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A Biokinetic Model to Describe Consequences of Inhibition/Stimulation in *DNA*-Proofreading and -Repair, Part 3. Application of the Model-1

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Summary. Using a previously reported physical-mathematical (biokinetic) model which dealt with the factors influencing the development of mismatch-dependent cells and DNA-proofreading and -repair and which model has been calibrated according to related experimental data available in the literature or determined from own preliminary tests, the known efficacy of classical cancer-therapies like surgical-tumor-extraction, or chemotherapy can be demonstrated via biokinetics. On the other hand, also other effects, as they have been reported recently in the literature upon a significant increase of mutants in cases of an inhibition of the proofreading and repair system, can be well described by the model.

Following the predictions of the model also in an opposite way, *i.e.* as to the consequences which arise, if the enzymatic proofreading- and repair-machinery were stimulated instead of inhibited, an interesting chance for a new, "soft" cancer-therapy results. According to this, the administration of proofreading- and repair-stimulators like f.e. equimolar combinations of purine- and pyrimidine-nucleotides' precursors should open the possibility for an adjuvant cancer-therapy, especially as a cancer-prophylaxis (*i.e.*, against cancers "*in statu nascendi*") but also as postsurgical safety-measure. The results of first preclinical tests are reported.

Keywords. Biokinetic model; Proofreading-stimulation; Equimolar combinations of nucleotides' precursors; New adjuvant cancer-therapy; First preclinical tests.

Introduction

Zhang and *Mathews* [1] recently reported results upon replication-fidelity. The authors detected in *in vitro* experiments a significant increase of the mutant-fractions, if *DNA*-replication was done in the presence of proofreading-inhibitors. Inspired by these findings, a biokinetic model was developed [2, 3] to test the

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consequences, if there was also the opposite effect possible, *i.e.* a proofreading-stimulation.

The model's outputs were demonstrated at the example of the timely development of *DNA*-mismatches-dependent cells (malignant cells) in a kinetic competition to the development of normal somatic cells (cells with correct genetic information).

In that way it has been shown [3], that the model answers with showing a break-through of cancer, if the organism was even slightliest exposed to a cancerogen, while its enzymatic proofreading- and repair-ability was inhibited. This result is absolutely in accordance with the findings of *Zhang* and *Mathews* [1]. The model further demonstrates the efficacy of classical cancer-therapies, like surgery and chemotherapy (Fig. 4b and 4c of Ref. [3]) from a biokinetic point of view. Chemotherapy is described by simulating the biokinetic effects reached with the administration of malignotoxic substances.

Based upon (a) this theoretical approach, in connection with (b) the huge volume of significant progresses in biokinetic data reported in recent literature plus (c) the exciting therapeutic successes with nucleotides' precursors [4–10] which led to a special conference on aminoimidazole carboxamide (AICA) in Japan, and (d) the amazing successes of *Ackermann* [11–15] in his cancer therapy using human placenta-extracts. Also the potential opposite effects to the inhibition of the proofreading and -repair-system – *i.e.* the chances which were implicated if a stimulation of the *DNA*-proofreading and -repair-system is possible – have been studied theoretically. The results lead to the consequence, that a stimulation of the *DNA*-proofreading- and repair-machinery might be the key to an interesting new cancer-therapy.

Modrich [16] and *Wagner* and *Meselson* [17] reported that also a postreplication mismatch-correction and -repair is possible. Following these results and considering the efficacy or inefficacy of the enzymatic systems involved in proofreading and *DNA*-repair (inefficacy in the case of a lack of just only one of the nucleotides), and while also keeping in mind the regularities due to the physical properties of nucleic bases in base-pairing, establishing hydrogen-bonds and as to their chemical reactivity, there is some indication, that also for these systems and not only in procaryotes, there might exist a similar ''*bottle-neck-effect*'' as it was described by *Kornberg* [18, 19] and which is also called ''*Kornberg*-effect''. According to *Kornberg*, the repair-systems stop their activity if not all of the 4 nucleotides which are responsible for the genetic code, are locally available enough, where a *DNA*-replication might start. Therefore, administrations of ''adequate'' combinations of nucleotides' precursors have been suggested (*Haschke* [3]) for the creation of depots at as many positions as possible in an organism to act as ''stand-by-effector-molecules'' from which nucleotides may be biosynthesized in only a few biochemical steps locally there, where such nucleotides are needed by the repair-machinery. Thus, a stimulation of the repair-machinery should be possible by activating those enzymes of the repair-machinery which otherwise were not able to do their job due to a lack in the nucleotides' pool.

According to further findings of *Zhang* and *Mathews* [1], mutant fractions are reduced to a minimum if replications occurred in a ''symmetric'' environment of nucleotides. From this, it seems important, that this adequacy is also kept while nucleotides' precursors are administered in a therapy. This means that the dosages

of the precursors are adjusted in such a way that equimolar concentrations of purine- and pyrimidine-nucleotides are reached on the cellular level. An equimolarity which should be reached including the local concentrations of the natural nucleotides' pool.

Precursors would have the advantage, that they might have better chances to ''undertunnel'' the many biochemical regulation-mechanisms in eucaryotes, which mechanisms are focused on stabilizing intracellular nucleotides' concentrations. Due to such regulatory mechanisms, administrations of nucleotides are not easily accepted *in vivo*, but rather rejected and biodegraded [20]. Thus, to create depots of nucleotides' precursors at as many positions as possible in the extra- and intracellular system of an organism, might be helpful to overcome *Kornberg*'s bottleneck-effect and to stimulate proofreading and repair-systems, which otherwise were present but inactive.

Due to the biochemical pathways of the nucleotides' biosynthesis, there are only two precursors necessary (a purine-nucleotides' precursor: *PUNP* plus a pyrimidine-nucleotides' precursor: *PYNP*) to establish a pool for all the 4 main-nucleotides (*i.e. ATP*, *GTP*, *TTP*, and *CTP*). Therefore, if it is possible to stimulate *DNA*-proofreading- and -repair-systems, not only the number of mismatches which are formed during *DNA*-replication or during normal mitosis, respectively, is reduced. *Sancar* and *Sancar* [21], *Modrich* [16], *Wagner* and *Meselson* [17], and *Hanawalt et al.* [22] demonstrated at the example of *DNA*-lesions, which were triggered by UV-radiation leading to the formation of dimers of pyrimidine-nucleotides and their excision and repair, that there should also be a possibility for a depression of the propagation of wrong genetic information *via* the activity of specific repair-mechanisms of which some show also a repair-efficacy at *DNA*-double-helices even after an attack by a cancerogen. By this, a depression of the propagation of malignant cells against normal somatic cells could be reached, showing a similarity to an attack of malignant genetic information or malignant cells by an immuno-system.

In addition to such an influencing of (malignant) cells' propagation, also the influenceability of the cells' dying away rates is expressed by the kinetic model. This is possible for the cells' normal life-cycle, but also under the influence of chemotherapeutica or by induced apoptosis. In the model, these effects are reflected in the form of a shifting of the pseudo-stationary states of growing/dying of malignant cells in competition to growing/dying of normal somatic cells (*Pseudo*-Stationarity No. 2 [2]). Depending upon a successful therapy, or in contrast to this an unsuccessful one or no therapy, the kinetic calculations show a shifting into the direction of cancer-recession or towards a final exponential break through, respectively. By this, the model is able to describe the timely development of a cancer and thus, to some extent, to help to optimize the scheduling of therapeutic measures.

Further, the model puts out that there should be at least three fundamentally different possibilities for a cancer-therapy:

1) The removal (by surgery) or deletion (by chemo- or by radiotherapy) of malignant cells and of their aggregations (tumors)
2) Triggering *apoptosis* of (preferably) malignant cells and/or blocking their energy-supply (like blocking *angiogenesis*)
3) *DNA*-proofreading and -repair and its stimulation

Results and Discussion

To demonstrate the model's effectiveness, some examplatory, typical cases are fed into the computer-program CANCER.xls, which is designed to deliver solutions (by numerical integration) of the equations-system according to *Haschke* [2] (see there: equations: 3–5d or see *Haschke* [3], the ''cancer-equation'' (2c)). The automatically generated results, which are forcing biophysical results of the model, are given and discussed below:

Case 1: Example for a short (0.2 periods of 20) cancerogenic impact (C.I.) by a cancerogen with low activity [ACG = 0.1 (= 10% relative to benzo[a]pyrene)].

ACG means a measure for the Cancerogenic Activity of a substance or of radiation or of a virus acting via viral integration. ACG might be expressed on a scale between 0 (0%) to 1 (100%). The top-value 1 expressing the cancerogenity of benzo[a]pyrene as a reference.

Result: The impact can be compensated by a healthy organism ($ADPoI_{rel} = 1$ ($ADPoI_{abs} = 1 \cdot 10^{-6}$); time of observation = 2000 weeks, *i.e.* time per period = 100 weeks; Fig. 1).

The acronyms $ADPoI_{rel}$ and $ADPoI_{abs}$ represent the relative and the absolute activity of a *DNA*-repair-system, respectively. The part ''DPoI'' in the acronym should just remind that there is described a system for which the enzyme *DNA*-Polymerase I is a good example. However, it must be kept in mind, that the repair-systems in eucaryotes are much more complicated than this simple single-enzyme: Eucaryotic repair-systems are complex and involve up to even cascades of enzymatic activities, but on the other side also with a capability for post-replication-repair and even further going repair-capabilities. (For $ADPoI_{abs}$ which is based upon kinetic data related to the literature and for its corresponding relative values see Ref. [3]).

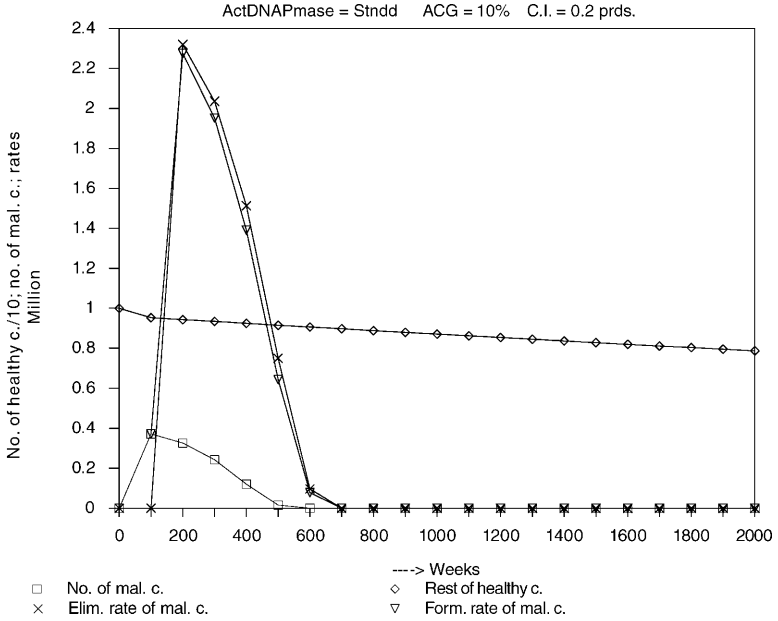

Fig. 1. Case 1: Short cancerogenic impact by a cancerogen with low activity (healthy cells scaled to 1/10)

Case 2: Example for a long lasting (C.I. = 20 periods), but very slight (ACG = 0.04 = 4%) cancerogenic impact.

Result No. 2/1: Cancer (*i.e.* some malignant cells) may be developed, but it is not breaking through due to the fact that in healthy organism the natural proof-reading and repair system (as long as still intact) can repair *DNA*-lesions ($ADPoI_{rel} = 1$; $ADPoI_{abs} = 1 \cdot 10^{-6}$; time of observation = 2000 weeks, *i.e.* time per period = 100 weeks; Fig. 2a).

Result No. 2/2: However, in an organism which contains only even 2% of the affected organ of malignant cells – f.e. due to an older cancerogenic impact or due to an incomplete surgical extraction of an old tumor – cancer breaks through under these conditions within approximately 900 weeks (= 17 years, Fig. 2b).

This example shows the immense importance of a real complete surgical extraction of the malignant cells and/or a postsurgical therapy to kill any potential rest of malignant cells.

Case 3: Example for a strong (ACG = 1 = 100%) and long lasting (C.I. = 20 periods) cancerogenic impact.

Result No. 3/1: With no therapy, cancer breaks through under such conditions within a period of approximately 1 year (Period of observation = 100 weeks, *i.e.* time per period = 5 weeks; Fig. 3).

Result No. 3/2: However, if the activity of the repair-system was stimulated up to 30-times of its normal activity, cancer seems already to be stabilized (Even if there were 2% of residual malignant cells (Fig. 4a).

Result No. 3/3: Nevertheless, extending the period of observation to 600 weeks (Fig. 4b, *i.e.* time per period = 30 weeks) it turns out, that only a postponing (a pseudo-stabilisation, which means rezidive after approximately 8 years) has been reached.

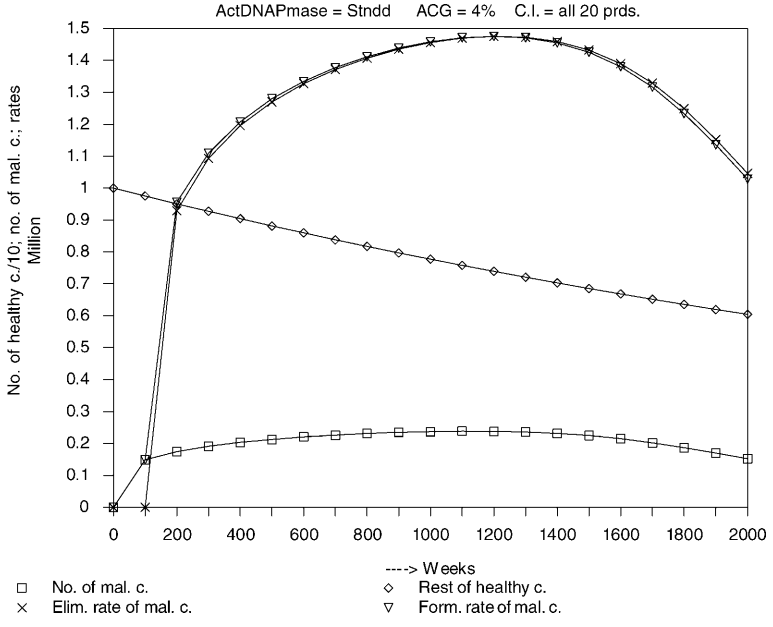

Fig. 2a. Case 2: Long lasting, but very slight cancerogenic impact (healthy cells scaled to 1/10)

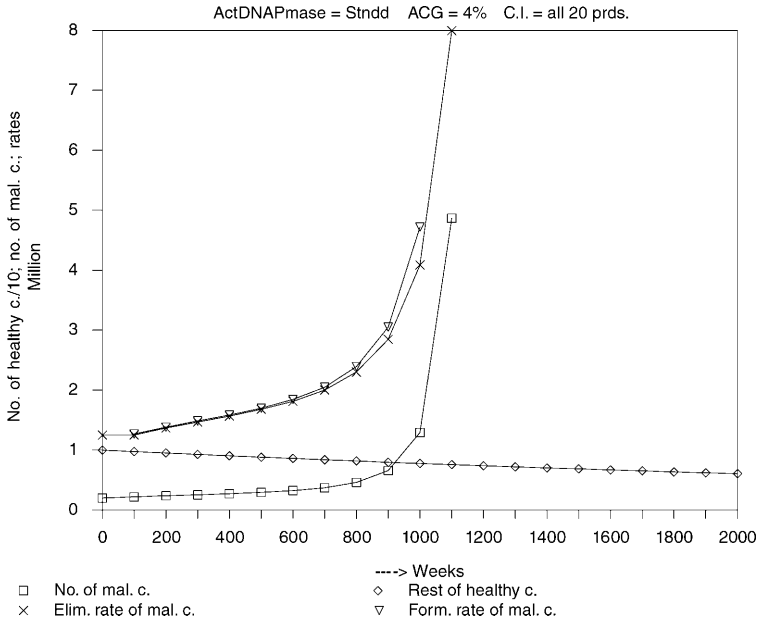

Fig. 2b. Case 2: Long lasting, but very slight cancerogenic impact with 2% residual malignant cells at the beginning (healthy cells scaled to 1/10)

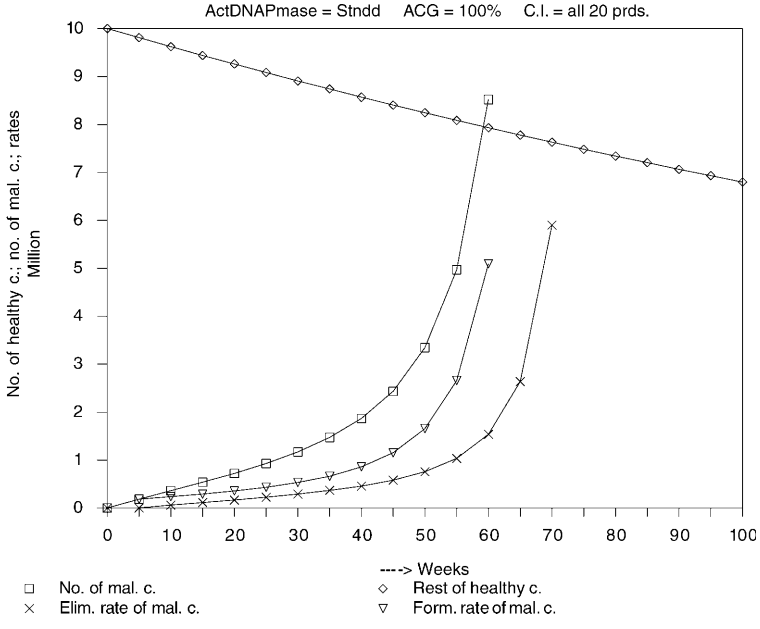

Fig. 3. Case 3: Long lasting and strong cancerogenic impact (healthy cells scaled to 1/10)

Result No. 3/4: By a further increase of the *DNA*-repair-mechanism up to 50-times of its normal activity, which seems advisable according to the result No. 3/3 above, the model shows an already rather long pseudo-stabilisation of the disease. But again it reflects just a postponed break-through of cancer (rezidive) after approximately 1000 weeks (*i.e.* 20 years, if the patient ''lives to his cancer''), as it

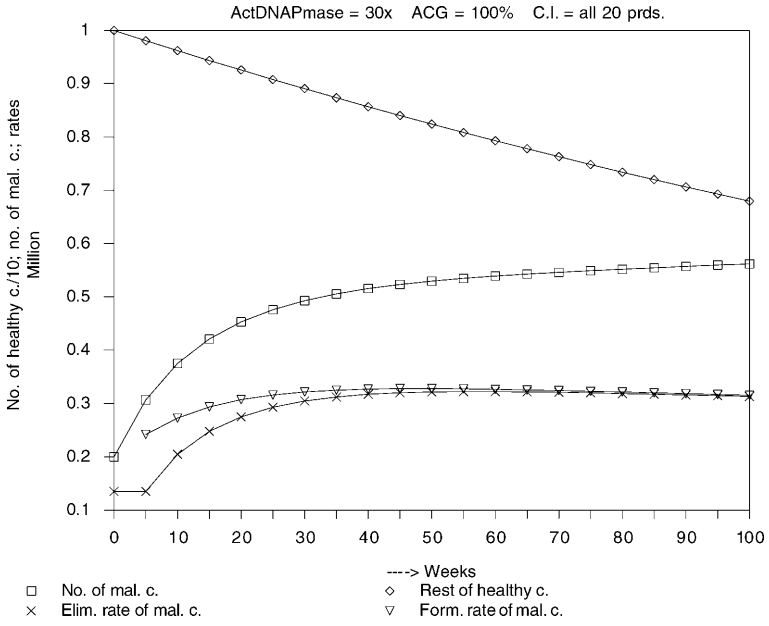

Fig. 4a. Case 3: Long lasting and strong cancerogenic impact with stimulation of the repair-system by 30-times (healthy cells scaled to 1/10)

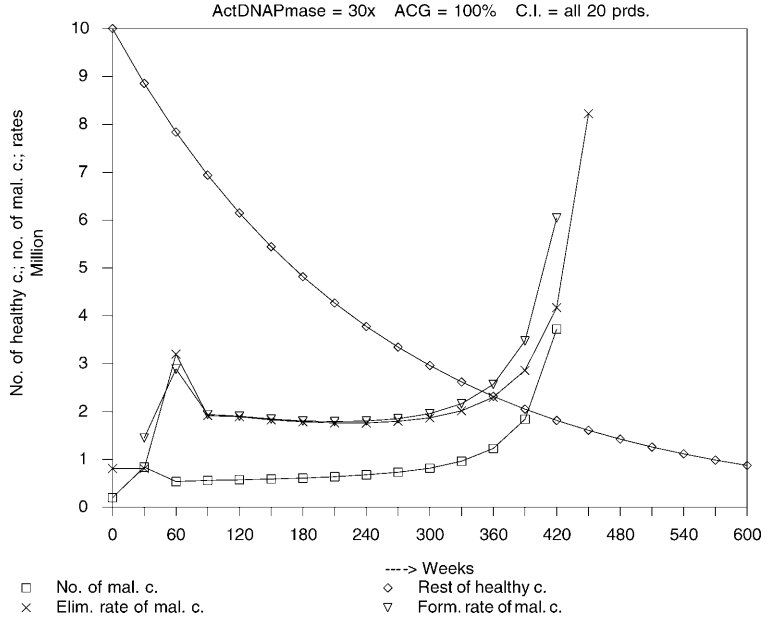

Fig. 4b. Case 3: Long lasting and strong cancerogenic impact with stimulation of the repair-system by 30-times and extension of the period of observation (healthy cells scaled to 1/10)

turns out when the period of observation is extended up to 1400 weeks (*i.e.* time per period = 70 weeks; Fig. 4c).

Result No. 3/5: By further increasing of the stimulation of the *DNA*-polymerase-I-analogous-repair-system's activity (as a consequence of correct

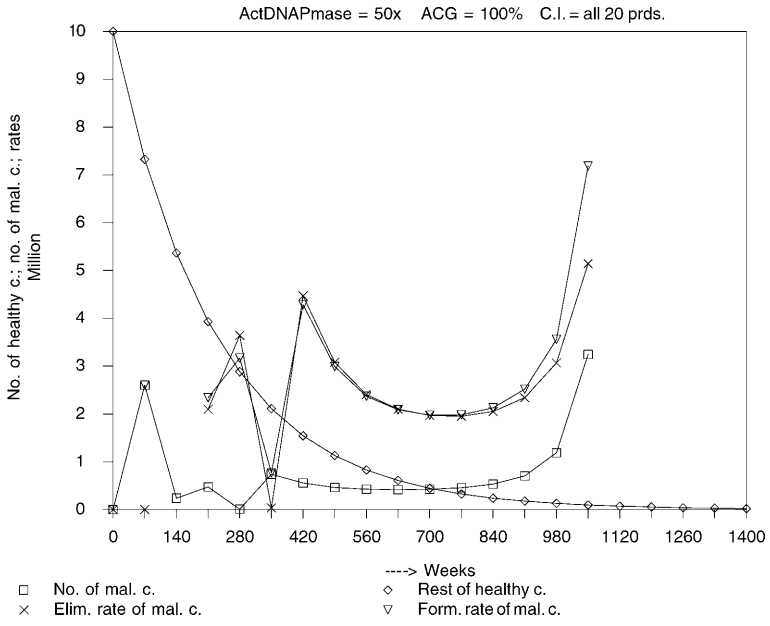

Fig. 4c. Case 3: Long lasting and strong cancerogenic impact with stimulation of the repair-system by 50-times (healthy cells scaled to 1/10)

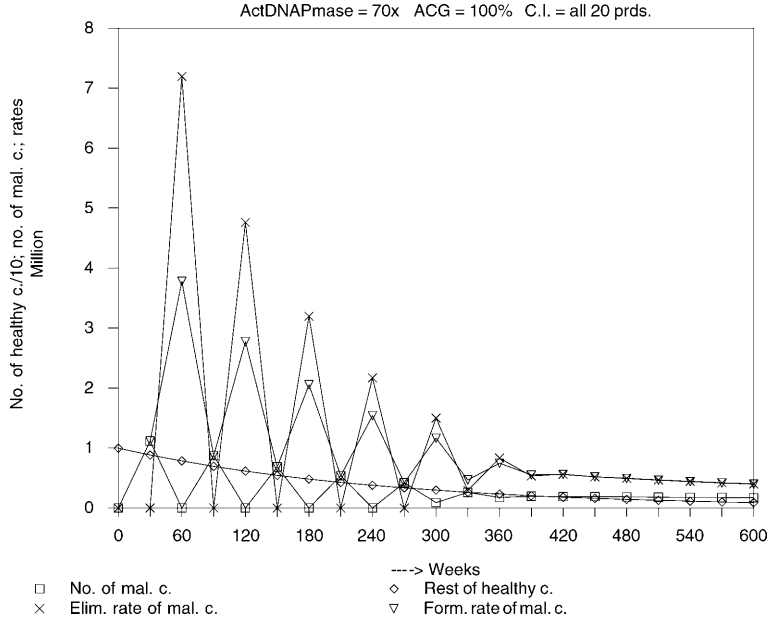

Fig. 4d. Case 3: Long lasting and strong cancerogenic impact with stimulation of the repair-system by 70-times (healthy cells scaled to 1/10)

dosage of $PUNP + PYNP$-stimulators) up to 70-times of the enzymatic standard-activity, the result is principally changed (Time of observation = 600 weeks, *i.e.* time per period = 30 weeks; Fig. 4d).

In spite of the strong and lasting cancerogenic impact studied in this case, due to the strongly stimulated *DNA*-repair-activity, the model answers automatically with simulating pseudo-periodic solutions with diminishing amplitudes. These oscillations may well be triggered, or expressed stronger, by the method of the iteration process. It is true that real oscillations should be based on another type of differential equations, *i.e.* of such of second order, f.e. such equations which describe the well known harmonic oscillator. However, the ''oscillations'' signalized by the model do have other reasons, but they may at least be taken as symbols indicating that the therapy enters into a critical phase. The model indicates, that the therapy begins significantly to influence the malignant system with higher efficacy. It symbolizes further the timely development in an organism where much more complicated mechanisms as those which can be included in the simple model are active, and where real oscillations may be observed, which latter have to be interpreted as back-falls and temporary stabilisations.

In any way – interpreted biologically – a behaviour of the models-outputs as shown in this example should mean: After an initial period of alternating improvements and relapses (analogous to the generation-phases as they are typical for tumor-cells), the last relapse occurs after approximately 10 years. However, the ''amplitudes'' of the back-falls diminish and to the end of the period of observation there is reached a stabilisation at a nearly zero-level of malignant cells.

Nevertheless, biophysically and mathematically it might still be of interest, that the model – without any change in its algorithm – suddenly puts out such pseudo-periodic solutions. Solutions which are similar to the timely development of the disease as it were also to be expected in a real therapy. And this only by feeding-in higher values of the input parameters characterising the *DNA*-repair-system's activity.

More detailed explanations are given in the section ''mathematical method''. Especially, concerning the effects of an overswinging and swing back during the iteration-process. It must be kept in mind that the partial solutions of the differential equations on which the model bases, are mainly exponential functions. However, this pseudo-periodic behaviour is desirable, because it is a good indicator for the point at which the system enters into a critical phase where, due to a favourable ratio of repair-system-stimulation to cancerogenic impact, a significantly positive influence to the further development of the disease is reached. (As to the reciprocal of the mentioned ''ratio of repair-system-stimulation to cancerogenic impact'' see below ''the cancerogenic/cure-ratio'' (''c/c-ratio'')).

Because negative values of numbers of cell-populations do not make sense, all solutions of such periodic functions for the time t at which they went through negative ''half-waves'' have been set to zero in the calculation.

Result No. 3/6: A further increasing of the stimulation of the repair-system's activity up to 100-times of its standard-activity, if such were possible, leads to a reduction of the number of periods of improvements and relapses at the beginning of the therapy and to a rather complete elimination of any residual malignant cells (Period of observation is extended to 2000 weeks, *i.e.* time per period = 100 weeks.)

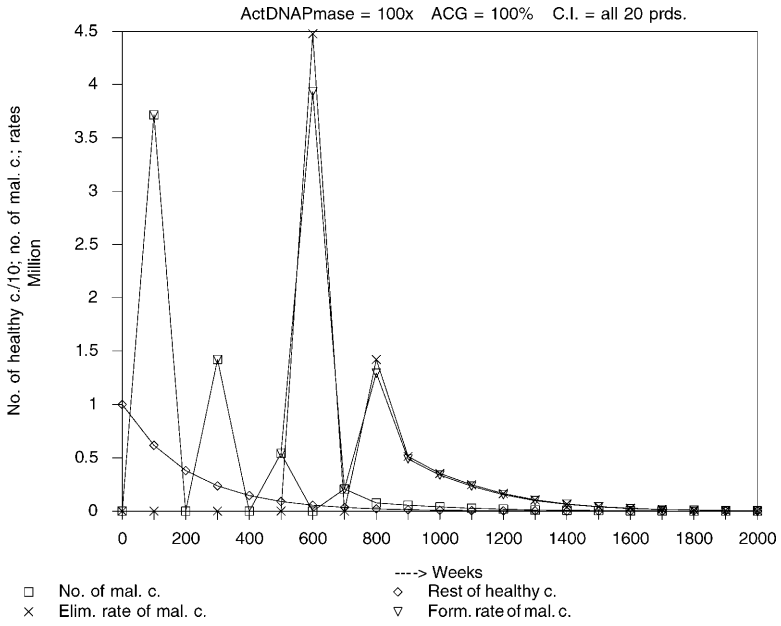

Fig. 4e. Case 3: Long lasting and strong cancerogenic impact with stimulation of the repair-system by 100-times (healthy cells scaled to 1/10)

By this model, it shall not be shown that cancer is calculable, nor that the combined administration of a precursor for purine-nucleotides like 4-carboxamido-5-amino imidazole (''Amino-Imidazole-Carbox-Amide'' = AICA), in combination with orotic acid (OA) must be the new way in cancer-therapy, but the model seems to demonstrate – at the example of a biochemically-sound *PUNP* + *PYNP*-therapy – that there are some physico-chemically based reasons which influence a cancer-development, just due to simple and well proven/established biophysical lawfulnesses. It is a forcing consequence of kinetics, that some positive effects might be achieved by stimulating auto-repair-mechanisms.

The kinetic lawfulnesses predict, that

1) with cancer usually there must be observed some apparently contradicting effects like periodic relapses during a therapy, – at least and especially at the beginning of the therapy; additionally, however – as trivial as it might seem at the first glance – in this context it is the result of the mathematical solution of a biophysical system of equations:
2) for cancer – compared to other diseases – a rather long lasting therapy is necessary.

But these are not the only consequences of kinetics. By the same physico-chemical reasons, a serious cancer-therapy must be based upon a strategy, which aims to eliminate not only the tumor, but also to eliminate the sources for the cancer-development. Therefore, a description and a survey of a cancer-development and a strategy to fight cancer must not be only based on pure phaenomenology, *i.e.* it must not only be a tumor-addressing therapy. This means that a therapy which is directed just only to eliminate the symptom

by which the disease has manifested locally, *i.e.* the tumor, is insufficient. Due to this,

3) cancer has to be understood as a multi-parameter-system. I.e., cancer should be understood as a complex development, triggered by molecular-biological disorders and processes arising therefrom, occurring already long before the local manifestation as a tumor is detectable. A complex development for which also interaction-effects can become even more dominant than the influence of single parameters.

Methods to identify and quantify interaction-effects in so called multi-factorial-systems have been well established by *Box* [23], *Box* and *Hunter* [24], and by *Bandermann* [25]. Especially to come to really scientific conclusions as to efficacy or inefficacy of cancer-therapies – as to the state of science – it seems inavoidable, that such methods for the detection of interaction-effects are also employed in addition to the standard-methods of a simple evaluation of standard-deviations within confidence-intervals as it is "usance" in medicinal practise for testing new therapies and therapeutica in clinical series.

For example, a multi-factorial design and its exploitation according to the *Box*-method may help to avoid wrong conclusions about the ineffectivity of a drug in cases where the effectivity of this drug is hidden in interaction effects.

Cf. Summarizing the Results: Because of the fact that effector-molecules stimulate an enzymatic repair-system rather than attack the malignant cells directly, such a stimulation-therapy cannot be effective in vitro, if no repair-enzymes are present.

Further on, the method of the multifactorial design of test-arrays may even help to get statistically significant results even from series where no placebo-group (no so called "blind-tests") have been used. This possibility is of extreme benefit, especially in testing drugs or therapies for cancer-fighting with the ethic problem of how to nominate patients for placebo-groups and let them by doing this untherapied for the series.

According to these standards, such interactions have to be studied and measured before any final decision. Such interactions were:

1) the interactions of different therapeutica and therapeutic measures among each other
2) interactions of the therapeutica with the organism's own enzymatic system
3) interactions with its hormone-system
4) interactions with the over-all-status of the organism
5) interactions with the age of the organism (*cf.* case 5)
6) interactions with any further exposure to cancerogenic and/or cancer-promoting influences. For example, cancerogenic might be a further, *i.e.* by unchanged life-style, inhalation of benzo[a]pyrene containing exhaust-gases in heavy *Diesel*-traffic – but also radiation and/or some other kinds of intoxination.

Therefore, classical cancer-therapies like radio- or chemotherapy might act themselves to some extent/under some conditions as sources of above mentioned interactions: By this, such a therapy with radiation or with cytostatics might be cancerogenic at other places of the organism [26].

Furtheron, as to the parameters involved, the kinetic model predicts, that the success of such a therapy will depend on the factors listed below:

1) The seriousness of the cancerogenic impact (C.I.): Represented in the model by the value of ACG (abbreviation for Activity of a Cancerogen) and which – together with the duration of the C.I. – defines the ''cancerous violation of the organism'' or at least ${}_{o}N_{M}$).
2) The duration for which the influence of such a cancerogenic impact is present. This reflects the therapeutic experiences, that a cancer-therapy may fail, if the patient is not able to change his stressing or cancerogenic environment or life-style.
3) The status in which the cancer is already at the beginning of the therapy (see f.e. Fig. 2b). This is represented in the model by any value of ${}_{o}N_{M}$. Showing the importance of classical cancer-therapies like surgery or radiotherapy in heavier or more established cases, which underlines the importance of early detecting measures and organisations.
4) Chemotherapeutic treatment might be essential to improve the starting-conditions (*i.e.* at least the N_H/N_M-ratio) before any ''stimulation-therapy'' could make sense.
5) The duration of the therapy. By effects of induction-periods, alternating phases, periodical relapses, and hidden activity of malignant cells, it is essential for a therapeutic success that too early finishing of a therapy is avoided as it might cause a just postponed break-through of cancer. Nevertheless, due to such alternations, especially at the beginning of a therapy, appearently disappointing results might be deducted.
6) For the same reasons and for reasons of not properly adjusted starting-conditions for such a stimulation-therapy, but also by over-dosage (according to the submodel's predictions of inhibiting effects (Fig. 1 of Ref. [3])), also disappointing results of the stimulation-therapy might be found as it was shown by *Karmali* and *Pokotilow* [27] if too high doses of the stimulation-therapeuticum were chosen.
7) Because of the fact that the (''adequate combinations'' of) $PUNP + PYNP$-therapeutica administered, do not attack malignant cells nor tumors directly, but they do act via an enzymatic repair-mechanism, effectuated by an organism's-own enzyme-/protein-system, it is to be expected, that *in vitro* tests with such a therapy might give negative results (because of a possible lack of enough and/or enough active repair enzyme-systems), while the same therapy will work *in vivo* (see again the results of *Karmali* and *Pokotilow* [27]).
8) Due to the mathematical consequences of the kinetic laws, also rather different responses to the stimulation-therapy might be observed from case to case.

Generally it should be confirmed, that such a strongly simplifying model as presented here, can only describe some principal relations and effects, especially for a rather newly developed cancer. Above all, the model should demonstrate which interactions and dependences are to be anticipated and how these are reflected in the timely development of a cancer. The model is not designed to overrule, or to replace, the very complex mechanisms of cancer-development, as

they are described by medicine. Nor does it want to replace the highly valuable and well established biochemical methods of the parameters for prognosis by biophysical ones, nor to lead to an omission of any one of them. Such methods are well described by *Eder* [28]. They are and will remain important, as they are essential tools in the detection of the status of a cancer and so define the emergency- and start-conditions necessary for the prescription of the therapeutic measures required in a case.

Nevertheless, any tumor-diagnostic method (like the TNM-system) can only start if a tumor is already detected, *i.e.* when the aggregation of malignant cells has already grown from the introduction-period of the exponential development into the ''explosion-phase''. This means, that any of today's usual medicinal methods of tumor-detection – according to the data following from the model – starts already in the above mentioned very critical phase of its development and not in the early introduction-period nor *in statu nascendi* of a cancer. Therefore the biochemical methods like the PSA-test, the use of markers or the analysis for amplified proto-onkogenes *etc*. are extremely important supporting methods, helping to shift the detection of malignant developments to as early as possible, *i.e.* towards the introduction-period (see Fig. 4 of Ref. [2]).

A detection, as exactly as possible, of the status of a cancer is one of the essential inputs for the model presented here and for the calculations given by it. Thus, as far as proofreading-stimulation-therapies (*i.e.* a $PUNP + PYNP$-therapy) may be concerned, the model does not diminish the importance of the classical and established methods of diagnosis, prognosis, or therapies. Moreover, the classical therapeutic measures are the emergency methods necessary in cases of all established forms of cancer, before a proofreading-stimulation-therapy might make sense at all.

On the other hand, it is an advantage of kinetics, that many very complex chemical and/or biochemical steps occuring during the propagation of a mechanism might only be reflected in one simple kinetic constant (especially, if in a chain of steps, only one is the rate-determining one). Thus, a kinetic approach might correctly describe the development of a cancer even in a very complex system, simplified and by this better surveyed and understood in its causal connections, but nevertheless accurate. For example, it is certain that different cancerogens do trigger different responses of an organism. This is reflected in the model by the choice of values for the relative activity-indicator for the cancerogen (ACG) and by the time-period during which this cancerogen is anticipated to be active (both factors together exprime the intensity of the ''cancerogenic impact'' (C.I.)).

There are also other known external factors which influence the development of a cancer: For example the *cancer-promotors*, so called: ''*cocarcinogens*'', *i.e.* substances which do not create malignant cells, but which promote the propagation of malignant cells, if such do already exist in an organism. Examples of such cancer-promotors have been newly detected in certain mushrooms such as the *Saffron milk-cap* (*Lactarius*, sect. *Dapetes*) or in plants such as the *Symphytum officinale*).

However, also the effects of such factors can be well described by the model. A cancer-promotor would just increase more or less distinctly the kinetic constant k_{bM} which is chosen for the not autocatalytically stimulated part of the formation

(autopropagation) of the malignant cells in the model according to the kinetic equation:

$$+\mathrm{d}N_{\mathrm{M}}/\mathrm{d}t = k_{\mathrm{bM}} \cdot N_{\mathrm{M}} \tag{1}$$

Analogously, k_{bH} is the kinetic constant in the model's kinetic equation describing the part of the normal growth of the number of healthy cells by cell-division (see Eq. (4) in Ref. [2]). Consequently, the model automatically delivers a cocarcinogens'-effect adjusted forecast-calculation.

In contrast to this increase in the autopropagation-rate for simulation of the effect of a cancer-promotor, the opposite effect could simulate the effect of ageing, with the known reduction of the danger of a breakthrough of a cancer in senile organisms, due to a reduction of the cells' mitosis-rate, especially of the malignant cells'. This effect is also easily reflected in the biophysical model by decreasing the k_{bM}-values:

Case 4: Example for cancer which was triggered during a life under exposure to medium active cancerogenic environment (ACG = 0.3, C.I. = 20 periods, time of observation = 500 weeks, *i.e.* time per period = 25 week).

Result No. 4/1: The model's output shows that without any earlier therapy such C.I. leads to death of a middle-aged organism within 150 weeks (about 3 years).

Result No. 4/2: If the kinetic rate-constants of the cell-formation (*i.e.* the k_{bH}- and k_{bM}-values) are reduced for example to 60% of their default-values to simulate the situation in a rather aged organism, the model's output by biophysical calculation suggests, that in such a case of a senile patient with a high risk as to the responses of this aged organism to any cells-attacking therapy (like cytostatics) the danger of a too strong intoxination of the healthy cells is too high (see Fig. 5c).

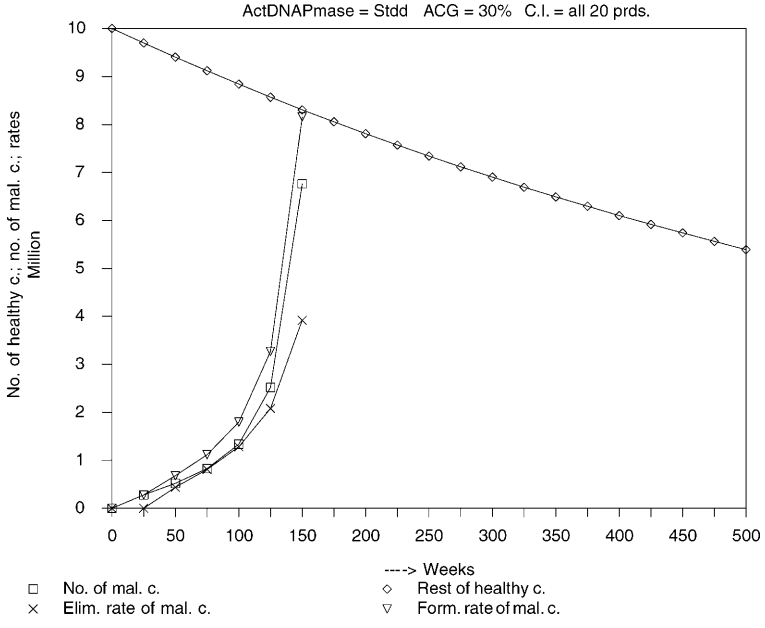

Fig. 5a. Case 4: Cancer which was triggered during a life under exposure to medium active cancerogenic environment (healthy cells scaled to 1/10)

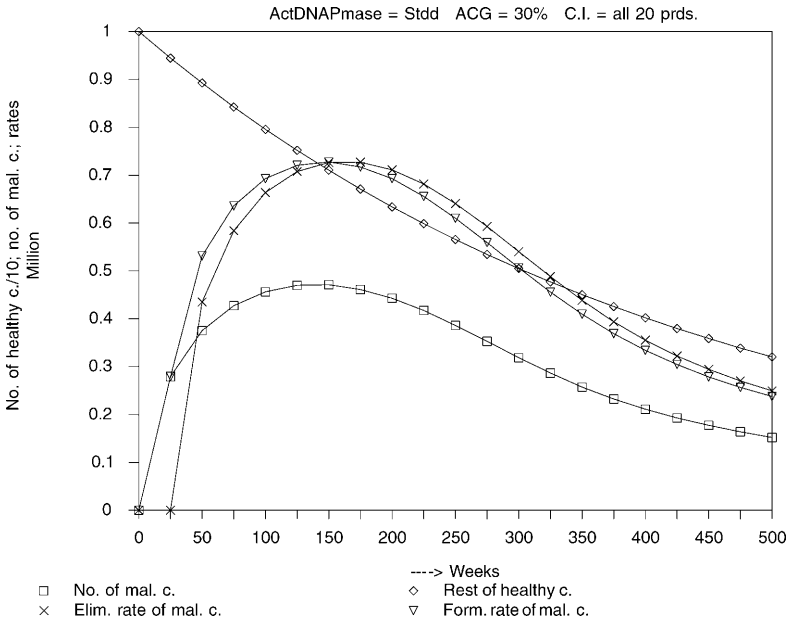

Fig. 5b. Case 4: Cancer which was triggered during a life under exposure to medium active cancerogenic environment with reduction of rate-constants of cell-formation to 60% (healthy cells scaled to 1/10)

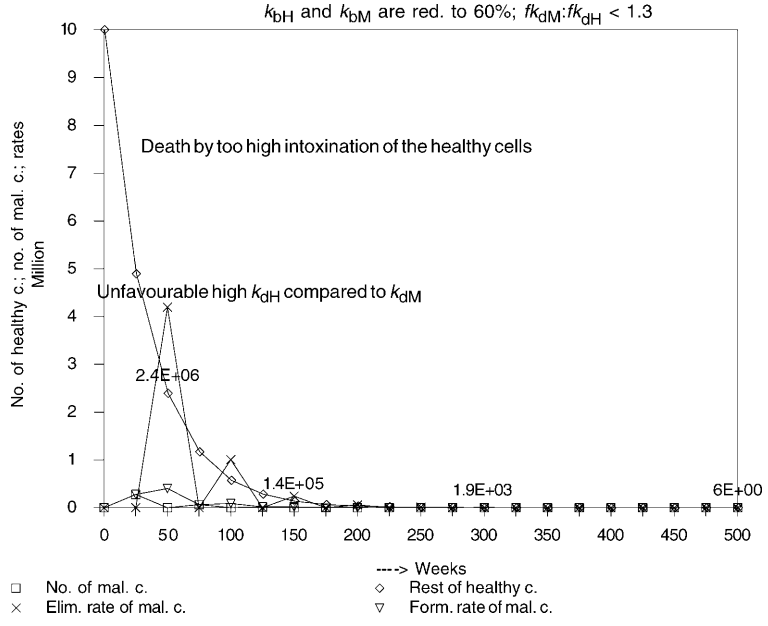

Fig. 5c. Case 4: Cancer which was triggered during a life under exposure to medium active cancerogenic environment with reduction of rate-constants of cell-formation to 60% under chemotherapy (healthy cells scaled to 1/10)

Thus, it is better just only to stabilize the organism's functions rather than to start a chemotherapeutical attack or a surgical extraction of the tumor as the therapy (see Fig. 5b). While it is obvious, that such measures are only acceptable, as long as the

tumor itself is not of acute danger and a stressing of the labile organism by surgical tumor-extraction is an uncalculable risk.

Vice versa, the model might help to understand the consequences of different influence-factors. After adjusting the model's input-parameters according to the typical situation of the definite case, what will be best done, by adjusting also the unmeasurable parameters until the graphical output of the model coincides best with the case-history of clinically detected development. Then, the model's biophysical results and predictions for the further development will allow to play through the different options of further therapy and it will also help to understand the cases of apparently unmotivated relapses. Furtheron, it might give a first guess of the chances, which can be expected due to different therapeutic measures or different doses of a therapeuticum.

For example, studying the effects of a chemotherapy which is usually successful at middle-aged patients, how it influences a senile, exhausted organism as described above.

Result No. 4/3: Same assumptions as above, *i.e.* the kinetic rate-constants of cells-formation (*i.e.* the k_{bH}- and k_{bM}-values) are *reduced* to 60%, but the dying-rates of the malignant cells are increased by a chemotherapy, for example, by a factor 10 (*i.e.* $fk_{dM} = 10$). However, in this special case, due to the fact that it is dealt with a senile, exhausted organism the (desired) increase of the dying-rate of the malignant cells by chemotherapy is accompanied now by an also rather strong increase of the dying-rate of the (weakened) healthy cells. For example, $fk_{dH} = 8$ instead of 2, as it were in a younger, not exhausted organism (see Fig. 5c).

Nomenclature: fk_{dM}:fk_{dH}-ratio (in the examples given = 10:8 and 10:2, respectively), *i.e.* a measure for the quality of the cytostaticum for a therapy at the specific organism with respect to the chemotherapy-correlated damage at healthy cells. Sometimes it is reasonable to express the reciprocal of this fk_{dM}:fk_{dH}-ratio in % as a relative violation-number for the healthy cells. In the examples given above for the young organism this was $2/10 = 20\%$, for the exhausted, senile organism it was $8/10 = 80\%$.

Safety-remarks to a DNA-Proofreading and -Repair-stimulation by Combined Administration of PUNP + PYNP

It must be kept in mind, that just only an equimolar mixture of any two precursors, one of them is of the type of a purine-nucelotides'-precursor and the other one is a pyrimidine-nucleotides'-precursor, *i.e.* for example *AICA* or *AICAR* (''aminoimidazole-carboxamide-ribonucleoside-monophosphate'') combined with for example *OA* (orotic acid) in Ref. [3] are not necessarily the optimum to check the hypothesis. The administration of such a mixture does not exclude that it may be necessary to administer also substances which support the body-own reservoir of proofreading and repair enzyme(s). Such supporting substances could be enzymes or at least proteins (so called ''protoenzymes'') from which such enzymes may be easily biosynthesized. Generally, a *DNA*-repair-stimulation-therapy will make necessary to offer the whole triple: a) *PUNP* plus b) *PYNP* plus c) *DNA*-repair-system (respectively its enzymes, protoenzymes, enzyme-precursors, and proteins).

Anyway, in spite of these facts, a first, time-saving preliminary check of the hypothesis is possible. There is a drug available with which clinical experiences and all data necessary for approbation do already exist. The medicine is named

AICORAT (see Table 1 in Ref. [3]) and has been used until now as therapeuticum in cases of chronic hepatitis, liver-cirrhosis, or fat-liver. However, it contains equimolar amounts of *AICA* and *OA* by which first *in vivo* tests should be possible. The results of such preliminary tests could be indicators for the reasonability for further, more distinct research (see also Ref. [27]). The very low toxicity of OA is known. Data on the toxicity of *AICAMIN* ($=AICA$) are reported by *La Barre* [30] as $LD_{50} = >6\,\mathrm{g/kg}$ b.w. (mice female oral administration) and $0.615\,\mathrm{g/kg}$ b.w. (mice female; intraperitoneal administration). Furthermore, for the pharmaceutical preparation *ORAZAMID* experiences of approx. 20 years, including clinical results, do exist, but as mentioned above, so far only as a liver-therapeuticum. Due to this fact, and as it is shown by the kinetic-model's data, such a period of experience is not long enough for a significance for a new cancer-therapy. However, taking also into account the successes of *Ackermann* [11–15], covering experiences of another 17 years, the idea of a stimulation-therapy seems founded.

Taking into account also the recent medicinal reports in the media describing surprising successes in cancer-therapy by administrations of umbilical-cord's blood, which successes are said to be based upon embryonal stem-cells, this situation with stem-cells in contrast to *Ackermann*'s cell-free human-placenta-extracts seems to be partially comparable to the 19th century, when the great *Louis Pasteur* still taught that the alcoholic fermentation is effectuated only by living yeast-cells, while *Buchner* (1897) demonstrated that fermentation can also be triggered by juices produced from yeast, but containing not any more any living cell.

Nevertheless – as favourable as the toxicity-data of such substances might be and as much as data upon subacute toxicities might be already known – it is obvious that any long-time therapy, as it seems to be required as a consequence of the competing effects, should be executed only under a steady medicinal control of all key-parameters of the organism. Apart from the trivial effect, that any such therapeutic substance, as well accepted by the organism it might be, will be handled by the liver and, therefore, will stress it. Thus, careful control is necessary. Especially with respect to the fact, that an accumulation of extraordinary high concentrations of orotate in the organism is known to lead to hypochrome megaloblasterial anaemia, and that in such cases of an administration-caused hyperorotic syndrome, also the standard-therapy to fight such disease, *i.e.* high dosage ($\sim$150 mg/kg b.w.) of uridine as a feed-back-blocker would fail, as such orotate were not the product of a biochemical hyper-production. Another effect observed in preliminary tests at a prostate-cancer-symptoms-patient (*H.H.*) is the likeliness of inducing slight diabetes-mellitus by long-time administration of higher doses of *ORAZAMID*, but seemingly stabilizable until partially reversable within approximately one year after ceasing the *ORAZAMID*-therapy.

Experimental and Method

Animal Tests

First experimental tests with the androgen-independent *Dunning* R-3327-AT-1 rat prostate tumor model in *Copenhagen* rats have been investigated by *CONSTANTIA*-Group and have been executed by *Karmali* and *Pokotilow* [27]. Unfortunately, these tests designed by *F. Wehrmann* were focused predominantely

on a potential efficacy of *AICA*-salts, like especially an "*AICA* · HCl-salt" or L 651 582-Orotate, and only to a minor part on equimolar combinations of purine- and pyrimidine-nucleotides' precursors as they are suggested by the model presented in this paper. However, these tests prooved, that there is no significant positive effect in cancer-therapy with *AICA* · HCl and other *AICA*-salts, like lactate *etc*., nor with combinations of L 651 583 as the amine-component with orotic acid (except the cytostatic activity of L 651 583 itself), but there is a significant effect in cases of administrations of equimolar *PUNP-PYNP*-combinations (like *AICA*-orotate, generic name: *ORAZAMID*) and this effect diminishes according to Fig. 2 in Haschke [3] with overdosage.

Test-Series #1: Preliminary Test (in vivo)

60 copenhagen male rats were each inoculated s.c. with $0.8 \cdot 10^6$ R-3327-AT-1 tumor cells. Five groups of rats (12 per group) were treated as follows:

Group 1.1: 100 mg/kg b.w. of *ORAZAMIDE* (*AICA*-Orotate, see *Haschke* [3])
Group 1.2: 100 mg/kg b.w. of *AICA* · HCl
Group 1.3: 26 mg/kg b.w. of L651 582 (see *Kohn* [29] and Fig. 3a in *Haschke* [3])
Group 1.4: 26 mg/kg b.w. of L651 582-Orotate.
Group 1.5: Untreated control-group.

Body-weight, overall survival, tumor-growth (measured on a weekly basis), and tumor-weight at the end of the experiment were measured.

Results

There was no significant difference in body-weight gain over time among the 5 groups: 250 ± 3 to 280 ± 10 g within 31 days. Mean tumor-weights (at the 31st day) in the L651 582-Orotate treated rats were lowest (4.5 with a std.dev. of 1.5 compared to an average over all groups of 5.7 g), however, with no statistical significance. Mean tumor-volume in the *ORAZAMID*-treated group (3516 ± 1885 mm^3) was lowest (control-group: 4990 ± 2344 mm^3), but also with poor significance.

Test-Series #2: Test to Compare Any Inhibitory-Effects

125 male Copenhagen rats were each inoculated s.c. with $8 \cdot 10^6$ R-3327-AT-1 cells.

Again 5 groups (25 per group) were treated as follows:

Group 2.1: 200 mg/kg b.w. of *ORAZAMID* (*AICA*-Orotate, see *Haschke* [3])
Group 2.2: 100 mg/kg b.w. of *ORAZAMID*
Group 2.3: 200 mg/kg b.w. of *AICA* · HCl
Group 2.4: 100 mg/kg b.w. of *AICA* · HCl
All agents were suspended in medium-chain triglyceride (*MCT*) by sonication.
Group 2.5: Control-group – just vehicle (*MCT*)-treated.

Body-weight and tumor-diameters were measured on a weekly basis and tumor-weight at the end of the experiment (31 days).

Results

Tumor-growth inhibition: There were no significant differences in body weights among the 5 groups over the growth period (220 to 280 ± 5 g). Over the growth period, the mean tumor-volume in the low-dose orazamid-group (group 2.2: 4000 mm^3) was significantly lower than that in the control group and also of that in the other groups (average 5000 mm^3).

Immunohistochemical effects: Proliferating cell nuclear antigen (*PCNA*): There are indications of greater frequency of active *DNA*-synthesis in tumors of the control-group compared to those with *ORAZAMID*-treatment. Assay of apoptotic cells (*Klenow*): There are indications for a greater frequency of apoptotic nuclei in the *ORAZAMID*-treated tumors.

Summary of the Results of the Animal Tests and of Cell-Culture Tests

The experimentators concluded: "Orazamide was ineffective *in vitro* but effective *in vivo* in inhibiting the growth of AT-1 prostate cancer cells" and "Administration of orazamide (10 mg/100 gm b.w.) to *Copenhagen* rats challenged with the highly agressive R-3327-AT-1 prostatic tumor cell line resulted in significant inhibition of tumor growth ($P = 0.01$); – however, at the higher dose orazamide was ineffective suggesting a non-linear dose-response curve in this model".

According to the biokinetic model, both results were to be expected: 1. The *PUNP* + *PYNP*-therapy does not attack the malignant cells directly (as it would do a chemotherapy by cytostatica), but the stimulation therapy does need an enzymatic *DNA*-repair-machinery to be stimulated. Thus, it cannot work in a system, where such repair-enzymes/proteins are not active enough as it is usually the case for *in vitro*-experiments in contrast to a living organism. 2. According to the submodel in *Haschke* (Formula 2 in Ref. [2] and Fig. 1 in Ref. [3]) the maximum of the orazamide-efficiency due to the *pseudo-Michaelis-Menten*-effect and inhibition is approx. at 14 mg/kg b.w.;- a dose beyond 100 mg/kg b.w. is aready below 20% of the max. efficiency, decreasing to below 5% at 200 mg/kg b.w.

Clinical Tests

Encouraged by these positive results in the a.m. animal tests, *Karmali* and *Pokotilow* [27] also made some "human studies" with the administration of "*AICA*-Orotate" (ORAZAMID 1-2 tablets à 100 mg × 3/day administered to patients having prostate cancer) resulting in the finding: "Patients having prostate cancer, on orazamide-therapy felt better and their prostate specific antigen (*PSA*) level fell to normal level (0–4 ng/ml)".

Concerning the Model: Mathematical Method

The model is based on a set of differential equations which may be summarized to Eq. (2), which leads to the solution Eqs. (3) and (4) or after substitution of $N_H \equiv x$, $N_M \equiv y$, $a \equiv (k_{bH} - k_{dH}) - k_{cG} \cdot \xi \cdot ACG$, $b \equiv k_{cG} \cdot \xi \cdot ACG$, $c \equiv k_H \cdot ADPoI$, $d \equiv k_{bM} - k_{dM}$, and $e \equiv k_E$ to the better readable form Eqs. (5) and (6).

$$-dN_H/dt = (k_{bH} - k_{dH}) \cdot N_H - k_{cG} \cdot \xi \cdot ACG \cdot N_H \tag{2}$$

$$N_H = {}_oN_H \cdot e^{-[(k_{dH} - k_{bH}) + k_{cG} \cdot \xi \cdot ACG] \cdot t} \tag{3}$$

$$dN_M/dt = k_{cG} \cdot \xi \cdot ACG \cdot N_H + k_{bM} \cdot N_M + k_E \cdot {N_M}^2 - k_{dM} \cdot N_M - k_H \cdot ADPoI \cdot N_H \cdot N_M \tag{4}$$

$$dy/dt = b \cdot x - c \cdot xy + d \cdot y + e \cdot y^2 \tag{5}$$

$$dx/dt = a \cdot x \tag{6}$$

$$dy/dx + c_1 \cdot y - d_1 \cdot y/x - e_1 \cdot y^2/x = b_1 \tag{7}$$

For $c_1 \equiv c/a$, $d_1 \equiv d/a$, $e_1 \equiv e/a$, and $b_1 \equiv b/a$, this gives an inhomogenous differential equation in only two variables (y, x):

To integrate the differential equations a simple numerical method has been chosen and a computer-program named CANCER.xls or CANCER.wr1 in a spread-sheet-calculation has been designed. A

diskette with this computer-program, which gives the results in a numerical and, especially, graphical form, is available for academic purposes on request. The program is running under SYMPHONY (ext.: ".wr1") or EXCEL (ext.: ".xls"). An example which allows to compare a correct mathematical integration with the results of such simple iteration is given by the programs INTEGITER.xls or INTEGITER.wr1.

For the purpose of this iterative integration, a time-axis, which is divided into 20 periods is defined in the programs. The number of weeks in each of these "periods" can freely be choosen. For a long-term-observation, *i.e.* for example, for a total of 2000 weeks (about 38 years), it is advisable to chose 100 weeks per period.

To see "survival/healing-scores" according to presently accepted usual medicinal definitions, a choice of 15 weeks per period delivers a time-axis for observation of approximately 5 years. To see immediate effects, a down-scaling to a total of 100 weeks (*i.e.* approx. 2 years) is preferable by choosing only 5 weeks per period.

The duration of the cancerogenic impact, *i.e.* how many periods a cancerogenic impact by which the cancerous result is triggered in the organism, is assumed to last, may be adjusted separately. For example, simulating a long lasting unchanged cancerogenic life-style as it might be a daily exposure to cancerogens like benzo[a]pyrene or similar active condensed aromates by exhaust-gases inhalation in a daily heavy traffic with many *Diesel*-engines, the duration of the C.I. is set to all the 20 periods.

The activity (efficiency) of the cancerogen (abbreviated to ACG) can be assigned and might be understood as a quantifier. It correlates the effect of a definite dose of the well known cancerogen benzo[a]pyrene being defined as 1 (corresp. to 100%) with that of weaker cancerogenic impacts, which are represented in this model by smaller figures, f.e. 0.01 if the effect is 1% of the cancerogenic efficiency of benzo[a]pyrene.

The "absolute" activity of the repair-system (*i.e.* the *DNA*-polymerase-I-similar "repair-machine" in eucaryotes) by stimulation is to be inserted into the calculation as given by Eq. (2) in *Haschke* [2] and Table 2 in *Haschke* [3] or by the submodel (computer-program: CSUBMOD.xls and CANCDOS.xls; see Fig. 1 in *Haschke* [3]).

To adjust to the type of cancer, there might be chosen also other "cancer-aggressiveness"-indicators than the default 1, which is chosen in connection with the k_d-values based on an average half-life time of normal average human body-cells. Consequently, this "type-of-cancer-classification-parameter" alters automatically only the biokinetic "constants" used by the program, according to the following selection: Formation- and decay-constants for healthy cells and for malignant cells are adjusted as well as the "metastasisation-constant" k_E. The biokinetic rate-constant of the repair-mechanism (because this indicates the usual, a priori cell-type-independent, biochemical *DNA*-repair reaction) is not altered. Only partially altered is the biokinetic constant k_{cG}, which is derived from $k_{cM,}$ describing the susceptibility of the typical (cancer-type-specific) cell to a cancerogenic impact and which is by this also – at least partially-dependent on the type of cancer, *i.e.* on the type of cells which are converted by the cancerogen to become malignant, and to another part dependent on the reactivity of the cancerogen against this type of cells.

The calculation is also designed to simulate the effects if the starting number of malignant cells is not zero, *i.e.* to show the influence, if, for example by a surgical extraction of a tumor, a rest of malignant cells is not removed.

By these assumptions, the iteration starts with the calculation of the increase of the number of malignant cells according to the differential Eqs. (5), (5a), and (5b) in *Haschke* [2]. Analogously, the diminishing of the number of malignant cells according to differential Eqs. (3) and (5d) in *Haschke* [2] (Eq. (5d) reflecting the repair-activity of the *DNA*-repair-system) is calculated. By the same iterative method the diminishing of the number of healthy cells according to differential Eqs. (3) minus (4) and (5) in *Haschke* [2] (*i.e.* the (pseudo-)-stationarity resulting out of the difference from cells' decay and normal cells' propagation and Eq. (5) reflecting the conversion of healthy cells to malignant cells) is determined.

The model is adjusted to start the calculation with a number of cells (*i.e.* "cell-group under observation") of ${}_{o}N_{H} = 10^{7}$ healthy, normal cells, of which for example (adjustable in the model) 30% are anticipated to be susceptible to be reached by the cancerogenic substance or radiation. ${}_{o}N_{H}$ is chosen rather small as a symbol for malignant cells' developments in the very beginning, *i.e.* far long before a tumor were detectable for example by x-ray-diagnosis, even if all these cells under observation (by the model) were already turned to be malignant. Although ${}_{o}N_{H}$ is also adjustable to higher values, if an extension of the model to bigger cell-aggregations was desirable. In that case the output and some other parameters have to be adjusted as well.

However, from the point of view of molecular biology, and as it is the approach of the model presented here and as it is shown by this, it seems reasonable to study the developments of malignant genetic information *in statu nascendi* (Fig. 4 in Ref. [2]), *i.e.* at such relatively small cell numbers (compare to the note in *Haschke* [3] at Summarizing (page 103): approx. 10^{7} cells for a $1\,mm^{3}$ tumor and Fig. 2b).

For this reason and as shown by the model with its first calibrations and consequent predictions thereof, cancer-therapies, as early detected the cancer might be, usually have no chance to interfere already in the above mentioned induction-period, but usually start after, *i.e.* beyond that "tg $\alpha = 1$-point", *i.e.* already in the explosion-phase of a cancer seen along its exponential timely development. From this it has to be concluded, that practically every cancer, as soon as it is diagnosed, is already an emergency case for which the rather radical methods of surgery, chemo- and/or radiotherapy are necessary. (For the reason of graphics' scaling the graph for the healthy cells usually is shifted to $1/10$. However, its labels are printed unchanged).

Conclusion

A biophysical/kinetic description of growth-rates and dying-away-rates of somatic cells, *i.e.* of the cells' "life-cycle" as given in a previous paper [2], delivers as their sum the picture of a pseudo-stationary state. Such a kinetic "life-cycle"-description can also be applied to cells which contain wrong genetic information. If their development is set in a kinetic competition to the mentioned normal somatic cells' development, including the effect of an inhibition of a *DNA*-repair-mechanism, the model delivers similar results [3] as they are to be expected according to the results of *Zhang* and *Mathews* [1] with their *in vitro* experiments.

Inserting higher values for kinetic constants of the cells' dying-rates, especially for those of malignant cells, as a trivial solution, the model reflects also the efficiency of cytostatics [3].

Switching from inhibition of the repair-mechanisms to an a) stimulation and including also b) mechanisms of feed-back by signal-transductant-substances which are emitted by malignant cells, c) auto-stimulation of malignant cells, and d) metastasis, but also making allowances in the model for taking into calculation e) accelerated cells'-death by chemotherapy or by induced apoptosis, the model answers by delivering interesting predictions of therapeutic successes. The results predicted do also strongly depend on the degree of the repair-systems' stimulation. These predictions, applied to typical examples, might be interesting for the description of timely developments of cancer and, therefore, for planning therapies.

This does not mean, that this paper does suggest, that cancer is easily calculable, nor does this paper present a new cancer-therapy which is ready for application. The suggested stimulation of the repair-systems still needs appreciable additional research and that is what this paper wants to propose.

For example: Further research is necessary as to the influenceability of *DNA*-repair- but also of other (especially post-replication-) repair-systems. Further on, as to the optimization of the *PUNP*/*PYNP*-combinations administered, the way of their administration (p.o. or i.m. *etc*.), but especially also concerning the detection of co-factors necessary. Such co-factors might be some activating protoenzymes and/or proteins and/or signal-substances. According to the findings of *Ackermann* [11–15], research on the latter items should start with the identification of effector-molecules and search in the components of placental-substances and embryonal-systems for those cells which have been damaged (or ''squeezed-out'': giving the low-molecular weight components according to *Ackermann*) and in which the cell-membranes have been eliminated. The *AICA* + *OA*-combination mentioned examplatory, is just one pair of *PUNP* + *PYNP*-precursors, but not the only one. This combination is not necessarily the most effective. It is well possible, that combinations of other precursors are much more active (see *Haschke* [3]).

Superior may be combinations with other substances with different (among another) biochemical-/biokinetical distances to the 4 main-nucleotides or with better depot-character. By this, such other combinations could fit better in accordance with the generation- and susceptibility-phases of malignant cells. Further on, comparable preparations from natural raw-materials (like placentae) and combinations with them may by promising.

The model should show how biochemical and clinical effects and results of modern research in biochemistry, molecular-biology, and medicine fit together in a framework of biophysics, biochemistry, plus physical-chemistry, and mathematics, building an interdisciplinary bridge and by this, suggesting the possible ''screws'' which may be turned, showing-up their interactions to reach therapeutical effects or at least to trigger a further direction of research and to encourage a partner for this research program.

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