Special Lecture

Oxazaphosphorine Cytostatics: Past–Present–Future
Seventh Cain Memorial Award Lecture
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Abstract

The development of the oxazaphosphorine cytostatics cyclophosphamide, ifosfamide, and trofosfamide was based on the idea of applying the transport form/active form principle to the highly reactive nitrogen mustard group. A critical analysis and synopsis of the available results and knowledge will include examination of the extent to which the hypotheses on which this concept is based have been confirmed by experimental and clinical findings:

1. Chemical synthesis succeeded in converting the reactive nitrogen mustard into an inactive transport form (latiation).
2. The requirement that the transport form be enzymatically activated to the active form in the target organ (the cancer cell) has been achieved by a sequence of metabolic reactions.
3. The aim of considerably increasing the therapeutic index of alkylating agents has been achieved by the oxazaphosphorine cytostatics. The greater cancerotoxic selectivity is closely correlated with the cytotoxic specificity of their activated primary metabolites.
4. The cancerotoxic selectivity of oxazaphosphorines was further increased when mesna was introduced as a regional uroprotector. Mesna eliminates the risk of therapy-limiting urotoxic side effects of oxazaphosphorines. With mesna protection, these cytostatics can be given in higher doses with increased safety, and their therapeutic efficiency can be enhanced.
5. Stabilization of the primary oxazaphosphorines, e.g., by attaching 2-mercaptoethanesulfonic acid (madosfamide), opens up new possibilities in preclinical investigations and in therapy, e.g., for the clonogenic stem cell assay, for in vitro purging in autologous bone marrow transplantation, for regional perfusion of tumors, and, in small doses, for immunomodulation, where appropriate, in conjunction with "biological response modifiers."

Introduction

The great distinction conferred by the Cain Memorial Award is evident from its stated objective "to give recognition for outstanding preclinical research leading to the discovery of a significant new therapeutic agent for the improved care of cancer patients." It is thus a great pleasure for me to join the list of award winners, whose contributions are regarded as milestones in the advance of cancer chemotherapy.

The acknowledgement of the pharmacologist's work in the development of the oxazaphosphorine cytostatics must take into account a number of scientists from other specialties who, in the past, have made essential contributions, and it suggests that the future prospects in this area of research should be outlined: "To see the future requires the memory of the past."²

Environment and Personal Background

Among the personalities I remember with particular respect from the 1930's when I was becoming a physician and researcher are the physicians Ernst Edens from Düsseldorf and the pharmacologists Wolfgang Heubner and Hermann Druckrey in Ber-
which received governmental support; only a few pharmaceutical companies were carrying out their own cancer research. Asta-Werke has kept faith with its decision for more than 35 years now, the only pharmaceutical company in Germany to do so.

To gain this objective it was necessary to have a group of workers able to see and to some extent master the problems in this area. ASTA then had had competent chemical, pharmacological, and clinical research departments. For experimental oncology, immunology, biochemistry, and biometry we sought cooperations with universities who provided continuous conceptual and methodological support. Thus, our research group can be regarded as an early and very efficiently functioning model of targeted collaboration between researchers in industry and the universities, and I would like to pay a grateful tribute to the pharmacologist and oncologist Hermann Druckrey of Freiburg, the biochemist Hans-Jürgen Hohorst of Frankfurt, the microbiologist and immunologist Jürgen Potel of Bielefeld and Hannover, and the biometrician Berthold Schneider of Hannover for many years of friendly cooperation.

Transport Form/Active Form as a Therapeutic Principle

We were aware from the outset that, in view of the financial limits, it was not possible to carry out an extensive screening program analogous to the testing of thousands of substances each year by the large national cancer research centers. The important point for our research group was to go beyond the empirical procedure which had predominated hitherto and to base the development of cancer chemotherapy on theoretical concepts (2) or, as Wolfgang Heubner had said, to follow “creative ideas” (3). Our aim in this was to develop substances with a greater selectivity of cancerotoxic action and to reduce the risks to patients by increasing the therapeutic range. This became the guiding principle of our subsequent work.

Druckrey proposed that a reactive, toxic drug should be administered not in the active form but in a chemically masked, inactive transport form. This should be converted into the active form in the body where possible, preferentially in the tumor cell (4). The first successful implementation of this idea was fosfostrol (Honvan), the diphosphate derivative of diethylstilbestrol, which is still widely used in the treatment of metastatic prostate carcinoma.

From the outset we regarded the basic idea as a hypothesis or theory, the validity of which can be examined objectively (2). The history of the oxazaphosphorine cytostatics is a good example of the interplay between idea and reality since intensive research worldwide in the decades following the formulation of the primary idea has confirmed the concept by experimental and clinical studies and by specific investigations. Three ideas are crucially involved:

1. The extension of the “transport form/active form” principle to highly reactive nitrogen mustards; this resulted in the oxazaphosphorine cytostatics cyclophosphamide, ifosfamide, and trofosfamide.
2. The introduction of the terms “cancerotoxic specificity” and “cancerotoxic selectivity” exemplified by the oxazaphosphorines. This made the mechanism of action of this compound class understandable and established their special position in the group of alkylating agents.
3. The development of regional, and thus of an organ-specific, detoxification of the urototoxic oxazaphosphorine cytostatics by detailed investigation of the metabolism and pharmacokinetics; this resulted in a further considerable increase in the cancerotoxic selectivity.

Oxazaphosphorine Cytostatics

After the success of fosfostrol, our team, including Arnold, Bourseaux, and Wilmanns, tried to apply the transport form/active form principle to the group of alkylating nitrogen mustards. The structure of these compounds appeared to be particularly suitable for designing a prodrug (5). Their cytotoxic action is closely related to the reactivity of the 2-chloroethyl groups, which in turn is linked with the basicity of the central nitrogen atom. Thus, chemical synthesis can be used to alter the reactivity of the functional groups in a specific manner. Ishidate et al. (6) were the first to demonstrate this relationship by describing chlormethylene-Oxide as an antitumor drug.

One of the earliest attempts to utilize chemically derived structural variations of the nitrogen mustard molecule for the synthesis of compounds with greater tumor selectivity was the work of Friedman and Seligman with open-chain phosphoramide mustard compounds (7). These compounds are chemically stable but, according to our own experiments (8), unsuitable as substrates for enzymatic activation; their oncocidal efficacy was insufficient, resulting in a narrow therapeutic range.

Cyclophosphamide. Our approach was aiming at obtaining cyclic N-phosphorylation products of nor-nitrogen mustard as prodrugs. These chemically and pharmacologically inactive transport forms should offer opportunities for enzymatic activation to the cancerotoxic active form, e.g., by the incorporation of phosphoramido and phosphoric ester bonds into the molecule.

These novel compounds were synthesized by reacting N,N-bis(2-chloroethyl)phosphoramid dichloride with α,ω-alkanolamines of various chain lengths. Further cyclic variants were produced with appropriate bifunctional alkanes yielding mono-, di-, or triamides of phosphoric acid (9, 10). From the pharmacotherapeutic viewpoint, the diamides, especially the nitrogen mustard phosphoramide esters (or oxazaphosphorines), were most attractive since they were largely inactive chemically and biologically in vitro but highly active in vivo. Of the more than 1000 derivatives that were synthesized, some compounds were found to possess particularly favorable properties (Fig. 1). Cyclophosphamide, the prototype of this class, was the first oxazaphosphorine cytostatic which accorded with theory; it was a chemically and pharmacologically inactive transport form, a prodrug of nor-N-mustard, which was therapeutically active in vivo (5, 8). Table 1 shows the results of early comparative experiments on Yoshida ascites sarcoma of the rat receiving a single i.v. administration of cyclophosphamide. It is evident from Table 1 that the curative activity of cyclophosphamide is about as high as that of the reference substance chlormethylene-Oxide, but it is far less toxic than this highly reactive nitrogen mustard derivative, the result being a distinctly larger therapeutic index.

The first publications on the pharmacology of cyclophos-
phamide were soon followed by confirmation of its superior chemotherapeutic properties (11, 12). The assessment of Sugiu et al. (13) was that “Among 1,000 selected compounds and antibiotics tested against all or portions of the tumor spectrum (33 tumors) cyclophosphamide was the most effective.” The product also rapidly attracted great attention in clinical oncology. The initial clinical results from Germany (14, 15) were soon confirmed and extended internationally (16). Even now, 30 years after its introduction, cyclophosphamide is one of the most widely used cytostatics and is a constituent of many polychemotherapy regimens. There have been more than 15,000 scientific publications on this product, which demonstrate the wide interest in it. This wide interest in the unique features of cyclophosphamide not only accelerated and augmented the scientific knowledge but also yielded a number of worldwide deep personal friendships.

Ifosfamide. From the viewpoint of pharmacology, cyclophosphamide appeared to have reached a certain optimum status, but it subsequently emerged that ifosfamide is a cytostatic with its own remarkable chemotherapeutic properties. In ifosfamide, one of the two 2-chloroethyl groups on the extracyclic nitrogen mustard moiety in cyclophosphamide has been transferred to the nitrogen in the oxazaphosphorine ring, so that there are now two independent functional chemical groups which are further apart (Fig. 1). This apparently small difference in the chemical structure alters the metabolism in vivo (17) and results in a cumulative action in vivo (17) and results in a

successful introduction of the currently used fractionated ifosfamide dose schedules in the clinic (19). Recently, this principle has been extended by administering ifosfamide as a continuous infusion for 1 to 5 days. This diminishes the toxicity, allows the total dose to be increased by nearly 50%, and improves the therapeutic results further (20, 21). The particular characteristics and clinical importance of this product, which was initially underestimated in some countries, have now received wide recognition (22–25).

Reliability of Experimental Findings on Cyclophosphamide and Ifosfamide to Clinical Experience

This point requires special discussion because important fundamentals of tumor pharmacology were not established until cyclophosphamide and ifosfamide were available as test substances. Both drugs were particularly suitable for a wide range of experimental and clinical uses because of their favorable physicochemical and biological properties, their high chemotherapeutic efficacy, and their relatively low toxicity. In particular, it proved possible to develop a large number of pharmacological test models for clinical oncology. These models have a crucial bridging function because they provide a scientific basis for the results of clinical trials on the effects of the drugs in patients and make them more reliable (26). They have made a considerable contribution to the development of a strategy for cancer chemotherapy.

Druckrey et al. (11) were aiming at optimization of the dose/time relationship when they developed massive-dose therapy. As the dose of cyclophosphamide increases, there is not only a corresponding improvement in the prospects of curing a particular tumor type but also a widening of the range of tumor types which can be influenced by the therapy. On the other hand, experiments showed that the development of secondary resistance of tumors was explained by treatment with fractionated low cyclophosphamide doses. The idea of massive-dose therapy with cyclophosphamide was taken up by clinicians. They found that the results of therapy of rapidly proliferating tumors were considerably better than with low cyclophosphamide doses (27).

Cyclophosphamide also played an important part in the development of rational polychemotherapy by Goldin et al. (28) and Schabel (29). When cyclophosphamide was included in new combination regimens, it was found that the clinical result depended not only on the particular chemotherapeutics chosen,

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**Table 1 Parameters of the curative and lethal effects of cyclophosphamide compared with chloromethine-N-oxide and non-nitrogen mustard**

<table>
<thead>
<tr>
<th>Agent</th>
<th>LD₅₀ (mg/kg)</th>
<th>CD₅₀ (mg/kg)</th>
<th>% of LD₅₀</th>
<th>Therapeutic index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>160</td>
<td>4.5</td>
<td>2.8</td>
<td>8.5</td>
</tr>
<tr>
<td>Chloromethine-N-oxide</td>
<td>50</td>
<td>5.4</td>
<td>10.9</td>
<td>2.2</td>
</tr>
<tr>
<td>non-Nitrogen mustard</td>
<td>100</td>
<td>40</td>
<td>40</td>
<td>0.65</td>
</tr>
</tbody>
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*LD₅₀, 50% lethal dose; LD₅₀, 5% lethal dose; CD₅₀, 50% curative dose; CD₅₀, 95% curative dose.*
the efficacy of which varied with the type of tumor, but also on appropriate dosage and a suitable time sequence of the individual substances.

The design of scientifically based multiple chemotherapy regimens demands not only knowledge of the mechanism of action and the pharmacokinetics of the chosen cytostatics but also detailed information on the kinetics of proliferation of the tumor cells which are to be treated and of the normal cells which must be protected. There have been many studies with cyclophosphamide as the test substance which have deepened and extended our knowledge in this difficult area. The phase specificity of many cytostatics in the cell cycle has been determined, and animal models for specific sequential cytostatic treatment of tumors have been developed by Skipper (30) and his group. This has made it possible to carry out logical sequential therapy, which results in greater clinical efficacy and higher selectivity.

Cyclophosphamide and ifosfamide were also used to work out the methods for determining the cumulative properties of cytostatics (11, 31). Although cumulative properties are unwanted and hazardous when they relate to the toxic effect of chemotherapeutics, they may be beneficial when they relate to the desired therapeutic effect. Results of pharmacological studies have crucially influenced the clinical use of cyclophosphamide and ifosfamide in patients.

The fundamental studies on cyclophosphamide in postoperative and preoperative adjuvant chemotherapy are still of great importance today. Thirty years ago (32) it was shown very clearly that chemotherapy is effective as an adjuvant measure in the scheme of postoperative prophylaxis of recurrence and metastasis. Suitable experimental models have also been developed for preoperative chemotherapy (33). Thus, for example, in chemotherapeutically incurable Shay chloroma of rats, the tumor weight was greatly reduced by treatment with cyclophosphamide (30 mg/kg), and subsequent removal by surgery resulted in a high percentage of definitive cures. The importance of this animal model for clinical oncology has only recently been pointed out by Van Putten (34).

All the important organotoxic components of the effect of cyclophosphamide have been analyzed and quantitatively determined resulting in the creation of the term danger coefficient (1). This coefficient indicates the probability of particular toxic effects, e.g., leukotoxicity, immunotoxicity, or vesicotoxicity associated with a particular curative dose, e.g., the 95% curative dose. These data have also proved to be clinically relevant. Thus, e.g., the fact that the leukotoxic effect of cyclophosphamide and ifosfamide is experimentally far less than that of directly alkylating agents has been widely confirmed in the clinic (16).

The clinical relevance of the experimental testing of cytostatics and its predictive value have been investigated by Goldin et al. (12); the relevance of results from animal experiments on cyclophosphamide was found to be particularly great (i.e., the predictive value for the treatment of human tumors was very high). This is why cyclophosphamide was recommended by the International Conference on Screening Methodology for Antitumor Drugs as a standard against which all new developments should be compared (Geneva, 1974).

**Cytotoxic Specificity and Cancerotoxic Selectivity of Oxazaphosphorines**

**Relationship to the Metabolism.** Once the relative selectivity of the oxazaphosphorine cytostatics had been demonstrated, the task was to find the biochemical and pharmacological reasons for this phenomenon and to elucidate the mechanism of action. A particularly interesting question was how a nitrogen mustard compound is able selectively to damage tumor cells since, after all, alklation, which is the basis for the cytotoxic action, is relatively nonspecific. Together with Hohorst, we carried out experiments attempting to explain the specificity and selectivity of alkylating nitrogen mustards, especially oxazaphosphorines (35, 36). This problem also attracted wide international interest and has been extensively investigated by many researchers, e.g., Refs. 37-42.

Cyclophosphamide and other oxazaphosphorine cytostatics differ from the directly alkylating substances in that they must undergo biotransformation before they can exert their alkylating oncoidal action. The metabolism of oxazaphosphorines in warmblooded species can be divided into three stages: activation, toxification, and deactivation (36, 43) (Fig. 3). The initial activation is based on hydroxylation of the ring at C-4 to give 4-hydroxycyclophosphamide by mixed function oxidases in the liver (cytochrome P-450). The increased reactivity conferred by this enzymatic hydroxylation leads to the toxification by spontaneous elimination of acrolein and formation of the directly alkylating phosphoric acid diamide derivatives. The sequence of enzymatic activation and spontaneous, rate-limiting toxification allows intermediate reactions to take place in vivo on the oxazaphosphorine ring, and these result in reversible or irreversible deactivation. An irreversible enzymatic deactivation by further dehydrogenation to give the 4-keto or carboxy compound is important for excretion. This process has also been suggested as the reason for the development of resistant tumor lines (44).

A step which is crucial for the selectivity is a nonenzymatic reversible reaction of 4-hydroxycyclophosphamide with sulfhydryl compounds to give 4-thioxazaphosphorines. Thus, for example, free sulfhydryl groups on proteins may slow down the toxification during transport in the blood and thus contribute to delaying the toxification until the tumor cell is penetrated (45).

**Cytotoxic Specificity.** When examining the problem of selectivity, the concept of cytotoxic specificity was introduced as a new and crucial parameter (36). It is defined as the biological efficacy in vitro of the alkylating reaction on which the cytotoxic effect depends (cytotoxic units per μmol and min). Surprisingly, the values for the cytotoxic specificity of the primary oxazaphosphorine metabolites are 10 to 100 times higher than those of simple alkylating agents. Comparison of these values with the therapeutic indices determined in vivo (corresponding to cancerotoxic selectivity) indicates (Fig. 4) that these two measures of the biological activity, which are basically independent from each other, show a largely parallel behavior. The high therapeutic indices of the oxazaphosphorines correspond to the high cytotoxic specificities of their active metabolites in vitro; in contrast,
simple nitrogen mustard derivatives have only low cancerotoxic selectivity in vivo, consistent with their low cytotoxic specificity. Hence the selectivity of the oxazaphosphorines in vivo derives mainly from the greater cytotoxic specificity of the primary metabolites and from the particular reactivity of the oxazaphosphorine ring hydroxylated on C-4.

Recent investigations by Hoborst et al. (45) have shown that it is possible to follow further the processes taking place in the cancer cell and thus to elucidate the actual mechanism of the high specificity and selectivity. Various 3',5'-exonucleases and phosphodiesterases catalyze the intracellular release of the alkylating metabolites from 4-hydroxycyclophosphamide, which is crucial for the oncocidal action (toxification). Particularly active 3',5'-exonucleases are those associated with DNA polymerases. They can be regarded as specific targets for the primary oxazaphosphorine metabolites. The intracellular release of the alkylating agent results in specific inhibition of the DNA polymerase enzyme moiety and thus in inhibition of DNA polymerization and to specific alkylation of the DNA.

Fig. 5 summarizes the present knowledge on the mode of action of the oxazaphosphorines and compares it with the initial idea (2). Even though the original hypothesis proved to be too simple, the high degree to which the original concept has been translated into reality is none the less remarkable. The aim of having a transport form activated enzymatically to the active form in the target organ has been achieved (as a sequence of various intermediate reactions), and the desired increase in cancerotoxic selectivity has been convincingly demonstrated. However, as the mechanism of action became clearer, and this is another benefit, new ideas for rational further development continually emerge, so that even now, 30 years after the introduction of cyclophosphamide, understanding is still increasing, and new projects are suggested; the development of stable metabolites is in progress, and there are now signs that these may be suitable for specific immunomodulation (44).

Organ-specific Detoxification of Urotoxic Oxazaphosphorines by Mesna

Despite all the advances, it cannot yet be said that the selectivity and therapeutic index of the oxazaphosphorines and other currently available cytostatics are satisfactory. Toxic side effects, which are often very organ specific, limit their use. Acute urotoxic effects must be expected as a consequence of the therapeutic use of the oxazaphosphorine cytostatics. These effects mainly take the form of hemorrhagic cystitis and not uncommonly limit the therapy. A typical, although rare, late consequence of successful chemotherapy with cyclophosphamide which has been completed many years earlier is the occurrence of bladder carcinoma. This led to the idea of developing a uroprotector which, on systemic administration, was intended to act like an antidote by detoxifying the toxic metabolites in the kidney and urinary tract (46-49).

The urotoxicity of oxazaphosphorine cytostatics was found to be caused by the primary 4-hydroxy metabolites, specifically by the acrolein which they release. These metabolites are excreted with the urine and cause concentration-dependent damage to the kidney and bladder. An effective uroprotector ought therefore to stabilize the 4-hydroxy metabolites in the urine, and thus prevent the release of acrolein, or to detoxify directly the acrolein being generated. A large number of substances, especially sulfur compounds, were examined for their ability to act as regional antidotes. Apart from the uroprotection, attention was directed at the pharmacokinetics, the intrinsic toxicity of the compounds, and the question of interactions. It emerged from these extensive studies that most of the tested substances were not capable of ensuring regional detoxification of the urotoxic oxazaphosphorine cytostatics. This also applies to N-acetylcysteine which has been repeatedly recommended for the uroprophylaxis of oxazaphosphorine cytostatics, despite clear evidence that no effective thiol concentrations appear in the urine after administration of N-acetylcysteine (50).

A special position is occupied by the mercaptoalkanesulfonic acids, and the compound sodium 2-mercaptopetanesulfonate (INN mesna) meets the requirements in an almost ideal manner (Fig. 6). Mesna is able to inactivate the toxic metabolites even after high doses of cyclophosphamide or ifosfamide and brings about dose-dependent prevention of the urotoxic side effects without reducing the efficacy of the cytostatic therapy itself.

The uroprotective properties of mesna are determined by its particular pharmacokinetics (51, 52). After parenteral or oral
administration, mesna is rapidly converted in the blood into the biologically inactive mesna disulfide (dimesna), which remains in the intravascular space and is rapidly eliminated via the kidney. Following glomerular filtration, mesna disulfide enters the epithelial cells of the renal tubules where it is reduced by the glutathione system of these cells and is excreted with the urine as a reactive thiol compound (Fig. 7). Only this detoxifies the aggressive oxazaphosphorine metabolites in the urine (51) (Fig. 8).

In clinical practice the administration of mesna prevents the urotoxic side effects of oxazaphosphorine therapy allowing higher doses of these cytostatics to be given, so that the therapeutic efficacy is improved and new indications have emerged (23–25, 53).

Experimentally, it was found that mesna can also inhibit or suppress the occurrence of bladder tumors when administered simultaneously during long-term treatment with cyclophosphamide (54). It is to be expected that effective prophylaxis of this tragic late effect will also be possible clinically. Thus, in future, the therapeutic use of oxazaphosphorines, especially cyclophosphamide and ifosfamide, should always be combined with uroprotection in order to circumvent reliably the risk of inflammation and of urinary bladder tumors.

Future Prospects in Oxazaphosphorine Research

The metabolites of the oxazaphosphorine cytostatics which play a key part are the 4-hydroxy compounds. They are the only ones which share the cytotoxic specificity in vitro and the can-

cerotoxic selectivity in vivo with the parent substances; in this respect they differ very considerably from all the directly alkylating compounds. The difference from the parent substances, e.g., cyclophosphamide, is that they no longer require enzymatic activation for their action; the release of the primary activated metabolite (e.g., 4-hydroxycyclophosphamide) takes place spontaneously in aqueous solution and depends on the chemical reactivity of the particular compound and the conditions prevailing, such as the pH and temperature. The pharmacokinetics and the biological variability in both the initial enzymatic activation and the competing deactivation reactions made it appear desirable to test the 4-hydroxy metabolites therapeutically. For a long time this was impossible due to the chemical instability. It has recently been possible to synthesize a number of new and more stable compounds by replacement of the 4-hydroxy group, and these are sufficiently stable in the crystalline form at room temperature but spontaneously liberate the 4-hydroxy compound in aqueous solution (5).

The prototype of this class of substances is mafosfamide (Asta Z. 7557, Z 7634) which has 2-mercaptoethanesulfonate as substituent in position 4 of the oxazaphosphorine ring (Fig. 1). The drug offers new and unexpected therapeutic approaches (44). Pretherapeutic evaluation in clonogenic stem cell assays had been impossible with the parent compounds, which required enzymatic activation. Intracavitary administration or site-directed perfusion can be carried out with mafosfamide. An interesting aspect now under clinical investigation is the extracorporeal purging of bone marrow before autologous transplantation in acute leukemia. Even more important in the near future might be the evaluation of the immunomodulating potency of low-dose mafosfamide, which in some experimental models induces permanent cures from cancer, simply by modulation of the host's defense system. An increase of this type in the immune response has also been reported with low cyclophosphamide or ifosfamide doses. Analysis of these findings by immunological methods suggested that the therapeutic efficacy of oxazaphosphorines in low, nontoxic doses derived from elimination of suppressor mechanisms (55). Mafosfamide, the stable metabolite, is very suitable for preclinical and clinical immunopharmacological research. The first clinical investigations of this new and fascinating aspect of oxazaphosphorine cytostatics have been initiated. These will also examine whether and how this new principle can be utilized therapeutically in conjunction with "biological response modifiers" (44, 56).

Conclusion

The research results which I have summarized arose from the desire to increase the selectivity of cancer chemotherapy. I would like to conclude with the forward-looking thoughts of Dr. Gertrude B. Elion, a past recipient of the Bruce F. Cain Award: "Chemotherapeutic agents are not only ends in themselves, they are also beginnings. . . . Selectivity must be our goal and understanding its basis our guide for the future." Further advances will depend more than ever on our intuition and the courage of new ideas, since, as Elion says "the basic knowledge and serendipity are not opposites but integral parts of the process of discovery" (57).

References

2. Brock, N. Ideas and reality in the development of cancer chemotherapeutic
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