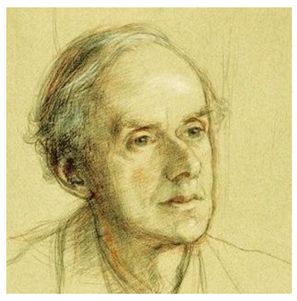
ANTIPROTON CANCER THERAPY

Niels Bassler[1,2] <n.bassler@dkfz.de> and the AD-4/ACE collaboration[*].
[1] Dept. Clinical Experimental Oncology, Aarhus University Hospital, Denmark
[2] Deutsches Krebsforschungszentrum, Heidelberg, Germany

ANTIMATTER

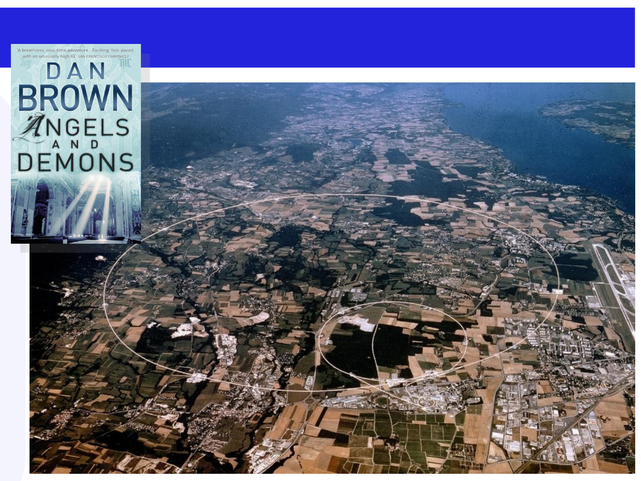
The existence of **antimatter** was first proposed by P.A.M. Dirac in 1928. He examined the wave equation of an electron in an arbitrary electron magnetic field. This **equation** had a **quadratic form**, and could be solved for an **electron with negative charge**, but also for a similar particle with **positive charge**. The **antielectron** was discovered 5 years later by C.D. Anderson. Similarly, the proton has an antiparticle, which is the **antiproton**. Antiprotons were already discovered in 1955 by Chamberlain et al.



Antimatter is similar to normal matter, just where the **charge sign is reversed.** Thus, the antiproton has a **negative** charge. When matter and antimatter meets, they **annihilate**, releasing their rest mass as energy according to $E=mc^2$. An antiproton annihilating on one proton results in **1.88 GeV** released energy. Thus, **one gram** of antihydrogen annihilating on matter releases energy corresponding to **3 Hiroshima** nuclear bombs.

ANTIPROTON PRODUCTION

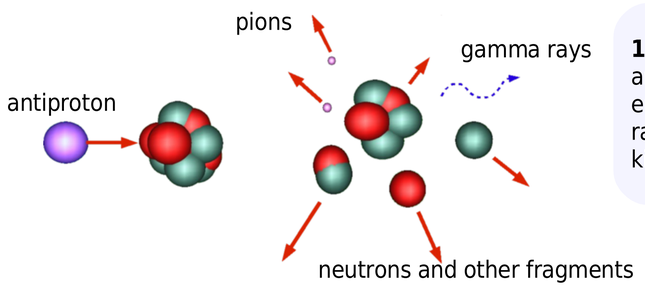
In spite of the popular perception of the availability of antiprotons (as in **Dan Brown's** bestseller "Angels and Demons"), it must be mentioned that the **production of antiprotons is very cumbersome.** Currently, only the European Organization for Nuclear Research **(CERN)** at Geneva, can provide a beam of antiprotons with low enough energy. Here, a 26 GeV proton beam from the proton synchrotron (PS) is dumped into an iridium target. For each spill, a few antiprotons are produced, which then are being collected and cooled at the **antiproton decelerator** (AD). The energy is reduced to almost **50 MeV**, giving a spill of **3e7** antiprotons (50 billionth of a nanogram!) every 90 seconds.



CERN. Geneva airport is seen to the right. The large ring is the LEP accelerator which currently is being upgraded to the LHC, using superconducting technology. (The circumference is 26 km.)

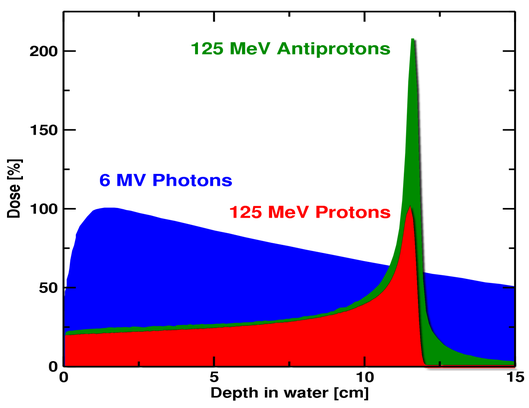
ANTIPROTON THERAPY

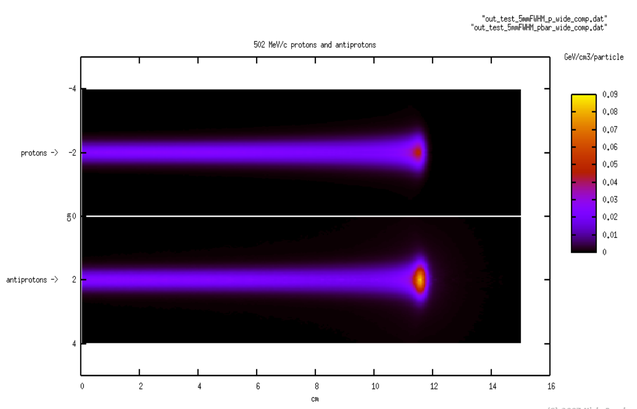
Antiprotons have some properties, which make them very relevant for radiotherapy:



1) When an antiproton stops, it will immediately annihilate on another nuclei. Most of the 1.88 GeV energy released is carried away by pions and gamma rays, but roughly **30 MeV** is **deposited locally** as kinetic energy from recoiling heavy nuclei.

2) Antiprotons behave like ordinary protons in the **plateau** region. Therefore the dosimetry is known. Also this is **Low-LET** radiation, just as protons, with known radiobiology. **Fractionation** benefits are **maintained**. **High-LET** radiation from the annihilation fragments is found at the **Annihilation-peak**. Antiprotons thus features low RBE in the plateau and high RBE in the peak.





3) The pions and gamma rays emerging from antiproton annihilations can directly be used for **online monitoring** of the irradiation process with similar techniques known from PET. One may get an **instant** image of the dose deposition.

To the left : FLUKA calculation of the relative dose deposited by a ~126 MeV proton and antiproton beam in a water target. (iso-fluence)

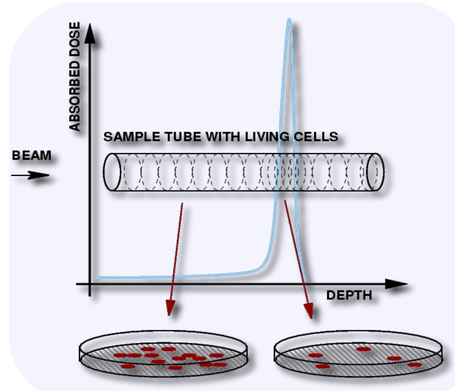
* THE AD4/ACE COLLABORATION

Michael H. Holzscheiter[1], Niels Bassler[2,3], Jan Alsner[2], Gerd Beyer[4], John J. DeMarco[5], Michael Doser[6], Dragan Hajdukovic[7], Oliver Hartley[4], Keisuke S. Iwamoto[5], Oliver Jaeckel[3], Helge V. Knudsen[8], Sandra Kovacevic[7], Raymond Miralbelle[4], Søren Pape Møller[8], Jens Overgaard[2], Jørgen B. Petersen[2], Osman Ratib[4], Timothy D. Solberg[9], Sanja Vranjes[10], Bradly G. Wouters[11].

[1] University of New Mexico, Albuquerque, NM, USA
[2] Dept. of Medical Physics and Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark
[3] Deutsches Krebsforschungszentrum, Heidelberg, Germany
[4] Hospital Universitaire de Geneve, Geneva, Switzerland
[5] David Geffen School of Medicine, UCLA, Los Angeles, CA, USA
[6] CERN, Geneva, Switzerland
[7] University of Montenegro, Podgorica, Montenegro
[8] Dept. of Physics & Astronomy and ISA, University of Aarhus, Aarhus, Denmark
[9] University of Nebraska Medical Center, Omaha, NE, USA
[10] VINCA Institute for Nuclear Sciences, Belgrade, Serbia
[11] University of Maastricht, Res. Institute Growth and Development, The Netherlands.

ANTIPROTON EXPERIMENTS AND RESULTS

In 2003 the **AD4/ACE collaboration** was formed in order to investigate the **biological effect** of the antiproton beam. We designed a setup, where a standard cell line (Chinese hamster cells, V79, WNRE) were irradiated with antiprotons. The most convenient thing to do now, would be to measure the RBE along the beam. This is also possible in the plateau region of the depth
dose curve, but it is more problematic in the **peak region**:
The dosimetry is here **complicated** by the **mixed radiation field** arising from the annihilating antiprotons. To overcome the trouble in an elegant way, a method was invented where the peak to plateau ratio of the **biological effect** of the antiproton beam could be measured, and compared to that of a proton beam. In this way, a **fourfold increase of the biological effec**t in the spread out peak region was recorded, **relative to** the similar situation of a **proton beam**. The findings are published in "Radiotherapy and Oncology".



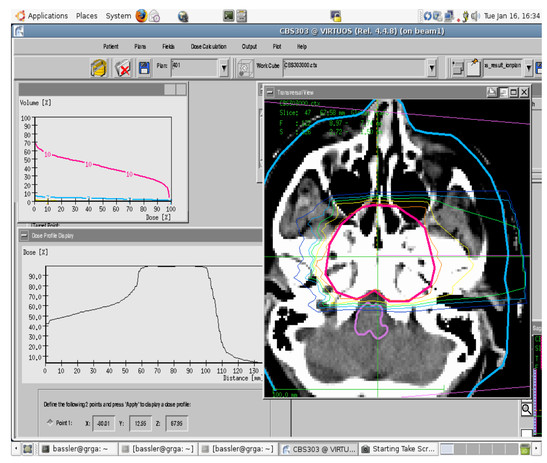
The AD4/ACE biology experiment. The tube containing the hamster cells was irradiated with antiprotons. The gel matrix was extruded and cells were plated from several slices along the axis.

Still, it could be desirable to directly **measure the RBE in the peak region**. As the time structure of the antiproton beam made standard dosimetry methods such as **ionization chamber dosimetry** and **calorimetry** difficult, we attempted alternative methods such as thermoluminescent detectors (TLDs), alanine and GAFChromic films. Monte Carlo calculations with SHIELD HIT v2 were used to map the annihilation spectrum of secondary particles. This spectrum was used with various detector models for TLDs and alanine, in order to calculate a response.

In the end, it is possible to get an idea of the dose in the peak region. From these estimates, a **RBE** in the region **1.3 - 2.6** was found (20% survival of the Chinese hamster cells).

CURRENT DEVELOPMENT

At the time writing this, we work on **improving the dosimetry** of the antiproton beam. October 2006 additional experiments took place at CERN, including **ionization chamber** measurements. Simultaneously, SHIELD-HIT v2 and FLUKA is being used for detailed analysis of the data acquired 2003 and 2004. This is done in close collaboration with the **DKFZ**, due to their valuable **experience** on **mixed particle fields** from clinical **carbon ion** beams. The goal is, to do planning studies with antiprotons using the knowledge gained about the dosimetry, the particle spectrum, and the **RBE** in the annihilation peak. The dose planning system **TRiP**, which is used by the DKFZ for carbon ion beams, is modified to **feature antiproton beams as well**. Planning studies may give a clearer picture of the anticipated benefits of antiproton radiotherapy.
The cell experiment was repeated with carbon ions in 2007 at GSI. These results are compared with the biological effect of antiprotons as well.



Above: The very first treatment plan with antiprotons using TRiP. The input data for the antiprotons are based on benchmarked Monte Carlo simulations. Currently only physical dose is modeled, but work is done to include the radiobiology using the **Local Effect Model**.

FAQ

Q: Your cell experiments were carried out with a beam, which only had a penetration depth of 2 cm. What about tumours which are seated deeper than that?

The **range of the antiprotons** can be adjusted by varying their initial **kinetic energy** - i.e. the speed of the antiprotons. The position of the annihilation peak can be calculated with more than **1 mm** precision, if the material in the entry region is known. This is analog to what is done with proton therapy and carbon ion therapy. In fact, the range of antiprotons is **almost identical** to that of protons for a given energy. Using the Bethe-Block equation, or online stopping power tables, you can see that e.g. a **200 MeV** proton reaches almost **26 cm** into a water target.

Q: Do you plan to repeat the cell experiment at higher energies?

This has already happened In October 2006 we used a beam of 502 MeV/c (equal to about **125 MeV**) for new dosimetry and biology experiments. The data is currently being processed.

Q: Almost 2 GeV are being released by a single antiproton annihilation. Only 30 MeV are being released "locally". Isn't that extremely dangerous for the patient?

Most of the energy by annihilation are carried away by particles with low mass and high energy. These are mostly pions, gammas by the instantaneous decay of pi-zero particles. These particles are **weakly interacting**, thus only contributing less to the dose. Furthermore, as the **secondaries are emitted isotropically** (same amount of particles in any direction), there is a $1/r^2$ dependence of these. We have in fact measured the dose in the **peripheral region**. The results have not been published yet, but our findings indicate that the dose here is **several magnitudes lower** than in then antiproton beam. The effects of the particles in the peripheral region is expected to be of **stochastic** type, and **not deterministic** as in the beam itself. Said in other words, the secondary particle spectrum may increase the risk of developing a **secondary cancer**.

Q: What secondary particles are seen for an antiproton beam annihilating in tissue like media?

Mostly pions, protons, gammas and neutrons. Then there are heavier particles, such as deuterons, tritons, He-3 and He-4 nuclei. There is also a some Lithium nuclei which contribute with about 5 percent of the total dose.