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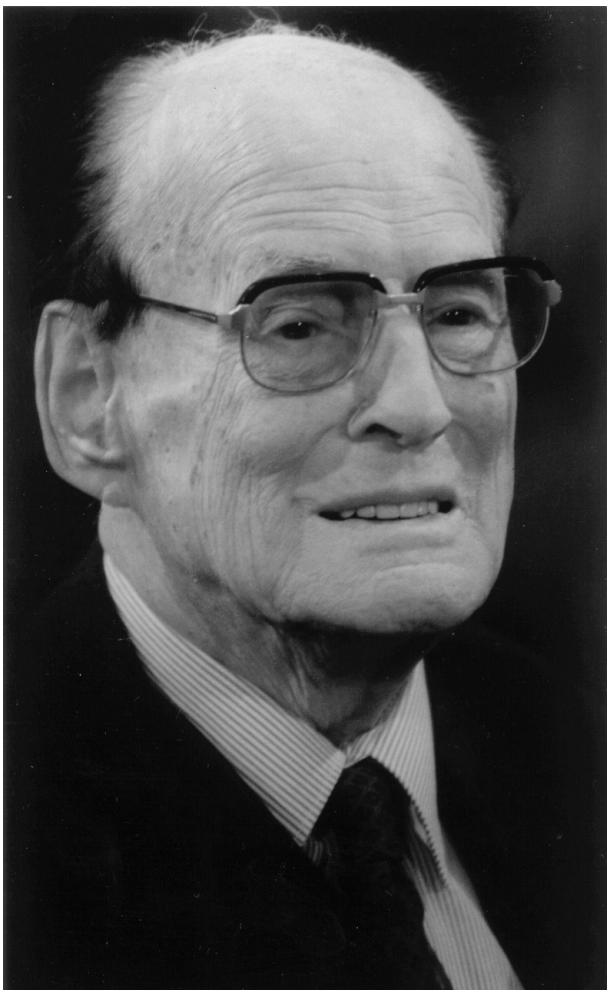
Experimental ONCOLOGY

ANNIVERSARY
PROFESSOR, DR. M. VON ARDENNE
(TO THE 100 BIRTHDAY OF M. VON ARDENNE)



In oncology it is continued to be actual the problem of working out the effective and selective modificators of action of conventional cytostatic means, that has to enhance their antitumor effect as well to decline their toxic influence upon the normal tissue and organs. Among the variety of modificators of traditional antitumor therapy hyperthermia has a special place. Hyperthermia has been known from Hippocrates time and turned attention of the medical scientists in the end of the 19th century and received the principal new technical and biological impact in 60-th of the past century.

One of the initiators of the modern development of hyperthermia was the outstanding scientist-physicist Professor M. von Ardenne, who has contribute much for develop this promise and effective method, especially as a whole body hyperthermic influence.

Institute of Experimental Pathology, Oncology and Radiobiology (IEPOR) of National Academy of Sciences of Ukraine (Kiev) has started to work in the hyperthermia field since 1972 owing to the proposition from famous scientific triumvirate: Prof. M. von Ardenne, Prof. B. Paton — President of National Academy of Sciences of Ukraine and Prof. R. Kavetsky — founder of IEPOR. At present the great interest is shown in Ukraine for hyperthermia, especially for the using of local heating in the treatment of patients with malignant tumors. Special care was given to the problem of tumor microphysiology modulation with the aim to enhance the hyperthermia efficacy. The 18th International Symposium on clinical Hyperthermia was held in Kiev on May, 1995.

In January 2007 M. von Ardenne will be 100 years old. He was the promoter of the developing of the hyperthermia problems in our Institute that allow to extend this promising method into combined treatment of oncological patients in Ukraine, and pay show much respect to this great scientist the Editorial Board propose some material devoting to this date.

Ardenne, Manfred von

20.01.1907–26.05.1997

Physicist and Cancer Researcher, Prof. Dr. h. c. mult

1925–1926 two years study of physics, chemistry and mathematics at the university of Berlin

1928–1945 erection and managing of a private research institute of electron physics in Berlin

1945 member of the German “Reichsforschungsrat”,

1945–1955 nuclear physicist in the USSR leader of a research institute for the development of industrial technologies for isotope separation in Sinop near Suchumi

1955–1990 CEO of the “Manfred von Ardenne Research Institute” in Dresden

1956 Professor at the Technical University of Dresden

1957–1989 member of the “Research Council of the GDR”

1961 chairman of the “Society of Medical Electronics” of GDR

1963–1989 vice chairman of the “Kulturbund-Fraktion der Volkskammer der DDR”

1965 member of the “Internationalis Astonautica Academia” Pans

1991–1997 CEO of the “Von Ardenne Institut fur Angewandte Medizimsche Forschung GmbH”

Main fields of research. Pioneer work in the field of radio- and television engineering, of electron- and ion physics of biomedical engineering, first realization

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of an electronically wideband amplifier, development of the electron beam oscilloscope of compact design, first realization of the full-electronically television, invention of the night vision equipment and X-ray image converter, invention and development of the scanning electron microscope of high resolution, R & D work at the electron microscope for Siemens, methods to magnetically isotope separation, electron beam multy chamber melting furnace, plasma torch with finest plasma beam of high density, Oxygen Multistep Therapy and development of the systemic Cancer Multistep Therapy until the clinical application in conventional incurable patients suffered from cancer with metastasis 600 patents in Germany and abroad.

Publications. More than 32 scientific books, beside them "Funk-Ruf-Buch" (1924), "Verstärkermeßtechnik" (1929), "Die Kathodenstrahlröhre" (1933, 1939 engi), "Fernsehempfang" (1935, 1936 engi), "Elektronen-Übermikroskopie" (1940, 1942 jap), "Tabellen zur Angewandten Kernphysik" (1956), "Tabellen der Elektronenphysik, Ionenphysik und Übermikroskopie" (1956), "Tabellen zur Angewandten Physik" (1962, 1973), "Krebs-Mehrschntt-Therapie" (1967, 1971), "Sauerstoff-Mehrschntt-Therapie" (1978, 1981, 1983, 1987, 1990 engi) "Systemische Krebs-Mehrschntt-Therapie" (1997) and more than 700 further publications.

Awards. Leibniz-Medal of Prussian Academy of Science (1941), State prize of USSR (1947), Stalin prize of USSR (1953), Dr. rer. nat. h. c. / University of Greifswald (1958), National prizes of GDR (1958/1965), Dr. med. h. c. / Medical Academy of Dresden (1979), Dr. paed. h. c. / Dresden College of Education (1982), Wilhelm-Ostwald-Medal of Saxon Academy of Science (1985), Diesel-medal of German Patent-Office (1988), Fnednch von Schiller Prize (1988), honorary citizen of city of Dresden (1989).

WHOLE-BODY HYPERTHERMIA IN THE-SCOPE OF MANFRED VON ARDENNE'S SYSTEMIC CANCER MULTISTEP THERAPY (SCMT)

(A short statement to the 100 birthday of M. von Ardenne (1907–1997))

*A. von Ardenne**

B. Van Ardenne Institute of Applied Medical Research, Dresden, Germany

In 1924 Otto Warburg (1893–1979) published his discovery of aerobe glycolysis of cancer cells [1]. *In vitro* he could proof and in 1962 confirm that tumor tissue in contrast to normal tissue has in presence of oxygen a prominent glycolytic metabolism. Only retina and brain tissue show partly glycolysis under aerobe conditions whereas in all other examined normal tissues no such process was observed. Warburg considered this peculiarity of cancer tissue as a "disturbances of the respiration" [2]. Aerobe glycolysis of the tumor tissues causes the production of lactate, which leads to a reduction of the extracellulary pH-value in the tumor tissue. This effect was observed in human tumors, too. This phenomenon can be used to differentiate normal from tumor tissue [3]. The longstanding partnership between von Ardenne and Warburg was intensified in the beginning of the sixties when von Ardenne developed ideas for cancer treatment based on Warburgs experiments and findings of cancer cells growth. Discussions and experimental investigations were intensified in such a way that Warburg convinced von Ardenne to quit physics and concentrate on medicine, especially to focus on cancer research [4].

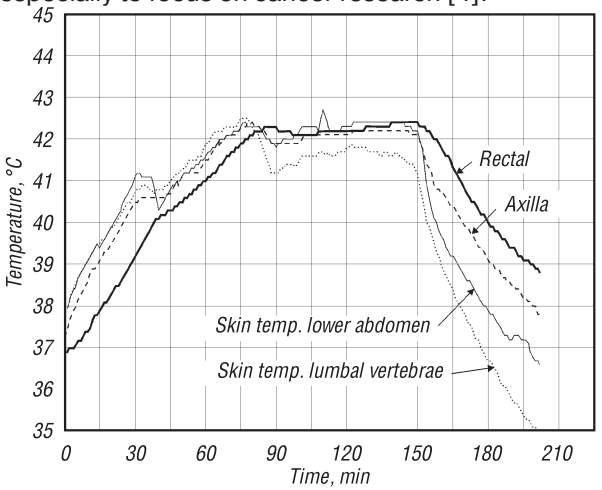

Fig. 1. Typical temperature-time course of systemic cancer multistep therapy (sCMT)

As early as 1935 Voegtiin observed a decrease of the pH-value in tumor tissue upon application of glucose [5]. He measured the pH-value with a pH-electrode on sarcomas and carcinomas of rat. To our best knowledge it was Naeslund, who performed first measurements on human gynecological tumors under intravenous application of glucose in 1953 [6].

Von Ardenne and his team in Dresden investigated the acidification of different tumor tissues also. They proposed an "*in vivo* theory of glycolytic metabolism of tumors and their hyperacidification by hyperglycemia" and explored the dynamic of selective hyper acidification of tumors by application of glucose [7, 8]. They discovered that no pH-decrease occurred during glucose infusion over many hours in the skeletal musculature and in the myocardium of rat [8, 9]. Even in the brain of rats under such conditions (33 mM/l) occurred no considerable pH-reduction [10]. This and other observations lead to the conclusion that tumor tissue can be selectively over acidified.

Von Ardenne's main goal — was to damage metastasis of unknown localizations in the body. Thus he had to elaborate to what extend metastasis are over acidified. Experimental data lead to the conclusion that metastases even smaller then 1.5 mm^3 (approx 10^6 cancer cells) show a clear over acidification [11].

"Classical" denaturants of proteins are acid and/or heat. This was the starting point for von Ardenne and his co-worker of many years Reitnauer to elaborate on the synergy of hyperthermia and over acidification in 1968 in order to study cancer cell damage through thermo sensibilization due to low pH-values [12]. They discovered later on that this effect can even be outperformed by extreme whole-body hyperthermia (body core temperature > 40.5 °C). Animal models provided experimental

data for selective tumor acidification. By increasing the temperature of the tumor to 42 to 43 °C the pH-value in such tissue decreased about 0.5 pH-units [13].

Usually metabolism is strongly activated during hyperthermia also in normal cells. A lack of oxygen and glucose as basic elements for the ATP-synthesis would be a disadvantage for normal cells in terms of their stability. This is one of the main reasons that application of oxygen was implemented into the hyperthermia cancer therapy also [14]. This results lead to the three main steps of systemic Cancer Multistep Therapy (sCMT), which are:

extreme whole-body hyperthermia
+ induced hyperglycemia
+ relative hyperoxemia

In 1974 in the sCMT it was suggested already a combination with cytostatics and radiotherapy [15]. The principle of the sCMT is represented by those three steps with selective labilization of cancer tissue while stabilizing the healthy tissue. It should be complemented by further selective steps, damaging the cancer tissues and stabilizing the normal tissues.

Over a period of 25 years many methods were investigated for systemic heating treatment of patients such as water bathes, extra corporal heat or high-frequency hyperthermia. As the most promising method was found water-filtered infrared-A heat radiation (wIRA) in terms of tolerance to human bodies simplicity and at the same time potency. In wIRA about two thirds of the irradiation energy is released in the corium and in deeper skin tissue. Once the heat radiation reaches the vessel bed of the skin, the blood flow distributes the applied energy through the whole organism. This principle is similar to an outer body shell heating and allows a simple temperature control of the outer body shell and the body core. Such a whole-body hyperthermia system was realized in the whole body hyperthermia device called IRATHERM® 2000. The temperature-time course of sCMT (Fig. 1) shows that it is possible to reach a final temperature of over 42 °C and to apply a high dose of heat within 90 minutes [16].

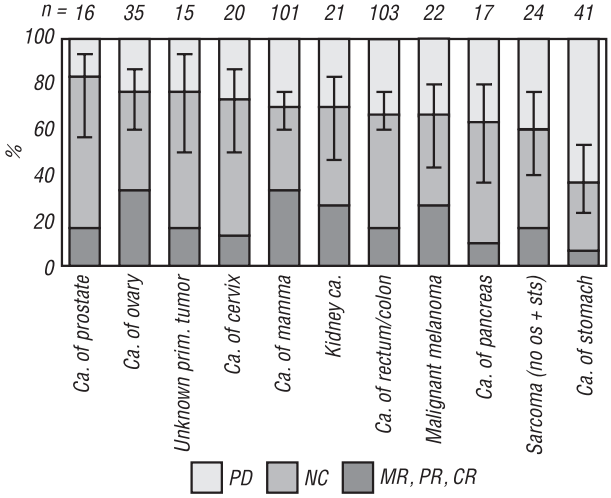

Fig. 2. Individual evaluations related to diagnosis acc. To UICC criteria in different tumor entites; 5% confidence interval for nonPD-PD limit

In 1990 Manfred von Ardenne founded at his institute in Dresden a research clinic for evaluation of sCMT During a phase-I-study it was proofed that patients in the stage of conventional uncontrollable progression show a good systemic tolerance of sCMT with wIRA hyperthermia with only "minimal side effects" [17]. Five years later a research group at an university demonstrated in a phase-I/II study that this therapy "does not lead to any serious or sustained organ dysfunction and can therefore be regarded as a safe therapy" [18].

In Dresden's sCMT clinic were given 490 sGMT one-time treatments in combination with adapted chemotherapy to patients mostly with metastasis in the stage of uncontrollable progression between 12/90 and 12/95. The mean body-core temperature had a value of 41.9 °C ± 0.3 °C and the maximal blood glucose level one of 27.0 ± 3.7 mM/l during the sixty minutes temperature plateau Fig. 2 shows the results of different tumor entities evaluated on the base of UICC criteria [19].

Furthermore sponsored by the "German Cancer Aid" a prospective phase-I/II study was performed on patients with metastatic colorectal cancer at the University Hospital Virchow. Herein was tested a combination of sCMT and chemotherapy protocol (folic acid + 5-Fluorouracil + Mitomycine-C). The whole-body hyperthermia was realized by application of wIRA, where the body-core temperature increased to 41.8 °C over 60 minutes as well as a 50% enrichment of oxygen through inhalation. The induced hyperglycemia had a value of 22 mM/l. During this study ten patients who did not responded to three cycles of chemotherapy were treated then with three cycles of sCMT plus the same chemotherapy. Three patients responded with partial remission (PR) and in six patients progression of the disease (PD) was prevented. Furthermore despite the negative selection of patients in the control group almost the same results were obtained in the progression free survival in the control and-test group [20].

During a pilot study 19 patients with metastasized adenocarcinomas (breast, n = 7, ovarian, n = 5, colorectal, n = 7) were treated with sCMT plus chemotherapy. All patients were refractory to standard chemotherapy and lived in progression (PD). The result of this study showed that nine patients reached a PR and seven a No Chance (NC). It was impossible to stop progression in four patients [21].

Two patients with refractory germ cell tumors were treated three times with sCMT plus chemotherapy (Ifosphamid + Carboplatin + Etoposid). In both cases a PR was reached after therapy completed [22].

Besides the above mentioned studies there are three extreme whole-body hyperthermia phase-II and two phase-III studies right now (2006) on-going in Germany. All these studies are performed under induced hyperglycemia and relative hyperoxemia as well as combined with chemotherapy. They all follow the sCMT procedure.

Manfred von Ardenne is without doubt one of the most influential protagonist of hyperthermia in oncolo-

gy, who fought over 40 years for the vision that cancer cells can selectively be damaged in combination with hyperthermia. Many groups are working today in the area of hyperthermia with the focus on oncology, what is a proof for the rightness of his idea post mortem, Manfred von Ardenne envisioned the sCMT in combination with chemotherapy and/or radiotherapy as an complementary method to conventional cancer therapies. In his opinion the best timing for this therapy was an early stage of cancer, preferably perioperatively. This will be hopefully proven in the future.

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