motion by such an interaction, would acquire a mass. The beauty of this apparently contrived mechanism is that *it hides but it does not destroy* the underlying symmetry that allows one to derive the existence on the force-particles from the matter-particles. Obviously this last Standard Model prediction needs an experimental verification.

The field cannot be measured directly, but its localised oscillations behave as particles, as for any other field. As the electromagnetic field has his particles, that we call 'photons', also the Higgs fields must have its particles. The search of these putative '*Higgs particles*', faithful testimonies of the underlying scalar field, has been going on since the start-up of LEP in 1989. The signature of the annihilation events in which a Higgs particle is produced is known from the Standard Model and this simplifies our task. However no event having the signature of a Higgs particle had been seen at LEP till few months ago.

But then the LEP machine experts have done their best to push all the parameters of the collider so to increase the collision energy to the maximum. Thus in the last months we have collected data with electrons and positrons circulating in LEP at 103 GeV, an energy that is higher than ever thought possible. Eventually in the electron-positron annihilations taking place at 206 GeV, the four Collaborations (ALEPH DELPHI, L3 and OPAL) – by combining their data – have detected a signal that could correspond to the creation of a Higgs particle of mass equivalent to 115 GeV. The few events observed have a probability of about 1% to be compatible with no Higgs produced, so that today the issue is hot but no definite claim can be made.

* * *

In summary, fifty years of accelerator developments have brought to a new and satisfying view of the fundamental particles and of the forces that act among them. The final needed touch, the check of the existence of the scalar field, is not yet there, but we have interesting hints. What is sure is that the technique of constructing and running very sophisticated particle accelerators and detectors are in hand and they have wide range applications. But before discussing their applications let us go back to the question: can one envisage some new basic knowledge, some new discovery, that would be directly 'usable' as X-rays have been?

Various proposals found in the literature leave some hopes, mainly related to *energy production*. For instance the stable particles predicted by some version of the Standard Model called 'Q-balls', if they exist, would produce energy when fed with nucleons. In general many long-lived charged particles, which are predicted by theories that go beyond the Standard Model, could catalyse fusion, as first proposed by A.D. Sakarov in 1940.

Considering the whole picture it is certainly not excluded that discoveries of this type will bring very important and practical consequences. Most particle physicists doubt that this dream will be realised, but the final answer has to be left to future experiments.

3. PEOPLE

The scientists and engineers who have successfully worked at the frontier of a challenging problem, in particular on basic science, are much sought after by high-tech companies and by groups working in other fields of science. In high-energy physics various more or less formal enquires have been made to ascertain the reasons why these persons are wanted. The major points are:

the analytical thought and systematic approach to new problems,
the experience in designing and carrying out complex projects,
the habit of documenting and presenting the work done,
the experience in working in International teams at the edge of knowledge and
the specific knowledge in science and technologies.

It is interesting to note that the knowledge in subatomic physics is by far not the main reason. The skills developed in the environment of large collaborations working in International laboratories are much more important.

Three groups of people are involved in it: students, research scientists and senior staffs.

Concentrating on the students, I want to quote a recent study performed on the carrier of the many students who have obtained their masters and/or PhD working in the DELPHI Collaboration. As I said, ours is a typical high-energy physics collaboration formed by about

50 groups belonging to almost 20 different nations. About ten years have elapsed from the conception of the so-called "detector" to its realisation. Data taking at LEP started in 1989 and is now ending after more than ten years. We have collected about five million events in which an electron and a positron annihilate with centre-of-mass energies in the range 90 – 205 GeV. The present DELPHI spokesman, Tiziano Camporesi, has recently published interesting information on the first occupation of our students [3].

Table 2. *First occupation of the 670 master and PhD students who obtained their degree(s) utilising DELPHI detectors and/or data in the years 1982-2000 [3].*

OCCUPATION	*PERCENTAGE*
Research	44%
Teaching	6%
Public sector	**50%**
High Tech	25%
Computing	15%
Business	7%
Management	3%
Private sector	**50%**

Of the 670 master and PhD students who obtained their degree(s) utilising DELPHI detectors and/or DELPHI data, 44% continued to do research and 6% went to teaching. The other 50% found their first job in the private sector. The percentages are: 25% in high-tech companies, 15% in computing, 7% in business and 3% in management positions. By extrapolating these numbers, one can estimate that in Europe about 200 students having completed their high-energy physics PhD thesis, move every year to companies of the private sector: the relevance of such a human spin-off should not be underestimated.

To complete the argument I want to consider the well-known scientists and engineers who have left subatomic physics for directing prestigious institutions. The examples in the field of science and education are too numerous to be quoted, but it is worthwhile listing some of those who went to direct applied science projects. John Adams (who in the sixties directed the UK fusion project), Hans Otto Wurst (Joint European Torus in Culham), Paolo Zanella (European Biological Institute in Cambridge) and recently Carlo Rubbia (ENEA in Rome). In connection with his new job Zanella said "*CERN is a very special case where you get to learn how to face very complex things. When you reach a certain age, you know how to solve big problems. And this is what I brought to the European Biological Institute*".

4. METHODS

The technologies and methods of subatomic physics become more and more sophisticated because the collision energies has to increase with time and the probability of interaction of the colliding particles decreases with the energy. The result is that, for instance, data acquisition rates have increased by more than a factor of ten every decade while the accelerator energy has increased – together with the dimension of the detectors and the number of the collaborating scientists. This has been possible because better technologies and better methods have been developed.

The first method to recall is condensed in a world wide used word: the *Web*, with its famous symbol "www". The idea of marrying Internet with hypertext was born at CERN when data taking was starting at LEP. Tim Berners-Lee e Robert Callieau wanted to help us, physicists, to communicate from laboratory to laboratory by exchanging huge amounts of data and putting together information. I still remember their effort to create a first software product that had to be so user friendly to convince the physicists, who were only thinking of their detectors and computer programmes. Luckily CERN — according to old-rooted attitudes and following also the formal rules— did not take any patent and the Web rapidly became a tool freely usable by everybody.

Moreover in subatomic physics sophisticated simulation programmes, in short 'Montecarlos', are used to design the experimental set-ups and to interpret the data. These Montecarlos have found use in practical applications, as the design of the future (futuristic?) reactors based on inertial fusion and of the spallation sources needed for the incineration of radioactive wastes. Recently they have also been used to plan X-ray treatments of tumour patients. This application has become possible because of the low cost and dimensions of very fast computers.

The methods, and sometimes also the tools, for handling huge amounts of data and to perform sophisticated statistical analyses have also been exported to other fields of science, biology in particular, and to medicine and industry.

5. TECHNOLOGIES

The list of the technologies used in nuclear and subatomic physics to construct accelerators and detectors is long: mechanical engineering, electromechanical engineering, material science, radio-frequency and microwave engineering, geodesy, superconductivity, cryogenic technologies, ultra high vacuum, radiation detection, electronics, computer systems, data networks. Sometimes a spin-off is the application in another field of a particular advance in *one of these technologies*, in other cases the marketable product is *a complete integrated system.*

As far as single technologies I limit myself to illustrate some of them.

Nobody doubts that the needs of high-energy physics have been instrumental to the development of large and sophisticated systems based on low temperature superconductivity. Among these one can quote the routine use of SC solenoids for hospital-based Magnetic Resonance Imaging and the first full-scale models of Maglevs, the magnetically levitated trains.

The long range consequences of the advances in ultra high vacuum techniques done at CERN mainly by C.Benvenuti who invented a new coating, based on a zirconium-vanadium-titanium alloy, which acts as a distributed pump. This may open the way to cheap and long lasting displays for TV sets and computers.

The applications of the continuous developments of new radiation detectors are numerous. The sciences which have most benefited are biology and medicine. It is enough to recall the

Positron Emission Tomographs based on BGO crystals. In industry the most spectacular applications are probably the systems sold by EUROPSCAN (a company created by Schunberger and Rheinmetall) and installed at the harbour of le Havre and in the de Gaulle airport in Paris. Here trucks and containers are radiographed in few minutes with many square metres of multiwire proportional chambers.

* * *

As far as the spin-offs of *full integrated systems*, they concern mainly applications of particle accelerators to other fields of science, medicine and industry. The list is long: synchrotron radiation sources, X-ray Free Electron Lasers (FEL), neutron spallation sources, inertial fusion plants based on the bombardment of pellets by ion beams, accelerators for waste incineration, production of medical isotopes and hadrontherapy.

X-ray FEL will open the way to the imaging of very small biological structures. On the long term they will have the same impact on biology as the by now standard synchrotron radiation sources, maybe even more. Two projects based on high current linear accelerators are under way. The first one by a Stanford-UCLA collaboration and the other by DESY in connection with the development of TESLA, the superconducting positron-electron linear collider.

As far as neutron spallation sources it is not by chance that the project leaders of the two design studies were CERN senior staff: Herbert Lengeler for the European Spallation Source and Philip Bryant for the AUSTRON project.

Cyclotrons for medical isotope production are usually low energy accelerators and are thus spin-offs of nuclear physics. In this field Europe is well placed with Ion Beam Application (IBA), which is a spin-off of the nuclear physics group of the University of Leuven and is grown so much to have recently acquired Scanditronix and two major companies in the field of food sterilisation.

In the *Energy Amplifier* proposed by Carlo Rubbia the spallation neutrons produced by a megawatt beam of 1 GeV protons are multiplied in a sub-critical reactor and slown down in its bismuth-lead moderator. In each collision with a heavy nucleus of the moderator a neutron looses a very small fraction of its kinetic energy, so that at a given point, even outside the sub-critical unit, the neutron spectrum covers almost uniformly the range which goes from 1 eV to 1 MeV. These neutrons can perform two different tasks, possibly in different facilities. The first scope is the incineration of radioactive wastes, in particular of the long-lived actinides that are contained in the spent fuel extracted from standard fission reactors. The second use is in the production of medical isotopes with a new method named '*adiabatic resonance crossing*' (ARC). Such an 'activator' can produce large quantities of the isotopes ^{99m}Tc and ^{129}I, which alone cover about 85% of all medical examinations.

The design of prototypes of the Energy Amplifier are well advanced and the European Union has set-up a committee of advisors to review the progress and advice on the strategy to follow. This spin-off of subatomic physics is thus moving towards its first realisation.

6. HADRONTHERAPY

Till now I have discussed the main *science challenge* facing the physicists working with particle accelerators and have presented some of the spin-offs of this activity as far as *people, methods* and *technologies* are concerned. It is now time to move to the technology that is explicitly announced in the title - *accelerators in cancer therapy* – to which I will devote the rest of my talk.

Table 2. *Accelerators in the world [5].*

CATEGORY	*NUMBER*
Ion implanters and surface modifications	7'000
Accelerators in industry	1'500
Accelerators in non-nuclear research	1'000
Radiotherapy	5'000
Medical isotopes production	200
Hadrontherapy	20
Synchrotron radiation sources	70
Research in nuclear and particle physics	110
TOTAL	**15'000**

At present about 15'000 particle accelerators are running in the world. Only about 100 are used for basic research in nuclear and subatomic physics while 55% of these 15'000 accelerators are devoted to ion implantation, surface modification, sterilisation and polymerisation.

As far as medical applications are concerned, about 200 cyclotrons are used to produce medical isotopes, mainly for diagnostic purposes, and as many as 5'000 electron accelerators used in radiotherapy to treat cancer patients. This number amounts to one third of the total amount of accelerators running in the world.

These 5'000 accelerators are mainly *linacs*, in which electrons - brought to about 10 MeV by a high-frequency oscillating electromagnetic field – hit a heavy target and produce a beam of high-energy X-rays. As the name '*linac*' says, the accelerating copper structure is *linear* and its length is typically 1.5 metres. Such a light system is mounted on a frame and can thereby rotate around the bed where the patient is laying. Thus the X-rays, produced when the electrons hit the target radially, can be sent on the patient body from any direction and the radiotherapist can maximise the dose given to the tumour by minimising the one absorbed by the healthy tissues.

In our advanced European societies every 10 million inhabitants about 20 000 patients are irradiated every year. Indeed about half of the cancer patients are irradiated at least once in the course of their cures.

For X-rays the dose – that is the energy given to a small mass of tissue - decreases roughly exponentially with the depth in the patient's body. Obviously this is not a very favourable situation because it implies that a tissue located at a depth of 25 cm receives a dose that is three time smaller (and thus is much is much less effective) than the one absorbed by a tissue that is only 3 cm under the skin. To reduce this problem since long radiotherapists irradiate the tumours with two crossed beams. Recently the techniques used have been greatly improved with the use of multiple successive irradiation from many directions. In such an *Intensity Modulated Radiation Therapy* (IMRT) up to *nine* different directions are used, so that the dose unavoidably going to the healthy tissues is distributed over a larger volume, while the tumour dose is very high where all the beams cross.

In this field a recent spin-off of nuclear and subatomic physics is '*hadrontherapy*', the modern technique of oncological radiotherapy which uses beams of *hadrons* instead of X-rays. (I recall that hadrons are particles made by quarks, so that the nuclei of all elements are hadrons because their protons and neutrons are themselves composed of three quarks each.)

The depth-dose curves of proton and ion beams are *completely different* from those of X-rays because these charged particles have little scattering when penetrating in matter and give the highest dose near the end of their range in what is known as the "*Bragg peak*". By varying the energy of the particles during the irradiation, many narrow Bragg peaks can be superimposed to form a *Spread-Out Bragg Peak* (SOBP) which can cover a tumour of any thickness. Thus, due to physical reasons, protons and Carbon ions fully stripped of their electrons are *much more suited* than X-rays to spare healthy tissues. Already two crossed beams give a dose that is better conformed to any deep tumour than nine beams of X-rays.

Thus on the basis of purely physics arguments, radiotherapists should use charged hadrons instead of X-rays. But the costs are larger and the equipment is heavier. In fact, in order to reach depths of more than 25 cm – necessary to treat deep-seated tumours – proton and carbon beams must have an initial energy not lower than 200 MeV and 4500 MeV respectively. These energies are 20 times and 450 times larger than the ones needed for X-ray therapy. Moreover the hadrons weigh many thousands times more than an electron and they are consequently much more difficult to accelerate. The development of hospital-based hadrontherapy has been hampered by the cost and bulkiness of the accelerators, which are typically cyclotrons for protontherapy and synchrotrons for light ions.

Still by now about 26'000 patients have undergone *protontherapy* in the world (mainly in nuclear and particle physics laboratories) and very good results have been obtained in head and neck cancers. Today for a dozen of tumour sites protontherapy is a recognised modality based on well-defined protocols. For about 1% of the tumours, proton beams are certainly better than X-rays (and this corresponds to 200 patients per 10 million inhabitants). For about 10% of them (corresponding to 2000 patients on the same population) there are good indications but the results of ongoing clinical studies have to be completed before quantifying the advantages.

Companies, such as IBA in Belgium, sell key-in-hand systems ready to use. The first hospital based centre having more than a treatment room was the Loma Linda University Medical Center (total cost: about 80 million US$) is based on a 7 metre diameter synchrotron designed at Fermilab and in 1999 has reached the regime by treating in one year about 1000 patients. It is interesting to remark that the first proposal was published more than 50 years ago in a radiological journal by Bob Wilson, who later became the constructor and first director of Fermilab. Three rooms are equipped with 'gantries', which are rotating magnetic systems having a diameter of about 10 metres and weighing about 100 tons. On average each patient comes to the centre for 20 sessions distributed over four weeks.

More centres of protontherapy are running or under construction so that the overall picture is that in a couple of years *two centres* will be running in USA and *five centres* in Japan. It has to be remarked that the States have chosen only protontherapy centres. Instead Carbon ion therapy is and will be performed in HIMAC (near Tokyo) and in the Hyogo centre, at present almost completed not far from the town of Kobe.

* * *

This brings me to the last issue I want to discuss: the use of light ions, in particular of Carbon ions. The natural question here is: why use Carbon ions of about 4500 MeV when protons of 200 MeV have the same range in the body and display practically the same Bragg peak?

The characteristics which make light ion beams an interesting addition to protons, is the higher density of energy loss and thus the higher ionisation produced along the track. The argument is simple. A proton loses 200 MeV in 25 cm of tissue while a carbon ion loses 4500 MeV, so that on an average the energy lost every cm is more than 20 times larger for carbons than for protons.

This high density of energy loss produces a much denser column of ionised molecules around the track of a Carbon ion than around the track of a proton. Moreover, as I said, this loss is larger and concentrated towards the end of the range in the body where the tumor is. Summarising a wealth of physical and radiobiological data, one can state that the dense column of ionisation produced near the Bragg peak of a Carbon ion track gives rise to many *Double Strand Breaks* and *Multiple Damaged Sites* when it crosses the DNA of a cell nucleus. The effects on the cell are thus *qualitatively* different from the ones produced by 'sparsely ionising' radiations, as X-rays, electrons and protons, which interact *mainly indirectly* with the DNA through reactive free radicals that cause mostly reparable *Single Strand Breaks.*

Due to the much larger proportion of direct effects on the DNA, Carbon ions (and other light ions as Lithium and Beryllium) have a *Radio Biological Effectiveness* that is two-three times larger than that of X-rays and protons. They are thus suited for clinical situations where the cancerous tissue is characterised either by a reduced cell oxygenation (hypoxia) or by an intrinsic radioresistance, problems difficult to overcome *both* by conventional radiation therapy *and* by protons.

X-ray and proton doses much larger than usual should be given to produce the wanted death of the cancerous cells to about 20% of all tumours treated with X-rays (corresponding to about 4000 patients every 10 million inhabitants). Carbon ions (and other light ions) are the only known radiotherapy method that can control these 'radioresistant' tumours.

The use of light ions is substantiated by many radiobiological studies, and to some extent by clinical information gathered with neutron therapy and by the results obtained on about three thousand ion therapy patients. The first results were obtained at Berkeley over about 30 years (1957–1992) with Helium ions (2054 patients) and Neon ions (500 patients) using essentially conventional uniform beams of fixed Bragg peak modulation. Modern clinical results are mainly due to the work done since 1994 in Japan at HIMAC (*Heavy Ion Medical Accelerator Centre*, Chiba), where about 800 patients have been treated with rather high quality beams of light ions with very good clinical results. In the framework of the so-called "pilot project", the GSI nuclear physics laboratory in Darmstadt has treated about eighty patients in the last two years with a new Carbon ion beam line. It is still too early to talk about definite clinical results but one can conclude that they are very encouraging for tumours of the head and of the liver and are in agreement with the expectations derived from physical arguments and radiobiological data.

* * *

On the basis of these arguments, in 1992 in Italy the TERA Foundation was created. (TERA is the Italian acronym for *TErapia con Radiazioni Adroniche*, that stands for 'therapy with hadronic particles'). TERA is a non-profit Foundation recognised by the Italian Ministry of Health in 1994. Its main purpose is the introduction in Italy and Europe of the most recent techniques to treat cancer.

In Italy its main project is the realisation of a centre of excellence called *CNAO* (*Centro Nazionale di Adroterapia Oncologica* = National Centre for Oncological Hadrontherapy). Following the international spirit of its founders, at the end of 1995 the TERA Foundation drew the interest of CERN (the European Laboratory for Particle Physics in Geneva) on the design of an *optimised* synchrotron for proton and light ion therapy. Such a design, once completed, would have been freely available to all the European countries ready to invest the required funds in the construction of a national facility. At the beginning of 1996 the CERN management agreed on the proposal, and a study of such a synchrotron was started at CERN under the acronym PIMMS (*Proton and Ion Medical Machine Study*).

PIMMS was a collaboration among CERN, GSI (Germany), Med-AUSTRON (Austria), Oncology 2000 (Czech Republic) and TERA (Italy). The PIMMS study group had the mandate to design the synchrotron and the beam lines of *a proton and Carbon ion hadrontherapy centre without any financial and/or space limitation.* Over the years 1996-1999 CERN contributed with the full-time leadership of Phil Bryant and the invaluable part-time assistance on many of its staff members, mainly drawn from the PS Division. TERA, Med-AUSTRON and Oncology 2000 invested in the study 25, 10 and 3 man years respectively. GSI contributed with expert advice and participation in regular meetings of the Project Advisory Committee.

The outcome of this four years study is a complete design that features a proton and ion synchrotron having a diameter of 24 metres and combines many innovative features so to provide an extracted pencil beam of particles that can be varied in energy, is very uniform in time and can easily be adjusted in shape. These are pre-requisites for the application of the novel technique of *Intensity Modulated Hadron Therapy* pioneered GSI (Germany) and at PSI (Switzerland).

In 1997 TERA, on the basis of the ongoing work of PIMMS, prepared a detailed project for a centre of proton- and ion-therapy (the CNAO quoted above) to be built in Italy. This centre would be less expensive and still retain the most important features of the PIMMS design. Its Phase 1 features *three* treatment rooms. Rotating gantries, which are expensive, are an addition belonging to a second phase. The investment to realise Phase 1 of CNAO, including the buildings and the conventional plants, is 50 MEuros. The Health Ministry has inscribed 10 MEuros in the State budget of the year 2001 and other 10 MEuros in the 2002 budget. The budget bill is at present in front of the Parliament.

In spring 1998 the Med-AUSTRON team presented to the Austrian authorities a project that is identical with the design proposed in the PIMMS study. To reduce the initial cost of the facility, it has been proposed to build it in three successive phases.

To complete the information related to the possible uses of the PIMMS work, it should be added that in 1998 TERA prepared a preliminary design for the University Claude Bernard of Lyon (always based on PIMMS). Moreover at present we are working together with the Karolinska Institute for a centre to be built in Stockholm.

I told in detail the story of the recent developments of light ion therapy in Europe because, in my opinion, this is a good example of how complex instruments developed for fundamental research can become tools used in other fields. Six main steps can be recognised:

1. accelerators have been developed for basic research in nuclear and subatomic physics,
2. basic research in radiobiology has shown that radioresistant cells are sensitive to the high density of ionisation produced by ions at the end of their range,
3. first results on patients have been obtained in a research laboratory, the Lawrence Berkeley Laboratory, later confirmed at GSI (Germany),
4. a dedicated facility has been built as a prototype hospital-based Centre (HIMAC in Japan),
5. an industry entered the field producing a first expensive facility (Hyogo by Mitshubishi Electrics cost 200 M$),
6. a new design was made to improve the quality of the treatment and reduce the costs (PIMMS with its applications in TERA, Med-AUSTRON, Lyon and possibly Stockholm).

Hopefully some of these centres will irradiate patients in five or six years. Of course we cannot be sure today that all the efforts done for transforming completed integrated systems used in research laboratories into commercial products used in hospitals will bear fruits. But the probabilities are high, in my opinion, that in twenty years from now many hospitals will be equipped with accelerators of light ions (from Helium to Oxygen probably) which will have smaller dimensions and will be less costly than the ones we are now contemplating.

REFERENCES

[1] C. Holden, Nature 284 (1999) 145.

[2] L. Alvarez, in *Evolution of Particle Physics*, Academic Press, New York and London, 1970, pp 1-49.

[3] T. Camporesi, CERN Courier, 40(8) (2000) 20.

[4] P. Zanella, in *Basic Science and Technology Transfer,* F. Bourgeois ed., CERN/BLIT/98-101, Feb. 1998, p.22.

[5] U. Amaldi, *The Importance of Particle Accelerators*, Proc. EPAC 2000, Vienna, 26-30 August 2000, pp 1-5.