Medical Hypotheses 17: 47-65, 1985

FUNDAMENTALS OF COMBATING CANCER METASTASIS BY OXYGEN MULTISTEP IMMUNO-STIMULATION PROCESSES*

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ABSTRACT

Because more than 80 % of all cancer deaths are caused by metastases, development and evaluation of methods for fighting tumor dissemination should be major tasks of present cancer research. Formation of metastases is favoured by both reduced numbers of immune cells in the bloodstream and impaired oxygen transport into tissues. These closely related signs often emerge concomitantly when the organism is endangered by circulating tumor cells released from the original tumor by therapeutic manipulations. From knowledge of these facts the O_2-multistep immunostimulation technique has been developed as a way of diminishing the risk of tumor spread. The process combines temporary elevation of the number of circulating immune cells with continuous improvement of oxygen transport into tissues. The former is achieved by a peptide mixture isolated from thymus glands in combination with the chemical immunomodulator 2-cyano-ethyl urea; the latter is the outcome of several variants of the O_2-multistep therapy discussed here. The efficiency ranges of the different variants are quantified on the basis of findings that allow assessment of the number of tumor cells which can be destroyed by this treatment. This number may be about 100 times the number of malignant cells that must be killed in terms of an effective metastasis prophylaxis ($\approx 3 \times 10^5$). The estimated efficiency range represents therefore a not yet fully exhausted preventive and possibly even therapeutic potential. - To speed the introduction of the procedures described into practice, all clinical oncologists are encouraged to refer their patients to established facilities for O_2-multistep immunostimulation after termination of any conventional therapy.

* In remembrance of Gerhard Domagk (1895-1964)- Monuments should be erected on all mountains to his memory, because he saved more human lives than were wiped out by two World Wars (from the obituary to G. D. by Otto Warburg).

INTRODUCTION

It is known that more than 80 % of all cancer deaths are caused by metastases as compared to only 10 % by the primary tumor (1). It follows that the probability of dissemination depends strongly on the tumor stage and increases rapidly with the size of the primary tumor at the moment of first detection or treatment. This experience is exemplified for mammary carcinoma in Fig. 1 according to Haagensen (2). Even in the relatively early stages, when the first therapeutic measures are usually initiated, the probability of metastasis is already about 50 to 60 % or higher for frequently occurring tumors such as breast and lung carcinomas or melanomas. The detection of metastases is tantamount to the individual's sentence of death. These facts indicate that development and evaluation of methods for fighting tumor spread should be a major object of present cancer research. This issue must be taken very seriously because in the past few decades

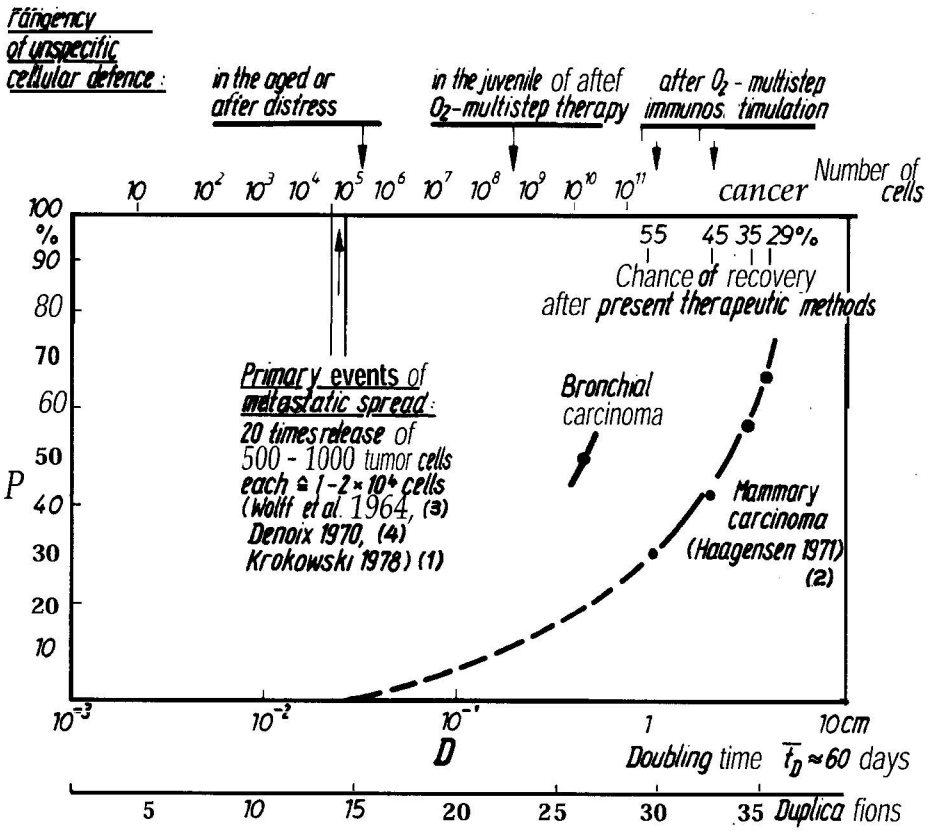

Fig. 1 - Primary events and probability P of metastatic spread vs. tumor diameter D exemplified by the mammary carcinoma after operation, radiation or chemotherapy. (Bronchial carcinoma for comparison). Adapted from data by other authors as indicated.

there has been no change in the relative number of cancer deaths despite billions of dollars invested worldwide in cancer research (5). In his profound cirticism of present cancer management, Krokowski (1) pointed out that in the past 20 - 25 years all attempts to improve the cure rate substantially have failed. He looks on prevention of metastatic spread, which should be initiated before and immediately after first treatment of the primary tumor, as the most promising method of guiding cancer treatment to new horizons, and he suggested the following measures:

1. Immunostimulation by BCG and levamisole;
2. Application of anticoagulants and aggregation inhibitors;
3. Application of radioprotective agents (6).

For the above-mentioned reasons, we have been dealing with the development and optimization of a particular process for reducing the probability of tumor spread since 1967. This has been described in a series of papers (7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18). Now the time has come to practise along these lines.

Promotion of Metastasis by Therapy-induced Decline of Circulating Immune Cells

It is obvious that in the phase of metastatic spread a maximum potency of the host defence system should be attained in order to minimize the probability of dissemination. However, established practice is in general still contradictory to this necessity.

Since about 1970 immunologic research has more and more shown that nonspecific cellular defence mechanisms contribute most prominently to cancer control. The number of immunocytes (leukocytes, T-lymphocytes etc.) per unit volume of blood is therefore of great importance for defence function. As shown in Fig 2, the concentration of immune cells, e.g., leukocytes, decreases regularly as a consequence of the three most important tumor treatment regimens of today. This leukopenia weakens the host defence mechanisms just at the phase of cancer cell dissemination and, inversely, promotes metastasis.

Promotion of Metastasis by Therapy-induced Debasement of Oxygen Transport into Host Tissue

Although we have proposed and investigated the improvement of host defence by O_2-multistep processes in a series of papers since 1971 (quotations see above), the impact of the individual's oxygen state has been widely recognized only recently.

Let the quantity of oxygen transport into host tissue be defined as O_2 state which can easily be calculated by the equation:

$$Q_{O_2} = \eta \times COP \times Hb_V,$$

where

η = utilization of the oxygen-binding capacity of blood, briefly

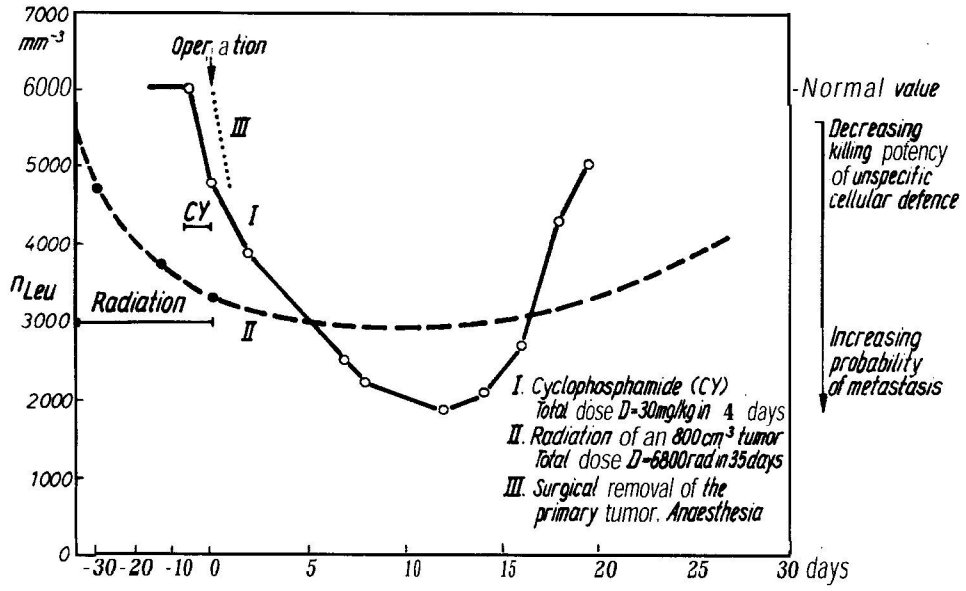

Fig. 2 - Examoles demonstratina leukopenia induced bv established tumor therapies as indicated. - Data obtained in part from (19, 20).

termed as difference of oxygen saturation, that can routinely be determined from the arterial and venous pO_2 resting levels (9, 21);

COP = cardiac output = stroke volume (SV) x pulse rate f. Due to the reciprocity of SV and f, COP remains approximately unaffected by changes of η (9, 21);

Hb_v = Content of hemoglobin in blood, constant for the individual case.

Under normal conditions, the value of η describes in rough approximation the magnitude of oxygen transport into tissues. Therefore, η may be considered a characteristic of the oxygen state and is used in this sense in the following.

The fact that the dynamics of the O_2 state was considered so late as a component of attempts at optimizing tumor control may be due to three reasons:

1. As late as 1980 it became evident that peroxides are the main effectors of phagocytosing cells (22). The concentration of these peroxides depends on the oxygen supply to tissues including the immune system.
2. As late as 1981 routine determination of sufficiently representative values for the O_2 state (η) and the discovery of its dynamics succeeded (21).
3. As late as 1981 we found that the O_2 state is severely impaired by conventional cancer therapies (23).

Typical examples of the critical deterioration of η (oxygen state) as a prompt response to cancer treatment by drugs, radiation or surgery

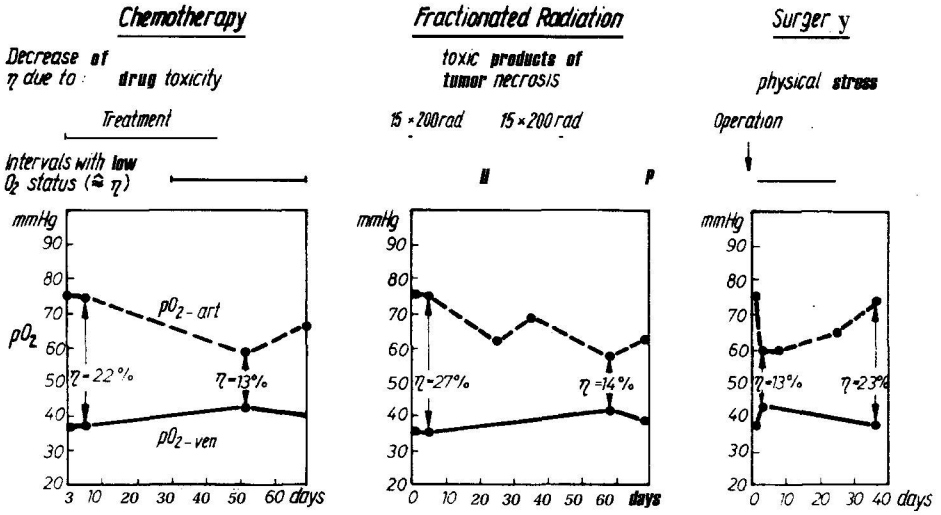

Fig. 3 - Remarkable changes of the O_2 status, i.e. decline of η as the main factor of oxygen transport into tissues, after tumor therapy by drugs, radiation, and surgery. - Typical examples for orientation.

are shown in Fig. 3. The decrease of η is therefore another accompaniment contributing to the further impairment of cancer control mechanisms in the phase of possible dissemination. The close correlation between the diminished value of η and the concomitant decrease of the number of circulating immune cells becomes evident as a very critical promoting factor of tumor cell spreading caused by established tumor therapies.

The Basic Concept of O_2-Multistep Immunostimulation

As outlined in the preceding Sections, pathophysiological findings and measurements reveal the reasons why the probability of metastasis is at present still about 50-60 % or more of all cancer cases under treatment and why nowadays about one million cancer patients per year must die prematurely. On the other hand, the same findings and facts indicate a method for diminishing tumor cell dissemination significantly. In order to approach this goal temporary elevation of the number of circulating immune cells has to be combined synchronously with a continued increase of oxygen transport into host tissues by intensive variants of the O_2 -multistep therapy (9). The judiciously timed concerted action of stimulated immune cell proliferation and improved oxygen supply is termed "O_2 -multistep immunostimulation" (10) and should be applied immediately after the first treatment of the primary tumor, i.e., in the hazardous phase of dissemination triggered by diagnostic or therapeutic interventions.

The interrelations between the two basic steps of this procedure and their synergistic effects are compiled in Table 1. The oxygen transport into tissue represents the limiting factor of (chemical) energy supply.

Table 1

Synergistic Effects of "O_2-Multistep-Immunostimulation"

step	Phenomenon	Effect*	References and Remarks
1. Chemical stimulation of cellular defence by BA 1-4 and/or ISTP peptide mixture from thymus extract	Temporary elevation of the number of leukocytes and lymphocytes	1. Significantly enhanced proliferation of immune cells over several days or even weeks	von Ardenne and Reitnauer (1975, 1977, 1981)
2. Increase of oxygen transport into all parts of the body by intensive variants of the O_2-multistep therapy	Temporary (3-4 days) elevation of O_2 transport up to 250 % of the average measured at 70 yr. of age Synergistic triple effect:	2.1. Stimulation of cell migration by improved energy supply	von Ardenne (1981)
		2.2. Stimulation of chemotaxis	Richter (1980)
		2.3. Enhanced peroxide formation in phagocytosing cells	Fischer et al. (1980): Peroxides as main contributing factors to phygocytosis

* Energy- and oxygen-dependent processes

It is therefore not surprising that continuous improvement of the O_2 state intensifies the many-sided energy-dependent mechanisms of cellular tumor defence remarkably (see column 3 in Table 1).

Synchronized Elevation of the Number of Circulating Immune Cells by Stimulation of Their Generation

Progress has been made very recently in the field of immunostimulation by thymus extracts. The whole extract can be separated into its immunosuppressive and immunostimulating peptide fractions; the latter is now available in purified form as 1 ml (6,5 mg) ampoules (ISTP thymus preparation). Fig. 4 shows increasing leukocyte counts in the peripheral blood of Wistar rats during three weeks after single application of various but well tolerated doses of this preparation. In this test system a corresponding amount of the whole thymus extract proved to be almost as fully active as the ISTP fraction (not shown here). Hence, that preparation ban ce used as well, if the purified ISTP fraction should not be available. The older immunomodulators such as BCG and levamisol are not nearly as effective. The usefulness of other substances such as lysolecithin, preparations from living cells, lithium carbonate etc. has not yet been evaluated definitely.

2-Cyano-ethyl urea (BA 1-4) was tested in the same way as ISTP (15, 17). The result is shown in Fig. 5. This substance exerts its maximum effect within 7 days after application, whereas the ISTP effects does not culminate before Day 16. On these grounds it seems probable that the preparations stimulate different sites of the cellular immune

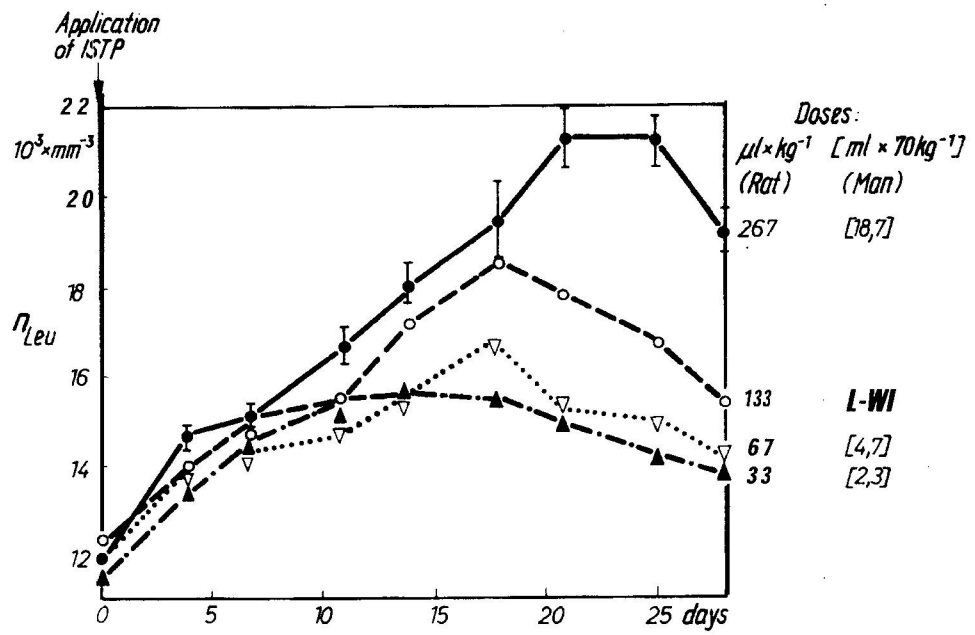

Fig. 4 - Dose-dependent increase of leukocyte counts (n_{Leu}) in the peripheral blood of male Wistar rats (mean body weight 150 g) after single im. application of purified thymus extract ISTP (without immunosuppressive fractions). - 5 animals per group; ISTP kindly provided by Dr. K. Mulli KG, D-7844 Neuenburg /FRG. - Doses for man are given at the right-hand ordinate in parentheses for comparison. - Unpublished results by W. Krüger and P.G. Reitnauer 1983.

system, and there is hope that a combination of them will act synergistically.

Animal experiments shown in Fig. 6 indicate that drug-induced leukopenia can be compensated or, at least, attenuated by modulators of this type.

Unfortunately, BA 1-4 is not commercially available yet. Presently this compound is synthetized on a loboratory scale in our Institute and will be manufactured later by VEB Arzneimittelwerk Dresden. Meanwhile O_2-multistep immunostimulation will have to be applied only with thymus preparations in most cases.

Synchronized Re-elevation of Decreased O_2 Transport into Host Tissues

In the course of our studies on the O_2 multistep therapy between 1977 and 1982 we found a cellular vessel wall trigger mechanism of the microcirculation that controls the bloodflow at the venous ends of all capillaries in the organism synchronously and equidirectionally in dependency On the oxygen (energetic) state (24). On passing a certain oxygen threshold the mechanism increases or decreases capillary

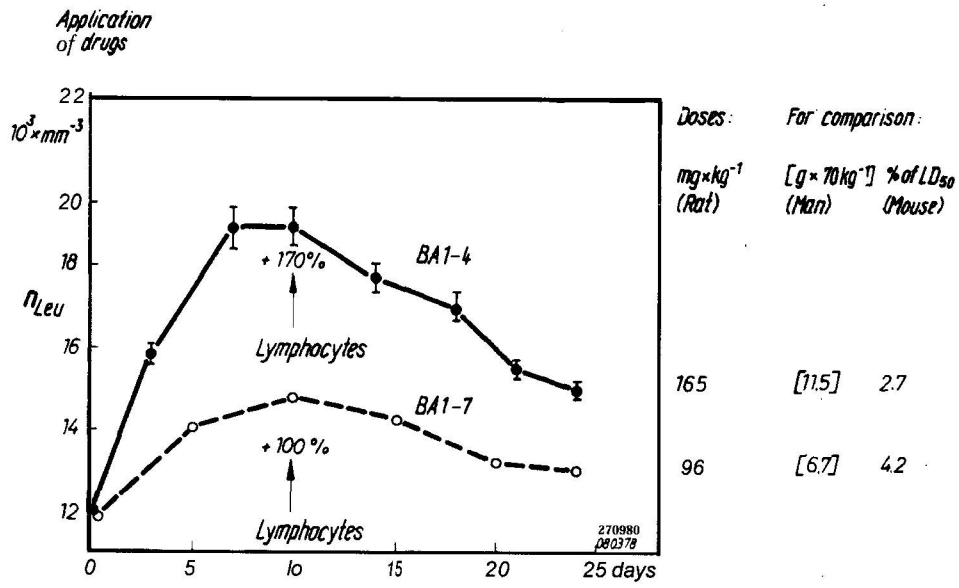

Fig. 5 - Increase of leukocyte counts (n_{Leu}) in the peripheral blood of male wistar rats after single iv. application of the immunomodulators BA 1-4 (2-cyanoethyl-urea) and BA 1-7. - At Day 10, differential blood counts were made additionally showing simultaneous lymphocyte peaks. In case of BA 1-4, a further slight increase of platelets (≈ 29 %) was found. Experiments by P. G. Reitnauer 1978/80.

bloodflow. Its integral effect is reflected in changes of the arterial and venous pO_2 resting levels and is, therefore, measurable routinely. This unexpected trigger effect is due to a feedback mechanism of bloodflow at the venous ends of capillaries (9, 24) and continues for weeks, months or even years until strong external influences on the O_2 (energetic) state shift the points to this or that direction. The discovery of this "switch" mechanism and of its response to variants of the O_2-multistep therapy enables the continued re-elevation of oxygen transport into tissues (expressed as η) after impairment by stressful events such as cancer therapy (9). For this aim the 36 h-multistep therapy process turned out to be the most practicable variant, which is described in the following Section. The increase of η attainable by this treatment is most pronounced for lowered initial values induced by stress, especially in old age. It should be mentioned in this context that in cases of physical weakness, circulatory lability and bedrest, values of η are generally of the order of only 12-15 % as compared to the normal of 20-25 % (21).

A typical example showing the improved oxygen transport into tissues by means of the 36 h-multistep therapy process after cancer therapy-induced distress is given in Fig. 7. When HOT*-UVI[1] treatment is added

[1] 'HOT* = hematogenic oxygenation therapy according to Wehrli (25) the asterisk indicates a special variant of it; UVI = Ultraviolet irradiation (of blood)

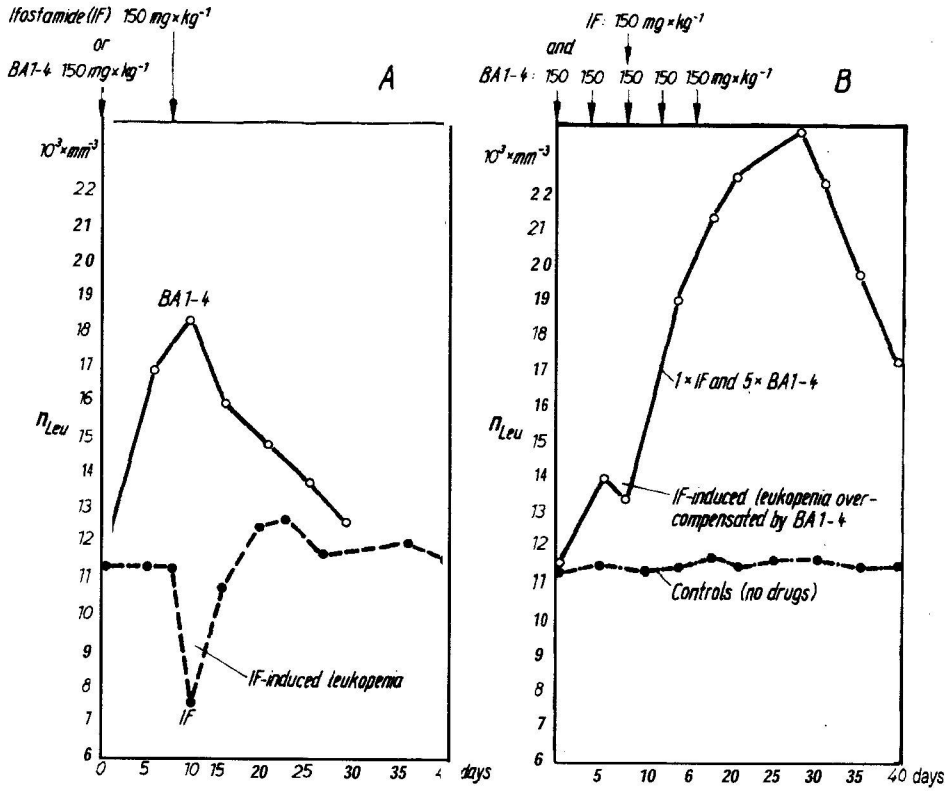

Fig. 6 - Changes of leukocyte counts (n_{Leu}) in the peripheral blood of male Wistar rats (8 animals per group) after single administration of BA 1-4 or Ifosfamide (A), and the effect of combined treatment (B).

as an adjuvant measure to the regu ar 36 h-process, the gain in η is even more prominent for some days. In the example shown, η is increased from 13 to 40 %, i.e. 3.7 fold!

For HOT*-UVI treatment according to Wehrli (25) about 70 ml of venous blood is withdrawn from the patient, mixed with citrate solution (12:1 v/v), uv-irradiated in a quartz cuvette for some minutes, and re-infunded intravenously. For this entirely risk-free procedure, which needs no bubble oxygenator, a special apparatus is commercially available (Manufacturer: VEK Pracitronic, DDR-8016 Dresden, GDR). The main parts are a quartz lamp emitting short-wave uv light and a quartz cuvette of small path length.

The effect of uv irradiation of the patient's own blood both on pO_2 and η is shown in the example of Fig. 8 (26). As can be seen, the positive effect of the additional HOT*-UVI treatment on pO_2 and η lasts generally only for few days as compared to the long-term effect of the O_2-multistep process itself. However, to overcome the problem

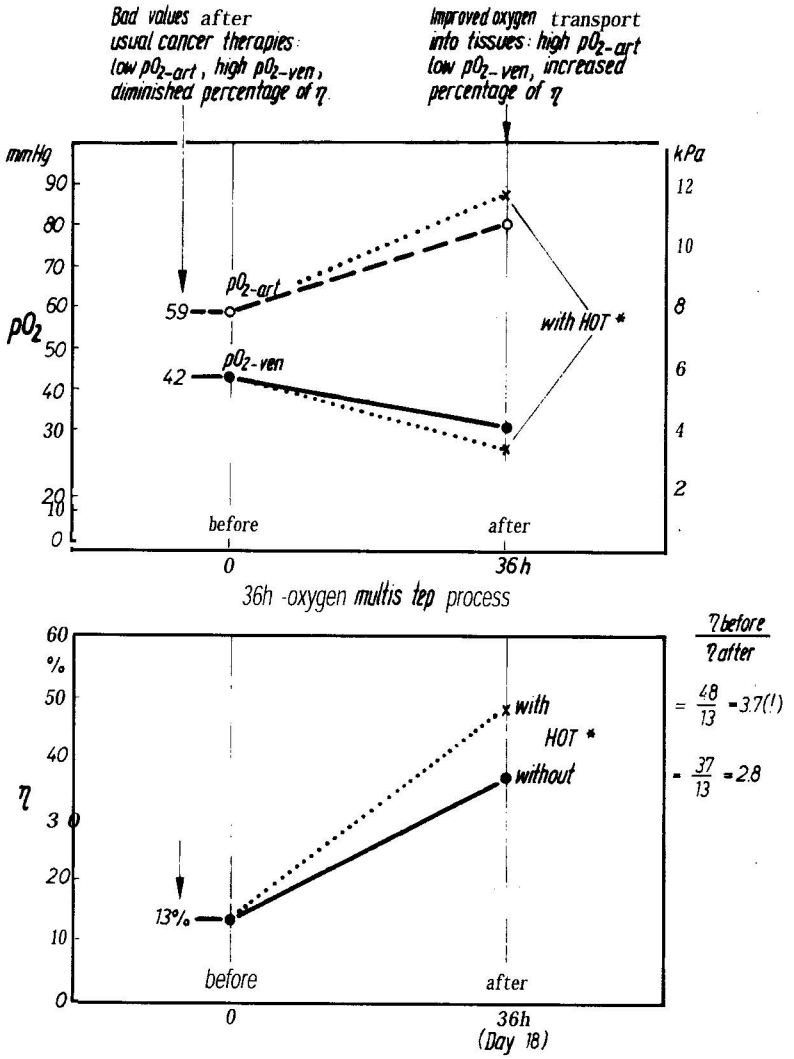

Fig. 7 - Example showing reduced oxygen supply due to distressing effects of usual cancer therapies and the reversal effect of the 36 h-oxygen multistep therapy process with or without HOT*-UVI treatment. The degree of improvement is approximately proportional to the increase of η. For details see text.

of metastatic spread every measure which will meet the general concept is welcome to improve the O_2 state, be it only for some days. Further research must clarify whether the adjuvant HOT*-UVI method is essential for metastasis prevention or the 36 h-multistep therapy process alone will succeed. At present, it seems opportune to us not to omit the HOT*-UVI step. It can be stated in conclusion that the O_2-multistep

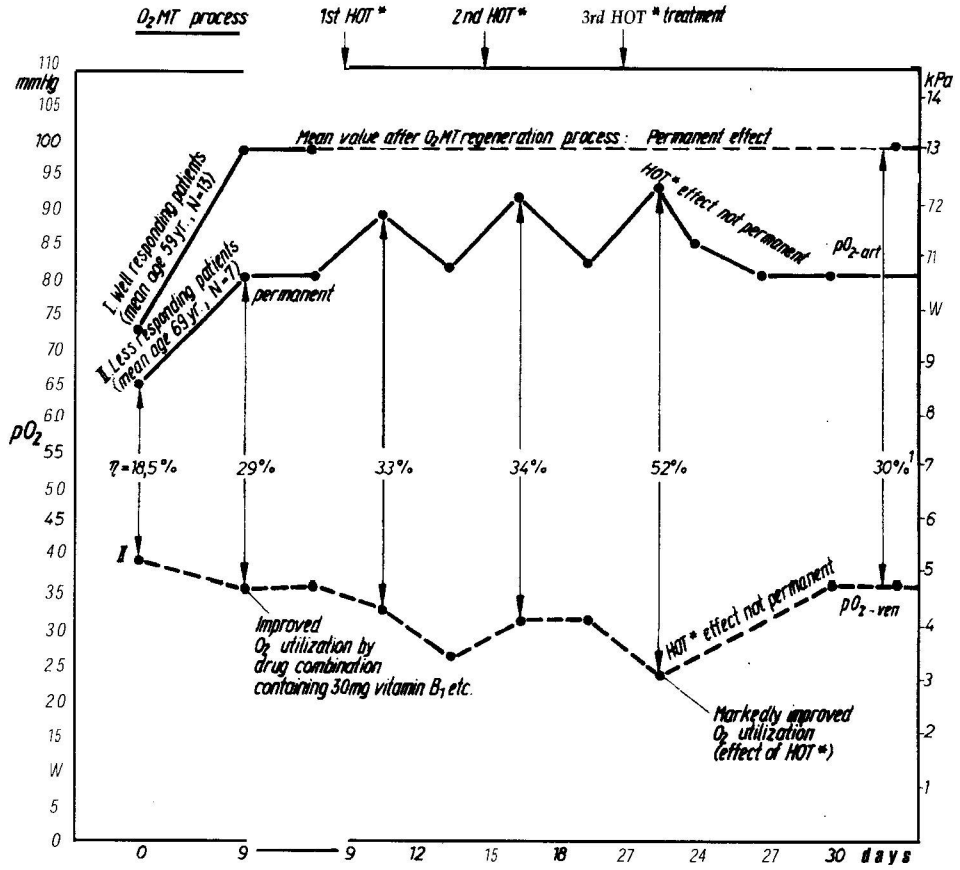

Fig. 8 - Examples showing the increase of arterial pO_2(-) and the decrease of venous pO_2 (--) by the O_2-multistep regeneration process combined with three times HOT*-UVI treatment. - η = degree of oxygen-binding capacity of blood.

[1] **on the fairly exact assumption that there is no essential drop of cardiac output**

measures discussed above are within a few days capable of increasing oxygen transport into host tissues, particularly into the body's defence system, up to three times the amount detectable after conventional tumor therapies.

Programming the O_2-Multistep Immunostimulation

The treatment schedule for the intensive variant of the O_2-multistep immunostimulation is presented in Fig. 9. The single steps are coordinated in such a way that their maximum effects coincide around Day 18. From this schedule several simplified variants have been derived which are summarized together with their indications and efficiency ranges in Table 2. For combating metastases it is recommended

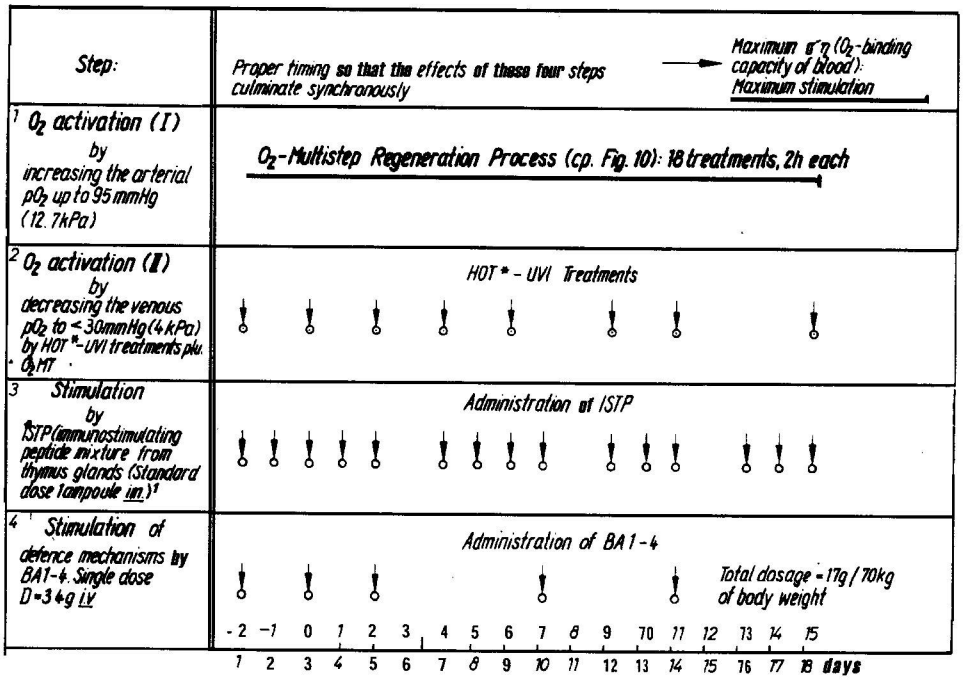

Fig. 9 - Schedule of O_2-mulstistep prophylaxis to cancer metastases and recurrencies by combining the O_2-multistep regeneration process + HOT*-UVI treatment with stimulation of body defence mechanisms by ISTP thymus extract + BA 1-4 (2-cano-ethyl-urea)[2].

As to the optimum starting point of this process, also such cases have to be considered, where metastasizing cancer cells arise simultaneously with the original tumor. In order to prevent metastases of this type, i.e. when the tumor cell emboli are still small, the process should be initiated as soon as ever possible after diagnosis of the primary tumor. Spreading cell aggregates like these are indeed thought to be destroyed by the body's unstimulated natural immune system, but they can attach to distant sites when the defence is severely weakened due to conventional therapeutic measures. These considerations indicate that even in case of earlydissemination the preventive process started immediately after treatment of the original tumor may also purposeful. When linked with the Cancer Multistep Therapy (CMT) this process is followed by hyperthermia (41°C - 120 min) combined with synchronous hyperglycemia (3-4 times the normal) on Day 18. For details of CMT see (7, 27).

[1] **1 ampule containing 1 ml = 6.5 mg of immunostimulating peptide mixture from thymus extracts (Manufacturer: Dr. Kurt Mulli KG, D-7844 Neuenburg/FRG). Total dosage: 15 ampoules. - Combination with Step 4: Stimulation by BA 1-4 (for details see (10))**

[2] **At present prepared by our Institute; prospective manufacturer: VEB Arzneimittelwerk Dresden (GDR)**

Table 2

Variants of O_2-multistep immunostimulation, their indications and efficiency ranges

Variant	Combination of steps as indicated in Fig.3	Efficiency range expressed as number of cancer cells killed[1]	Indication	Treatments per annum	Remarks
1 Intensive variant	1, 2, 3, 4	8×10^9	Therapy (also for palliative treatment)	1 - 2 (2 6)	(Life with cancer')
2 Standard variant[2]	1, 2, 3 or 1, 2, 4	1×10^9	Prevention of metastases (unexhausted reserves)		Treatment within 10 days after any conventional cancer therapy
3 Standard variant, simplified	1, 3 or 1, 4	$\approx 5 \times 10^8$	General cancer prevention (juvenile years)	1	
4 Non-invasive variant	1 with oral application of stimulants	$\approx 2 \times 10^8$	General cancer prevention	1	Orally applicable stimulants under investigation
5 O_2-multistep therapy alone	1 as 36 h-process	5×10^7	Prevention of metastases (no reserve)		Treatment within 3 days after any conventional cancer therapy

[1] These numbers are assessed from experimental observations

[2] Also as constituent of the Cancer Multistep Therapy

to apply initially the standard variant (no. 2), because it offers a certain "stand-by power". When this variant has undoubtedly proven effective, one can pass over carefully to simpler and less powerful variants.

Each variant of the O_2 -multistep immunostimulation includes the 36 h-oxygen multistep process (Step 1 in Fig. 9) divided into 18 treatments of 2 hours each. More details of this process can be taken from Fig. 10 (9). In brief, for a good response to this process consisting of three special measures, it is of great importance that the prescribed flow rate of 4 l/min O, is fully available for the lungs. This necessity is met well by using a special breathing mask made of flexible polyethylene (Fig. 11). By this mask, which can eventually be connected with a gas-storage ball for equalizing flow, oxyxgen is delivered without loss, even if the patient breathes through nose and mouth.

Investigation and design of the simplest possible variant for general cancer prevention is a future project, following effective development of metastasis prophylaxis. It seems not too utopian to suggest that in countries, in such a method is employed once a year, the incidence

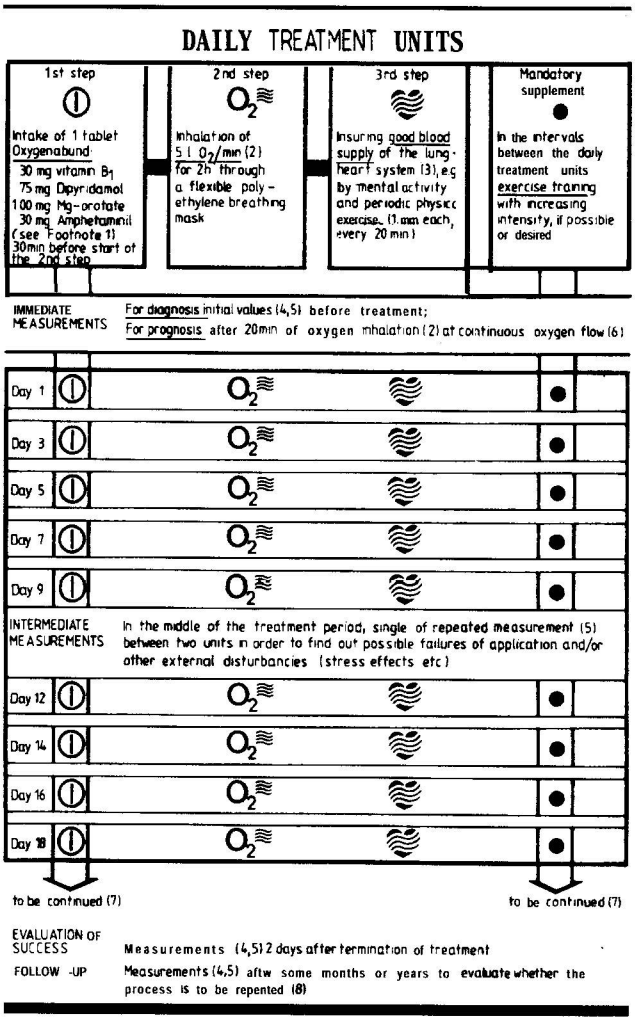

Fig. 10 - Leaflet for doctors and patients, which explains the protocol of the 36 h-02 multistep therapy exemplified by the "18 days cure".

(1) Add 1 g Vitamin C-if desired

(2) Monitoring oxygen flow

(3) For hypotensive patients: drugs (e.g. Novodral retard or Mephentemin) should be given for increasing blood pressure amplitude

(4) Measurement of arterial oxygen partial pressure ($pO_{2\text{-art}}$) in capillary blood from the "arterialized" (hyperemic) ear-lobe after 10 min rest about at the same time of day by using a special device, e.g., MO 10 Universal pO_2 Meter manufactured by VEK Pracitronic, 8019 Oresden/GDR

(5) Measurement of venous oxygen partial pressure

(pO_{2}-ven) in blood from the untied vena cubitalis (9)

(6) pO_{2}-art $\geq$ 125 mm Hg indicates good response

(7) Daily intake of Oxygenabund 30 min before starting exercise to decrease pO_{2}-ven

(8) Decreased values of η reflect stressful events such as cytostatic treatment, irradiation, operations etc.

Fig. 11 - The new oxygen applicator made of flexible polyethylene (Manufacturers: SM-Gesellschaft für Kur- und Sauerstoff-Mehrschritt-Therapie mbH, D-8942 Ottobeuren or G. Weinmann GmbH, D-2000 Hamburg 54/FRG) - Advantages: Oxygen applications through mouth and nose; reading also with glasses possible; comfortable enough for use at sleep; low oxygen loss; disposable material.

of cancer will be drastically reduced. For optimizing variants like these orally applicable stimulants or combined preparations as at-e presently designed might always play an important role. Further studies must clarify whether the 15 min-O_{2} multistep quick process, which is suitable also for outpatients, can be applied in the same way as the above-mentioned extended 36 h-process. Anyway, a variant for general cancer prevention is to be distinguished by extraordinary simplicity. This is, however, a future challenge.

Efficiency Range of the O_2-Multistep Immunostimulation

For designing metastasis prophylaxis two values should be known:
1. The total number of cancer cells spread during metastasis. This figure results from the number of cancer cells initially released, multiplied by the number of cell duplications until the onset of the immunostimulating process and by a safety factor.
2. The efficiency range of the different variants of O_2-immunostimulation.

The total number N of cancer cells to be killed by metastasis prophylaxis can be calculated according to the equation

$$N = N_{prim} \times 2^{ND},$$

where

N_{prim} = the number of initially relased cancer cells, i.e., 2×10^4 (see: (1), and Fig. 1)
ND = Number of duplications until onset of the prophylactic treatment.

Duplication times of metastases are in general much shorter than those of primary tumors and are of the order of 5-30 days, depending on type and localization of the original tumor (1). That is the reason why any prophylactic process should be initiated as soon as possible after termination of usual tumor treatments. On the assumption that
- the duplication time is (unfavourably) short, i.e. 5 days, and
- the prophylaxis process is performed 20 days (= 4 duplication times) after initial metastatic spread,

the number of cancer cells to be destroyed is approximately 3×10^5. This number is multiplied by a safety factor of 10^2.

Then, it must be checked which variant of the O_2-multistep immunostimulation is capable of killing tumor cell numbers of this magnitude. The effective range can be determined from the disappearance of tumor cell aggregates in humans. Table 2 indicates the efficiency of different variants of the O_2-multistep immunostimulation assessed from such observations. After performance of the standard variant (No. 2 in Table 2), disappearance of mammary tumor nodes 1 cm in diameter, i.e., about 10^9 tumor cells, could be seen repeatedly. By application of O_2-multistep therapy alone, i.e. without immunostimulants and HOT*-UVI treatment but by elevation of η up to 52 %, a basalioma consisting of about 5×10^7 cells disappeared as is shown in Fig. 12. From these measurements (note the values of η!) the correlation between oxygenation state and immune state is obvious.

CONCLUSION

The graph in Fig. 13 demonstrates the relations between the efficiency ranges of variants of the O_2-multistep immunostimulation and the different growth kinetics of tumors. At the right hand side of this graph, the numbers of tumor cells which have to be killed by effective metastasis prophylaxis as well as by a general preventive measure applied once a year are additionally indicated. This graph shows

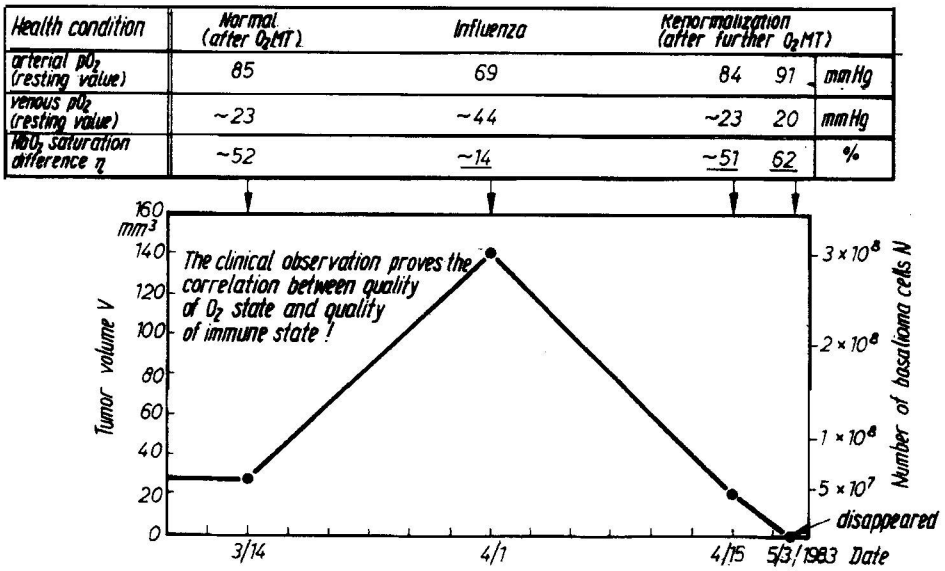

Fig. 12 - Dependency of the steady state between cell proliferation and cell-killing capacity of body defence mechanisms from the oxygen state of the organism (characterized by η) in case of a basalioma of a 76 yr. old male patient. - Destruction of at least 5 x 10^7 cells only by Or-multistep therapy without HOT*-UVI.

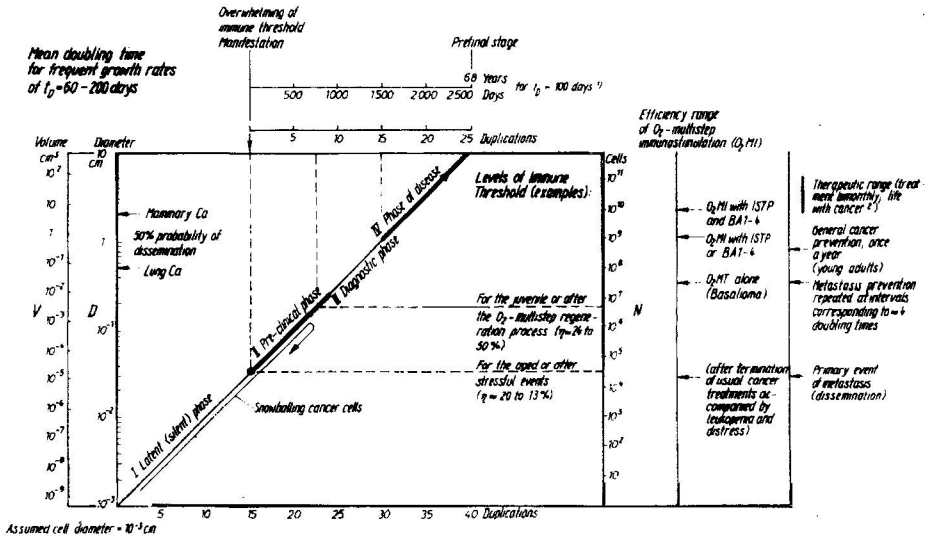

Fig. 13 - Efficiency ranges of variants of the O_2 -multistep immunostimulation in relation to the different growth dynamics of tumors.

'Actually, cancer cell doubling'time t_D is not constant but increases with increasing tumor diameters ($D \geq 1^D$ cm) (1).

clearly that in terms of the number ofdestructible cancer cells the variants of the O_2-multistep immunostimulation present an increased effectiveness of the order of some powers of ten. Whereas large parts of the host's defence system are daily bound up in removing decaying normal cells and in other "daily necessities", the additional defence capacity gained by the methods described can primarily serve to attack cancer cells.

As a consequence of further numerous clinical observations (pain relief, retardation or cessation of tumor growth, survival with increased quality of life despite cancer), a doctors' community for utilization of O_2 -multistep immunostimulation has been founded under the leadership of Or. S. H. Wolf of Bad Wildungen/W.-Germany. This group held a symposium attended by about 50 doctors in Bad Wildungen in late June of 1983. The results and further information can be obtained from the organizer of this symposium.

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