On Cancer Breathing: How Otto Warburg Led Manfred von Ardenne and then the Whole World into Temptation

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***Abstract*— The article relates to the history of science and technology, more precisely, to two giant inventions - the atomic bomb and the treatment of cancer with hyperthermia, and also to the invention of television, microwave ovens, and others. It is a story about two geniuses: Otto Warburg and Manfred von Ardenne and a fascinating story about the fight against cancer, describes hyperthermia technologies as a cancer treatment approach with their rise and decline.**

I. Introduction. Visiting M. von Ardenne (1907-1997)

I met the great German inventor Manfred von Ardenne on August 16, 1973, in his mansion in the proud Weißer Hirsch (White Deer) summerhouse district of Dresden, located opposite the center of Dresden across the Elbe River on its steep banks (Figs 1-3). The meeting occurred during the X International Conference on Medical and Biological Engineering. (Since 1961, Ardenne has been president of the "International Federation of Medical and Biological Engineering".)

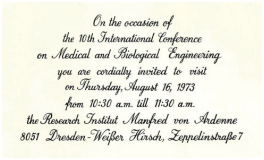

On the occasion of
the 10th International Conference
on Medical and Biological Engineering
you are cordially invited to visit
on Thursday, August 16, 1973
from 10:30 a.m. till 11:30 a.m.
the Research Institut Manfred von Ardenne
8051 Dresden-Weißer Hirsch, Zeppelinstraße 7

Fig. 1. Invitation to visit Ardenne Research Institute

At the meeting, he showed his institute in some 12 summer houses of former rich people and around 500 employees working there. The reception ended with a round table conversation in his villa. I remember, in the middle of the table there was a crystal of the Ural Mountains, about half a meter in size, in a violet shade. In the yard - a large aquarium like a swimming pool.

Fig. 2. Manfred von Ardenne at his villa

Fig. 3. Ardenne villa and private observatory

The 10th International Medical and Biological Technology Conference was opened on August 13, 1973, with a symphonic concert in the Palace of Culture (Figs 4, 5).

Fig. 4. Dresden Palace of Culture (1985)

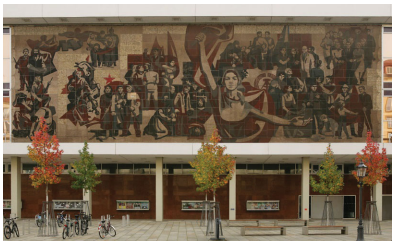
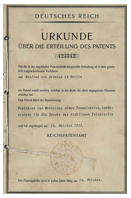


Fig. 5. "Road of the Red Flag" - mural on the outer walls of the Palace of Culture (hardly preserved after the reconstruction of the Kulturpalast and the change of ideology).

At the conference, von Ardenne gave an extensive paper on his multi-step therapy for cancer. The author (as well as the listeners) was confident of success in cancer treatment because his entire previous life had been brilliantly, even brilliantly successful. The following is about two giant inventions - the atomic bomb and the treatment of cancer with hyperthermia, as well as the invention of television, microwave oven, and many others. It is a story about two geniuses: Otto Warburg and Manfred von Ardenne. Section II is devoted to Ardenne's electrical engineering and nuclear physics achievements. Section III explains German scientists' part in the Soviet atomic project. Sections IV and VI are about the Warburg Effect. Section V describes hyperthermia technologies as a cancer treatment approach.

II. Miracle Worker of Electrical Engineering

The first patent. In 1924, as a 16-year-old schoolboy, Manfred completed his first significant work at Lingström's company, Berlin (Fig. 6), significantly improving the quality of mechanical recording of sound on a record, and registered a patent "Method for achieving sound selection, especially for wireless telegraphy" (Verfahren zur Erzielung einer Tonselektion, insbesondere für die Zwecke der drahtlosen Telegraphie).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ÜBER DIE ERTEILUNG DES PATENTS

Fig. 6. First Ardenne's patent

The first integrated circuit. In 1926-1927 Ardenne studied for four semesters at the University of Berlin. In 1926, Ardenne developed a combined radio tube by combining three lamps in one vacuum cylinder. This lamp is today considered the world's first integrated circuit. He assembled a radio receiver on this combined lamp, which was then mastered in serial production by Radiofrequenz GmbH (the owner Siegmunds Loewe), and produced in millions of quantities (Figs 7, 8).

Fig. 7. Ardenne's radio receiver on a combined lamp

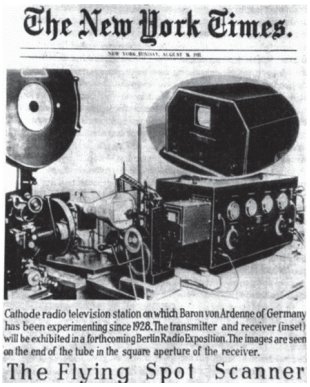
Fig. 8. Sigmund Loewe and M. von Ardenne in 1928

The famous creator of the tube triode, Lee de Forest (1873-1961), showed interest in the work of the young scientist, who specially sailed from overseas to meet the talented young man (Fig. 9) personally. Lee de Forest was an American inventor and a fundamentally important early pioneer in electronics. He invented the first practical electronic amplifier, the three-element "Audion" triode vacuum tube in 1906.

Fig. 9. Lee de Forest, M. von Ardenne

Private research institute. The money earned from this invention and a loan of 150 thousand marks were enough to buy 1928 a large house in Berlin-Lichterfelde and equip it for the private institute "Forschungslaboratorium für Elektronenphysik" (research laboratory for electron physics). In the building that now houses the Villa Folke Bernadotte youth cultural center.

Television. Ardenne was particularly motivated by his visit to the International Radio Exhibition (IFA) in 1928. The experimental apparatus presented by the Hungarian Dénes von Mihály with a Nipkow disk - a purely mechanically controlled process for transmitting images - appeared to him to be "useless". Ardenne tinkered and experimented and created the world's first electronic image decomposition and reproduction on a cathode ray tube. The funds came from the proceeds of Loewe Technology. On December 14, 1930, he made the first television broadcast in Germany. In 1931, Ardenne's transmit-receive electronic TV system with 6000 elements (100 lines) at 20 frames per second, manufactured by Loewe, became the decoration of the Eighth Berlin Radio Exhibition. On August 22, 1931, his "Flying Spot Scanner" was presented at the IFA, and even the New York Times reported on the invention on the front page (Fig. 10).


The New York Times.

Cathode radio television station on which Baron von Ardenne of Germany has been experimenting since 1928. The transmitter and receiver (inset) will be exhibited in a forthcoming Berlin Radio Exposition. The images are seen on the end of the tube in the square aperture of the receiver.

The Flying Spot Scanner

Fig. 10. New York Times (1931): the front page on Ardenne's achievements in TV

The Lichterfeld Ardenne Laboratory was visited by the pioneer of English mechanical television, John Logie Bird, who got acquainted with his achievements and became convinced of the advantage of electronic scanning over mechanical scanning (Figs 11-13). John Logie Baird (1888-1946) was a Scottish inventor, electrical engineer, and innovator who demonstrated the world's first live-working television system on 26 January 1926.

Fig. 11. Ardenne with a Braun tube in his laboratory, 1931. The earliest version of the cathode-ray tube was known as the "Braun tube", invented by the German physicist Ferdinand Braun in 1897.

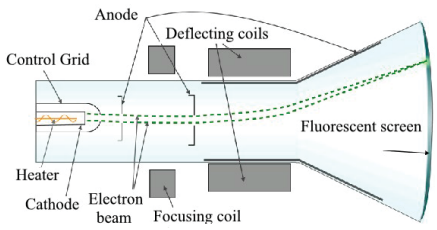


Fig. 12. Cathode-ray tube cross-section diagram with its focused and deflected electron beam

Fig. 13. Lorenz television receiver from 1936 with the television tube invented by Ardenne

TV triumph: Berlin Olympic Games. On January 15, 1936, regular television broadcasting began in Berlin. The highlight of Ardenne's life was the 1936 Summer Olympics in Berlin. More than 150 thousand spectators watched the Olympic competition on TV clubs. It was the first show of this level and scale in world history (Figs 14-16).

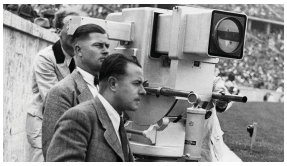


Fig. 14. Manfred von Ardenne (foreground) Berlin Olympics 1936

Fig. 15. Opening of the Berlin Olympic Games in 1936: The Olympic Stadium welcomes A. Hitler

Fig. 16. Berlin Television Exhibition 1936. Above is the stand of the Lichterfeld Laboratory: on the right is a model of a polar-coordinated oscilloscope for radar; on the left are indicators on the Ardenne tubes. Below are two designs of the Leibold and von Ardenne association.

Scanning electron microscope. In 1937, Ardenne pioneered the scanning electron microscope with an electron beam diameter on a target of ~10 nm. This allows the smallest molecule structures to be made visible for the first time (Figs 17, 18). Through his development of amplifier tubes, he is also significantly involved in the further development of radar in Germany. Siemens-Schuckertwerke produced the first commercial electron microscope in 1938. From this point onwards, transmission electron microscopes became more readily available in other areas of the world. During World War II, the installation was destroyed and work on electron microscopy was stopped.

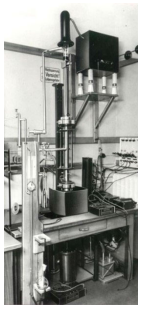


Fig. 17. Scanning electron microscope

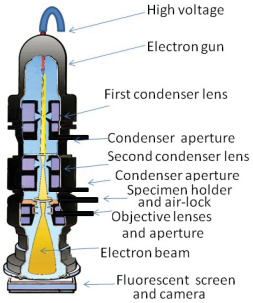


Fig. 18. Diagram of a transmission electron microscope

German atom project. Always looking deeply and broadly at problems, von Ardenne recruited the theoretical physicist Friedrich Houtermans (1903-1966), who in August 1941 proved that isotopes of transuranium elements such as neptunium and plutonium could be used as nuclear fuel instead of uranium. In 1941 experimental (60-ton cyclotron) work on nuclear physics began at the institute in Lichterfelde. The institute to be set up by Ardenne was integrated into the atomic bomb project *(Kerwaffenprojekt).* It was commissioned to develop an electromagnetic process for the industrial separation of uranium isotopes.

The Ardenne laboratory had a special government order, but it operated separately from Germany's main uranium project - under the auspices of the Reich Ministry of Posts (Reichspostministerium). In 1942, the laboratory developed a new method of electromagnetic separation of uranium isotope 235. Linear and circular accelerators were created for the separation of uranium isotopes. Ardenne received the personal patronage of Reich Minister Wilhelm Ohnesorge (1872-1962). He is also known to have contributed heavily to research towards a German atomic bomb. However, by order of A. Hitler, all scientific work that did not have a quick military effect in 1943-1944 was deprived of funding. During the Second World War, he took part in the research and application of radar technology. in January 1945 Ardenne received the title of “Reich Research Adviser” (Reichsforschungsrat). His private institute operated under the command of SS troops, and he received the rank of Standartenführer (Colonel). For his many achievements, Hitler personally presented Manfred von Ardenne with the Knight's Cross with Oak Leaves (Fig. 19).

Fig. 19. Knight's Cross with Oak Leaves

III. GERMANS IN THE SOVIET ATOMIC PROJECT

The war had not yet ended when special teams were already sent to the territory of Germany occupied by the Red Army, looking for physicists, engineers, and other specialists who could help the USSR in the development of nuclear weapons.

Anticipating the future fate, four German scientists:

- Manfred von Ardenne,
- Gustav Hertz, Nobel laureate and director of Research Laboratory II at Siemens,
- Peter Adolf Thiessen, ordinarius professor at the Humboldt University of Berlin and director of the Kaiser-Wilhelm Institut für physikalische Chemie und Elektrochemie, and
- Max Volmer, ordinarius professor and director of the Physical Chemistry Institute at the Berlin Technische Hochschule

had made a pact. The pact was a pledge that whoever first contacted the Soviets would speak for the rest. The objectives of their pact were threefold:

(1) Prevent plunder of their institutes,

(2) Continue their work with minimal interruption, and

(3) Protect themselves from prosecution for any political acts of the past.

All four of the pact members were taken to the Soviet Union. Von Ardenne was made head of Institute A, in Sukhumi. In his first meeting with Lavrentij Beria (1899-1953), von Ardenne was asked to participate in the Soviet atomic bomb project, but von Ardenne quickly realized that participation would prohibit his repatriation to Germany, so he suggested isotope enrichment as an objective, which was agreed to. Beria oversaw the Soviet atomic bomb project; which Stalin gave absolute priority.

Goals of Ardenne's Institute A included:

(1) Electromagnetic separation of isotopes, for which von Ardenne was the leader,

(2) Techniques for manufacturing porous barriers for isotope separation, for which Peter Adolf Thiessen was the leader, and

(3) Molecular techniques for the separation of uranium isotopes, for which Max Steenbeck was the leader; Steenbeck was a colleague of Hertz at Siemens. A unique bearing unit for uranium gas centrifuges was created in Max Stenbeck's group.

Gustav Hertz (1887-1975) made discoveries in the 1910s confirming the quantum theory of the atom, for which he was awarded the Nobel Prize for Physics in 1925. He later developed a method of separating isotopes using diffusion, which was the basis for the enrichment of uranium by gas diffusion centrifuges. He headed the institute "G" (from the first letter of the Russian name Герц), which was specially created for him in the sanatorium of the time of the proud tsar in the Agudzera, near Sukhumi (Fig. 20). It has now become the Sukhumi Institute of Physics and Technology (SIPT). The task of the institute was to develop the enrichment of uranium isotope 235 on an industrial scale. (Due to the conflicts in Georgia since 1992, SIPT could no longer operate in Sukhumi, so in December 1993, the institute moved to Tbilisi.)

Fig. 20. Institute “G”

A) On the institute "A”

On May 21, 1945, M. von Ardenne arrived in Moscow with his family. He was given a cottage in the Serebrjannij Bor district (Moscow region), where a piano, paintings, and other family belongings were brought from Lichterfelde (as von Ardenne writes in his autobiography, they even brought children's toys). Von Ardenne lived in a two-story mansion, on the stairs was a full-length painting of M. von Ardenne by the Führer's artist, in which Hitler presented him with the Knight's Cross with Oak Leaves - the highest award of the Reich. Now the Russian National Research Center "Kurchatov Institute" is located in this area.

The Soviet Union obtained the entire von Ardenne laboratory, its scientific staff, all equipment, a pre-built uranium centrifuge with all documentation and reagents, paper stocks for recorders, photographic records, wire tape recorders for telemetry and optics, electrical transformers, etc., as well as all the equipment of the Kaiser Institute in Berlin and 15 tons of metallic uranium.

Manfred von Ardenne and his German staff put the Sinop sanatorium (near Sukhumi) at their disposal, where they established a research center for the Soviet atomic project. It dealt with the problems of enriching and separating uranium isotopes. Thus, M. von Ardenne became the scientific head of a secret NKVD institute (with the code "A"). The institute's most important task was the development of a centrifuge for separating uranium isotopes. The development of the centrifuge was led by the German engineer Max Steenbeck (1904-1981).

Manfred von Ardenne became the scientific director of Institute "A". There, von Ardenne built a new powerful ion source mass spectrometer, necessary for the analysis of uranium isotope mixtures. Peter Thiessen (1899-1990) was one of the experts in the field of physical chemistry in pre-war Germany, he became the deputy director of Institute "A" (Figs 21,22). The task of the scientist was to develop methods for the production of tubular filters, they are very important elements of uranium gas diffusion enrichment equipment (gas centrifuges).

Fig. 21. Institute "A": main building

By the end of the 1940s, nearly 300 Germans were working at the institute, and they were not the total workforce. At the suggestion of authorities, Ardenne eventually shifted his

research from isotope separation to plasma research directed toward controlled nuclear fusion.

Institutes "A" and "G" were supplied with German equipment and devices exported from Germany (mainly from the Kaiser Institute in Berlin and the Ardenne Institute). At first, the Germans who came with their families worked in facilities A and G. Then it was supplemented with specialists from German prisoners of war and German-speaking Soviet specialists (to take over the knowledge of the Germans).

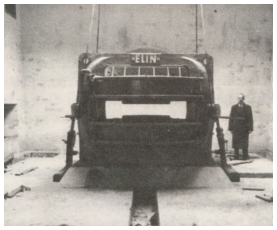


Fig. 22. Cyclotron was transported from the Ardenne Institute (Berlin) to Sinop

German specialists lived in a guarded area, behind a high green fence, literally in a "corn field" a hundred meters from the institute. They had five long two-story houses with a corridor system of rooms and common areas. Next to the park, there were also five Finnish-style houses where higher-level scientists and their families lived. At any time, the Germans could leave the zone - even if only accompanied by a convoy - 24 hours a day, to go on a trip to the city, to the market, or to a shop (Figs 23-25).

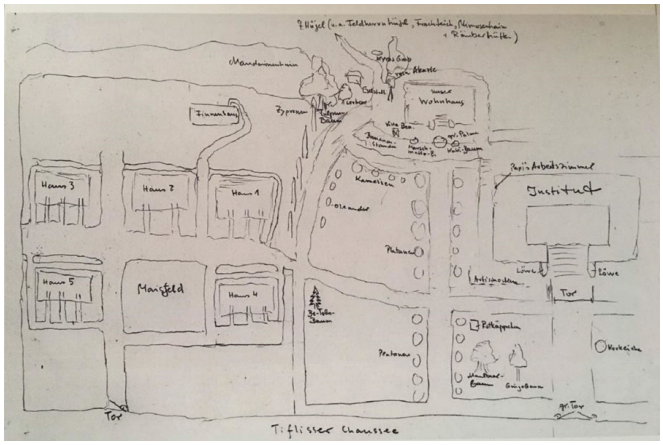


Fig. 23. Scheme of Institute "A" drawn by M. von Ardenne's daughter (father's office was located in the upper left corner of the institute building, a little higher - also a private home for living).

Fig. 24. Ardenne with his family on the way to Svaneti (1946)

Fig. 25. Sukhumi in vinter, 1950

*Electron microscope***.** Ardenne twice became a laureate of the Stalin Prize: for the first time in 1947 for the invention of the electron microscope.

Mass spectrometer. One of the first achievements of Institute "A" was two mass spectrometers designed by Ardenne with sector magnets at an angle of 60 degrees. The first of them was with a single focus, the second - with a double focus. The mass spectrometer made it possible to accurately measure the atomic nuclei and isotope masses of all known elements.

Duoplasmatron. In 1948 Ardenne constructed the Duoplasmatron — ion source for use in large particle accelerators and ion-propelled cosmic rockets. Ion sources are necessary to form ions for mass spectrometers and other types of instruments.

The Duoplasmatron is an ion source in which a cathode filament emits electrons into a vacuum chamber. A gas such as argon is introduced in very small quantities into the chamber where it is charged or ionized by interacting with free electrons from the cathode to form a plasma. The plasma is then accelerated through a series of at least two highly charged grids and becomes an ion beam traveling at a fairly high speed from the device aperture (Fig. 26).

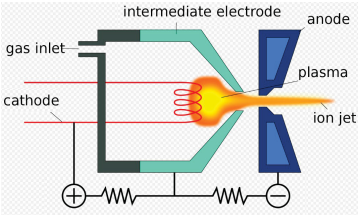


Fig. 26. Illustration of a Duoplasmatron

Cyclotron. In 1953, a cyclotron with a voltage of 10-20 megavolts was put into operation, which made it possible to accelerate deuterons and protons with an intensity of more than 100 mA and to study the nuclear reactions of radioactive isotopes in a wide mass range. In the same year, the institute created the first Soviet mass spectrograph with high light output and extremely small errors in the optical image of ions, which made it possible to significantly improve the accuracy of measuring the masses of atomic nuclei. This was an important scientific achievement and contributed to the further development of spectral analysis (Fig. 27).

Fig. 27. This is what Ardenne's secret underground laboratory looks like today. The two main underground tunnels of gigantic size, which could easily fit two railway cars, had many more branches (all long since ruined and overgrown).

Atomic bombs and uranium-235. The nucleus of this substance is very unstable. When an extra neutron appears in it, it collapses, forming two nuclei of other matter, and also releasing two neutrons and releasing a relatively large amount of energy. The released neutrons get into other U-235 nuclei and fission takes place again, etc. The fission of nuclei spontaneously releases enormous amounts of energy. For a chain reaction to start, there must be a certain mass of substance. The critical mass of uranium-235 is 52 kg. The ball body can be made of ordinary steel or duralumin. Inside the case, there is a chemical (or some other) explosive. In the center are two pieces of the radioactive substance U-235. The mass of each piece is less than the critical mass, but the total mass is greater. When a chemical explosive detonates, it compresses two pieces of radioactive material into one. When they connect, a spontaneous nuclear chain reaction begins.

Gas centrifuge. Uranium enrichment is one of the main steps in the creation of nuclear weapons. Uranium-235 is an isotope that makes up less than 1 percent of all-natural uranium and provides fuel for nuclear reactors and atomic bombs. 99 percent of natural uranium is the isotope uranium-238, which is not used in nuclear weapons. To make an atomic bomb, uranium-235 must be obtained. This can be done (albeit with great effort) because uranium-235 atoms weigh slightly less than uranium-238 atoms. To separate the tiny amount of uranium-235 found in each piece of natural uranium ore, engineers first convert the uranium into a gas. After that, gas centrifuges are used, that is, uranium gas is introduced into cylindrical tubes. Each tube rotates on its axis at an incredibly high speed (around 1500 rpm), pulling the slightly heavier uranium-238 gas molecules to the sides of the tube, leaving the lighter uranium-235 gas molecules near the axis of rotation where they can be sucked out. After separating gaseous uranium-235, uranium gas is converted into a solid metal in many centrifuge stages. This metal is then used in either nuclear reactors or bombs (Fig. 28).

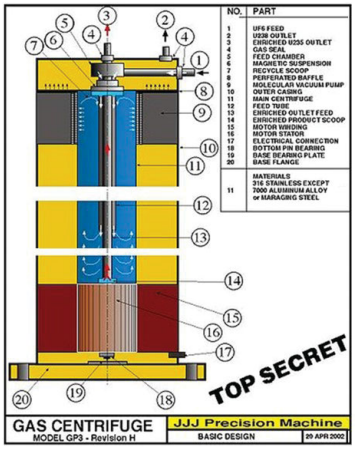


Fig. 28. Scheme of the gas centrifuge: tubes (in blue) rotate around the axis, exit 3 sucks enriched U-235, and exit 2 sucks U-238.

In 1953 M. von Ardenne became a laureate of the Stalin Prize for a second time: for the production of lithium-6, which is an essential component of the atomic bomb (Fig. 29).

Fig. 29. Stalin Prize

B) On the First Soviet atomic bomb

The atomic bomb is being developed in two versions: using "heavy fuel" (plutonium) and using "light fuel" (uranium-235). The nuclear bomb had to be manufactured in the form of an aerial bomb weighing no more than 5 tons, with a diameter of no more than 1.5 meters and a length of no more than 5 meters. These restrictions were because the bomb was developed for the TU-4 aircraft, the bomb bay of which allowed the placement of a "product" with a diameter of no more than 1.5 meters.

An option with plutonium was implemented. In a plutonium bomb, the transition through the critical state must be achieved by symmetrically compressing the spherical plutonium with a conventional explosive. The initiator is a polonium-beryllium system with a radius of 1 cm. A neutron flux is created by an impact on the initiator, as a result of which α-particles of polonium interact with beryllium nuclei. The active material of the bomb is the δ-phase of plutonium with a specific gravity of 15.8 g/cm^3, made in the form of a hollow ball consisting of two halves, which are then compressed. The outer diameter of the ball is 80-90 mm.

The tamper is a hollow ball of uranium metal with an outer diameter of 230 mm. The aluminum shell surrounding the tamper is a hollow ball with an outer diameter of 460 mm. Behind the aluminum layer is a layer of explosives. The total weight of the explosive is about 2 tons. The explosive layer is covered with a duralumin shell, to which a blasting device weighing 180 kg is attached. The internal diameter of the shell is approximately 1400 mm, weight together with the blasting device is about 700 kg (Figs 30, 31).

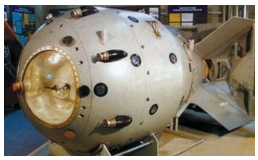


Fig. 30. First Soviet atomic bomb

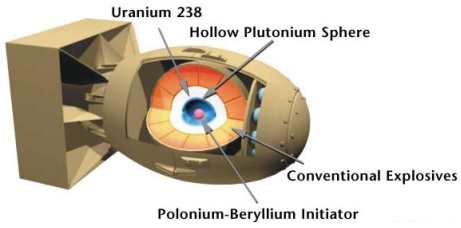


Fig. 31. The scheme of the atomic bomb

Fig. 32. Nuclear mushroom of the atomic bomb ground explosion on August 29, 1949

On 29 August 1949, the Soviet Union secretly conducted its first successful weapon test at the Semipalatinsk-21 in Kazakhstan (Fig. 32). Stalin alongside Soviet political officials and scientists was elated at the successful test. A nuclear-armed Soviet Union sent its rival Western neighbors, and particularly the United States into a state of unprecedented trepidation.

At the end of the war, the USSR's atomic bomb project was far behind the Americans. Then 12 Nobel laureates, 15 thousand scientists, engineers, and technicians, 45 thousand workers, 4 thousand stenographers, typists, and secretaries, and a thousand security personnel already participated in the Manhattan Project. There were only 80 people in Igor Kurchatov's laboratory No. 2, of which only 25 were researchers. However, the Soviet Union soon overtook the United States in the resources involved in developing nuclear weapons. In the summer of 1949, when the bomb was ready, more than 700 thousand people worked in the nuclear industry. Among them, about 7,000 German specialists worked on the atomic energy project, and another 3,000 were employed by Sergey Korolyov (1907-1966) on the rocket project (Fig. 33).

Fig. 33. USSR nuclear facilities in the 1950s

Since 1949, the Soviet Union has been producing and testing nuclear weapons on a large scale. In total, the Soviet Union conducted 715 nuclear weapons tests during the Cold War. In addition, the Soviet Union's nuclear capabilities escalated the Cold War with the United States to the point of nuclear war and introduced the doctrine of mutually assured destruction.

C) Back to Germany

In 1953, before his return to Germany, Ardenne was awarded a Stalin Prize, first class, for contributions to the atomic bomb project; the money from this prize, 100,000 Rubles, was used to buy the land for his private institute in East Germany. According to an agreement that Ardenne made with authorities in the Soviet Union soon after his arrival, the equipment that he brought to the Soviet Union from his laboratory in Berlin-Lichterfelde was not to be considered "reparations" to the Soviet Union. Ardenne took the equipment with him in December 1954 when he returned to the then East Germany.

The new Manfred von Ardenne Institute started work in electron, ion, and nuclear physics, as well as electron microscopy, and later in medical electronics and the biochemical industry. The field of work was very broad and focused on practically important things, including Vacuum melting of reactive and reflective metals, Cutting and welding, Thermal and non-thermal micro structuring, Textured surface coating, Rapid evaporation of metals and dielectrics, Radio-polymerization of synthetic materials, Rational sterilization of cereal seeds or disposable medical products.

An electron beams multi-chamber furnace went into operation here in 1959, with which steel blocks weighing up to 20 tons could be melted and refined. In 1963, the plasma fine jet torch with a high-pressure arc was invented for cutting extremely brittle materials. With the development of systems for vapor deposition of thin layers in a high vacuum, the phase of dominance of technical and physical interests ended in 1965.

The institute carried out work important for the industry in both the USSR and the GDR, for which it received awards from both sides (Figs 34, 35): twice the National Prize of the GDR (in 1958 and 1965) and the Lenin Medal in 1970 (on Lenin's centenary).

Fig. 34. National Prize of the GDR (with a portrait of Goethe)

Fig. 35. Lenin Medal

Magnetron. In October 1974, the first magnetron discharge supported by a pot magnet was carried out successfully This magnetic field arrangement kept the electrons with a lateral drift along the path as long as they could provide energy for the ionization process. It caused the decisive increase of the ion current density on the target by up to 30 and similarly influenced the deposition rate. the first tests were made in 1974 in a straightforward setup using a pot magnet from an ion-getter pump, combined with an uncooled copper plate target. Last year, these initial tests were repeated with the original equipment to commemorate their importance

The success of the first tests led to rapid development. In less than one year, the first planar magnetron PPS-5 was available for IvA purchase. At the time it was called the Planar Plasmatron (Fig. 36). Its performance of 5 kW discharge power

by a 500 V discharge voltage and a sputter rate of 0.7 g/min for copper seemed to be very impressive in those days.

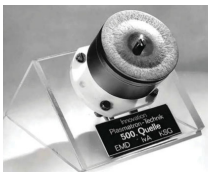


Fig. 36. Design of the first Planar Plasmatron PPS-5 with 5kW power developed at Ardenne Institute

Today, magnetron sputtering is a reliable, highly developed, and industrially proven technology (Fig. 37).

Fig. 37. Actual design of high power rotatable dual magnetron RDM with 3750 mm target length for architectural glass coating (developed at Ardenne Institute).

IV. Otto Warburg: How the Cell Breathes

Otto Warburg (1883-1970) - a German biochemist, doctor, and physiologist - pursued his path as a scientist very purposefully and in 1931 received the Nobel Prize in Physiology and Medicine (Fig. 38). The wording of the Nobel committee was as follows: "For his discovery of the nature and mode of action of the respiratory enzyme."

Fig. 38. Otto Warburg

Otto Warburg tried to uncover the secret of cancer - based on cellular respiration. Warburg's goal was to find the biochemical triggers that turn normal cells into cancer cells with their inherent uncontrolled growth. Warburg began measuring how much oxygen was consumed by normal and tumor tissue. It turned out that both cells "eat" the same amount of oxygen, however, cancer cells release much more lactic acid in the presence of oxygen. Warburg began to investigate why this happens and discovered an important feature of cancer cells.

As early as 1924, Warburg discovered that healthy cells obtain energy in the mitochondria during the oxidative breakdown of organic acids, but tumor and cancer cells, on the contrary, receive energy through the non-oxidative breakdown of glucose (Fig. 39). The transition to an oxygen-free energy regime, according to Warburg, leads to an autonomous uncontrolled existence of the cell: it begins to behave as an independent organism and tries to divide (reproduce). Based on this discovery, Warburg proposed that cancer can be considered a mitochondrial disease [4].

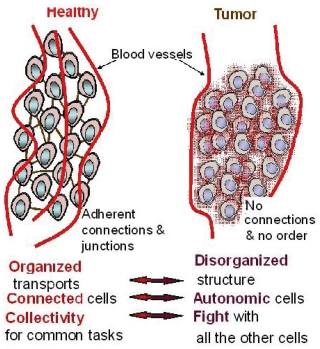


Fig. 39. Blood flows inside healthy and tumor cells

When the Nazis came to power, Warburg was forbidden to teach as a person of Jewish origin. In 1941, he even allowed himself to criticize the authorities and immediately lost the position of director of the institute. Maybe he would have lost his life, but Hitler was terrified of oncological diseases - it saved him. A few weeks later, Warburg received personal permission to continue his scientific work, which came directly from the Führer's office.

Nobel laureate Otto Warburg's theory caused controversy in the scientific world for many years. Researchers discovered that malignant changes in cells and uncontrolled cell growth lead to genetic mutations, so most scientists began to believe that Warburg's discovery was only a side effect, not the cause of cancer.

It is worth recalling the words of Otto Warburg: "Cancer has only one primary cause. The main cause of cancer is the replacement of normal cellular respiration by anaerobic (without oxygen)". Thus, the scientist formulated the following conclusion: cancer cells will never live in an oxygen-saturated environment, because they cannot survive in the presence of oxygen.

V. Hyperthermia as a Cancer Treatment Method

A) Ardenne and hyperthermia

In 1959, Ardenne met Nobel laureate Otto Warburg. After a long discussion about the characteristics of cancer cells, Warburg convinced Ardenne to focus on cancer treatments. And Ardenne tackled this exciting job with all his zeal, even beyond measure. As a result, in the 1970s, the scientist suffered a very serious illness — he was diagnosed with "general exhaustion of the body". Doctors gave him no more than two years to live. Disregarding the advice of doctors, von Ardenne started treatment himself — he developed a new multi-stage oxygen therapy. Simply put, several times a day he breathed pure oxygen according to a certain schedule. Today, this technique is used all over the world. And Manfred von Ardenne himself stood up in a couple of days — literally to the amazement of the specialists.

Hyperthermia as a treatment method was already known in ancient times. Already in Indian Ayurvedic treatises dating from the 10th - 8th century BC, one can find a reference to a method that can without exaggeration be attributed to local oncological hyperthermia, that is, there is talk of placing a heated stone on tumors in the abdomen. In ancient Greece, hyperthermia was practiced deliberately and methodically. The

ancient Greek philosopher Parmenides (540-480 BC) said: "Give me the power to cause fever and I will cure any disease."

Otto Warburg convinced Manfred von Ardenne to practice medicine, namely the treatment of cancer: cancer cells heat up more than healthy ones and therefore die faster than healthy ones - because they conduct heat worse (they simply overheat).

Ardenne's range of research is unprecedentedly wide, he explored all available options for increasing the effectiveness of hyperthermia: infrared hyperthermia, microwave hyperthermia, and many others in combination with anticancer drugs and irradiation.

One important fact of physiology that complicates the use of hyperthermia should be noted. It is the concentration of hydrogen ions (pH level). The target pH level of the body is 4.35-7.45, so - slightly alkaline. From 0 to 7 the solution is "acidic" and from 7 to 14 it is "alkaline". So, the body is constantly working to generate the necessary balanced pH of 7.4. Going beyond the permissible range (7.35-7.45), protein denaturation occurs: cells are destroyed, enzymes lose their ability to perform their functions, and the body may die. Therefore, the acid-base balance in the body is strictly regulated. Several buffer systems reversibly bind hydrogen ions and prevent any change in pH (Fig. 40).

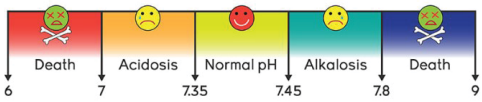


Fig. 40. Blood pH Levels

According to von Ardenne's theory, hyperglycemia causes the activation of anaerobic metabolism in tumor tissue, which leads to lactate accumulation and tumor acidification; erythrocyte membranes become rigid in an acidic environment, which prevents them from passing through the capillaries normally and leads to their blockage and a decrease in blood flow through the tumor. At the same time, a decrease in pH to 6.5 and below causes destabilization of lysosomal membranes, and hyperthermia causes subsequent release of lysosomal enzymes and tumor autolysis. However, whole-body hyperthermia can also cause increased metabolism in healthy tissues, where the aerobic nature requires high oxygen consumption; oxygen is also necessary for recovery from hyperthermia.

General hyperthermia. Ardenne began experiments with general hyperthermia in a bath, and as early as 1965 he presented his concept of "multilevel cancer therapy" at the Heidelberg Cancer Institute, based on hyperthermic effects on tumor tissue: metabolic acidosis results in hyperglycemia. To warm the patient, he was placed in a special bath and, using hot water jets, achieved an increase in body temperature to 42-43 °C. The patient's head was cooled with a special helmet. The duration of the procedure was about 6 hours (Fig. 41).

Fig. 41. Hyperthermic bath

Extracorporeal hyperthermia. In 1966, Ardenne created a heat exchanger for extracorporeal hyperthermia, which became the forerunner of all subsequent extracorporeal hyperthermia systems, and in 1975, the first high-frequency hyperthermia system, which became the prototype of all subsequent electrohyperthermic systems.

Search for thermosensibilizers. Meanwhile — it seems, already in 1967 — von Ardenne had stumbled upon the phenomenon of incomparability of results in vitro and in vivo and also faced the problem of insufficient effectiveness of hyperthermia, which was reflected in the active search for thermosensibilizers, many of them were tested between 1967 and 1969. (Menadione, atebrin, progesterone, dimetilstilbestron, Tween 80, vitamin A, dimethyl sulfoxide, and antibodies were tested.)

Radiotherapy. In 1969, he started experiments in vivo on mice based on the combination of hyperthermia, hyperglycemia, and soft X-ray.

The complete concept of cancer therapy. In 1972, Ardenne introduced the complete concept of "selective multiphasic cancer therapy" (sCMT), in which "long-term acidification by activation of glycolysis" was mentioned for the first time as the primary mechanism of cancer treatment, while mild hyperthermia (40°C) was considered only as an auxiliary modality.

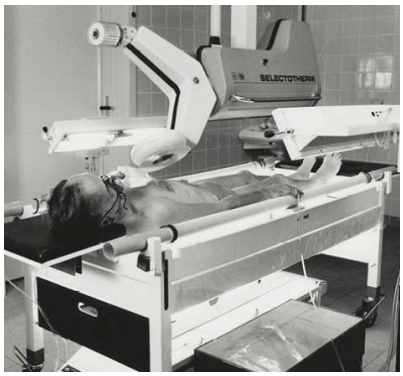


Fig. 42. Oxygen therapy equipment

Oxygen therapy. As a consequence, in 1973 the concept of von Ardenne had been replenished with the last component — the multistep oxygen therapy considered as a multiplier of sCMT (Fig. 42).

Anticancer drugs. In 1976, the idea of selective anticancer agents activated by the acidic environment of the tumor was published. This idea is currently being actively developed, that is, von Ardenne was again ahead of his time by 20-30 years.

Microcirculation in tumor tissue. About 10 papers were published by von Ardenne on the selective inhibition of microcirculation in tumor tissue. In particular, he examined the role of pH-modified red blood cells and the change in their size in hyperglycemic environments, etc. In 1985, the impact of microcirculation was acknowledged by von Ardenne as a central mechanism of sCMT.

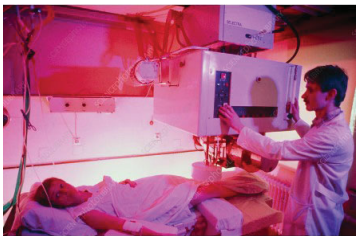


Fig. 43. Selectotherm machine uses radio waves to treat malignant tumors

In the Selectotherm concept, the phenomenon of complete blockade of tumor blood flow at pH 6.1 and 41^{0}C was discovered soon (Fig. 43).

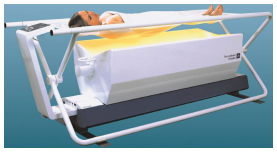


Fig. 44. Whole-body infrared range hyperthermia

Infrared range hyperthermia. In 1992, a new system for extreme whole-body hyperthermia IRATHERM 2000 (infrared range, IRA) was launched, and in 1993 the final version of sCMT was completed: extreme whole-body hyperthermia + selective hyperglycemia thermopotentiation + supportive hyperoxemia (Fig. 44). Meanwhile, hyperthermia was ready for the battle for recognition.

B) Hyperthermia – the rise and decline

Oncological hyperthermia was pioneered by Manfred von Ardenne in the 1960s. He announced his discovery of a "zone of selectivity between malignant and healthy cells in the treatment of cancer with extreme hyperthermia". This marked the beginning of the world's "hyperthermia race". In 1971, von Ardenne published a fundamental monograph on multi-stage cancer therapy, and already in 1975, the first international hyperthermia and radiotherapy cancer symposium was held in Washington, where the North American Hyperthermia Group (NAHG) was founded; it was followed by the second symposium in 1977, the third in 1980 and the fourth in 1984. Around 1981, the US National Cancer Institute (NCI) funded comparative studies of hyperthermia devices (more than 20 prototypes were tested). In 1981, the North American Hyperthermia Society (NAHS) and the International Clinical Hyperthermia Society (ICHS) were founded. In 1978, the Hyperthermia Research Group was established in Japan, and in 1984 it became the Japanese Society of Hyperthermic Oncology (JSHO). Since 1985, hyperthermia treatment began to be insured in Japan. Together with large subsidies from the Japanese government, this led to the rapid development of hyperthermia in Japan. Around 1985, the European Society for Hyperthermic Oncology (ESHO) was founded, in 1985 NAHS, ESHO, and JSHO founded the International Journal of Hyperthermia. In 1985, hyperthermia was considered a promising method in oncology. It was many times called the potential fourth basic method of treatment in oncology, after surgery, chemotherapy, and radiotherapy.

Thus, from 1965 to 1975 hyperthermia experienced considerable progress. At the same time, the negative results had been accumulated. The initial enthusiasm for the "virtually unlimited selectivity" of hyperthermia quickly gave way to the understanding of the inefficiency of hyperthermia as a separate method, as is seen from von Ardenne's research progress.

Despite many "positive" studies and some meta-analyses of hyperthermia, these results were not considered obvious by the medical community. Hyperthermia is not approved as a standard treatment method in oncology. The hyperthermia of the world is now in ruins. This is especially evident when comparing the current state with the 80s and 90s. Analysis of biases in randomized trials has not confirmed the efficacy of hyperthermia. The growing evidence of athermal effects and their wide application has led to the development of some athermal cancer treatments. The concept of hyperthermia (HT) now needs to be radically re-evaluated to establish the obvious bankruptcy of the temperature concept and the development of the athermal concept.

The initial hyperthermia concept of the 60s was straightforward. It was based on the known imperfect of tumor bloodflow: hypovascularization makes the tumor a "heat trap" and allows it to overheat more than surrounding tissues because of their cooling with thermoenhanced bloodflow.

It is well known that the direct cell-damaging effect of hyperthermia is connected with protein denaturation. Reversible denaturation of proteins starts already above 41°C, which is a physiological limit of body temperature.

Instead of triumph, the hyperthermic community was in for a huge disappointment: all the trials had failed to prove the benefits of hyperthermia. Nothing was confirmed: thermal parameters were mostly uncorrelated with endpoints, heating was insufficient within the extreme HT concept, toxicity was too high, and multiple sessions had no effect. The result of 25 years of boiling activity was nothing. It was the dawn of hyperthermia.

C) Technologies based on nonthermal effects

Nonthermal effects have been gradually becoming the mainstream of electromagnetic research since 1985. By the end of the XX century, the number of nonthermal publications (more than 20,000 Pubmed publications) had reached the critical mass, making the transition to practical application inevitable.

TABLE. NONTHERMAL ALTERNATING ELECTROMAGNETIC FIELDS (AEMF) IN CLINICAL ONCOLOGY [5].

Technology	Trademark	Company	Since
Electrohyperthermia	Oncothermia (modulated electrohypethermia)	OncoTherm Group (Germany-Hungary)	1988
Electroporation	electrochemo therapy (ECT)	IGEA Srl (Italy)	~1980
	electro gene therapy (EGT)	Genetronics Biomedical Corp. (USA)	~1997
		Ichor Medical Systems Inc. (USA)	1994
Electric field therapy	tumor treatment field (TTF)	NovoCure Ltd. (Israel)	2000
Magnetotherapy	therapeutic electromagnetic field (TEMF)	EMF Therapeutics Inc. (USA)	~2000
Galvanotherapy	electro cancer therapy (ECT)	CUTH Meditech GmbH (Germany)	2006
		Ionix Medical Inc. (USA)	~2000

Currently, the nonthermal effects of alternating electromagnetic fields could be classified as follows:

(1) ponderomotoric effects due to polarization of dielectrics: (a) dielectrophoresis; (b) rotation of cell and nucleus; (c) orientational effect ("pearl-chain" formation),

(2) membranotropic effects: (a) electropermeabilization and electroporation; (b) cell fusion; (c) changes of transmembrane transport; (d) changes of membrane structure; (e) membrane destruction,

(3) molecular effects caused by direct impact of AEMF on macromolecules: (a) genotropic effects on DNA; (b) proteinotropic effects.

There are several directions and technologies based on the nonthermal effects: (1) dielectrophoresis; (2) electroporation; (3) bioelectric effect; (4) galvanotherapy; (5) electrotherapy; (6) electric field therapy; (7) magnetotherapy; (8) electro hyperthermia (see Table). Some nonthermal technologies have been commercialized or close to commercialization [5].

At the same time, the history of electromagnetic therapy in oncology is only at its beginning. New methods of electromagnetic treatment, some of which already exist and some are in development, will replace hyperthermia, and, probably, we will see the "fourth basic method of cancer treatment" at last.

In the application of oncological hyperthermia, which uses nanoscale heating technology (called oncothermia); a radio frequency (RF) current flows through a selected volume of the body, separately heating the cell membrane. The cell membrane is a good insulator and therefore the current is densest in the extracellular electrolyte near the cells. Of course, when the absorbed energy is too much, individual cell heating does not work, the whole volume will be heated equally. This is again the declaration of the well-known rule: "The difference between the poison and the medicament is only their dose".

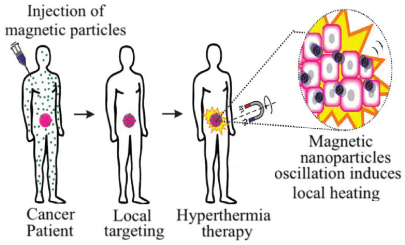


Fig. 45. Magnetic nanoparticles for cancer therapy.

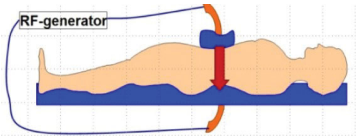


Fig. 46. The oncothermia principle [6].

Both electrodes are always active, independently of their size or form. The current starts in one and ends in the other. The energy density is different, and many safety functions differ (Figs 45,46).

Although oncothermia is currently the hyperthermia world leader with more than 250 devices installed, it is impossible to resume its final success before obtaining trial results because there was the same "success" with other hyperthermia technologies before phase trials. Anyway, we will receive the answers soon.

VI. The Warburg Effect Renaissance

As Otto Warburg discovered, the malignant cells behave completely differently from their healthy counterparts, having mitochondrial dysfunction to produce ATP. (For this discovery a Nobel prize was granted to him.) Warburg's work nowadays has its renaissance [7]; showing the validity of the dominance of the non-mitochondrial (fermentative) way of ATP production. The enzymatic form of metabolic ATP production is still an "ancient" chemical reaction that was typical early in the evolution of life when oxygen, the general electron acceptor, was only available in small amounts in the atmosphere. It is an enzymatic way of using glucose energy, converting it into lactic acid, producing only 2 ATP per cycle. The metabolism of whole cells is mainly regulated by the ATP-convertible energy source. The citrate (Krebs) cycle, carried out by the mitochondria, the "energy plant" of the cell, produces 36 ATP with excellent efficiency with the help of oxygen (Fig. 47a). The fermentative ATP production is a low-efficacy process in malignant cells, (Fig. 47b), however, (due to its simplicity) it can occur in large amounts, and its overall energy-flux can be higher than obtained from the high-efficacy process.

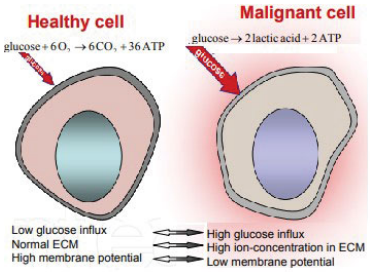


Fig. 47. Differences in healthy and malignant cells: a) healthy cell: glucose+ $6O_2 \rightarrow 6CO_2 + 36ATP$; b) malignant cell: glucose $\rightarrow$ 2lactic acid + 2ATP [7].

Malignant cells divide frequently and constantly. The energy consumption of intensive division is greater than the energy consumption of healthy cells in homeostasis. This is available only when the glucose intake is at least 18 times higher because its ATP (adenosine triphosphate) production is 18 times less than normal. This allows the cell to supply energetically all the normal processes and make differentiation, development, adaptation, and evolution possible. This is a huge additional part of the glucose influx to the anyway high Warburg process.

Nowadays, the Warburg Effect has been studied extensively (Fig. 48).

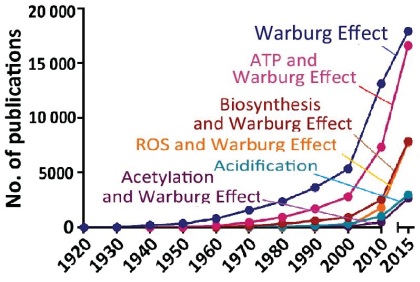


Fig. 48. An exponential growth of publications on the Warburg Effect [7].

What happened?

Today, mutations in oncogenes and tumor suppressor genes are believed to be responsible for malignant transformation, and the metabolic changes that Warburg considered the cause are now believed to be the result of these mutations. Recent re-evaluation of data from nuclear/cytoplasmic transfer experiments, in which cancer cell nuclei are placed in normal cytoplasm and normal cell nuclei are placed in cancer cytoplasm, supports the role of cancer metabolism and mitochondria in promoting tumor suppression. However, as can be seen from the references therein, this promising phenomenon cannot explain the origin of cancer, as Warburg originally proposed.

Warburg's hypothesis has certainly inspired the scientific community to further explore the field of cancer metabolism. His tendency to oversimplify may have prevented him from accepting the extremely complex role and interaction between mitochondria and the nucleus, or, more generally, metabolism and mutation.

The connection between cancer genetics and metabolism shed new light on Warburg's observations. Activation of oncogenes or deactivation of tumor suppressor genes reprograms the cancer cell's metabolism, increasing glucose uptake to provide the fuel the hungry cancer cell needs to continue growing and enhancing anabolic pathways that produce needed molecules. Metabolomics – the identification and quantification of these small molecule metabolites – is an application for which mass spectrometry with gas and liquid chromatography as a pre-separation is ideally suited.

VII. Conclusion

Ardenne constantly fought with medical resistance, so in 1991 he founded his Institute of Applied Medical Research and opened his Multi-Step Therapy Clinic in Dresden. In 1997, his monograph "Systemic multistage cancer therapy" [8] was published, and in the same year, Manfred von Ardenne died.

Ardenne founded the only private research institute in the GDR in Dresden, which employed around 500 people in 1989. He led the institute named after himself for 35 years — from 1955 to 1990. It gained worldwide fame as an important birthplace of innovation.

Fig. 49. Professor Manfred von Ardenne 1988

Evaluating M. von Ardenne's achievements in life (now more than 25 years have passed since his death), for the sake of truth we have to admit that his achievements in the world of technology are admirable, but not so successful in medicine (Fig. 49). Live nature turned out to be much more complicated. He overestimated his abilities as an inventor. His proposed multi-level oxygen therapy and cancer treatment with hyperthermia attracted many followers and research in these directions is still ongoing worldwide, but there is still a long way to go before the final results.

In a television interview, looking back on his life for 85 years, M. von Ardenne spoke about love: "*Love, the most successful phenomenon given to mankind by God, or in other words, the knowledge of the infinite wisdom of nature, has guided my entire life, giving me the strength to achieve more than the world expected.*" It should be added here that love, as a passion for learning the wisdom of nature, is the essence of the life of every real scientist.

He compared the long memory of a composer's work with the fleeting succession of an engineer's work: "*I am most admired by Mozart's genius. It is incredible that a man who lived a little over 30 has made such a great contribution to a particular field and that his influence on it continues for centuries.*"

Here are excerpts from "*Baron unter Kommunisten: Manfred von Ardenne*" [9] published in *Hamburger Abendblatt*:

"Hamburg. No sign, no plaque, nothing on the house at Grindelhof 56 reminds us that one of the most interesting and at the same time contradictory German scientists and entrepreneurs was born here — a television pioneer, co-developer of the Soviet atomic bomb, and holder of more than 600 patents. (...) Manfred Baron von Ardenne died on May 26, 1997 in Dresden at the age of 90. In the meantime, the memory of this extraordinary radio and television technology pioneer and natural scientist has faded somewhat."

Sic transit gloria mundi!

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