## ABOUT THE AUTHOR

Graduated from New York University College of Medicine in 1952, Dr. Greenwald received his training at Kings County Hospital and Montefiore Hospital. It was at the latter hospital that he came under the influence of Dr. Daniel Laszlo and Dr. Herta Spencer. Their work in the field of neoplastic disease was the impetus for Dr. Greenwald's interest in this subject. Since 1958 he has been associated with the Division of Neoplastic Medicine Montefiore Hospital and Medical Center. He is now an Adjunct Attending on this service, helping to supervise medical students and house staff. He also does neoplastic consultations at Morrisania City Hospital. He is also in the private practice on Internal Medicine and Neoplastic Diseases in New Rochelle, New York and on the staff of New Rochelle Hospital.

# CANCER CHEMOTHERAPY

## Medical Outline Series

By

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# PREFACE

It was after many hours spent in the library, that the idea for this manual arose. Because of the lack of a reference book, questions about cancer chemotherapy are often difficult to answer. Such questions as: "What chemotherapy is best for one of the rarer tumors? How long after surgery must one wait to institute nitrogen mustard? Will nitrogen mustard give as good results in ovarian carcinoma as ThioTEPA?" cannot be readily answered by existing books. Reference to original articles is often necessary. But where to find the original article, is often a problem. Many of the articles are in journals not immediately available in community hospital libraries. The best source material on recent advances is contained in journals such as *Cancer Chemotherapy Reports, Cancer Research,* and *Proceedings of the American Association for Cancer Research,* journals not always at hand. Even if articles are available, several may be read before the answers are found.

This manual is not meant to be a "cookbook" for any physician who decides he would like to use cancer chemotherapy. It is directed to the internist, surgeon, or general practitioner who has had some formal training or supervised experience with chemotherapy. Perhaps he has used one of the agents, but would like to check on some aspects of this agent. Or perhaps he would like to use one of the newer agents. It is hoped that the clinician will find in this book most of the answers he seeks, or that the bibliography will provide the source of the required information.

The bibliography does not pretend to be complete. Rather, it contains several of the more useful original articles for each subject. Readily available journals and English language sources are stressed.

The problem of "keeping up to date" is of course insoluble. However, in cancer chemotherapy many of the so-called recent advances do not bear the test of time. Therefore, the tested and lasting material of the past eighteen years is available in this book. This material will not become easily dated. With this as a background, the recent literature on chemotherapy can be evaluated and utilized more intelligently.

# INTRODUCTION

The most frequent question asked the clinician interested in cancer chemotherapy is whether this type of therapy is of any benefit to the patient. This question may often arise in the mind of the therapist himself, particularly after treating patients with very advanced malignancy.

This question is difficult to answer. Certainly there are few statistical studies which attempt to answer the question of whether cancer chemotherapy prolongs life. Probably the only good studies in this area are those from the Veterans Administration hospitals,[1] which show that mechlorethamine therapy does not prolong life in carcinoma of the lung. There is strong evidence that our current treatment prolongs life in childhood acute leukemia,[2,3] and that cyclophosphamide prolongs life in multiple myeloma.[4] Also, one cannot doubt the prolongation of life in choriocarcinoma.

Many studies have shown that patients with chemotherapy-induced remissions live longer than those who fail to respond. However, the two groups are not comparable, and it is entirely possible that the tumor which is more likely to respond to chemotherapy is the one which is less likely to be rapidly lethal. Criteria for remission in such studies is often failure of the tumor to progress, rather than significant decrease in tumor size. Thus the very fact that the patient lives, may be falsely interpreted as a remission.

Fortunately, prolongation of survival is not the only aim of cancer chemotherapy. At this point, I think it is important to digress, and discuss the whole problem of treatment of incurable cancer. It is the duty of a physician not to abandon his cancer patients, even though cure is impossible. His treatment of the cancer patient involves the total care of the patient, including concern for the patient's family. Involved in total care are supportive care, relief of pain, control of other disease present in the cancer patient, and attempts to control or reverse the growth of the malignancy. Cancer chemotherapy, if used, may represent only a small portion of the entire care of the patient.

This is not to say that cancer chemotherapy should be used merely so that the patient feels something is being done. If there is a reasonable expectancy of palliation with anticancer drugs, they should be offered to the patient. It should always be the aim

of the physician using chemotherapy not to cause greater discomfort with the medication than improvement in the disease.

Whenever therapy is used in any area of medicine, the benefits to be gained should be weighed against the dangers of the treatment. This is true for even such a routine medication as aspirin, so it is certainly true for cancer chemotherapy.

At present, unfortunately, even the palliation produced by cancer chemotherapy is limited. There is little that can be achieved in most of the carcinomas. Palliation of adenocarcinoma of the gastrointestinal tract, lung carcinoma, and even breast carcinoma is slight. However, there are other areas where significant improvement can be achieved. The leukemias and lymphomas, and choriocarcinoma, are outstanding examples, and hormones have been of moderate usefulness in breast cancer.

The plan of this book is to discuss thoroughly the use of each cancer chemotherapeutic agent. Indications, dosage, and toxicity are stressed. The physiology, chemistry, and pharmacology of the agents are presented in a separate chapter.

After the series of chapters devoted to the specific agents, there is a chapter on special toxicity. The final chapter covers the various tumors, and briefly discusses the agent or agents of choice for each tumor. This chapter can be used to give one an idea of whether cancer chemotherapy has anything to offer in a particular patient. Details of therapy will usually be covered in the chapters devoted to the chemotherapeutic agents.

The agents discussed in this book include all but one of the commercially available agents. This is triethylene melamine, which is only mentioned briefly, because its erratic absorptions from the gastrointestinal tract make it a less useful agent. Mithramycin and methylhydrazine are the only agents, not commercially available, which are discussed. New and experimental techniques which are not accepted for routine clinical use are, to a great extent, omitted.

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# CHAPTER I

## PHARMACOLOGY OF CANCER CHEMOTHERAPY

The pharmacology of cancer chemotherapy is a fascinating field, for it touches on the most basic processes of life. To understand the mechanism of action of the anticancer drugs, one must understand the recent advances in molecular biology. While molecular biology has contributed greatly to our understanding of cancer chemotherapy, the debt is mutual. Actinomycin-D, a powerful tumoricidal agent, is a valuable tool in studying the mechanism of action of hormones and other substances. The reason for this will be discussed later in this chapter.

In a book such as this, aimed at the clinician, details of pharmacology cannot be included. The author's aim in this chapter is to whet the reader's appetite. An outline of the pharmacology of the chemotherapeutic drugs will be given. Stress will be placed on those aspects of immediate practical value, and enough basic science will be included to provide an outline for further study. Therefore, this chapter's bibliography will contain mainly review articles. Original references must be obtained by consulting these review articles, however some of the more interesting original references will be discussed. The pharmacology of the steroid hormones will be discussed briefly in Chapter 9.

In addition to mechanism of action, traditional pharmacology (absorption, excretion, distribution and metabolism of the drugs) will be discussed. Unfortunately, these areas of the pharmacology have not been explored extensively. For this latter area, the chapter in the new Goodman and Gilman textbook of pharmacology is especially recommended. Calabrese and Welch[1] have done a superb job of collecting the available data. A recent review by Oliverio and Zubrod[2] is also highly recommended.

In order to present the mechanism of action of the cancer chemotherapeutic agents, a preliminary outline of some basic biochemistry is needed. The major factor which makes cells of an organism different from one another is the proteins they synthesize. These may be enzymes, structural proteins, or other proteins with specialized functions. The structure of these proteins is determined by the genes operative in the cell at that time. As an aside, it should be noted that within any organism (and this includes mammals) every cell has the same genetic make-up. However, it is currently thought that the vast majority of genes in each differentiated cell are *repressed* and therefore not functioning. The area of genetic control mechanisms is unfortunately beyond the scope of this chapter. For those who are more adventurous I recommend articles in the last three years of Scientific American and Watson's book *Molecular Biology of the Gene.*[3]

To return to our brief outline of Biochemistry, it is now time to discuss how the active genes control protein synthesis. The gene is a packet of deoxyribonucleic acid (DNA). DNA is a double coiled helix. That is, two chains wound around each other in a fashion similar to the familiar medical symbol (the two coiled serpents). The backbone of each chain is a recurring sequence of a sugar and a phosphate group. The sugar is deoxyribose. The two chains are held together by specific pairing of the bases through bonds, which though individually weak, when cooperating render this double helix more stable to denaturation than most proteins. Each sugar has a purine or pyrimidine base attached which faces inward toward a purine or pyrimidine base attached to a sugar on the other chain. Thus the double coiled helix resembles a spiral ladder or stair case, the rungs consisting of a purine bound to a pyrimidine by hydrogen bonding. These purine or pyrimidine bases, which, as pairs, form the rungs of the ladder are universally present in all nature. There are four bases which predominate in DNA, although a number of other bases appear occasionally as minor components. For the purposes of coding (this term is being used somewhat ahead of its place) these other bases probably act as one of the four main bases.

Purines and pyrimidines are ring compounds containing carbon and nitrogen atoms in the ring. Adenine and guanine are the purines, and cytosine and thymine are the pyrimidines. Cytosine is always bound to guanine and adenine to thymine. This is very

useful for the theory of cell replication. For when the cell divides it is thought that the double helix unwinds, and each chain separates from the other. Each chain then contains the structure to synthesize its own partner. Since, wherever there is a cytosine a guanine must join, and wherever there is an adenine, a thymine must join.

At this point one may wonder as did molecular biologists several years ago, how does DNA control protein synthesis? This leads to the next cell component, ribonucleic acid (RNA), for it is on RNA molecules that protein is synthesized. RNA is identical in structure to one chain of DNA except for two things. First, the sugar in the backbone or chain is ribose instead of deoxyribose, and second, instead of thymine, it contains a different pyrimidine, uracil.

The alert reader will now see that as each chain of DNA can synthesize its partner, the DNA contains the *information* to synthesize an RNA molecule. Base pairing according to the predetermined code is the key. It should be noted that the adenine in DNA will lead to a uracil in the RNA.

Therefore, the first step in protein synthesis is the production of an RNA chain by DNA. The RNA so produced is called "messenger RNA." The sequence of bases in this RNA determines the structure of the protein produced. This process is one of the most fascinating in nature.

Proteins consist of long chains of amino acids known as polypeptides. Approximately twenty different amino acids are used to build these chains. An important discovery was that the sequence of three adjacent bases in RNA may act as a coding unit for one amino acid. For example three uracils in a row code for the amino acid phenylalanine.

The actual synthesis of proteins involves a structure containing messenger RNA, transfer RNA, amino acids, the peptide chains to be completed, and possibly DNA. Different amino acids are attached to specific transfer RNA molecules by specific enzymes. These amino acids containing RNA molecules now transfer their amino acid moiety to the growing peptide chain one at a time. The sequence in which the amino acids are attached is determined by the messenger RNA which, as you remember, was itself determined by one of the DNA chains. The role of the ribosomes (which contain ribosomal RNA and protein) is not yet

known, however they are thought to position the messenger RNA, transfer RNA, and growing peptide chains to facilitate formation of the next peptide bond. This process is explained clearly in a recent article in Scientific American.[4]

The introductory basic biochemistry is almost complete. The only remaining aspect is the synthesis of DNA. There are many reactions concerned here. Lest the reader grow weary, he can be reassured that these reactions will not be discussed. As was mentioned earlier, the DNA molecule is a double coiled helix, the backbone of which is made up of a repeating pattern of deoxyribose and phosphate with a base attached to each sugar. This unit of sugar, phosphate, and base is called a nucleotide, and therefore DNA is a polynucleotide. Nucleotides can be formed from preformed pyrimidines and purines, but the major production of nucleotides occurs from precursors such as amino acids. The purine or pyrimidine ring is closed after the sugar and phosphate are attached. The nucleotides are then joined to form the DNA molecule, this reaction being catalyzed by the enzyme DNA polymerase.

The last step in the synthesis of one of the nucleotides, thymidilic acid (thymine-deoxyribose-phosphate) is the placing of a methyl group on the 5 position of the uracil in uradylic acid (uracil-deoxyribose-phosphate). This methyl group is donated by a tetrahydrofolic acid derivative, formaminotetrahydrofolic acid. The methylation is catalyzed by an enzyme called thymidilate synthetase. It should be remembered that this reaction is not involved in RNA synthesis, because RNA contains no thymine.

Several good review articles on the mechanism of action of the antitumor drugs have appeared.[5,6] The chapter by Calabrese and Welch[1] in the new edition of Goodman and Gilman is excellent. Articles reviewing the pharmacology of specific groups of drugs will be mentioned in the appropriate sections.

## Alkylating Agents

The original derivation of the term alkylating comes from the word alkane. An alkane is any hydrocarbon chain with the general formula $C_NH_{2N+2}$. Warwick[7] in his outstanding review article has defined alkylating agents as "those compounds capable of replacing a hydrogen atom in another molecule by an alkyl radical."

Alkylating agents are highly reactive chemical compounds

capable of reacting with nucleophilic groups such as amino or sulfhydryl groups. Some of the alkylating agents are so chemically active that they will react with water within a few minutes. For this reason, mechlorethamine is stored as a dry powder, and only dissolved immediately before administration.

There are two types of alkylating agents: monofunctional and bifunctional. Monofunctional alkylating agents have only one active alkyl group, while the bifunctional alkylating agents have two. The monofunctional alkylating agents have far less antitumor activity. When the mechanism of action of these drugs is explained the reader will see why this is so.

There are two types of alkylation. One is called first order or $S_N1$ nucleophilic substitution. This type involves carbonium ion formation and occurs rapidly. Its rate is dependent on the concentration of the alkylating agent. Second order or $S_N2$ nucleophilic substitution involves formation of a transition complex which includes the alkylating agent and the substance with which it reacts. Its rate depends on the concentration of both reactants.

There is no strict separation of alkylating agents into $S_N1$ and $S_N2$ because many agents can react in either way depending on pH and other factors. Those that tend to act by the $S_N1$ reaction, such as mechlorethamine, are very unstable after administration, and react rapidly with tissues. The $S_N2$ reactors such as busulfan and triethylenethiophosphoramide react more slowly, but some $S_N1$ reactors such as chlorambucil have decreased rate of carbonium ion formation because of the electron withdrawing capacity of its aromatic ring. These latter $S_N1$ reactors are also slower acting.

As has been emphasized, alkylating agents are highly reactive chemical compounds. They have been shown to react with so many body substances, that for many years there was a great deal of controversy as to which of the reactions was important for the action of these agents.

Since alkylating agents react most readily with thiol groups, many authors thought that their reaction with these groups in proteins was the major site of action of alkylating agents. However, recent studies, most notably those by Lawley and Brooks, but also by Roberts and Warwick, and Wheeler have shown that alkylating agents act by binding to DNA.

The evidence for this is as follows:

1. Alkylating agents are mutagenic and carcinogenic.
2. *In vivo* and *in vitro*, alkylating agents produce fragmentation and clumping of chromosomes.
3. They inactivate DNA containing viruses much more readily than RNA viruses.
4. Alkylating agents are relatively inefficient inhibitors of protein function, but readily inhibit mitosis.

Evidence is rapidly accumulating that alkylating agents produce their effect by interstrand binding from the $N^7$ in the guanine of one strand to the $N^7$ of guanine in the opposite strand. Interestingly enough, these experimental results had been predicted on theoretical grounds. This interstrand binding prevents the separation of the two strands of DNA in the double coiled helix necessary for cell replication.

Interesting evidence for this interstrand linkage is that alkylating agents do not inhibit a bacteriophage containing a single stranded DNA. Evidence for the interstrand guanine $N^7$ linkage has been produced most forcefully by Brooks and Lawley.[8,9] They have shown that "the more reactive the alkylating agent and the greater its tendency to react with nucleophiles, the greater the extent of the reaction with the guanine moiety." In *in vitro* experiments they have isolated di-(guanin-7-yl) derivatives of sulfur mustard when this agent was reacted with DNA.

Lawley and Brooks[9] have recently published results of an elegant series of experiments carried out with strains of E. Coli sensitive and resistant to sulfur mustard. They showed that both strains had initially equal uptake of $S^{32}$ labelled mustard in their DNA, but that the resistant strain was able to enzymatically remove the cross-linked di-guaninyl mustard.

The cross-linking hypothesis explains why monofunctional alkylating agents are 50 to 100 times less effective than bifunctional agents.

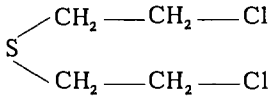
The question of whether there are any basic differences in mechanism of action of the alkylating agents is a difficult one. Much work has been done, but there are many gaps in our knowledge in this area. It would appear that outside of busulfan, no basic differences in mechanism of action have been demonstrated on a biochemical level for the alkylating agents discussed in this book. I have seen no explanation for the unique action of cyclophosphamide against childhood acute leukemia. Studies with three

strains of animal tumors resistant to 1-phenylalanine mustard show that these cells are also resistant to other alkylating agents.

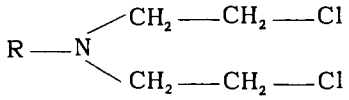
Busulfan appears to be a unique case. Busulfan and the other methanesulfonates do not appear to act by interstrand cross-linking to DNA. Cross-linked products have not been produced *in vitro* when busulfan was reacted with DNA. This is in contrast to the mustards. It is thought that the great reactivity with thiol groups in proteins may explain the action of busulfan. Later in this section, some other differences in busulfan's actions on a cellular level will be discussed.

Most of the alkylating agents in clinical use are modifications of the basic mustard structure.

Mustard gas (Fig. 1) is a sulfur mustard. The basic nitrogen mustard structure differs in that the sulfur is replaced by a nitrogen atom. The nitrogen atom has a valence one less than sulfur, allowing an extra radical besides the two chloroethyl groups.



*Mustard Gas*



*Basic Mustard Structure*

Figure 1

In mechlorethamine, commonly known as nitrogen mustard, the R is a methyl group. Mechlorethamine is highly reactive, and therefore an irritant to skin or mucosa. For this reason, it cannot be given orally, even though it is absorbed through the gastrointestinal tract. The half-life of mechlorethamine after parenteral administration is only a few minutes. Less than .01% is excreted in the urine.

In chlorambucil, the R is aminophenyl butyric acid. The aromatic ring's electron withdrawing capacity decreases the rate of carbonium ion formation and permits chlorambucil a longer half-life in serum. This permits oral administration, and makes the compound less reactive.

Chlorambucil is absorbed orally, but to what extent is not known. There appears to be even absorption from day to day, as the patients do not have wide fluctuations in blood count while on maintenance therapy. Little is known of the metabolism and excretion of chlorambucil.

In cyclophosphamide the R is a cyclic phosphamide ester. Cyclophosphamide was synthesized because it is inactive until the cyclic group is cleaved enzymatically at the phosphorus-nitrogen linkage by a phosphatase or phosphamidase. Since some neoplastic tissues contain higher concentrations of these enzymes than normal tissue, it was hoped that malignant cells would preferentially activate the agent. However, plasma and liver can both activate cyclophosphamide, so it is likely that the drug is active before it arrives at the tumor sites.

Cyclophosphamide is partially absorbed orally, 17 to 31% being found in the stool unchanged. There is a fairly short half-life in plasma, but it is measured in hours rather than minutes. While most of the drug is excreted in metabolized form in the stool, a significant amount is excreted in the urine as metabolites with locally irritating properties. This is the reason for the sterile cystitis produced in some patients by cyclophosphamide.

The last mustard derivative to be discussed in this book is melphalan or 1-phenylalanine mustard. In this case, the R is 1-phenylalanine, an amino acid. This compound was synthesized with the hope that it would be more active against malignant melanoma. The amino acid phenylalanine is a precursor of melanin pigment. Unfortunately, melphalan is no more active against melanoma than other agents.

Melphalan is well absorbed orally. Its half-life in the blood is somewhat longer than cyclophosphamide. Little data are available on excretion and metabolism.

Triethylene thiophosphoramide is closely related to the mustards. It contains three ethyleneimonium groups. This compound, along with other similar compounds not in clinical use, was synthesized because formation of the ethyleneimonium ion constitutes the initial reaction of the nitrogen mustards. This compound is poorly absorbed orally. It has a half-life in plasma similar to cyclophosphamide, and 75 to 80% of the compound is excreted in the urine as metabolites.

Busulfan, chemically unrelated to the mustards, is well absorbed orally. It has a very short half-life in serum, on the order of a few minutes. Despite this it is not clinically a rapidly acting agent. The drug is excreted in the urine mainly as methane sulfonic acid. Chemically, busulfan is an alkanesulfonic acid ester.

Two areas of the pharmacology of the alkylating agents remain to be discussed. The first of these is whether the alkylating agents are truly radiomimetic. This subject is discussed in great detail in Warwick's article.[7] He stresses that the alkylating agents are radiomimetic or not, depending on what biological phenomena are being considered. He states "the term 'radiomimetic' is often applied far too indiscriminately to sometimes ill-defined biological phenomena, and it would seem more profitable and less misleading to define carefully the biological effects manifested by each alkylating agent, rather than to refer some property as 'radiomimetic' because it may vaguely correspond to a particular property of radiation. Any apparent similarity between the biological properties of radiation and alkylating agents undoubtedly results from the capacity of each entity to modify cellular structure and function by direct combination with cellular components such as nuclear and cytoplasmic material. The most 'radiomimetic' chemicals will be those capable of penetrating deep into the cell, and reacting with a diversity of cellular sites, whereas less reactive chemicals or those which alkylate by a different basic mechanism may possess far fewer 'radiomimetic properties.' "

Similarities between alkylating agents and radiation include (1) marrow depression, (2) teratogenicity, (3) mutagenicity, (4) production of chromosomal breaks and clumping, and (5) antibody suppression. The last will be discussed in more detail below.

Interestingly, busulfan appears to resemble radiation more closely in its effects than the other alkylating agents. For example, busulfan like x-rays, does not inhibit mitosis until at least one division has occurred. Mechlorethamine immediately arrests cell division.

In its effects on fertility, busulfan again more closely resembles radiation. Melphalan and chlorambucil do not interfere with fertility of male rats in leukopenia-producing doses. Other mustards act on late stages of spermatogenesis and produce infertility within four weeks in male rats. Busulfan, like radiation, acts on early stages of spermatogenesis, producing sterility after eight weeks. This is because the germinal cells present continue to develop normally. Hence, there is a sequential deple-

tion of the germ cells in order of their immaturity, spermatogonia disappearing first and spermatozoa last.

The final pharmacologic effects of alkylating agents to be discussed are their immunosuppressive actions. Unfortunately, these have not been studied extensively. Busulfan, like radiation, exerts its inhibition of antibody production best when given two to four days before the antigen, whereas mechlorethamine exerts its maximum effect when given two days after the antigen. None of these suppress antibody formation once it has started. This has been explained by a greater action of busulfan and radiation on primitive stem cells from which the antibody-producing cells arise, and the greater effect of mechlorethamine on the cells that produce antibody. It is of interest here that the most sensitive cell to mechlorethamine is the lymphocyte, a cell which is almost untouched by busulfan. Much more study is needed in this field.

## Folic Acid Antagonists

At present, methotrexate is the only folic acid antagonist in clinical use. Many of the biochemical studies have been carried out with another antifol, aminopterin which appears to act identically with methotrexate. A great deal is known of the pharmacology of methotrexate, and many of this compound's effects can be explained on the biochemical level. However, as for all the anticancer drugs, little or nothing is known to explain its selective toxicity for certain neoplasms over normal tissues.

There are a number of excellent review articles on the mechanism of action of methotrexate.[10-15] Only the major aspects of the biochemistry will be outlined here.

Folic acid, as such, is inactive in biochemical reactions in most cell systems. It must be reduced to tetrahydrofolic acid (THF) by the enzyme dihydrofolic acid reductase (DHFR). This reaction takes place in two steps with dihydrofolic acid being formed as the intermediate. The enzyme for both stages of the reaction is probably the same. Once THF is formed it can be readily transformed into other derivatives. These THF derivatives are important as coenzymes which function as carriers of "one-carbon" units in many biosynthetic reactions in the body. These reactions are well reviewed by Delmonte and Jukes.[10]

The two most important reactions in which the THF coenzymes are involved are: (1) the thymidilate synthetase reaction in which

deoxyuridylic acid is transformed to thymidilic acid by addition of a methyl group to the 5 position of the uracil ring. The coenzyme for this reaction is 5,10-methylene THF. (2) The $N^5$, $N^{10}$-anhydroformyl derivative of THF is required for the transfer of formyl groups into the 8 and 2 position of the purine ring, and therefore is intimately involved in the synthesis of purines. Apparently, the former of these two reactions is the one whose inhibition leads to the antitumor and toxic effects of the folic acid antagonists.

Methotrexate acts by preventing the reduction of folic acid to THF. It does so by binding to the enzyme DHFR. Its affinity for DHFR is more than 100,000 times that of folic acid. *In vivo* this binding is essentially irreversible. However at alkaline pH *in vitro* this reaction between methotrexate and DHFR has been shown to be reversible. Studies in rats have shown that minute quantities of methotrexate are still present in kidney and liver bound to DHFR, eight months after administration of a single dose.

After a single dose of methotrexate there is binding of the drug by DHFR. Any excess unbound methotrexate is rapidly excreted. (Details of absorption excretion and distribution will be described later in this section.) Since the binding of DHFR will prevent further DNA synthesis cell division will be prevented. However, protein production under the influence of RNA already formed, and the production of RNA from preformed DNA will not be prevented. Therefore, cells will be able to produce new DHFR. If subsequent doses of methotrexate are not given, the cells will be able to recover, when sufficient DHFR is produced to initiate DNA synthesis. It can thus be seen that duration of contact of methotrexate with tissues, rather than the height of the blood level of the drug, is the critical factor in determining drug effects. This point will be reemphasized when we discuss the influence on toxicity of rate of absorption, route of administration, and dosage regimens.

It can be seen from the above paragraph that rapidly dividing cells such as bone marrow elements, hair follicle cells, and intestinal mucosal cells will be most susceptible to folic acid antagonists. Less rapidly dividing cells, since they do not need to produce DNA as rapidly, can exist without DHFR for longer periods of time.

It is important at this time to discuss the various means of preventing or reversing methotrexate toxicity. Unfortunately, toxicity cannot be diminished without proportionately reducing antitumor effects.

The direct antagonist of methotrexate and other antifolics is THF, since by administering THF, the block in reduction of folic acid is bypassed. In practice, a THF derivative citrovorum factor (Leucovorin®, Lederle) is used. Chemically this is $N^5$ formyl-THF. It is effective if given before or within four hours of administration of methotrexate. After this, irreversible toxicity will occur.

Folic acid pretreatment is able to protect against a single dose of methotrexate, but not against multiple doses. Werkheiser[13] states that this is due to conversion of this folic acid to THF by the liver, with resultant high blood levels of THF.

Pharmacologic doses of dihydrofolic acid but not folic acid can partially reverse methotrexate toxicity when given after the methotrexate. Dihydrofolic acid and folic acid can replace some of the methotrexate bound to DHFR if given in sufficient quantities. However, folic acid is a competitive inhibitor of dihydrofolic acid with respect to DHFR. If folic acid is given, it as well as the methotrexate will compete with dihydrofolic acid for the DHFR, and prevent formation of THF. If dihydrofolic acid alone is given it will displace the methotrexate from DHFR and form THF.

Natural and acquired resistance to methotrexate are unfortunate properties of tumors. This subject has been only partially elucidated. Induction of increased production of DHFR has been shown to occur when normal leukocytes are incubated with methotrexate. This occurs too rapidly to be explained by selection of resistant cells. This may also occur in leukemia cells.

However, the major reason for development of resistance to methotrexate appears to be selection of tumor cells which produce high concentrations of DHFR. While these cells are still susceptible to methotrexate, the concentrations required are lethal to normal cells. In bacteria, and in murine neoplasms resistant to methotrexate there has been an almost constant marked rise in production of DHFR.

Another mechanism of development of resistance to methotrexate appears to be the appearance of decreased permeability

of the cell to this drug. This also occurs by selection of genetically resistant cells. Other mechanisms have been postulated but not demonstrated.[12]

A discussion of absorption and excretion is more important for methotrexate than for any other antitumor drug. As will be seen, rate of absorption and/or excretion can be a critical factor in toxicity. First the known facts will be outlined, and then the implications will be discussed.

Although it has been deduced on clinical grounds that methotrexate was well absorbed after oral administration, the exact degree has been in some doubt. Recent studies with tritiated methotrexate in humans have clarified this problem.[16] At small oral dosages there is essentially complete absorption. Dosages in the range of those used clinically (0.1 mg/kg/day) are completely absorbed, as blood levels are comparable to those following i.v. administration. Large oral dosages of methotrexate lead to prolonged and incomplete absorption.

There is little if any metabolism of methotrexate in the human.[16] Following i.v. administration or a small oral dosage, 58-92% of the drug was excreted in the urine within 24 hours, and less than 10% was found in the stool. After large oral dosages, large amounts (39%) were recovered in the stool and significant urinary excretion continued for several days.

Thus it can be seen that any impairment of urinary function will delay excretion and maintain a high blood level for a longer period of time. High oral dosages with delayed absorption will also permit maintenance of high blood levels for a longer time. With the same high dose given intravenously, peak levels would be higher, but duration of significant blood level is shorter.

The importance in toxicity of the cumulative effects of methotrexate cannot be emphasized too strongly. This fact has been utilized in adjusting dosage regimens. Traditionally, methotrexate is given once daily orally. A four times a day regimen for five days has been utilized in treating adult acute leukemia (see Chapter 3 on methotrexate). The pharmacology of methotrexate has been utilized by Hertz to plan an effective regimen for treatment of choriocarcinoma (see Chapter 3). This regimen utilizes the fact that host tissues recover more rapidly from the effects of methotrexate than the tumor tissue (presumably by the synthesis of new DHFR). The patient is given five daily single injections of a high dose of methotrexate. As soon as toxicity clears the

next five day course is given. This is continued until cure. While this therapy is intermittent for the normal tissues, it is cumulative for the tumor.

In this last paragraph, we see one of the few areas where there is at least a partial explanation of selective toxicity for tumor. Werkheiser[13] has also contributed to the speculations in this area. He points out that methotrexate enters cells of different types at widely different rates. If the rate of entry is too slow, the rate of formation of new DHFR may exceed the rate of entry of methotrexate, and the cell will not be affected by the drug.

## 6-mercaptopurine

Up to this time the mechanism of action of the purine antagonists has eluded investigators. It is known that 6-mercaptopurine interferes with reactions involved in purine synthesis, both in the early stages of synthesis and in the interconversion of purines. Brockman[17] has made the suggestion that 6-mercaptopurine as the ribotide acts at the site of end-product inhibition of purine synthesis by purine ribonucleotides. The clearest discussion of the present state of knowledge is contained in the article in Goodman and Gilman's textbook.[1]

6-mercaptopurine is well absorbed from the gastrointestinal tract, but the exact extent is not known. The drug is rapidly metabolized, the major excretion product in the urine being 6-thiouric acid. Xanthine oxidase seems to be extremely important in the metabolism of 6-mercaptopurine as allopurinol markedly decreases the tolerance to 6-mercaptopurine.

## Fluorinated Pyrimidines

When reading the literature on the fluorinated pyrimidines one is reminded of a Russian novel. The list of compounds, all with similar names leads to confusion. The usual aid in understanding *War and Peace* is a list of characters, with a small description accompanying each name. Such a list of the characters in *The Fluorouracil Story* is now presented.

1. *Uracil:* A pyrimidine base. One of the two major pyrimidine bases present in RNA.
2. *Thymine:* One of the two major pyrimidine bases present in DNA. Not found in RNA. It has the same structure as

uracil, except for the replacement of a hydrogen atom by a methyl group in the 5 position.

3. *5-fluorouracil (FU):* The commercially available antitumor agent. It has the same structure as uracil except for a fluorine atom in the 5 position. Note that it also differs by only one group from thymine which has a methyl group in the 5 position.
4. *5-fluorodeoxyuridine (FUdR):* Another antitumor agent, not commercially available, but studied extensively in humans. Its structure is made up of FU attached to deoxyribose. Deoxyribose is the sugar molecule present in the DNA backbone.
5. *5-fluoro-2'-deoxyuridine-5'-phosphate (FUdRP):* Also known as fluorodeoxyuridylic acid. It is the deoxyribonucleotide of FU. It is also the metabolically active form of FU, being formed from FU *in vivo*.
6. *5-fluorouridine (FUR):* The riboside of FU. In other words it is FU attached to ribose. It is readily formed in the body from FU, and can be converted readily to fluorouridylic acid (FURMP).
7. *Fluorouridylic acid (FURMP):* This is the ribonucleotide of fluorouracil. Its structure is 5-fluorouracil-ribose-phosphate. FURMP is readily incorporated into RNA.

There are several good discussions in the literature of the mechanism of action of the fluorinated pyrimidines.[1,6,18] A great deal is known, far more than is known about 6-mercaptopurine, an agent that has been available for a much longer time.

To understand the action of the fluorinated pyrimidines, one must first know something of their metabolism. When we talk of the fluorinated pyrimidines, at present the field is limited to 5-fluorouracil (FU) which is commercially available and 5-fluorodeoxyuridine (FUdR), which some claim is more effective than FU. FUdR is in short supply, and is only available for research.

FU can be involved in all the catabolic and anabolic reactions of uracil except for one. This is the 5-methylation reaction of the anabolic product FUdRP. This last fact is of some importance, as will be seen later.

The catabolic reactions leading to the degradation of 5-fluorouracil account for most of its metabolism, and will be discussed later. It is the anabolic reactions which are important in its mechanism of action. The most important of these reactions are

the production of FUdR from FU and the subsequent transformation of FUdR to FUdRP. FUdRP is the active form of the drug. FU may also combine with ribose to form FUR. FUR may in turn be transformed to FURMP.

The way in which FUdRP exerts its action is by competing with deoxyuridylate for the enzyme thymidylate synthetase. (Deoxyuridylate is the deoxyribotide of uracil, and the thymidylate synthetase reaction involves methylation in the 5 position to produce thymidylic acid, the deoxyribotide of thymine. The methyl group is provided by $N^5N^{10}$ methylene tetrahydrofolic acid. The formation of this compound was discussed in the earlier section on methotrexate, because methotrexate inhibits production of tetrahydrofolic acid compounds.)

Sufficient quantities of FUdRP will inhibit the production of thymidylic acid by the thymidylate synthetase reaction. Thymidylic acid is present in DNA, but not in RNA. Therefore FU and FUdR prevent DNA but not RNA synthesis. FUdRP when given to the intact animal is unable to penetrate cells. It must first be dephosphorylated to FUdR which will be rephosphorylated when it enters the cell.

FUdR, when given as a single injection is rapidly converted to FU, so that it is no more active than FU mole for mole. However, when FUdR is given by prolonged intravenous infusion it is 30 to 60 times as potent. That is 1/30 to 1/60 of the dose is given over a 24 hour period as when a single intravenous dose is given.

Sullivan and Miller[19] have given an excellent explanation of this phenomenon.

"The increased biologic activity of 5-FUdR resulting from continuous i.v. administration measured in terms of dose-toxicity and therapeutic response may be explained, in part, as follows: In a given cancer-cell and other vulnerable tissue-cell (for example, bone marrow) population only a small percentage of such cells will be, at any given time, in the process of nucleic acid production prior to cell division. If, and this premise is based upon a large body of evidence, only those cells in a specific stage of nucleic acid production will be adversely affected by the anti-metabolite at any given moment, then a large percentage of potentially vulnerable cells will not be affected by the temporary exposure to anti-metabolite when it is given by *single* daily injection. A large percentage of the potentially vulnerable

cell population will be insensitive to the drug during this temporary period of exposure. Thus, when the drug is given by single daily injection, a large segment of the cell population may escape its effects during the period in which the blood level of the drug is below the threshold of pharmacologic activity. However, when the drug is given by *continuous* i.v. infusion at a rate adequate to produce a continuous blood level above the threshold of pharmacologic activity, all cells sequentially entering a sensitive phase of metabolic activity may be affected.

There is convincing evidence that the prolonged i.v. infusion of 5-FUdR results in an altered metabolic pathway and an altered mechanism of action of the compound as compared with rapid single daily i.v. injection. When 5-FUdR is given by the latter relatively massive dose schedule, probably most of it is rapidly cleaved to 5-FU as there is insufficient enzyme to anabolize it to 5-FUdRP. With small continuous doses of 5-FUdR, however, most of the compound is anabolized to 5-FUdRP, the compound-inhibiting thymidylate synthetase. Thus, a single daily i.v. injection of 5-FUdR produces its biologic activity largely by way of its catabolite 5-FU while by continuous i.v. infusion it is acting to interfere with the synthesis of thymidine, essential to deoxyribonucleic acid synthesis."

As was stated earlier, some FU is converted to FUR. FUR is readily incorporated into RNA as FURMP. One would think that RNA containing a false pyrimidine would not code properly. It is interesting that in some species such RNA has functioned normally while in others it has not.[18] While FU may be incorporated into RNA it cannot be incorporated into DNA.

The natural antagonist of FU is thymidine. However, Calabresi and Welch explain why this is of no practical value except in prolonged infusion of FUdR.[11] "Given as single daily intravenous doses, the effects of neither FU nor FUdR can be prevented by large doses of thymidine; in fact, under these conditions this precursor of DNA *increases* the toxicity of the nucleoside. This apparent paradox is explained by the very rapid metabolic conversion of thymidine to the corresponding base, thymine, which competes with the enzyme that can attack either FU, uracil or thymine. In this manner, an increased concentration of fluorouracil is made available for anabolic utilization. On the other hand, when thymidine is given by intravenous infusion, together with FUdR the effect of the latter can be nullified, since in this

manner, enough thymidine can be provided simultaneously to susceptible cells to circumvent any inhibition of thymidylate synthetase caused by FUdR, acting as the 5'-phosphate ester."

The liver is the major area of catabolism of FU and FUdR. These compounds follow the same pathway as uracil. $CO_2$ and urea are major metabolic products. With rapid intravenous injection of FU, a significant amount of the drug is excreted unchanged in the urine, but when given as a slow infusion less than 5% is so excreted, most of the drug being catabolized. This probably explains the decreased toxicity and effectiveness of FU when given by slow intravenous injection. On the other hand, when FUdR is given by slow infusion less appears unchanged in the urine than when given as a single intravenous dose.

In the preceding pages we have seen the explanation for a seeming paradox. FU is more toxic by single injection, while FUdR's toxicity is increased by slow infusion.

Oral administration of FU and FUdR is not used because of increased catabolism of the compounds by the liver.

## Vinca Rosea Alkaloids

Vincristine and vinblastine are naturally occurring alkaloids, extracted from the Vinca Rosea plant (periwinkle). Although cross resistance between vinblastine and vincristine does not seem to occur in tumors in humans, the mechanism of action of these two complex compounds appears to be the same. These two agents are large molecules, but they only differ in chemical structure by the replacement of a methyl group in vinblastine with a formyl group in vincristine.

Very little is known of the mechanism of action of the vinca rosea alkaloids. While they inhibit mitosis in metaphase they do not appear to decrease DNA formation.[20] It is currently believed that their effect on tumors is mediated through their ability to produce metaphase arrest.

Oral absorption of vinblastine is poor, but a recent report[21] has appeared describing an improved oral form. Both drugs are rapidly removed from the blood stream, and their excretion is almost entirely by the liver into the bile. Local uptake or destruction is rapid, as considerably higher doses can be given intraarterially than intravenously.

## Actinomycin D

Actinomycin D is the most active, and least toxic of a group of antibiotics isolated from a culture broth of a species of *Streptomyces*. This compound has excited a great deal of interest not so much because of its antitumor actions, but because of its great usefulness as a tool in molecular biology. The reason for this will become apparent in the next few paragraphs.

Several excellent review articles have discussed the biochemistry of actinomycin D. Samuels[22] has stressed its role in determining the mode of action of hormones, but also reviews other actions. Goldberg[23] has given an especially complete discussion of the latest knowledge of the mechanism of action of actinomycin D.

Actinomycin D binds to DNA, but not to RNA to form a relatively stable complex. This binding requires the presence of guanine in a double helical configuration. Synthetic polynucleotides which do not contain guanine do not react with actinomycin D. Synthetic or naturally occurring DNA's containing even small quantities of guanine do react with actinomycin D. The degree of binding roughly parallels the amount of guanine in the DNA molecule. Single stranded or heated DNA binds less actinomycin D than natural DNA of similar base composition. When DNA-actinomycin complexes are heated, dissociation of the DNA from the actinomycin begins at onset of heat-induced strand separation. These facts emphasize the necessity of the double helical structure of DNA for maximum binding of actinomycin.

It is this binding of actinomycin D to DNA which explains its biological effects. Actinomycin D selectively inhibits RNA synthesis by RNA polymerase in microorganisms and mammalian cells. It does not directly inhibit RNA polymerase. (Effects of actinomycin D can be overcome *in vitro* by excess DNA, but not by increasing the concentration of RNA polymerase, precursors, or cofactors.)

It is thought that actinomycin D inhibits RNA synthesis by binding to the site on the DNA template where RNA polymerase ordinarily functions. Goldberg[23] has proposed a molecular model which shows the peptide chains of actinomycin filling the minor groove of DNA for a distance of 3 base pairs.

Actinomycin D also inhibits DNA synthesis, but only in concentrations which affect the physical properties of the DNA

molecule. The concentrations required for inhibition of RNA synthesis are much less and do not affect the heat stability of DNA.

As further evidence for these theories, RNA directed RNA synthesis is not inhibited by actinomycin D.

As a result of this action in preventing RNA synthesis, actinomycin D has been a useful tool in understanding the biochemical actions of hormones. Any hormone whose action is inhibited by low concentrations of actinomycin D can be considered to produce this action by increasing DNA dependent RNA synthesis. Growth hormone, ACTH, adrenal steroids, estrogen, testosterone, insulin and thyroxine have been shown probably to exert at least part of their action, by RNA production stimulation. Actinomycin D is useful in studying other biochemical reactions than those involved in hormone actions.

The actinomycins are potent immunosuppressive agents, and they are commonly used in renal transplantations. However, little is known of their exact site of attack on the immune mechanism. Actinomycin D is a potent additive agent to x-rays, and may actually potentiate radiotherapy. This is discussed in Chapter 7.

Actinomycin D is absorbed poorly from the gastrointestinal tract. It is cleared almost completely from the blood in less than two minutes. About 50% of the drug is excreted unchanged in the bile, and 10% is excreted in the urine.

### Mithramycin

Mithramycin, like actinomycin, a product of a *Streptomyces*, has similar biochemical actions.[23] It binds to DNA and inhibits RNA synthesis.

### Methylhydrazines

It is believed that the methylhydrazines produce their antitumor effects by forming hydrogen peroxide and hydroxyl radicals within the cells.[24,25] However, this is based on preliminary studies. Methylhydrazines, like x-rays and alkylating agents, cause fragmentation of DNA. This action of methylhydrazines can only occur in the presence of oxygen. The only methylhydrazine in clinical use at present is RO 4-6467/1 (Natulan). This compound is also a strong immunosuppressive agent.

Very little is known of the absorption, metabolism and excretion of the methylhydrazines. RO 4-6467/1 has been studied to some extent.[26]

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## CHAPTER II

## ALKYLATING AGENTS

The alkylating agents are the single most useful group of cancer chemotherapeutic agents. Despite this, there is little evidence that they prolong survival significantly. Studies with cyclophosphamide in multiple myeloma indicate that life is lengthened. I am not aware of similar studies with alkylating agents in other malignancies.

There has been a great deal of controversy as to whether there are basic differences among the various alkylating agents. The pharmacologic evidence is beyond the scope of this section. For clinical purposes, a few differences are extremely significant, even if not based on different mechanisms of action.

The most interesting of these individual clinical effects of alkylating agents is the limited but definite remission of childhood acute leukemia produced by cyclophosphamide. The marked alopecia-producing action, and urinary bladder irritation of cyclophosphamide are also unique.

Outside of these differences, the reasons for favoring a particular alkylating agent for any disease are usually based on clinical experience. This clinical experience is partly based on pharmacologic factors such as speed of action, duration of action, and rate of administration. It was often based on what patients were available to the original investigators.

For this reason, the so-called alkylating agent of choice for any disease is often somewhat arbitrary. However, it is best to stick to the accepted drug or drugs, except in the course of a planned investigation in a large series of patients.

As was stated, evidence for prolongation of life with alkylating agents is limited. The outstanding achievements to be discussed in this chapter are the palliation of Hodgkin's disease,

other lymphomas, ovarian carcinoma, chronic leukemias, and multiple myeloma.

In general, when a patient's tumor becomes refractory to one alkylating agent, it will not respond to another. Rare exceptions to this have been reported.

## Mechlorethamine

Mechlorethamine, commonly known as nitrogen mustard or $HN_2$ and commercially available as Mustargen® (Merck & Co.), is a member of that group of alkylating agents known as *nitrogen mustards*. It is the only nitrogen mustard in clinical use, and for almost ten years was the only alkylating agent released commercially.

The indications for and dosage of mechlorethamine are perhaps clearer than for any alkylating agent except busulfan (Myleran®, Burroughs-Wellcome & Co.). This is undoubtedly because the earliest studies were carried out by men who are giants in the fields of hematology, pharmacology, and neoplastic diseases. The initial clinical article was by C. P. Rhoads,[1] and the names on the second clinical article[2] include Goodman, Gilman, Wintrobe, and Dameshek. Other early investigators include Karnofsky,[3] Gellhorn,[4] and Leon Jacobson.[5]

The earliest successes with mechlorethamine were in the lymphomas, and it is still the most widely used drug in Hodgkin's disease. Although there are studies which indicate that triethylene thiophosphoramide[6] and cyclophosphamide[7] can give equally good results in Hodgkin's disease, mechlorethamine must remain the drug of choice at this time.

For anyone who plans to use mechlorethamine in patients with Hodgkin's disease, I would strongly recommend reading Dameshek's article published in 1949.[8] This article contains a clear and detailed description of the clinical changes which occur with therapy. It emphasizes time of onset and duration of improvement in different clinical parameters as well as similar chronological data for toxicity. Other excellent clinical articles have appeared[3,9-11] which include treatment of other lymphomas and carcinomas. An excellent description of hematologic toxicity can be found in articles by Dameshek,[8] Gellhorn,[4] Jacobson et al,[5] and Wintrobe.[10]

Although mechlorethamine is the chemotherapeutic agent of choice in the treatment of Hodgkin's disease, the mainstay of therapy in this condition must still be radiotherapy. All authors agree that widespread disease and systemic toxicity are the criteria for using chemotherapy. However there are some differences of opinion as to the interpretation of these terms. Certainly all physicians who have treated a number of patients with Hodgkin's disease have seen high fever, anemia, weight loss, anorexia, and fatigue, reversed by radiotherapy of large paraortic abdominal nodes or extensive mediastinal disease. In the lymphoma group at Montefiore Hospital, we have emphasized radiotherapy, searching for all areas of involvement that can be treated by localized radiotherapy. Chemotherapy is reserved for patients who have systemic findings without discernible tumor deposits, or patients who have received maximum tolerated dosage of radiotherapy to areas of still active Hodgkin's disease.

We have followed this approach because of the prolonged remission of disease in the area treated by radiotherapy, as compared to the relatively brief remissions produced by mechlorethamine (median 12 weeks). By properly timing the treatment to different areas, it has been possible to treat many patients with extensive stage III disease by radiotherapy alone. This has been best applied when disease is confined to the lymph nodes and spleen. Radiotherapy has also been quite successful for epidural and lung parenchyma involvement. We have been impressed with the disappearance of systemic toxicity with radiotherapy alone. Lymph node involvement in the iliac and paraortic nodes in the abdomen have been a common cause of systemic manifestations. Radiotherapy for extensive bone marrow involvement has not been of great use.

This approach is not universally accepted, although all authors believe in using radiotherapy to localized areas of Hodgkin's disease. Many would add mechlorethamine for patients with more than minor systemic signs and symptoms. Several eminent investigators recommend giving a course of mechlorethamine to even those patients with a small localized deposit of Hodgkin's disease (stage I) after completion of the radiotherapy.[8,12,13] These authors argue that small foci of Hodgkin's disease may exist outside of the area treated. However, no one has ever shown that mechlorethamine does more than temporarily suppress the growth of Hodgkin's disease. This suppression is

rarely for more than a year, and usually for a much shorter time. I can see no logical reason for use of a potentially toxic agent such as mechlorethamine in stage I and early stage II Hodgkin's disease. Certainly there is a much stronger argument for using mechlorethamine early in the treatment when systemic symptoms are severe. Radiotherapy to extensive disease may take many weeks, and mechlorethamine can relieve systemic symptoms within a few days to weeks. However, the use of systemic therapy by suppressing the bone marrow may slow down the rate at which radiotherapy can be given, and we prefer not to do this.

A very high percentage of patients with Hodgkin's disease will respond to mechlorethamine. Wintrobe et al[14] have stated that only "truly terminal" cases will not respond. For this reason, response rates quoted by various authors depend to a great extent on the condition of their patients prior to treatment. Dameshek[8] reports remissions in 79.4% of courses (34.3% complete and 45.1% partial). Karnofsky in a review of the literature[3] states that 80 to 90% will respond, and Spurr et al[15] report 72% good or fair response in Hodgkin's granuloma or paragranuloma. Gellhorn et al[9] have attempted to assess the effect of mechlorethamine on survival in Hodgkin's disease. They compared 67 patients with generalized disease treated with radiotherapy and mechlorethamine in alternating courses to 65 previous patients treated with x-ray alone. There was no difference in survival between the groups. However, the chemotherapy permitted shorter treatment periods of radiotherapy with a greater amount of useful time available to the patient. The reduction in radiotherapy days was approximately 50%.

Wintrobe et al[14] state that there is "no question that patients have been maintained in an asymptomatic state for a greater proportion of their disease courses than had been achieved with radiotherapy alone, the amount of time spent undergoing therapy and hospitalization has been shorter, and total economic burden has been distinctly lower."

The response of patients with Hodgkin's disease will be described in some detail. The most dramatic changes are in symptoms such as fever, fatigue, anorexia, weight loss, and weakness. However, objective changes in tumor deposits also occur. Within four days of mechlorethamine therapy in almost all but very advanced cases fever will start to drop. Spurr et al[15] noted that all patients who responded had lysis of fever within

96 hours of treatment. These authors spaced the mechlorethamine dosage over four days and do not state whether the 96 hours was from start or completion of therapy. I would suspect the latter is correct. These authors state that if fever does not return to normal, remission in other features does not occur. Wintrobe et al[14] noted disappearance of fever within a week.

Anorexia is completely relieved in over 75% of patients, and fatiguability in over 50%. Almost all patients have improvement in strength with some patients returning to full sense of well-being. Relief of anorexia is accompanied by weight gain. Pruritus is less often relieved. This is partially because of secondary skin changes that have occurred as a result of scratching. Dameshek[8] gave 15 courses of mechlorethamine to patients with pruritus. Six had complete relief and 5 had partial response of pruritus.

Anemia will often respond, although not necessarily completely. Dameshek[8] noted complete disappearance of splenomegaly in 39.1% of patients and some decrease in size of the enlarged spleen in another 32.6%. Spurr[15] stated that degree of resolution of splenomegaly varied from complete to partial. Hepatomegaly responds to a lesser extent. Dameshek[8] noted return to normal size in 26.6% and partial response in 10% of patients with enlarged livers. Lymphadenopathy responds about as well as splenomegaly. Wintrobe et al[14] noted changes in nodes within a week of therapy. Dameshek[8] noted complete disappearance of enlarged nodes in 38.1% of patients and partial response in 32.1%. Spurr[15] stated that completeness of resolution of nodes varied from moderate softening and reduction in size to complete reduction. This change was noted to a greater extent in earlier cases. Apparently mediastinal nodes are about as responsive as peripheral nodes. It should be emphasized that the primary therapy for mediastinal Hodgkin's disease is radiotherapy. This form of therapy usually produces permanent resolution of mediastinal Hodgkin's disease.

Although hepatomegaly may respond to mechlorethamine and jaundice responds in some patients, hepatic involvement sufficient to cause jaundice is a poor prognostic sign. Unfortunately, the tolerance of the liver for radiation makes it difficult to deliver a large dose of radiotherapy to this organ. There are very little clinical data as to the preferred method of therapy for advanced hepatic Hodgkin's disease.

Extensive Hodgkin's disease of the lung parenchyma is also a poor prognostic sign. However, localized deposits respond well to supravoltage radiotherapy. There are little data on the response of parenchymal involvement to mechlorethamine.

Bone involvement must be distinguished from widespread bone marrow involvement. The latter condition is not very common and is most often found in Hodgkin's sarcoma. It responds poorly to any therapy. Localized bone involvement is best treated by radiotherapy. This treatment will relieve pain and may cause some radiologic improvement. Mechlorethamine will usually relieve bone pain but did not cause improvement in radiologic appearance of bone lesions in a single one of 21 courses.[8]

Two situations which are supposedly prime indications for immediate mechlorethamine therapy in Hodgkin's disease are spinal cord compression and superior mediastinal syndrome (superior vena cava syndrome). There is some rationale for this in spinal cord compression where speed is imperative. Mechlorethamine may be somewhat more rapid than radiotherapy. When signs and symptoms of cord compression develop slowly, radiotherapy alone is probably just as effective. There is no good study comparing the effectiveness of radiotherapy alone with combined therapy.

In superior mediastinal syndrome rapid tumor lysis is not imperative. Low salt diet, diuretics, and elevation of the head of the bed will almost always relieve the acute symptoms. Mechlorethamine administration into upper extremity veins is somewhat hazardous with the slowed blood flow of the superior mediastinal syndrome. Severe thrombophlebitis has occurred. For these reasons, radiotherapy alone is the treatment of choice for this syndrome. There appears to be no evidence for the idea that initial radiotherapy may produce swelling and temporary worsening in cord compression, or superior mediastinal syndrome.

Mechlorethamine has been used extensively in lymphosarcoma. However, chlorambucil is probably safer and possibly more effective in small cell lymphosarcoma and its close relative, chronic lymphatic leukemia. The same holds true for giant follicular lymphoblastoma. Mycosis fungoides has been successfully treated with mechlorethamine.[16-18] However, remissions tend to be very brief (usually less than three months). Repeat courses may be as successful as the first, but eventually resistance develops.

Mechlorethamine has been used extensively in lung carcinoma. Although subjective relief has been reported in a number of patients, almost all patients who have objective response belong to the small cell anaplastic (oat cell) variety of lung cancer.[19,20] About 50% of these patients with oat cell carcinoma have objective regression of tumor, and 90% are subjectively improved. However, duration of remissions are very short, averaging two to six weeks. Second remissions may occur after a repeat course, but oat cell carcinoma is such a lethal disease that almost all patients are dead within a year of diagnosis despite chemotherapy and radiotherapy.

Wolf et al[21] treated 296 bronchogenic carcinoma patients with 0.4 mg/kg of mechlorethamine. A second course was given six weeks later. The survival rate was no better than in 327 control patients. However, there was a slight prolongation of survival within the subgroup of squamous cell carcinoma. Spear et al[7] found cyclophosphamide equally as effective as mechlorethamine in bronchogenic carcinoma. Studies of intravenous mechlorethamine as an adjuvant at the time of pulmonary resection for bronchogenic carcinoma in over 500 patients showed this agent to be ineffective in improving survival.[22] Thus it can be seen that mechlorethamine has a small, but definite role to play in the palliation of bronchogenic carcinoma.

It is of interest that mechlorethamine has had little trial in ovarian carcinoma, a disease where chlorambucil and triethylene thiophosphoramide have produced a good percentage of remissions. Hreshchyshyn[23] in his review of chemotherapy in gynecologic cancer, published in 1962, was able to find nine patients with ovarian carcinoma treated with mechlorethamine. None had responded.

Palumbo et al[24] in 1962, reported nine patients with ovarian carcinoma who did not respond to mechlorethamine. However, they found several other alkylating agents effective in this disease.

Mechlorethamine is considered a standard form of treatment for recurrent malignant effusions. It is conventionally given directly into the pleural, peritoneal, or pericardial cavity after removal of most or all of the effusion. Details of the technique will be described below. However, the role of intracavitary mechlorethamine in malignant effusions is based on uncontrolled studies and clinical impressions.

The best results have been reported by Weisberger.[25,26] Fifty-six of 88 patients were improved, and 17 of the 32 nonresponders were preterminal. Of the 56 patients improved, 43 had no re-accumulation of fluid and 13 had a significant decrease in the rate of accumulation.[26] The improvement rate was somewhat higher in patients with pleural effusion (67%) as compared to those with peritoneal effusion (53%).

Weisberger[26] found failures to be more common in those patients with chylous effusions. He also found poor results in patients with pleural effusions of low specific gravity. This was attributed to the fact that pathogenesis of such effusions was usually mediastinal compression. Large mediastinal masses, such as these, would not be expected to respond to intracavitary therapy which bathes the surface of the tumor.

Other authors have reported good results with intrapleural mechlorethamine.[27-30] In general, the best results have been reported in ovarian and breast carcinoma, tumors which are more sensitive to alkylating agents. It has been noted that in some patients intrapleural mechlorethamine has caused adhesive pleuritis.[27] For this reason most clinicians have shied away from using intraperitoneal mechlorethamine. It is feared that adhesive peritonitis might lead to intestinal obstruction. However, Weisberger[26] did not mention this complication in thirty patients who received intraperitoneal mechlorethamine. He did note pain and cramps in the first three days after injection.

Before the degree of usefulness of intracavitary mechlorethamine can be determined, a controlled series must be carried out comparing this therapy with intravenous mechlorethamine administration after removal of the effusion. A second control group who merely had removal of the malignant effusion should also be included.

Despite these reservations, at present intrapleural mechlorethamine seems to be occasionally useful in the palliation of malignant pleural effusions.

The use of intraarterial mechlorethamine either by infusion or isolation perfusion has been of little value.[31]

Mechlorethamine is supplied, as Mustargen, in the form of a sterile dry powder, 10 mg of the agent in an ampul. For intravenous administration it is dissolved in 10 cc of sterile water. The required amount of solution is injected into the rubber tubing of a rapidly flowing intravenous infusion. Great care is taken to

prevent any of the solution from infiltrating into the tissues of the patient. The package insert also cautions against spilling any of the solution on the skin because of its vesicant action. However, Goodman and Gilman's textbook[32] states that the solution (10 mg/10 cc) is not concentrated enough to cause skin damage. These authors do caution against getting any of the solution onto the cornea where it may cause serious damage.

The standard dosage is 0.4 mg/kg, usually given as 0.1 mg/kg/day for four days. This dose is lowered in patients whose marrow might be more sensitive to alkylating agents. (See Discussion in section on chlorambucil.) Occasionally, higher dosages have been used in patients with lung cancer.

The main reason for dividing the dosage into four daily injections has been tradition. There seems to be little rationale for this, and at Montefiore Hospital we give 0.4 mg/kg in a single injection. There is no more nausea and vomiting with this dose, and the patient has these side effects on one day only instead of four. Premedication to minimize nausea and vomiting is important and will be discussed below.

There are several variations on the technique for intracavitary injection of mechlorethamine. Weisberger et al[26] first remove approximately one-half of the malignant effusion. For intrapleural administration 0.4 mg/kg is given through the same needle used for the thoracentesis. The strength of the solution is the same as used for intravenous administration, 1 mg/cc. Saline or sterile water may be used as the diluent. For intraperitoneal effusions, the solution is administered through a rubber or plastic catheter inserted into the trochar used for paracentesis or through an 18 gauge needle inserted at another site. Free flow of fluid through the needle or trochar should be ascertained frequently by aspiration during the slow injection of the mechlorethamine solution. This is important in intrapleural, intraperitoneal, and intrapericardial injections, as localized collections of the solution in loculated effusions or outside the serous cavity can cause tissue necrosis.

Weisberger then advises a repeat tap the next day to remove the remainder of the fluid. A reactive effusion may occasionally occur within the first few days after administration of the mechlorethamine. Weisberger[26] regards this as favorable, and indicative of a probable response.

Other authors have used variations on Weisberger's technique.[27-29] An indwelling catheter in the pleural cavity under suction to remove as much fluid as possible, has been suggested.[27,29] In this case, it is probably better to use 50 to 100 cc of normal saline as the diluent for the mechlorethamine. This technique encourages an adhesive pleuritis which may aid in preventing fluid reaccumulation.

No matter what technique is used, once the agent is instilled, efforts should be made to insure contact of the drug with all surfaces of the affected cavity. The position of the patient should be changed frequently in the first fifteen minutes after injection. A tilt table will be of aid in this aim.

Systemic toxicity of mechlorethamine lies in two areas: the nausea and vomiting which occur within the first day, and the bone marrow toxicity which is delayed for more than a week.

Nausea and vomiting occur in approximately 90% of patients. They occur within 1 to 3 hours of the injection, and severe symptoms usually last 2 to 4 hours. However, some degree of nausea may last for 24 hours. The vomiting may be very severe. Most physicians use some form of premedication in an attempt to prevent or lessen the nausea and vomiting. Heavy sedation with a barbiturate or phenothiazine usually gives partial protection. The mustargen package insert recommends a short-acting barbiturate shortly before or with the mechlorethamine injection.

Because of the severe nausea and vomiting it is best to hospitalize the patient for mechlorethamine administration. The patient can be heavily sedated (3 to 4½ grains of a barbiturate or equivalent dose of a phenothiazine) and the drug given at bedtime. The patient can then be discharged the next morning. With this regimen the patient usually sleeps through most of the night, awakening once or twice to vomit.

Other immediate toxicity has been chills, fever and diarrhea, but these are less common. Dameshek[8] reported chills in 12.4% of courses and fever in 6.8%.

Bone marrow depression, although less frequent than the immediate gastrointestinal disturbance, is a more formidable problem. The classic article on this aspect of mechlorethamine toxicity appeared in 1946.[5] Little has been added since that time. Other good discussions of hematopoietic depression due to mechlorethamine have appeared.[3,4,8-10,33,34] The article by Dameshek is especially recommended.[8]

It should be noted that dangerous bone marrow depression is uncommon with mechlorethamine if proper safeguards are taken. Death due to this drug should occur in less than 1% of courses.

The first effect noted is a drop in peripheral blood lymphocytes and monocytes. This occurs within 24 hours after the initial dose, with maximum drop in 6 to 8 days and return to normal by two weeks. It is of little clinical significance. (This description does not include patients with chronic lymphatic leukemia where maximum drop in lymphocyte count may take several weeks to occur.)

The total white blood count drop may start as early as 4 days after the initial dose, with maximum fall occurring by 14 to 25 days after start of therapy. Recovery usually is complete by six weeks, although occasionally, patients may have prolonged granulocyte depression.

The height of the white blood count prior to therapy influences the degree to which the granulocytes will be depressed. Wintrobe[10] found after a standard dose of 0.4 mg/kg that 53 of 88 patients with initially normal white blood counts had a drop to below 4000 wbc/mm$^3$. However, only 11 of 38 patients with initial leukocytosis fell this low. Only ¼ of patients whose white blood counts fell below 4000/mm$^3$ had a drop below 2000/mm$^3$, and only 3 of these 16 had a fall below 1000/mm$^3$. Two of the leukopenic patients had infections during the period of leukopenia.

Thrombocytopenia is less common after mechlorethamine than is leukopenia. Scott[33] noted transient thrombocytopenia in 12 of 84 patients with initially normal platelet counts. Five patients initially thrombocytopenic received mechlorethamine. One patient's platelet count rose to normal and four patients had no change. Dameshek[8] noted a platelet count drop in 20.5% of his patients. The average decrease in these patients was 69.4% of the initial platelet count. The maximum drop occurred between the 20th and 30th day after the initial dose of mechlorethamine. Wintrobe[10] noted a drop below 100,000 platelets/mm$^3$ in 20 of 93 patients with initially normal platelet counts. The maximum drop occurred between the 8th and 39th day (average 19th day). Recovery occurred between the 21st and 105th day after the initial mechlorethamine dose (average 46th day) in 14 of 17 patients in whom thrombocytopenia developed.

Most authors have noted a definite but unimportant drop in hemoglobin and reticulocytes after mechlorethamine. Jacobson

et al[5] noted a slight drop in hemoglobin and stated that decreased reticulocyte counts could be noted between the 1st and 2nd weeks after onset of therapy. Scott[33] noted development of anemia or worsening of preexisting anemia in 12 of 89 patients with Hodgkin's disease who were given mechlorethamine. Dameshek[8] noted a drop in hemoglobin in 58.5% of patients beginning on the 5th or 6th day after the initial dose, and lasting until the 21st day. The maximum drop was 16.2% of the initial hemoglobin. Wintrobe[10] noted a drop in hematocrit below 40% in 29% of patients who had normal values initially. The maximum drop occurred between the 7th and 31st day (average 15th day). Thirteen of 17 patients in whom anemia developed, had a return to normal hematocrit by the 20th to 75th day (average 52nd day) after onset of mechlorethamine administration.

Dameshek[8] noted a decrease in peripheral blood reticulocytes in 85% of patients, with the maximum drop occurring between the 6th and 10th day.

Extensive studies of the effect of mechlorethamine on the appearance of the human bone marrow aspirate have not been carried out. Jacobson[5] noted "cytotoxic" effects on both mature and immature elements. Dameshek[8] noted some effect on the marrow within 24 hours of the first dose and noted regeneration occurring six days after cessation of mechlorethamine therapy.

The overall effects of this marrow toxicity have not been too serious. Gellhorn[9] noted significant toxicity after 7% of courses. This was defined as white blood count depression below 1000/mm$^3$ or platelet count depression below 70,000/mm$^3$. He noted one death due to mechlorethamine in 144 courses. However, Mrazek[34] noted two deaths and one serious hemorrhage in 68 courses. He noted the greatest depression of white blood count in patients who had received previous alkylating agent therapy or radiotherapy.

This leads to the question of which patients are more sensitive to mechlorethamine. In general, patients who have had extensive radiotherapy to marrow producing areas and chemotherapy within the previous six weeks are more sensitive. Patients with myelophthisis, lymphosarcoma, and chronic lymphocytic leukemia also tend to be more sensitive. These patients should be given smaller initial doses than usual.

Two quotations from the literature are pertinent to this point:

"Cautious adjustment of dosage is necessary in initiating (mechlorethamine) therapy in cases with leukopenia. An excellent

therapeutic result may be obtained in those patients with a toxic or hypersplenic depression of hemopoiesis. However in cases with extensive myelophthisis, especially in lymphosarcoma and acute or chronic leukemia, late toxic manifestations may develop which may be aggravated by nitrogen mustard or roentgen therapy."[15]

"If there is prior bone marrow injury or a primary hematological disturbance, ordinary doses may cause profound and prolonged marrow depression. This may be due in part to the impaired regenerative capacity of the diseased bone marrow."[11]

From the above, it can be seen that the usual dose of 0.4 mg/kg gives little trouble in the average patient. Dosage must be adjusted downward in those patients who might be expected to have a more sensitive marrow. In general, it is best not to administer the drug sooner than six weeks after the last course, no matter how well the blood and marrow have recovered.

In addition to the previously described marrow and gastrointestinal toxicity, there have been isolated reports of other systemic toxic effects. The Mustargen package insert mentions that "occasionally a maculopapular skin eruption has been observed." This brochure also mentions amenorrhea of several months' duration and impaired spermatogenesis.

Smith et al[35] have described five patients in whom a prolonged coagulation time developed at the same time as a severe leukopenia and thrombocytopenia. This prolonged coagulation time was correctible by protamine or toluidine blue, and thus presumed due to hyperheparinemia.

A number of reports of women receiving mechlorethamine during pregnancy have appeared.[36-39] The article by Smith et al[38] gives a valuable discussion of this problem as well as a review of the literature. They conclude that it is safe to give the agent during the second and third trimester. Several patients have had spontaneous abortions, but no fetal abnormalities have resulted in babies born to mothers given mechlorethamine in the first trimester of pregnancy. However, experimental studies in animals were so "overwhelming" that Smith et al[38] strongly advised against mechlorethamine therapy in the first trimester of pregnancy.

The local toxicity of mechlorethamine cannot be neglected. Extravasation of the solution into subcutaneous tissues results in a painful inflammation. Sloughing may occur. Thrombosis and thrombophlebitis rarely occur in the vein in which the drug was

injected. For this reason, care must be taken in patients with elevated arm vein pressure due to the superior mediastinal syndrome.

If there is leakage of the solution into subcutaneous tissue, prompt infiltration of the area with 1/6 molar sodium thiosulfate is advised. Such a solution can be prepared by dissolving 4.14 gm of sodium thiosulfate U.S.P. or 2.64 gm of anhydrous sodium thiosulfate in water to make a total volume of 100 cc.

If such a solution is not available, the package insert advises local injection of isotonic saline.

In summary, mechlorethamine (nitrogen mustard, mustargen) was the first alkylating agent clinically available. It is still the most useful chemotherapeutic agent in Hodgkin's disease. It is also used extensively for palliation of lung cancer, but has given far from dramatic results. Its intracavitary administration for control of malignant effusions is almost standard therapy, but based on anecdotal type of studies. The standard dosage is 0.4 mg/kg intravenously, and its major toxicity is on the bone marrow.

## Chlorambucil

Chlorambucil, known chemically as p-(di-2-chloroethyl) amino-phenyl-butyric acid, is commercially available as Leukeran® (Burroughs Wellcome & Co.) in 2 mg tablets. This agent has been used extensively in the lymphomas, and is considered the drug of choice in chronic lymphocytic leukemia (C.L.L.). More recently, it has been found so useful in ovarian carcinoma that it may replace triethylene thiophosphoramide as the alkylating agent of choice.

Chlorambucil has become one of the most useful of the alkylating agents because of its relative safety, wide spectrum of usefulness, and above all, because it is administered orally. Its reliability of absorption is so great that it has almost completely replaced the erratic triethylene melamine. Sudden appearance of toxicity, a hazard, with the latter drug, does not occur with chlorambucil when properly administered. The onset of action of chlorambucil is quite slow compared to mechlorethamine, cyclophosphamide, and triethylene thiophosphoramide. This property, a disadvantage in the sicker patient, makes chlorambucil a safer drug to administer. Lethal toxicity is almost unheard of

with chlorambucil, and it is probably the easiest of the alkylating agents to administer.

The relative safety of chlorambucil should not lead to overconfidence, since the potential for complete marrow suppression is present. Carelessness in its administration can lead to death. However, cessation of chlorambucil at the early stages of toxicity will almost always be rewarded by rapid marrow recovery. This statement only holds true if the daily dosage prior to toxicity was not excessive.

The main usefulness of chlorambucil has been in chronic lymphocytic leukemia (C.L.L.). Its effects in this disease are not so dramatic as those produced by busulfan in chronic myelogenous leukemia. Complete remission with chlorambucil is uncommon in C.L.L. Furthermore, the indications for use of the drug in C.L.L. are not always clear-cut. On the other hand, the indications for busulfan therapy are quite definite in chronic myelogenous leukemia, an elevated white blood count (the absolute level varying with the therapist) being sufficient indication.

In C.L.L. an elevated white blood count, per se, even to levels of 200,000 w.b.c./$mm^3$ is not an indication for therapy. Nor do lymphadenopathy or splenomegaly require treatment, unless these enlarged organs produce symptoms by local pressure effects. When enlarged nodes or spleen cause symptoms, local radiotherapy is usually the treatment of choice. Anemia in C.L.L. when due to hemolysis is best treated by steroids, and will rarely respond to alkylating agents. When anemia in C.L.L. is not due to hemolysis, its response to chlorambucil is quite variable with the majority of cases not having significant hemoglobin rise.[40-43] Thrombocytopenia in C.L.L. is also, more often than not, unresponsive to chlorambucil therapy. The best responses seem to be in that vague area of "clinical improvement." This is not meant to imply that objective change does not occur. Objective improvement occurs in over two-thirds of cases, but is usually not complete or dramatic.[41-46] As previously mentioned, improvement in anemia and thrombocytopenia is a less common objective change. The more frequent objective changes of shrinkage of lymphadenopathy and splenomegaly, and drop in peripheral lymphocyte count, are of less clinical importance. Duration of remission without maintenance therapy is over six months in over half the cases.[42] Only 2 of Galton's 43 cases had remissions over two years, and they were on maintenance therapy.[42]

Thus it can be seen that the decision to start a patient with C.L.L. on chlorambucil is often not clear-cut. It cannot be emphasized too often that elevated peripheral white blood count alone, no matter how high, is not sufficient reason for therapy. Anemia in C.L.L. must be investigated first as to mechanism. If appropriate tests indicate active hemolysis, corticosteroids are the treatment of choice, with 6-mercaptopurine reserved for severe hemolytic anemia unresponsive to steroid therapy.[47] If the low hemoglobin is not due to hemolysis, and is of sufficient degree to cause symptoms, anemia becomes an indication for chlorambucil therapy. Hemoglobin under 10.0 gm/100 cc is usually sufficient to institute therapy, although many patients with hemoglobin levels between 8.0 and 10.0 gm/100 cc do not require treatment. A platelet count below 100,000 may cause one to consider treatment; however, chlorambucil therapy will not often be rewarded by a rise in platelet count. It then comes down to the fact that the usual reason for institution of chlorambucil therapy is that the patient does not feel well. Weakness and fatigue, symptoms difficult to evaluate, are usually improved, often dramatically within several weeks of institution of chlorambucil.

Splenomegaly decreases significantly in 25 to 50% of courses, and lymphadenopathy decreases significantly in over 50% of courses. Almost all patients have a drop in absolute peripheral lymphocyte counts. In Galton's[42] series, the lymphocyte count fell to less than 20% of its initial value in 53 of 67 courses, and all but 3 courses resulted in a fall greater than 50%. However, almost all patients in their series continued to have abnormal total lymphocyte counts after completion of chlorambucil therapy.

Therefore, while the indications for chlorambucil therapy are not always clear in C.L.L., such therapy usually brings benefit, but rarely dramatic improvement.

From the fact that chlorambucil is the alkylating agent of choice in C.L.L. it can be assumed that it should be a useful drug in lymphosarcoma (L.S.A.). This has been borne out in the literature.[41,44-46,48] Many authors feel that L.S.A., with the basic cell the small lymphocyte, is the same disease as C.L.L. The farther the basic cell in L.S.A. varies from the small mature lymphocyte, the less the disease corresponds to C.L.L.

It should be noted that the reported experience with chlorambucil in L.S.A. is less than in C.L.L. Radiotherapy to local tumor

deposits is more often indicated in L.S.A. than in C.L.L. Anemia and systemic symptoms are the common indications for chlorambucil therapy in L.S.A.

Without maintenance therapy, remissions probably average four to six months.[41,45] As in C.L.L., lymphadenopathy and splenomegaly often respond significantly. Improvement of anemia is less common. Objective improvement occurs in approximately two-thirds of cases, but is not always accompanied by subjective benefit.

Reticulum cell sarcoma responds to chlorambucil in a fairly high proportion of cases, but benefit is so short-lived that it is often not of much help. It is probable that cyclophosphamide is a more useful drug in this disease.

The usefulness of chlorambucil in Hodgkin's disease is more controversial than in the above conditions. Most authors would agree that mechlorethamine is the preferred drug in Hodgkin's disease because of its rapidity of action and the greater degree of improvement produced. (Because of the greater degree of sensitivity of the small lymphocyte to alkylating agents, mechlorethamine is considered more hazardous than chlorambucil in C.L.L. and L.S.A.)

However, Miller,[41] who noted 11 marked and 8 moderate objective responses in 32 patients with measurable Hodgkin's disease, concluded that chlorambucil was equally as effective as mechlorethamine in this disease. Doan et al[46] noted response in 32 of 47 patients, many of whom were unsuccessful with mechlorethamine and triethylene melamine. Doan[46] used a rather large dosage of 0.3 mg/kg/day. Galton[48] and Ultmann[44] had far less favorable results in Hodgkin's disease.

Doan[46] noted decrease of fever within 3 to 12 days of onset of chlorambucil therapy. Normal size of enlarged liver, spleen and lymph nodes was achieved in six weeks. Miller,[41] using 0.2 mg/kg/day found that it took an average of 77 days to achieve maximum response. In his 33 patients, 6 had a rise of hemoglobin greater than 2 gm/100 cc. Twenty of these patients had complete subjective improvement.

One study[33] has shown that chlorambucil maintenance therapy will significantly prolong mechlorethamine-induced remissions in Hodgkin's disease. In this study, the patients treated with a single course of mechlorethamine without maintenance treatment relapsed in an average of 11.7 weeks, but those placed on chlor-

ambucil 0.2 mg/kg/day after the initial course of mechlorethamine had remissions averaging 35.6 weeks. Chlorambucil was started as soon as white blood and platelet counts rose to normal after the mechlorethamine-induced drop. In half the chlorambucil maintenance patients, the dosage of 0.2 mg/kg/day had to be lowered.

Despite this impressive study, it is not widely accepted that chlorambucil maintenance should be used after mechlorethamine therapy in Hodgkin's disease. Most physicians would prefer to use a second course of mechlorethamine when the patient had relapsed to a significant extent.

One of the most important uses of chlorambucil is in the treatment of ovarian carcinoma. Only a small percentage of patients with ovarian cancer are cured by surgery. Radiotherapy is useful mainly in disease confined to the pelvis, although there have been some good results with "strip" radiotherapy to the whole abdomen.

Because of the limitations of surgery and radiotherapy in ovarian carcinoma, there is great need for effective chemotherapeutic agents. Triethylene thiophosphoramide has been used most widely, with objective remission in about 40% of cases. However, the published studies[49-51] and personal experience indicate that chlorambucil is just as effective. It is a safer agent because of the more gradual onset of toxicity, and its oral administration is preferred by the patients.

Masterson et al[49] treated 30 patients with advanced ovarian carcinoma with chlorambucil in a dosage of 0.2 to 0.4 mg/kg/day for four weeks. Excellent response, as defined by complete disappearance of all palpable tumor, ascites, and symptoms, occurred in 6 cases, while good response (considerable decrease in tumor size and major resolution of symptoms) occurred in 8 patients. The authors concluded that the 0.2 mg/kg/day dosage was just as effective as the higher dosage. Maintenance therapy was not given, and it was not known how long optimum improvement would last. Coonrad and Rundles[50] used triethylene melamine, mechlorethamine, or chlorambucil and produced remissions lasting from 4 months to 6 years. Galton[52] noted remissions in 26/72 patients with advanced ovarian carcinoma.

Parker and Shingleton[51] find chlorambucil the drug of choice in ovarian carcinoma because of its effectiveness, predictability, oral dosage, and low incidence of gastrointestinal side effects. These authors treated 95 patients with a variety of alkylating agents (mechlorethamine, chlorambucil, cyclophosphamide, tri-

ethylene melamine, and triethylene thiophosphoramide). Their overall results were 40 cases with good palliation for over six months out of 82 evaluable patients. Criteria for "palliation" were not as rigid as in some other studies, so that it is not certain that all patients had objective remissions. Four patients survived over five years after chemotherapy was started. Parker and Shingleton[51] attempted to keep the white blood count below 3,000 and continued chemotherapy as long as effective palliation continued. In general, they found that these patients who did not respond to radiotherapy did not respond well to chemotherapy. Only one patient in the series died from the chemotherapy.

I have preferred to maintain the patients on enough chlorambucil to keep the white blood count below 4,000. No statistical evidence is available to show that this is preferable to repeating short courses of chlorambucil at each relapse. In the discussion of dosage which follows later, the technique of maintenance chlorambucil therapy will be included. The necessity of watching the platelet count as well as the white blood count will be emphasized.

A further use of chlorambucil is in Waldenstrom's macroglobulinemia. The Mayo Clinic[53] has reported 9 patients treated with long-term chlorambucil therapy. All patients responded, and none of the six given continuous therapy have relapsed. One patient has been treated for five years. Hemoglobin rose to near normal values, and macroglobulins decreased significantly, although exact data are not supplied in the article. The initial dose was 12 mg daily, with maintenance dose varying from 2 to 8 mg daily.

Chlorambucil has also been used in the treatment of breast carcinoma. Remissions occur in a small percentage of cases. However, Freckman et al[54] reported objective remissions lasting 6 to 40 months in 33.8% of 71 patients using a combination of prednisolone and 14 to 20 mg of chlorambucil daily.

Chlorambucil is supplied in 2 mg tablets. The total daily dose is given orally at one time. The dosage varies with the condition being treated, and the state of the patient's marrow. As with all alkylating agents and almost all anticancer agents, dosage should be lower in patients who have had extensive or recent radiotherapy or recent previous cancer chemotherapy.

Patients with chronic lymphatic leukemia (C.L.L.) or lymphosarcoma (L.S.A.) are more sensitive to chlorambucil and are more

subject to its bone marrow toxicity.[41,46,48] Initial dosage as high as 0.2 mg/kg can be given safely to these patients if they are watched closely. At this dosage the patient should have twice-weekly blood counts until the dosage is lowered. As will be seen below, this frequent follow-up is not necessary in most patients with Hodgkin's disease or ovarian carcinoma. If the patient's condition is such that rapid improvement is not necessary, it is probably better to start with a dosage of 0.1 to 0.15 mg/kg. The blood count can then be followed weekly. Quantitative platelet counts are also necessary, as many patients with C.L.L. or L.S.A. have low platelet counts.

The question of maintenance therapy with chlorambucil in C.L.L. and L.S.A. is far from settled. Miller et al[41] felt that it was helpful in C.L.L. and possibly in L.S.A. but not in Hodgkin's disease, chronic myelogenous leukemia, and reticulum cell sarcoma. Ultmann[44] and Doan[46] used maintenance therapy, but Galton[42] preferred to retreat when relapse occurred. However, a few of their patients received prolonged therapy because of progressive improvement without appearance of toxicity. Maintenance dosage varies from as little as 4 mg/week to 6 mg/day. Lower dosages prevail in patients with C.L.L. and L.S.A.

In ovarian carcinoma, and the Hodgkin's disease patient with good marrow function, the starting dosage should be 0.2 mg/kg/day. Again the question of maintenance dosage is unsettled. In ovarian carcinoma, because of apparent better results with small tumor masses, I prefer maintenance therapy in those patients who have remissions. This is not supported (or contradicted) by any published studies.

This initial dose of 0.2 mg/kg/day should be lowered as the white blood count or platelet count falls significantly. The rate of fall is important as well as the absolute level of white blood count or platelet count. As a general rule, either a drop of 50% in an initially elevated white blood count or a total white blood count of below 5,000 should cause one to either temporarily stop or significantly lower chlorambucil dosage when treating ovarian carcinoma or Hodgkin's disease. For example, an ovarian carcinoma patient with an initial white blood count of 10,000/mm$^3$ is started on 12 mg chlorambucil daily. In four weeks the white blood count has fallen to 5,000. At this point, dosage should be lowered to 6 mg/day and lowered even further when the white blood count reaches 4,000. It may be anywhere from 2 to more

than 8 weeks before the starting dose is changed. Weekly white blood counts and hemoglobins or hematocrits, as well as estimation of platelet counts from stained peripheral blood smears are imperative.

In the following discussion of chlorambucil toxicity, it will be apparent that the above dose regimen must be modified in certain patients whose marrow may be more sensitive. The conditions that make the marrow sensitive will be discussed.

The major toxicity of chlorambucil is bone marrow depression. Granulocytes, platelets, and red cells have all been affected. Irreversible marrow toxicity is rare if proper precautions are followed. The granulocyte count is usually depressed by therapeutic courses of chlorambucil. Most patients will have the maximum drop within ten days of discontinuing therapy although rare patients have continued to have drops in the peripheral granulocyte count for as long as eight weeks.[42]

This depression of granulocyte count is usually rapidly reversible. However, death from infection can occur during the course of the white blood count depression. Galton,[42] in his series of 50 patients with C.L.L., had 7 cases in whom neutropenia was accompanied by and may have led to serious complications. In this series, 30 patients had falls in neutrophil counts below 1,000/mm$^3$ and 20 patients fell below 500/mm$^3$. In a previous report of 62 patients with various lymphomas, Galton[48] had 11 patients who developed total peripheral white blood counts below 1,000. Five recovered rapidly, but the others were in the terminal stage of disease and the neutropenia persisted until death. Doan[46] found marrow depressant effect to be moderate and readily reversible in most cases, even in patients with hypoplastic marrow before therapy. Altman[40] noted a white blood count rise in all eight of his patients with C.L.L. as soon as the drug was stopped.

If chlorambucil dosage is lowered as toxicity is approached, and stopped when total white blood count is still above 15,000 in patients with C.L.L., and above 4,000 in patients with L.S.A., Hodgkin's disease, and ovarian carcinoma, the very low neutrophil counts noted by Galton should usually be avoided. Lower white blood counts than the above limits (15,000 in C.L.L. and 4,000 in the other conditions) can be achieved by reinstitution of lower dosage therapy after maximum fall has occurred. This technique of cautious titration has been most useful in ovarian carcinoma, where patients can be safely maintained with total

white blood counts of 3,000 to 4,000/mm$^3$. Blood counts should be performed every two weeks, once the maintenance dose has been determined.

The Burroughs-Wellcome literature stresses data from Galton's article[42] in which he states that all but one patient with severe neutropenia received a total dose of 6.5 mg/kg or more in one course. Galton noted severe neutropenia in ¼ of patients receiving more than 6.5 mg/kg, and this figure rose to ⅓, if this total dose was given in less than eight weeks.

These rules are only approximate guide lines, since the patients with C.L.L. and L.S.A. are so much more susceptible to white blood count depression than most other types of patients who receive chlorambucil.

Platelet count depression has been somewhat less troublesome than neutropenia. Galton et al[48] in their series of 62 patients with various lymphomas, had 11 patients with platelet counts below 100,000/mm$^3$ prior to chlorambucil therapy. Yet only two of these had further platelet depression while on chlorambucil. In a later article, where treatment of C.L.L. only was discussed, Galton[42] noted platelet counts below 50,000/mm$^3$ in 11 of 83 courses of chlorambucil; 6 of these patients had platelet counts below 100,000/mm$^3$ before start of therapy. Two of 7 patients with platelet counts below 100,000/mm$^3$ before therapy had a rise above 100,000/mm$^3$ while on chlorambucil. In this group with C.L.L., the decrease in platelets was almost always transient and never serious when therapy was stopped. Miller[41] noted platelet count drop in 7 of 38 patients with Hodgkin's disease. In 3 patients with C.L.L. low platelet counts rose while on chlorambucil. In 6 others with initially low or borderline platelet counts, the platelet counts were further depressed or not affected by therapy. Masterson[49] treated 30 patients with ovarian carcinoma. Two of these developed platelet counts below 100,000. Ultmann[44] stated that he treated 14 initially thrombocytopenic C.L.L. patients with chlorambucil. He found that the thrombocytopenia presented no problem in the therapy.

Depression of the red blood cells is uncommon with chlorambucil. This may be partially due to the longer life span of the red blood cell. Galton[42] noted significant hemoglobin drop in 6 out of 83 courses of chlorambucil in patients with C.L.L. However, he concluded that one of these was due to development of a hemolytic anemia responsive to steroids, and in the other 5 pa-

tients, anemia was due to infection and not the chlorambucil. Miller[41] noted a drop in hemoglobin in 1 of 38 patients with Hodgkin's disease and 5 of 19 patients with C.L.L. treated with chlorambucil.

Certain situations predispose to marrow toxicity. Galton et al[48] discuss this problem in some detail. They noted that "in the lymphoma group most patients who developed severe neutropenia had infiltration of the bone marrow, but others who tolerated the drug (chlorambucil) well had similar infiltration." The patient with such infiltration did have a greater chance of developing marrow toxicity.

They concluded that the following circumstances made the marrow more vulnerable to chlorambucil:

1. Shortly after radiotherapy or cytotoxic drugs had been administered.
2. When the marrow is infiltrated with lymphomatous tissue. This would explain the greater sensitivity of the patients with C.L.L.
3. When the marrow is hypoplastic as a result of long-standing and usually extensively treated disease.

These authors also stated that patients with Hodgkin's disease with marrow fibrosis are not suitable for chlorambucil treatment. They also advised that chlorambucil should not be given within four weeks of the end of a full course of chemotherapy or radiotherapy. Radiotherapy confined to small fields not involving the bone marrow did not mean that therapy had to be delayed for this four week period.

Miller et al[41] also advised lower initial dosage (0.1 mg/kg/day) in patients with C.L.L., myelophthisis, or previous treatment, because of this increased marrow sensitivity. Bouroncle et al[55] also noted that the effect of chlorambucil on the marrow was greater after radiotherapy or previous cytotoxic drugs.

Toxicity other than marrow depression presents little problem. A few patients will have nausea or epigastric burning. Vomiting is rare. Liver damage has been suggested to be a rare form of toxicity.[56,57] In Koler's[56] case it was almost certainly an allergic reaction. Ambronin et al[57] reported three cases where there was strong evidence that chlorambucil had produced liver damage. He also noted three other patients where there was suggestive evidence that chlorambucil was the cause of liver damage. Ultmann[44] reports one patient with lymphosarcoma who developed

transient anuria from uric acid nephropathy. This patient was dehydrated.

Chlorambucil when given as the sole anticancer drug to pregnant women has not resulted in fetal damage.[46,58]

Wolfson et al[59] report an interesting case of a 2½ year old child who accidentally ingested 70 mg of chlorambucil at one time. Convulsions and coma lasting one day and temporary depression of peripheral blood lymphocytes and neutrophils resulted. No permanent damage occurred.

In summary, chlorambucil is the most versatile and safest of all the alkylating agents. It is the drug of choice in chronic lymphocytic leukemia and probably in ovarian carcinoma. It is also of some value in Waldenstrom's macroglobulinemia, breast cancer, and Hodgkin's disease. The average initial dosage in chronic lymphocytic leukemia, lymphosarcoma, and patients with depressed marrow is 0.1 to 0.15 mg/kg/day orally. Higher initial dosage can be used in Hodgkin's disease and carcinoma patients without depressed marrow. The major toxicity is bone marrow depression, and this is usually readily reversible.

## Busulfan

Of all the alkylating agents, busulfan is the one whose use and indications are best defined. The only condition in which it is useful is chronic granulocytic leukemia (C.G.L.), and for this disease it is the best drug available.

Busulfan (1,4-dimethanesulfonoxybutane) is available as Myleran® (Burroughs-Wellcome & Co.) in 2 mg scored tablets. It is very insoluble in cold water, making it impractical to prepare a parenteral form.

At present, busulfan and radiotherapy have approximately equal status as the method of choice in the treatment of C.G.L. Either method may be used when the patient becomes refractory to the other. Refractoriness to busulfan is uncommon in C.G.L. and often, but not always, heralds the onset of acute blastic crisis. This complication which is the usual terminal event in C.G.L. is relatively refractory to all methods of therapy. However, some patients with blastic crisis have had temporary responses to 6-mercaptopurine.

As has been stated, refractoriness to busulfan is uncommon. Almost all patients with C.G.L. not in the blastic phase respond

to this drug. There are numerous published series which bear this out. Some of the larger series are listed in the bibliography.[60-69]

Haut et al[69] found only 1 of 30 patients resistant to the first course; a second patient became partially refractory to the second course. All other patients who became refractory did so suddenly and completely, coincident with onset of the "acute phase." This was defined as 20% or more of the peripheral white blood count consisting of blasts or promyelocytes. This coincides with what other authors call "blastic crisis." Louis, Limarzi and Best[61] noted response in 100% of 24 patients, and Unugur et al[63] had a response in all 35 patients treated.

While there may be strong advocates of either mode of therapy, there is no great advantage of splenic radiotherapy over busulfan or vice versa in the treatment of C.G.L. The choice is generally made by what is most convenient for the patient and doctor. The danger of severe marrow depression is less with radiotherapy, but in experienced hands this danger is minimal with busulfan. Radiotherapy has the disadvantages of expense, and eventual maximal tolerated dose.

While busulfan is clearly the drug of choice for C.G.L., other drugs have been used and may occasionally replace busulfan. Rundles et al[70] compared busulfan and chlorambucil (Leukeran) over a 12 week period. They found busulfan gave a good response in 21 of 21 patients, but chlorambucil gave such a response in only 12 of 21. However, they did feel that higher doses of chlorambucil than the 12 mg a day used might have produced better results. Chlorambucil was also less toxic to the platelets, so it was suggested that this drug might be useful in cases where platelet toxicity prevented the use of busulfan. I have found no published evidence of this use of chlorambucil in cases where busulfan was discarded because of platelet depression. However, there is ample documentation both in animal and human studies[70-72] that busulfan specifically depresses production of granulocytes and platelets without effecting lymphocyte production, while the effect of chlorambucil on lymphocyte production is greater than its marrow depressant action.

Another drug that has been compared with busulfan in C.G.L. is 6-mercaptopurine. Shullenberger[73] found the two drugs equally useful, although the degree of control fluctuated less with busulfan. The Southeastern Cancer Chemotherapy Cooperative Study Group[74] found in a 12 week study that 89% of patients treated

with busulfan had a good response while only 33% treated with 6-mercaptopurine had a good response. The latter drug was harder to control because of fluctuation of the white blood count. However, there was little platelet depressant action of 6-mercaptopurine, so it was suggested that it might be the preferred drug in patients with initially low platelet counts.

Bethell[75] has found triethylene melamine, an alkylating agent, equal to busulfan as a treatment for C.G.L. However, this drug has largely been discarded because of uncertainty of absorption.

After initial uncertainty as to dosage, and experimentation with higher dosage regimens, most authors now recommend starting with 4 to 6 mg of busulfan daily until the white blood count is almost to therapeutic level, and then lowering dosage until a white blood count below 10,000 is obtained. There is still no general agreement as to whether maintenance dosage is better than repeated courses instituted at each relapse. This will be discussed below.

Busulfan therapy is very easy to control, as there is little or no further drop in the white blood count after the drug is stopped. Because of this, it is simple to titrate dosage and obtain white blood counts between 5,000 and 10,000. It is considered desirable to lower the blood count in this range, because remissions are prolonged when this is done.[63,64,66,69] This point is brought out very well by Haut et al.[69] These authors did not use maintenance therapy. They found that if the white blood count was brought below 10,000, 54% of 61 patients had remissions of six months or more. In 15 patients who had final white blood counts between 10,000 and 12,000, 33% had remissions lasting six months or more, and only 19% of 16 patients with final white blood counts of 12,000 to 25,000 had remissions over six months.

The starting dose of busulfan is 6 mg daily. If the platelet count is low, the white blood count under 50,000, or the patient weighs less than 120 pounds, a starting dose of 4 mg daily might be safer. Almost all patients will achieve desired white blood counts on this dosage within three months. White blood counts, platelet estimations (examination of stained smears will suffice as long as normal or excess platelets are present), and hemoglobin determinations should be done weekly. If the response is not unusually rapid within the first three weeks, this interval can be increased to every two weeks until the white blood count reaches 25,000. When the white blood count reaches approximately

15,000, the dosage should be lowered to 4 mg daily and when the white blood count falls below 10,000 the dosage should be lowered to 2 mg daily. When the white blood count reaches 5,000 to 7,000 the drug should be stopped. If maintenance therapy is desired, 2 mg/day should be instituted as soon as the white blood count rises over 10,000. This dosage should be adjusted to maintain normal white blood counts, and may be as little as 2 mg/week or as much as 4 mg/day.

Those who do not use maintenance therapy reinstitute busulfan in the 4 to 6 mg/day dosage when the white blood count rises to 25,000 to 50,000, or symptoms recur at a lower white blood count.

Maintenance dosage must be carefully individualized and usually varies between 2 mg twice a week to 4 mg a day. Once the dosage is regulated, blood counts may be done once every two to four weeks. The white blood count should be kept between 5,000 and 10,000. Platelet depression must be watched for by examination of the stained blood smear, and quantitative platelet counts should be done in patients with low or borderline numbers of platelet on smear.

Platelet count depression will be discussed later in this section. At this point it can be said that lowering of platelet count below 100,000, if due to the drug, is reason for stopping busulfan. If the platelet count is low prior to the start of busulfan therapy, it may be possible to continue the drug. This will be discussed in detail, as it may be quite important in a small percentage of patients with C.G.L.

Although the usual practice is to use maintenance therapy, there is little discussion in the literature of whether maintenance therapy is superior to repeated courses. In this latter method, busulfan is resumed in full dosage when symptoms recur, or the white blood count reaches an arbitrary level, usually around 30,000.

One author who discusses this problem in some detail is Galton.[60] He lists the advantages of maintenance therapy as: maintenance of high hemoglobin levels, good health, and sense of well-being for long periods. He found maintenance therapy was often successful after the remissions following interrupted courses had become short-lived. He felt that the one disadvantage of maintenance therapy was that resistance eventually developed. This point, however, was not well documented. Another disadvan-

tage of maintenance therapy is a greater incidence of toxicity other than marrow depression.

The response to busulfan starts within one to two weeks. The initial response is subjective improvement (improved appetite, sense of well-being, disappearance of night sweats, and improved strength). This occurs regularly in almost every case, so that there is no question of it being a placebo effect. Coincidentally with this subjective improvement, there is a decrease in the number of immature white cells in the peripheral blood and initial drop in the total white blood count.

Depending somewhat on the dosage and initial height of the white blood count, most patients have achieved normal white blood counts in two to three months. The hemoglobin starts to rise in the second or third week of therapy. Haut et al[69] found that the hemoglobin rise was greatest in those patients who were most anemic prior to therapy. They found hemoglobin continuing to rise even after the white blood count had reached normal levels. However, Unugur et al[63] found the hemoglobin peak reached in five weeks.

Splenomegaly responds less dramatically. Haut et al[69] found that in only 15% of patients did the spleen become impalpable. However, in most of the others the spleen size decreased more than 50%. These authors did not use maintenance therapy and did find further decrease in splenic size with subsequent courses of busulfan. Unugur et al[63] found disappearance of palpable splenomegaly in 16 of 35 patients, a somewhat higher figure than Haut's group. In Haut's series,[69] 5 of the 30 patients had lymphadenopathy. In none of these patients did lymphadenopathy respond to busulfan therapy.

In complete remission induced by busulfan not only the white blood count, but the differential, returns to normal. The bone marrow also will return to normal. Xeftoris[76] has shown that in prolonged complete remission with busulfan, the leukocyte alkaline phosphatase usually returns to normal levels.

Toxicity of busulfan is usually minimal. The most prominent is bone marrow depression, but several other interesting and bizarre forms of toxicity have occurred. Kyle et al[77] have reviewed the toxicity of busulfan in great detail. They list the following types of toxic reactions: Amenorrhea, skin hyperpigmentation, gastrointestinal reactions, hyperuricemia, testicular atrophy, gynecomastia and interstitial pulmonary fibrosis. In ad-

dition, these authors describe a syndrome resembling adrenal insufficiency which occurred in four patients after protracted therapy (1 to 5 years, total dose 820-5710 mg). This syndrome occurred in three patients while in remission, and one other just prior to appearance of a blastic crisis. It was characterized by hyperpigmentation of the skin, severe weakness, fatigue, anorexia, and weight loss. Laboratory tests excluded adrenal insufficiency. Smalley and Wall[78] also discuss other patients with this syndrome.

The bone marrow toxicity is a natural outgrowth of busulfan's suppressive effect on the production of granulocyte and platelets. Fortunately, platelet suppression to dangerous levels usually does not accompany therapeutic doses of busulfan. This complication as well as agranulocytosis is an ever present potential danger, but thrombocytopenia necessitating cessation of busulfan therapy occurs in less than 10% of cases. To give some idea of the degree of this problem, Haut et al[69] noted that in 11 courses of busulfan given to 5 initially thrombocytopenic patients, only three courses had to be stopped. In three patients, platelets actually increased to normal levels while on the drug. However, in a total of 30 patients receiving 114 courses of busulfan, thrombocytopenia was present on 16 occasions. This figure includes the five occasions when patients had thrombocytopenia before the drug was started or between courses. (Haut's group did not use maintenance therapy.)

Unugur[63] noted thrombocytopenia in 2 of 35 patients on busulfan. However, a far higher figure was noted by Wilkinson,[67] who used an initial dose of 25 mg of busulfan daily. He later discarded this high dosage, which is definitely a dangerous one, and noted bone marrow toxicity in only 2 of 34 patients treated with 2 to 6 mg daily.

Thrombocytopenia due to busulfan or occurring in the course of untreated C.G.L. can be a serious matter. Haut et al[69] noted hemorrhagic phenomena in 14 of 16 patients who were thrombocytopenic. This included cerebral hemorrhage. Severe thrombocytopenia was not always necessary for the development of hemorrhagic complications. One patient with 116,000 platelets/$mm^3$ had purpura, and a cerebral hemorrhage occurred in a patient with 109,000 platelets/$mm^3$. This implies a qualitative platelet defect.

Agranulocytosis has been a very uncommon complication and usually means hypersensitivity to the drug, or excessive dosage.

This complication occurred more frequently with high dosage regimens, now discarded.[67,78] However, hypersensitivity with sudden drop of white blood count to extremely low levels has occurred. Greig[62] described one patient in whom agranulocytosis developed 48 hours after a 4 mg dose of busulfan. This patient had a previous course of busulfan which had been stopped three months previously. Unugur et al[63] describe a similar, but less dramatic case. This patient who became pancytopenic after five months on 2 mg of busulfan daily was restarted on 2 mg daily after an interval of 19 months. The white blood count at the start of this repeat course was 30,000. Fifteen days after the start of this course "striking thrombocytopenia" occurred. Louis et al[61] used 8 to 10 mg/day in patients with initial white blood counts over 100,000 and lower doses in patients with lower blood counts. This is slightly higher than the presently recommended doses. Three of their 24 patients had precipitous drops in white blood counts after one week of treatment. One of these patients had a drop of 94% of the initial white blood count. These may represent patients with hypersensitivity to the drug.

Aplastic anemia was described in two of Wilkinson's[67] very high dosage patients.

To summarize the all important subject of bone marrow toxicity: Aplastic anemia should be a rare complication on usual dosages. Agranulocytosis may occur uncommonly as a sudden hypersensitivity reaction, or, if white blood counts are not taken frequently enough, agranulocytosis may appear gradually during initial or maintenance therapy. For this reason, weekly white blood counts are recommended at the onset of therapy. The interval between blood counts should probably never exceed two weeks while on busulfan therapy. Platelet counts should be followed at the same intervals. Qualitative estimate from stained smear will suffice unless platelet counts are low. Quantitative platelet counts should be done from time to time in all patients, since it is important to know if thrombocytosis, with its attendant dangers of hemorrhagic or thrombotic complications, is present. Initial thrombocytopenia is not a reason for lower dosage. In such patients accurate quantitative platelet counts every two to three days are important. Significant drop of an initially low platelet count should be the signal to stop the drug. Thrombocytopenia below 100,000 developing in a patient with initially normal or elevated platelet counts is another reason to stop busulfan.

Toxicity other than marrow depression has been previously mentioned. The syndrome resembling adrenal insufficiency was described above. Some discussion of other less important toxicity is in order at this point. Nausea is mild and uncommon; hyperpigmentation of the skin after prolonged therapy has been reported in small numbers of patients.[62,65,67,69,77] Amenorrhea occurs in most menstruating women on busulfan.[62,63,65,67] This is often accompanied by flushes and other menopausal symptoms. Mild gynecomastia in men has occurred occasionally.[65,77]

One group[79] has reported two patients who developed pulmonary fibrosis while on busulfan for treatment of C.G.L. Lung biopsy revealed diffuse interstitial fibrosis, and chest x-ray showed diffuse bilateral parenchymal infiltrates. One of the lung biopsies showed proliferative vasculitis in addition to the fibrosis. This patient's pulmonary infiltrates responded rapidly to steroids. It has been suggested that busulfan is a potential carcinogen in humans. This is based on the fact that several patients developed atypical large cells in many tissues while on long term busulfan therapy.[80] One of these patients died of breast cancer.

The final point in the discussion of busulfan toxicity is its potential toxicity to the fetus when taken by the pregnant woman. Reyes and Perez[84] review the literature on this subject and present one case of their own. Although the child born to the mother in their report died in the fifth week of staphylococcal infection, they felt there was no relation to busulfan. They found three other cases in the literature where normal babies were born to mothers on busulfan. A fifth child was born malformed but the mother also received radiation and 6-mercaptopurine therapy. White[85] reported a sixth case, also with no adverse effect on the fetus. Other single cases have been reported by Neu,[79] Dennis[80] and Smalley and Wall.[78] No ill effects to the fetus were reported in these three instances. As far as I know, these are the only case reports relating to this problem.

In summary, busulfan is an extremely useful agent in the treatment of chronic granulocytic leukemia (C.G.L.) rivaling radiotherapy as the treatment of choice. It is effective in over 85% of cases in an initial dosage of 4 to 6 mg daily. Most authors recommend maintenance therapy. Symptomatic improvement is almost immediate, and a normal white blood count is achieved in almost all cases by three months. It is best to bring the white blood count below 10,000. The major toxicity is on the bone

marrow, with thrombocytopenia being an occasional limiting factor. Refractoriness to busulfan often, but not always, means the onset of the blastic phase of C.G.L.

### Triethylene Thiophosphoramide

Triethylene Thiophosphoramide (TSPA) is commercially available as Thio TEPA® (Lederle). Its chemical name is tris (1-aziridinyl) phosphine sulfide. It is probably the most widely used cancer chemotherapeutic agent in office practice. There are several reasons for its wide acceptance by the physician outside the hospital. First, it has been available commercially longer than most other agents. Second, it is easy to administer to outpatients, usually being given directly intravenously at weekly intervals. Third, the side effects other than marrow depression are minimal, and fourth, the dosage is easily regulated by following the white blood count.

Triethylene thiophosphoramide is a very useful agent in several conditions. However, it is my opinion that its widest use has been for many solid tumors where there is little rationale for this application. The very ease of administration and relative safety have led to this overuse. It is difficult to condemn its administration in conditions where no other agent is available, and where isolated responses may be expected. Often the decision is one that the individual doctor must take after weighing the alternatives of no therapy, or other more toxic and possibly no more effective agents.

The main usefulness of TSPA is against ovarian carcinoma.[86-91] Remission rates of over 60% have been reported, some of these remissions lasting from many months to years. The median duration of remission seems to be 6 to 12 months. Objective criteria include disappearance or marked diminution in size of tumor masses, prevention of recurrent pleural or peritoneal effusions, or less significant, increase in interval between recurrent paracenteses or thoracenteses.

When tumor masses without effusion are present, intravenous therapy is best. Some authors recommend intracavitary administration when effusions are the problem. This will be discussed later in this section.

The only serious rival to TSPA in ovarian carcinoma is chlorambucil (Leukeran) although cyclophosphamide (Cytoxan)

may be equally useful (see the section on cyclophosphamide in this chapter). As will be discussed in the section on this drug, chlorambucil has the advantage of oral administration. TSPA is effective against all forms of ovarian carcinoma. However, there is some evidence that the papillary cystadenocarcinomas and highly anaplastic carcinomas are more likely to respond.[88]

The next most widely accepted use for TSPA has been intracavitary administration for control of malignant effusions.[87,91-93] This has been more effective for pleural effusions than for ascites, and has given the best results in ovarian and breast carcinoma. Effectiveness in these conditions is probably over 50%. However, second and third injections may be necessary at suitable intervals. The technique of intracavitary injections will be discussed below.

TSPA has one advantage over mechlorethamine for intracavitary injection. This is the fact that it is non-irritating, and there are no reactions to its use other than the bone marrow depressant action. However, the irritant action of mechlorethamine may result in an obliterative pleuritis which acts to prevent pleural fluid formation even if no specific antitumor action occurs. I would prefer TSPA in breast and ovarian carcinoma pleural effusions in severely ill patients. Mechlorethamine would be preferred in pleural effusions due to lung carcinoma or solid tumors usually resistant to alkylating agents, especially if the general condition of the patient was good. There is as yet no statistical evidence that intrapleural TSPA is more effective than intravenous therapy for malignant effusions.

The place of TSPA in the treatment of breast cancer is more controversial than its previously described indications (ovarian carcinoma and malignant effusions). Despite several very favorable reports,[92,94-96] most authors would favor using TSPA only after hormonal therapy had failed. In favorable patients, adrenalectomy or hypophysectomy would also be preferred first. Despite Bateman's report that two-thirds of her patients had objective remissions, the well-controlled studies of Sears,[97] Moore,[98] and Zubrod,[99] with remission rates of 10 to 36%, are closer to the generally accepted estimate of effectiveness of alkylating agents in breast carcinoma.

Despite the general acceptance of the fact that TSPA will give a low incidence of remissions in breast carcinoma, occasional spectacular and long lasting remissions make this the

drug of choice in cases no longer responding to hormones or surgical endocrine ablation. Bateman's work[91] suggests that this agent may be especially useful in the control of local recurrence or large breast masses which are technically inoperable (vide infra).

There are several other promising but still experimental areas for treatment with TSPA. One of these is its local instillation into the urinary bladder in bladder carcinoma.[100,101] There is no doubt that objective remission, and even complete disappearance of bladder carcinoma, can occur with this agent. Superficial tumors respond best, especially when they are less than 0.5 cm in size.[101] Jones et al[101] estimated that approximately one-third of the medication instilled into the bladder was absorbed systemically. These authors reported excellent responses in 8 of 13 patients, with partial response in three others. Two of the patients with excellent responses needed second courses for recurrence.

There are many questions still to be answered about the use of TSPA for local treatment of bladder carcinoma. Will any patients have permanent cure? Will repeated courses give permanent control? What is the role of this agent in making large bulky tumors locally resectable? What is the role of combined radiotherapy and chemotherapy?

At present, this use of TSPA had best be reserved for the urologist as an adjunct to, rather than a replacement for, surgical treatment.

TSPA, by arterial perfusion, has been useful as an adjunct to surgery and for palliation of malignant melanoma of the extremities.[102] However, melphalan seems to be the preferred agent. Perfusion for melanoma is still a technique reserved for the few centers equipped to carry out this treatment.

Isolated responses have occurred in other tumors. Enthusiastic reports of intratumoral injection for carcinoma of the prostate[103] and intracarotid injection for brain metastases from breast carcinoma[104] so far have not been duplicated by other authors.

TSPA, although showing antitumor effect in Hodgkin's disease, chronic lymphatic leukemia, lymphosarcoma, and chronic myelogenous leukemia,[88,99,105] has not been used extensively in these conditions. Mechlorethamine or cyclophosphamide are preferred for Hodgkin's disease; chlorambucil, for chronic lymphatic leukemia, and lymphosarcoma; and busulfan for chronic myelogenous leukemia.

The use of systemic TSPA at the time of surgery and for several days thereafter to prevent recurrence of carcinoma is still being investigated.[106-108] This technique has not proved useful in lung, gastric, or colon and rectum carcinoma. However, in breast carcinoma there has been a statistically significant decrease in recurrences in the treated over the control group.[106] Two dosage regimens were used. The high dosage regimen used in 58 patients gave better results in prevention of recurrence, but gave an increased incidence of postoperative complications. This regimen involved giving 0.2 mg/kg of the agent intravenously on the day of surgery and on each of the three succeeding days for a total of 0.8 mg/kg. The low dosage regimen is identical except that no medication is given on the third postoperative day, for a total dose of 0.6 mg/kg. This latter regimen when used in 329 patients gave better results than the control group. At 21 months there was 14% recurrence in the treated group and 20% recurrence in the control group.[106] The latter regimen gave no higher incidence of postoperative complications than in the control group. However, additional studies will have to be carried out before this becomes a standard procedure.

For systemic therapy, TSPA is usually given intravenously. The intramuscular route has not been used as extensively, but may well be equally effective. When used intravenously, the powder is dissolved in 1.5 to 5 cc of sterile saline or sterile water and given directly into the vein. Accidental infiltration is no problem as the solution is not irritating to tissues. Many different dosage regimens have been used with TSPA. Most popular has been an initial loading dose divided into five to seven daily doses given on consecutive days. Ten to 15 mg/day for five days is recommended if the patient has not had recent chemotherapy or extensive radiotherapy. Local radiotherapy not involving bone marrow sites is not a reason for lowering initial dosage.

After the initial loading dose, it is best to wait one to two weeks to see what changes take place in the white blood and platelet counts. Then a weekly maintenance dose is given. Fifteen mg/week is usual unless the white blood count is below 5,000 or the platelet count is below 200,000. In this case 5 to 10 mg is given. No medication is given if the white blood count is below 2,500 to 3,000 or the platelet count below 100,000. Even if these limits are not reached, if there is a rapid fall in white blood count or platelet count, it is best to wait three to

five more days, and then repeat the blood tests before giving another dose. Although the Lederle product brochure states that the platelet count usually falls after the white blood count, this has not always been true in my experience. I have found that early in the course of therapy the white blood count is usually the limiting factor in dosage, but that after prolonged administration, the platelet count becomes more important. I have several patients who maintained platelet counts below 100,000 for over eight weeks despite no further therapy, and white blood counts above 5,000. Ultmann[88] noted a similar phenomenon.

Although remissions can occur in ovarian carcinoma without marked lowering of the white blood count or platelet count, it is my personal prejudice to keep the white blood count between 2,500 and 3,500 with sufficient maintenance dosage. There is no statistical proof that this prolongs remission. However, I am unaware of any studies in this area.

The usual intracavitary dose is 45 to 60 mg dissolved in 5 to 30 cc of normal saline, injected directly into the pleural or peritoneal cavity after most of the fluid has been drained. After injection, the patient's position should be shifted frequently for 15 to 30 minutes to insure contact of the drug with all tumor deposits. Intracavitary dosage should not be repeated for two to three weeks until white blood count starts to rise.

As is apparent from the above discussion, the main toxicity of TSPA is on the bone marrow. The white blood count and platelet count are the most sensitive, but with prolonged dosage, moderate red cell depression is not uncommon. Bone marrow depression first appears 5 to 30 days after onset of therapy. Ultmann[88] noted toxicity 11 to 13 days after completion of a 5 to 7 day course. Moore[98] noted maximal white blood count depression 14 days after completion of a five day course.

Recovery from the marrow toxicity is usually noted within thirty days. However, prolonged leukopenia or thrombocytopenia is not rare. Patients who have had previous radiotherapy or chemotherapy are naturally more sensitive to the drug. It was Shay's[95] impression that marrow toxicity occurred more readily in patients with bone or marrow metastases. There are almost no human studies in this area to prove or disprove this point.

Other toxicity is minimal. Nausea, vomiting, headache, and anorexia occasionally occur. but are not severe. When they do occur they rarely last for more than 24 hours after the last injec-

tion. Ultmann[88] noted irreversible renal shut-down in two patients with reticulum cell sarcoma with preexisting hyperuricemia.

In summary, TSPA is a non-irritating injectible alkylating agent, which shares the position of agent of choice for ovarian carcinoma with chlorambucil. It is of some use in breast carcinoma, and for intracavitary administration in malignant pleural and peritoneal effusions. Toxicity is confined almost entirely to bone marrow depression.

## Cyclophosphamide

Cyclophosphamide has the chemical name N,N-bis ($\beta$-chloroethyl)-N′, o-propylenephosphoric acid ester diamide monohydrate. It was synthesized in 1957. It is available commercially as Cytoxan® (Mead Johnson) both as 50 mg oral tablets and in injectible form.

Probably more clinical studies of the use of cyclophosphamide have been published than for any other alkylating agent. Yet there is little agreement as to the place of this drug as a cancer chemotherapeutic agent. The reason for this is the poor design and inadequate documentation of so many of the studies. It is only more recently that comparative studies under the auspices of the CCNSC (Cancer Chemotherapy National Service Center) have appeared. These cooperative studies utilizing patients from several institutions require rigid criteria for definition of remission. Often double blind studies are carried out. It is hoped that within the next few years the place of this most interesting agent will be better defined.

At present, it would seem that cyclophosphamide is useful in almost any condition where an alkylating agent is useful, except perhaps, chronic granulocytic leukemia. It appears to be the alkylating agent of choice in acute leukemia, reticulum cell sarcoma, and the malignant tumors of early childhood. One recently published article[109] describing 165 well-studied patients with multiple myeloma, suggests that cyclophosphamide may be the drug of choice in this condition.

Cyclophosphamide is unique among alkylating agents in its ability to produce remissions in childhood leukemia in a significant number of patients. Fernbach[110] reported 8 complete and 5 partial remissions in 44 children with acute leukemia. Some degree of remission persisted from 100 to 453 days with a mean

of 206 days. Hoogstraten[111] reported a 15% remission rate with cyclophosphamide in childhood acute leukemia. The Acute Leukemia Cooperative Group B[112] reported 2 complete and 2 partial remissions and 9 patients improved out of 37 patients with acute leukemia under the age of 20. In 45 patients over the age of 20, there were 5 partial remissions and 5 improved patients. The two complete remissions in the childhood acute leukemia patients lasted 9 weeks and 17 weeks.

It is apparent from the above that cyclophosphamide is less useful than methotrexate, 6-mercaptopurine, steroids, or vincristine as the sole agent in the treatment of childhood acute leukemia. However, its usefulness as a component of alternating or combined regimens is being investigated.

Whether cyclophosphamide is more useful than other alkylating agents in the highly malignant sarcomas of children is not clear. It has been used more extensively in these tumors and in Wilm's tumor. The most favorable results have been in neuroblastomas. Kontras and Newton[113] using rather high dosages, had objective and subjective remission in 5 of 9 patients. Thurman[114] noted 19 responses in 24 patients. Ten of the 19 responses were considered good and 9 fair. Fourteen of these 19 responses occurred within the first 21 days of treatment. One patient was still in remission after 20 months. Pinkel[115] noted 3 brief responses in 8 children with neuroblastoma, and Sweeney[116] noted 3 responses in 6 children.

Kmetz[117] found significant prolongation of survival in cyclophosphamide-treated children with neuroblastoma. (Median survival 5.4 months in the control group as opposed to 8.5 months in the treated group.) Stephenson et al[118] reported 3 children with diffusely disseminated metastatic neuroblastoma who were still alive 17, 13, and 7 months after treatment with cyclophosphamide. Two of these, with initially inoperable tumors, later had successful surgical removal of the primary tumor. More recently, James et al[119] have reported spectacular results in neuroblastoma with a regimen involving alternate doses of vincristine and cyclophosphamide. (This will be discussed in Chapter 8.)

Five of 7 treated children with Ewing's sarcoma[115,116,120] have had short responses to cyclophosphamide. Results in Wilm's tumor have been poor.[121] Pinkel[115] noted 3 short responses in 7 children with rhabdomyosarcoma.

It would seem that cyclophosphamide is of some use in sarcomas of childhood, particularly in neuroblastoma, but that prolonged remissions are rare. Combination therapy with vincristine may prove very useful.

The medical literature pertaining to the role of cyclophosphamide in Hodgkin's disease is extremely confusing. This is because the various authors do not clarify whether their patients had become resistant to other alkylating agents. The stage of disease prior to therapy is not always clear, and exact criteria of response are not described in all series.

Perhaps the studies which are most useful are those of Spear[7] and Laszlo.[122] These are double blind studies comparing cyclophosphamide with mechlorethamine. Spear[7] found the two agents of equal value in 66 patients with Hodgkin's disease. In Laszlo's study[122] in 17 patients receiving mechlorethamine there were 3 excellent, 5 good, and 5 fair responses; while cyclophosphamide gave 3 excellent, 3 good, and 3 fair responses in 20 patients with Hodgkin's disease. These results were statistically significant in favor of mechlorethamine. However, the drugs were given intravenously at one to two week intervals after an initial loading dose. This is probably not the optimal method for using cyclophosphamide.

A similar study is being carried out by the Eastern Cooperative Group.[123] Preliminary results indicate equal results from mechlorethamine and cyclophosphamide.

Other less rigid studies[124-130] give varying results. The consensus seems to indicate that mechlorethamine is the superior drug.

Until recently, melphalan was considered the drug of choice in multiple myeloma despite occasional reports of good results with cyclophosphamide.[131] In September, 1964, a report from the Midwest Cooperative Chemotherapy Group appeared.[109] It was an analysis of 165 patients treated for at least two months with a daily oral dose of cyclophosphamide. Of the 78 patients on treatment for one year or more, complete remission occurred in only 1% and moderate remission in 6%. However, 48% of these 78 patients had some objective improvement and 23% had subjective improvement only. Only 3% of patients had progression of disease. Of the overall group of 165 patients, 11.6% were removed from the study for other treatment, 24% died, and 11.6% were lost to follow-up. The most impressive statistic from the study was the

median survival of 32 months from onset of therapy compared to a group of 70 patients receiving at least two months of urethane. This group had a median survival of 13.5 months from onset of therapy.

The objective changes noted in the patients receiving cyclophosphamide were "improvement in peripheral blood values" in 35%, and significant improvement in abnormal electrophoretic patterns in 24%. Only three patients had improvement in bone x-rays. These objectives changes are less impressive than those with melphalan. However, toxicity due to the drug was far less than with melphalan, the dosage was easier to regulate, and subjective benefit and performance status improvement were of the same order with the two drugs. The significant prolongation in survival was most impressive. A large controlled study must be done to decide which of these two agents is the drug of choice for myeloma.

Studies have appeared evaluating cyclophosphamide in chronic lymphatic leukemia, lymphosarcoma and reticulum cell sarcoma.[124-128,130,132] For the first two conditions, it would seem to be less effective than chlorambucil.[127,132] In the one double-blind study, chlorambucil was superior in chronic lymphatic leukemia, although the results were not statistically significant.[132]

Several authors who have treated reticulum cell sarcoma with cyclophosphamide agree that it seems to give results superior to any other alkylating agent.[126,127,133] Rundles[127] noted fair to excellent results for six months or longer in 11 of 14 patients with reticulum cell sarcoma, and the Midwest Cooperative Group[126] noted one complete remission and 2 patients with objective improvement (one of these for 256 days) out of 5 patients treated. More studies are needed before one can say that cyclophosphamide is the drug of choice in reticulum cell sarcoma.

From the results in a few cases of Waldenstrom's macroglobulinemia, it would appear that cyclophosphamide is an active therapeutic agent in this disease.[134]

While several groups have used cyclophosphamide in treating ovarian carcinoma[127,133,135] and breast cancer,[128,130,135-137] there are not enough data to show whether it is any more or less effective than other alkylating agents.

Cyclophosphamide is supplied as 50 mg oral tablets and as a powder 100 mg or 200 mg to an ampul. The powder is dissolved in sterile water to make 20 mg/cc and administered directly intra-

venously. The solution is stable for three hours after preparation. It may also be given intramuscularly, intrapleurally or intraperitoneally, as the solution is not irritating to tissues.

There is no general agreement as to the correct dosage regimen for cyclophosphamide. Basically, four different regimens have been used:

1. Approximately 30 mg/kg intravenously, then 10-15 mg/kg intravenously once a week.[125,129,138]
2. 30-50 mg/kg intravenously with a similar or slightly lower single intravenous dose at 6-8 week intervals.[135,136,139,140]
3. Intravenous loading 2-6 mg/kg/day for 4 to 10 days up to a total dose of 35 to 60 mg/kg followed by oral maintenance of 1 to 3 mg/kg.[110,120,124,130,135,137,139,141]
4. Daily oral dose of 2-3 mg/kg.[109,110,112,125,131,141]

Regimen 1 has been used less extensively than 3 and 4, and seems to be less popular. The reason for this is not clear except that nausea and vomiting are uncommon with doses of 200 mg or less. Regimen 2 has been used even less than the first, perhaps for the same reason. The fourth regimen is most useful in multiple myeloma, lymphosarcoma, giant follicular lymphoblastoma, and chronic lymphatic leukemia.[109,125,126] This regimen is best in the last three conditions because they are more sensitive to the alkylating agents, and there is less danger of toxicity with the moderately low daily oral dose. If cyclophosphamide is used in multiple myeloma, this regimen is almost completely free of toxicity, and would appear to give significant prolongation of life.[109]

Regimen 3 has been the most popular and is the one described in the Mead Johnson package insert. There is great variation in the application of this regimen. It is important to note first the findings of Bergsagel,[141] who tested a variety of dosage plans within the framework of regimen 3. He found that when 35 to 45 mg/kg total dose was given in less than 9 days there was a high percentage of toxicity.

Regimen 3 would not be recommended for lymphosarcoma, chronic lymphatic leukemia, giant follicular lymphoblastoma, or multiple myeloma. Regimen 4 is probably also the preferred one for Waldenstrom's macroglobulinemia. Regimen 3 would then be applicable in Hodgkin's disease, acute leukemia of children, reticulum cell sarcoma, neuroblastoma, perhaps other sarcomas of childhood, and possibly in ovarian and breast carcinoma. For

children, 5 mg/kg intravenously daily for ten days followed by oral maintenance of 2-4 mg/kg/day is suggested. Some authors have not used maintenance dosage, but rather, resumed intravenous therapy when relapse occurs. A good discussion of dosage in childhood acute leukemia is available in Fernbach's article.[110] For adults, I would suggest a total daily dose of 200 mg intravenously for ten days. It is best to wait seven days for maximum white blood count drop before starting oral maintenance of 100 to 200 mg/day. If bone marrow depression is present lower dosage should be used.

It has not yet been demonstrated whether it is preferable to continue oral maintenance therapy after maximum remission has occurred. Some authors would prefer to discontinue therapy and restart the initial regimen when relapse occurs. Continuous oral therapy for multiple myeloma would be indicated in view of the previously described data from the Midwest Cooperative Chemotherapy Group.[109]

As with the other alkylating agents, the major toxicity of cyclophosphamide is on the bone marrow. However, alopecia and bladder irritation are toxic effects of cyclophosphamide not found with the other alkylating agents.

An excellent discussion of the marrow toxicity of cyclophosphamide has been given by Pegg.[143] He confirms the much greater effect of this drug on the peripheral white blood count than on the platelet count. This dissociation has been noted by most authors.[125, 128, 130, 139, 141]

Pegg noted the following:

1. There appeared to be a relationship between the occurrence of leukopenia and the rapidity with which the treatment was administered. White blood counts below 4,000/mm$^3$ were noted in 13 of 14 patients in whom daily dose was over 4 mg/kg. The low white blood count occurred in 5 of 11 patients receiving a smaller dose.
2. A white blood count below 1000/mm$^3$ was reached in the shortest time by patients who received brief intensive treatments. However, it never took less than four days.
3. Platelet counts of 100,000/mm$^3$ or less occurred in seven patients and invariably were accompanied by leukopenia of at least 1,000/mm$^3$. Only one patient with a white blood count below 1,000/mm$^3$ failed to show a platelet count below 100,000/mm$^3$.

4. Speed of recovery of white blood count and platelet count was very rapid after stopping drug. (Less than 7 days with a mean of 4.5 days.)

From this, Pegg concluded that doses of cyclophosphamide sufficient to lower the white blood count to 1,000/mm$^3$, to all intents and purposes, stop production of granulocytes and platelets. However, the speed of recovery from cyclophosphamide as compared to the other alkylating agents is exceptionally rapid. This in conjunction with the longer life span of platelets (average 8 days) as compared to granulocytes (4 days) prevents platelet counts from dropping as greatly as the white blood count. This argument, while ingenious, would be easier to accept if supported by bone marrow studies. It would not explain the marrow findings of Coggins[139] and Wall[130]: that there appears to be suppression of granulopoeisis but not of megakaryocyte activity when cyclophosphamide is given.

In any case, there is little doubt that clinical toxicity of cyclophosphamide is somewhat greater on total white blood count than on platelets.

While Pegg's[143] conclusions may not be borne out by further studies, his findings have been duplicated by others. Kontras[113] using 5 to 10 mg/kg/day in children, noted drop in white blood count within 5 to 7 days of start of therapy. Stoll[136] noted maximum drop of white blood count within 7 to 13 days of administration of a single large dose, while Solomon[125] noted the peak drop in 9 days, and Thurman[114] in 8 days. Most authors noted return to normal of white blood count and platelets by 10 days after maximum drop.[114,125,133,137] The great majority of patients responded in less than 10 days, with severe depression usually not lasting more than 3 to 4 days. Stoll[136] noted somewhat longer time for recovery, but he used quite large doses (45-50 mg/kg in one dose).

As noted above, the maximum white blood count drop after a large dose of cyclophosphamide occurred in 7 to 13 days. However, when smaller doses are given daily, there is continued fall in white blood count for only 2 to 5 days after stopping the drug.[110,138]

In long continued treatment, or high dosage regimens, slight hemoglobin drop may be noted.[116,136] After stopping the drug, Sweeney[116] noted rise in hemoglobin, confirming the fact that the anemia was drug-induced.

There is general agreement that patients with marrow de-

pressed by previous radiotherapy, chemotherapy, or involvement by tumor are more sensitive to cyclophosphamide and should receive more cautious dosage. Kontras[113] noted that neuroblastoma patients with marrow metastases had greater toxicity than those without such involvement. Bergsagel[141] stated that patients with previously existing liver damage are also more sensitive to cyclophosphamide.

Considering the above facts, it is important that frequent white blood counts be taken when patients are on cyclophosphamide. On high dosage daily intravenous administration (over 3 mg/kg/day), white blood counts should be done every other day (daily after the white blood count falls below 5,000), with hemoglobin and platelet counts at 4 to 7 day intervals. On long-term low dosage maintenance, white blood counts can be done as infrequently as every two weeks after stabilization of the white blood count has been reached. One fact that should be emphasized is at what point the drug should be stopped.

When initial daily dosage is being given as in regimen 3, the drug should be stopped when the white blood count reaches 3,500/mm$^3$. Lower white blood counts can then be achieved with the oral maintenance by cautious titration. Anders,[137] using daily intravenous doses of 200 to 300 mg/kg/day, treated 92 patients until their white blood counts reached 2,000/mm$^3$. Twenty-eight of these patients had continued fall of the white blood count to below 1000/mm$^3$ after cessation of therapy, and 5 of these patients died with infection and bone marrow aplasia. This degree of morbidity and mortality is unnecessary with a drug as easily regulated as cyclophosphamide. With the short duration of marrow suppression with this agent, earlier cessation of the drug (white blood count below 3,500/mm$^3$) would obviate such toxicity.

Although the major toxicity of cyclophosphamide is on the bone marrow, bladder toxicity has been a problem, almost entirely in children. It is manifested as frequency, then dysuria, and finally hematuria.

It has been conclusively shown that the bladder toxicity of cyclophosphamide is due to contact of irritating metabolites with the bladder wall.[144] It has been usually possible to obviate bladder toxicity by high fluid intake or lower dosage.[117] However, reports have appeared of considerable bladder scarring at autopsy in children who received long-term cyclophosphamide,[116] and one case of exsanguinating hemorrhage with severe chronic fibrosing

cystitis has been reported.[145] Alopecia is an annoying, but not serious side effect. It is more common on higher dosage intravenous regimens and usually clears on continued oral maintenance therapy. It may be slight, but is often marked, and may be complete. Alopecia has been reported in as high as 90% of cases.[139] After approximately 2 to 3 months of maintenance therapy hair will start to regrow.[133, 136]

Nausea and vomiting are frequent with intravenous daily doses over 4 mg/kg. They do not appear until six hours after a dose is given, and last for approximately four hours. Slightly higher doses are tolerated intravenously than orally.[130] The nausea and vomiting associated with cyclophosphamide are less severe than with mechlorethamine.[128]

Other toxicity has been noted less commonly. Foley[128] noted a temperature rise in 5.8% of his patients shortly after an intravenous dose. Thurman[114] noted skin hyperpigmentation in 19% of children with neuroblastoma treated with cyclophosphamide. Acute Leukemia Group[112] noted mucosal ulcerations in 15.5% of children treated with cyclophosphamide. Fernbach[110] reported one case of transient jaundice almost certainly due to cyclophosphamide. Cannon[146] reported an unusual case of reticulum cell sarcoma of the small bowel where cyclophosphamide caused hemorrhagic necrosis of areas of tumor involvement in the jejunum. Greenberg[147] reported one case of a child born with multiple congenital abnormalities, whose mother had cyclophosphamide treatment during the first trimester of pregnancy.

In summary, cyclophosphamide, an alkylating agent, whose place as an anticancer agent is poorly defined despite extensive research, appears to have several unique and useful properties. Its most important distinction is its platelet sparing action in ordinary dosage. It is uniquely useful in acute leukemia, and neuroblastoma. It is probably the agent of choice in reticulum cell sarcoma, and may be very useful in multiple myeloma. Bladder toxicity and alopecia are unfortunate unique properties, but bone marrow depression is the major toxicity. Dosage regimens are still not standardized.

### Melphalan

Melphalan (L-phenylalanine mustard, L-sarcolysin, CB 3025) is a phenylalanine derivative of nitrogen mustard. Chemically it

is p-di (2 chloroethyl) amino-L-phenylalanine. It was released in February, 1964, by Burroughs Wellcome as Alkeran®, for use in multiple myelcma.

Although reports of the clinical use of melphalan date back to 1958[148] there are only a few reports of its usefulness in multiple myeloma.[149-154] The lack of reports is due to two factors: the relative infrequency of myeloma, and the delay in realizing that melphalan was somewhat unique among alkylating agents in its effectiveness against myeloma.

In the few published reports, it would seem that melphalan is effective in 33 to 70% of patients with myeloma. This is far better than with any previous agent. Its most striking effect seems to be in lowering the abnormal serum globulin. Improvement in performance status, rise in hemoglobin and normal gamma globulin, and decrease or disappearance of proteinuria were frequent enough to be of significance. Recalcification of bone lesions has occurred in a few cases.

The incidence of measurable objective change (marked decrease in abnormal globulin, marked decrease in proteinuria, rise in hemoglobin of greater than 2 grams per 100 ml, disappearance of hypercalcemia, or recalcification of skeletal lesions) is approximately 30 to 70% in the reported series. Although isolated reports of objective response to urethane and other agents have appeared, no agent except cyclophosphamide has been as consistently effective as melphalan in multiple myeloma. Remissions last from 6 to 36 months when maintenance therapy is given.[150]

Because of the recent introduction of melphalan, there is no general agreement as to the correct dosage schedule. The Burroughs Wellcome brochure suggests 6 mg once daily for two to three weeks. Weekly blood counts are advised during this interval, and dosage adjusted on the basis of these. After this initial course a wait of up to four weeks is advised, with a maintenance dose of 2 mg/day started when the white blood count and platelet count are rising.

Osserman,[151] who has a large experience with melphalan, advises 10mg/day for 7 to 10 days. Maximal suppression of white blood and platelet counts occurs within 3 to 5 weeks and recovery within 4 to 8 weeks. Continuous maintenance therapy with 2 mg/day is instituted when the white blood count has recovered to 4,000 and the platelet count has risen above 100,000. Maintenance dosage is adjusted between 1 and 3 mg/day depending

upon the hematologic response. Osserman advises keeping the leukocyte count in the range of 3,000 to 3,500 cells/cu mm.

The administration of melphalan in myeloma is probably more difficult to master than the use of any other alkylating agent in any other disease. This is because of the high incidence of leukopenia and/or thrombocytopenia in untreated multiple myeloma. One is always wary of using a full course of as potent an agent as melphalan in a patient with a very low platelet or white blood count. Bergsagel et al,[149] however, using an aggressive regimen of 0.2 mg/kg/day to the point of leukopenia, had only one death attributable to the drug in 38 courses. These investigators treated patients with initial white blood counts below 3,000 until the leukocyte count dropped below 1,000 or the platelet count fell below 100,000.

Osserman[151] feels that suppression of leukopoeisis appears to be an unavoidable counterpart of the tumor-suppression action of melphalan, and that the leukocyte count is the best index that an adequate dose is being given. Extreme care should be taken with melphalan if the patient has had recent chemotherapy or extensive radiotherapy.

Because of the fairly recent introduction of melphalan and the lack of an established dosage schedule, it is advised that several of the original references be consulted before using this agent. Osserman,[151] Bergsagel,[149] AMA Council on Drugs,[155] Speed,[156] and Brook[150] are suggested sources.

The need for prolonged therapy cannot be emphasized too strongly. Rapid objective response to melphalan is the exception. However, relief of bone pain may occur within two weeks. In Brook's[150] report of 36 patients the median onset of objective improvement was 53 days, with a range of 18 to 123 days from the start of therapy.

The toxicity of melphalan is almost purely on the bone marrow. Large oral doses over 20 mg may cause nausea. Such doses are not recommended. The bone marrow depressant effect may be on white cells, platelets or red cells. The dosage necessary to produce toxicity is quite variable from patient to patient, and also seems to depend on the dosage schedule. Brook et al[150] found toxicity occurring at a median total dosage of 3.3 mg/kg when a daily dose of 0.1 mg/kg was given, but when the daily dosage was 0.05 mg/kg, toxicity occurred at a median total dose of 1.32 mg/kg. It has been suggested that patients with uremia are

more susceptible to melphalan toxicity, and should receive a smaller initial dosage.

Because of these uncertainties, patients receiving melphalan should have frequent blood counts. Complete blood counts including platelet counts should be done weekly.

It should be mentioned that melphalan has been used by perfusion with some success in the treatment of malignant melanoma.[157-161] Krementz and Creech[160] review six years of experience in melanoma of the extremities. Melphalan alone, or in combination with triethylene thiophosphoramide, was used by regional perfusion. Results were so promising that these authors felt that there was no longer need for amputation or radical excision in the treatment of local recurrence or regional metastasis. Nine of twenty patients with satellite nodules and positive nodes were apparently cured four years after perfusion. However, technical problems still make this form of therapy one that can only be used by a few centers with specially trained teams and the proper complex equipment.

In summary, melphalan (Alkeran) is a useful agent for the treatment of multiple myeloma. In experienced hands the toxicity can be minimal. At the present time there is no agreement as to the best dosage schedule. Reference to original articles before using melphalan is recommended.

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## CHAPTER III

## METHOTREXATE

The major features of the pharmacology and clinical utility of methotrexate are readily available in the literature. An excellent review article on folic acid antagonists was published by Delmonte and Jukes.[1] M. Lois Murphy has reviewed the use of methotrexate in acute leukemia of children. Numerous other good clinical articles are available.[3,4,5]

Although many antifolics have been tested in tissue cultures and animals, and several have been tried in humans, methotrexate is at present the only such agent used clinically. Its chemical name is 4-amino-$N^{10}$-methyl pteroylglutamic acid, and it was formerly known as amethopterin.

Another agent, aminopterin, had fairly extensive clinical trial. However, its action was somewhat erratic, and it has been withdrawn from use.

Methotrexate is available from Lederle Laboratories in both an oral form, as 2.5 mg tablets, and a parenteral form. The parenteral form is available as a 5 mg and a 50 mg ampul.

The major use of methotrexate has been in acute leukemia of children, where remission rates varying from 40% to 68% have been reported.[1] About half of these remissions are complete, with return to normal of the bone marrow and peripheral blood, as well as the presence of a state of clinical well-being. Farber[6] has reported on 800 children with acute leukemia treated over an 11 year period with antifolics. The median survival was 14 months, and 10% of the children survived 32 months or more.

Because of the inadvisability of using untreated controls, there have been no studies to prove that antimetabolites prolong survival in childhood acute leukemia. All evidence in this area has been gained by comparing survival statistics from the immediate pre-chemotherapy era with those of the author, using

methotrexate or methotrexate plus corticosteroids.[7,8,9,10] This method is not foolproof, because it cannot take into account improvement in supportive care. However, most authors feel that the use of antibiotics and blood transfusions were developed to a sufficient degree so that most of the advance in survival must be attributed to specific therapy.

At present, the treatment of acute leukemia in children is in a state of flux. The best results are being reported with some form of sequential therapy involving planned alternation of active agents on a definite schedule.[11,12] These regimens are based on the principle of changing the drug before the leukemic cell has a chance to become resistant. Since these regimens are still experimental, detailed presentation is beyond the scope of this book. However, a more complete description of several of these regimens will be included in the final chapter, in the section on acute leukemia of children.

The best results with methotrexate have been in acute stem cell and acute lymphoblastic leukemia. However, acute granulocytic leukemia is rare in children, so it is not known definitively whether age or cell type is the basic factor in response. When methotrexate is used as the sole drug for acute leukemia in children, it takes two to six weeks to obtain a remission. The median duration of complete remission is about 4 months. Most authors would use concurrent corticosteroids for the first several weeks if the child is acutely ill. The response rate to methotrexate is probably the same whether or not the child has had previous therapy with 6-mercaptopurine.[13]

Combined therapy with 6-mercaptopurine gives a higher initial remission rate than using either drug alone, but overall results are no better than when sequential therapy is used. Sequential therapy as used here should not be confused with planned alternation of drugs as advocated by Brubaker[11] and Zuelzer.[12] By sequential therapy it is meant that either 6-mercaptopurine or methotrexate is given until relapse. At this point the drug is stopped, and the other drug is then started. This has been the traditional method of treating childhood acute leukemia. Steroids have generally been used for brief periods in the severely ill child with acute leukemia, and when the child is no longer responsive to an antimetabolite. Vincristine and cyclophosphamide were added to the sequence as it became apparent that they were effective agents. However, it is probable that regimens with alter-

nation of agents at shorter (usually monthly) intervals will prolong remissions.

It should be noted that when methotrexate is given, the blood picture may worsen for the first ten days to two weeks, although the bone marrow is starting to show favorable effects. When remission or relapse is starting, the peripheral blood picture and clinical state lag behind the bone marrow. For this reason, most authors have advocated bone marrow examinations once a month. This will allow switching to a new agent before the child feels ill, if the marrow starts to show relapse. In this way the child can be maintained in a state of continuous well-being. Murphy's[2] article is especially recommended for discussion of the traditional techniques of treating childhood acute leukemia.

Methotrexate is given daily, 1.25 to 2.5 mg for infants, 2.5 to 5.0 mg for children. If toxicity appears the drug is stopped for 7 to 10 days, and then resumed at a somewhat lower dose. In some cases, it may be necessary to produce moderately severe toxicity on several occasions before a remission occurs.[2] However, this is usually unnecessary, and most cases have little or no toxicity.

As with the use of chemotherapeutic agents in most neoplastic diseases, the question of whether to give maintenance therapy has not been settled. Murphy[2] stated that if maintenance therapy is decided upon, it should be in the full therapeutic daily dose. It is of interest that Selawry and Frei[14] have found that methotrexate 30 mg/m$^2$ BSA intramuscularly, twice a week, is more effective than 3 mg/m$^2$ BSA/day, orally, in maintaining remissions induced by a combination of vincristine and prednisone. Whether the intramuscular route or the intermittent treatment is the effective factor is not known. Delmonte and Jukes[1] discuss some aspects of this question.

Methotrexate by intrathecal administration, for treatment of cerebral leukemia, will be discussed later in this chapter. Remission of acute leukemia, induced by oral methotrexate, does not prevent central nervous system involvement by the leukemic process. This is because of the so-called "blood-brain barrier." Spinal fluid levels of methotrexate are extremely low after oral or intramuscular administration. For this reason, methotrexate has been used intrathecally, with great success for this complication (vide infra).

The response of adult acute leukemia to methotrexate is far less favorable than that of childhood acute leukemia. The dividing line between childhood and adult acute leukemia is not clear, but it seems to fall between the ages of 15 and 20. Ellison and Burchenal[15] have stated that less than 5 to 10% of adults with acute leukemia have a complete remission on methotrexate. They feel that previous treatment with 6-mercaptopurine enhances the response rate to methotrexate. Frei et al[13] did not find that pretreatment with 6-mercaptopurine had any effect on the low response rate to methotrexate. 6-mercaptopurine is the drug of choice for the treatment of adult acute leukemia.

Huguley et al[16] have attempted to improve these poor results in adults. They used a dosage schedule of 1.25 to 2.5 mg of methotrexate every 6 hours for 5 days. This course was repeated at 10 to 14 day intervals. They noted 4 complete remissions in 9 patients with acute granulocytic leukemia, and 1 of 2 with blastic crisis of chronic granulocytic leukemia. The only patient with erythremic myelosis had a complete remission, but none of 3 with monocytic leukemia. Two patients were still in remission at 49 and 164 days. The other 4 remissions varied from 72 to 109 days.

The outstanding triumph in all cancer chemotherapy is probably the long-standing remissions of metastatic choriocarcinoma produced by methotrexate. These remissions have been so remarkable that one can talk of cures.

The classic paper in this field is by Hertz, Lewis and Lipsett.[17] A follow-up paper from this group appeared in 1964.[18] Another excellent report, with a review of the literature, is that of Lamb et al.[19] There is no doubt that methotrexate has produced prolonged complete remissions in about 50% of patients with metastatic choriocarcinoma. However, even the best studied series present difficulties in interpretation. The reasons for this are very well discussed by Brewer et al[20] in their excellent article on the chemotherapy of choriocarcinoma. The major difficulty has been in documenting whether the patient has a true choriocarcinoma or a metastasizing mole (chorioadenoma destruens). Apparently spontaneous remission rate without chemotherapy is less than 10% in choriocarcinoma, but as high as 50% in metastasizing mole.[17]

Hertz et al[18] reported that 60% of 75 patients with metastasizing choriocarcinoma had complete remission without relapse

from 1 to 7 years after start of methotrexate therapy. With prompt use of other chemotherapy (actinomycin D, vinblastine or triple therapy) in those patients unresponsive or no longer responsive to methotrexate, overall prolonged remissions approach 90%.[20] The use of each of these other agents in choriocarcinoma is discussed in the chapter pertaining to that agent.

In the 1961 article, Hertz et al[17] discussed the use of methotrexate in choriocarcinoma in some detail. Of 63 patients, one was resistant to methotrexate, and 3 died very soon after start of therapy. Twenty-eight patients had no evidence of disease at the time of reporting, having received methotrexate alone. Two patients were alive with persistent disease, and 16 were dead after remission. Thirteen patients who had partial remissions to methotrexate received vinblastine. Two of these were free of disease, 5 were alive with persistent disease, and 6 were dead after remission. Only 3 patients who had complete remission later relapsed. However, Brewer et al[20] noted relapse in 7 of 20 with initially sustained response. These occurred in the first six months of remission. Twenty-seven of Hertz'[17] 29 partial responses to methotrexate lasted less than a year. Poor results were noted in patients with brain metastases.

Hertz[17] suggests that the response rate in metastasizing chorioadenoma destruens is not different from the spontaneous remission rate. However, Lamb et al[19] disagree. They report a 65% complete remission rate in forty patients, collected by reviewing the literature.

The results with chemotherapy in choriocarcinoma are now so excellent that hysterectomy plays little role, and is reserved for patients who have persistent elevation of human chorionic gonadatrophin (HCG) titres as the only manifestation of disease after treatment with chemotherapy. This should amount to less than 10% of cases. There have now been several reports of normal pregnancies after chemotherapy of choriocarcinoma.[19,20]

The details of methotrexate therapy in choriocarcinoma will be discussed later in this chapter.

Intrathecal methotrexate is the treatment of choice for intracranial manifestations of acute leukemia. The central nervous system complications of acute leukemia have become more prevalent as the life span of patients with this disease has been lengthened. The most effective drugs for acute leukemia, methotrexate and 6-mercaptopurine, do not cross the blood-brain barrier

in significant concentration. Therefore, patients in complete remission from these drugs can develop isolated central nervous system manifestations despite maintenance of a normal bone marrow.

When methotrexate is administered intrathecally, in the dosage used clinically, the cerebrospinal fluid levels of the drug are 30 to 100 times that achieved when the drug is given orally. The clinical results of intrathecal administration of methotrexate have been well documented.[2,21,22,23,24] Evans et al[23] have reported a large series comparing intrathecal methotrexate with lumbar puncture alone, and cerebral radiotherapy. Fifty episodes were treated by each of the three methods. Forty-nine of 50 patients responded to radiotherapy, and 44 of 50 to methotrexate. The median duration free of symptoms was 2.8 months after radiotherapy, 3.7 months after methotrexate intrathecally, and 0.6 months after lumbar puncture alone. These authors preferred methotrexate because of the longer duration of remission, and the fact that radiotherapy caused alopecia.

The best results with intrathecal methotrexate occur in those patients with elevated spinal fluid cell counts and elevated C.S.F. pressure.[2] Murphy[2] had a response in 12 of 14 patients with elevated C.S.F. pressure, but in none of 9 with lower extremity weakness and no cells. Intrathecal methotrexate is effective even in patients whose systemic disease is resistant to methotrexate. This is because of the high local concentration achieved in the spinal fluid.

There are several other less widely accepted uses of methotrexate. Nevinny et al[25] have been able to prevent hormone-induced hypercalcemia in six patients with breast cancer by giving methotrexate 2.5 mg/day by mouth until the white blood count fell below 4,000, and then reinstituting the offending sex hormone.

Friedman and Daly[26] report temporary regression of squamous cell carcinoma of the head and neck with oral methotrexate in about 50% of cases. Ten per cent of the tumors were highly sensitive and had greater than 75% disappearance. Unfortunately, remissions were usually very brief. These authors noted an "enhancement" of radiotherapy. However, an interesting editorial in *Lancet*[27] questions whether this "enhancement" benefits the patient. Toxicity with combined therapy is greater, and it may well be that more radiotherapy may be as effective as combined chemotherapy and radiotherapy.

Wright et al[28] have reported on the use of methotrexate in mycosis fungoides. They report responses in 9 of 16 patients. Duration of remission varied from 1 to 22.5 months.

Duvall[29] has reviewed the literature on the use of methotrexate in tumors other than acute leukemia and choriocarcinoma.

The infusion of methotrexate directly into the artery supplying a lesion, with protection of the remainder of the tissues by systemic administration of citrovorum factor, has been tried by a number of groups.[30,31] Lawrence[30] has reviewed these results. There is no doubt that marked objective tumor regression has sometimes occurred, especially in squamous cell carcinoma of the head and neck region. However, even with the most experienced groups, complications such as hemorrhage and arterial thrombosis are quite common, and the remissions are short-lived (1 to 3 months).

Methotrexate is one of the drugs used in the "triple-therapy" regimen. This will be discussed in a later chapter.

It should be mentioned that methotrexate has been quite effective in psoriasis[32] and psoriatic arthritis.[33] However, the potential toxicity of methotrexate makes it a drastic form of therapy. Attempts are being made to work out a non-toxic regimen. At present, methotrexate should be reserved for the most serious cases of these two illnesses. A more detailed discussion of this topic is outside the scope of this book.

Methotrexate is usually administered orally. Toxicity is related more to duration of drug contact with the tissues, rather than height of the blood level. For this reason, the same dose divided throughout the day is more toxic than when given as a single dose. Larger quantities can be given intraarterially, intravenously, or intramuscularly, than orally, for the same reason. This is discussed in greater detail in the introductory chapter on pharmacology.

The dosage for treatment of acute leukemia is approximately 3 mg/m$^2$ of body surface area daily. This works out to 1.25 mg to 2.5 mg/day for infants, 2.5 mg to 5.0 mg daily for children, and 5.0 to 7.5 mg/day for adults. If toxicity occurs before a full 6 to 8 week course can be given, the drug should be stopped for 7 to 10 days, and then resumed at a lower dosage level.

The bone marrow may show improvement as early as 10 days to 2 weeks. Improvement in the peripheral blood lags behind the bone marrow changes by 1 to 2 weeks. However, it may take 6 to

8 weeks of therapy to obtain a remission. Murphy[2] states that in some initially resistant cases it may be necessary to produce moderately severe toxicity, perhaps several times, in order to obtain a successful remission.

One of the most difficult problems in controlling dosage of methotrexate is that many of the children with acute leukemia have initial leukopenia and thrombocytopenia. Further drops in the white blood count or platelet count may be due either to the disease or the drug. Bone marrow examination is usually helpful here. If the marrow shows aplasia or marked megaloblastic changes, it is strong evidence of drug toxicity.

Blood counts should be done frequently, daily in the very ill patient, and 2 to 3 times a week in the less ill patient. When the patient is in remission, blood counts may be done as infrequently as every 1 to 2 weeks. Bone marrow aspirations should be done monthly, so relapse can be noted before clinical effects are apparent.

There has been some experimentation with other dosage schedules in treatment of childhood and adult acute leukemia.[14,16,34] Further work in this area is necessary, using larger series of patients.

The dosage schedule for methotrexate in choriocarcinoma has been very different. The usual dosage is a single dose of 25 mg/day orally, or intramuscularly for five days. Smaller doses are given if the marrow is depressed. Hertz et al[17] used 10 to 30 mg/day intramuscularly for five days. The course is repeated when toxicity has completely cleared. This is usually one to two weeks after completion of the last course. Subsequent courses may have to be given at slightly greater intervals (up to four weeks).[19] The courses are repeated until all evidence of disease is gone, and human chorionic gonadotrophin titres have returned to normal. Frequent determinations using a very sensitive method are needed.[19,20]

One to 12 courses may be needed, with an average of 5.[17,20] Maintenance therapy is not used after complete remission. Brewer et al[20] advise prompt switch to actinomycin D at the first sign of relapse, or soon after it is apparent that the patient will not respond to methotrexate.

Dosage schedules for head and neck cancers and mycosis fungoides have been similar to that for acute leukemia. Nevinny and Hall[25] used 2.5 mg/day by mouth to prevent hormone-induced hypercalcemia in breast cancer.

Intrathecal methotrexate dosage is not completely standardized. (Good references are Murphy[2] and Evans et al.[23]) A safe dose is 0.25 mg/kg every 2 to 3 days until the symptoms have cleared, the cerebrospinal fluid pressure has returned to normal, and the cell count in the fluid is normal. Murphy[2] suggests giving one additional dose after the cell count is normal. An alternate regimen is 0.5 mg/kg every 4 to 5 days. Murphy[2] found between 2 and 9 injections were needed. Evans et al[23] suggest dissolving the required amount of methotrexate in 1 to 2 ml of saline and further dissolving this solution in 5 to 10 ml of cerebrospinal fluid. If there is free flow of fluid in the spinal tap needle, they advocate forceful injection of the solution, followed by withdrawal of the fluid and forceful reinjection. Most authors have temporarily stopped oral methotrexate during the period of intrathecal therapy.

Toxicity of methotrexate has been well discussed in a number of articles.[1,19,20,34] The article by Delmonte and Jukes[1] is especially helpful. Because of the dose schedule, greater toxicity has been produced in the treatment of choriocarcinoma. Hertz,[34] referring to this tumor, has stated: "It is our aim to willfully induce a severe degree of toxicity to the point of maximum tolerance in anticipation of the recovery of the host tissues from such induced toxicity and the failure of recovery of the tumor tissue by the higher folic acid requirement of the tumor tissue."

The toxicity of methotrexate is probably due to the inhibition of synthesis of nucleic acids in rapidly proliferating cells. For this reason, toxicity is manifested by the hematopoietic tissues, oral and intestinal mucosa, skin, and hair follicles.

Delmonte and Jukes[1] state that: "Single large oral doses of antifolics, resulting in high but transitory serum levels and associated with rapid urinary drug elimination were better tolerated by normal animals and man than repeated smaller doses giving rise to moderately high, prolonged drug levels in the serum.... Impaired renal function resulted in delayed plasma clearance and drug excretion. This increases the danger of early systemic toxicity."

Delmonte and Jukes[1] quote R.D. Sullivan as postulating that toxicity depended on duration of drug contact with the tissues rather than on the concentration of drug in the blood. Sullivan found that a five-day course of continuous 12-hour intraarterial infusions of 5 mg/day resulted in toxic manifestations considered

quantitatively similar to those observed after a five-day course of single intraarterial doses of 25 mg.[1]

The major limiting toxicity of methotrexate may be either on the marrow or the gastrointestinal tract. Shallow ulceration on the buccal mucosa is the first sign of gastrointestinal toxicity. These are "shallow, painful, white or yellow, red-edged lesions on the lips, tongue or other buccal mucosa."[1] Therapy must be stopped at this time and not resumed for at least seven days. More severe gastrointestinal toxicity is manifested by diarrhea. Morphologic accompaniement of this diarrhea is extensive areas of atrophic degeneration and denudation of the villous epithelium of the small intestine. Multiple hemorrhagic areas and mucosal ulceration develop throughout the small and large intestine. A clinical accompaniment may be oral or rectal bleeding. If therapy is not stopped at this point, death will result.

Marrow toxicity may also be a limiting factor. Sudden onset of rapidly progressive leukopenia is a sign of marrow depression and requires interruption of therapy. However, Murphy[2] notes that in the first 10 days to 2 weeks of therapy in acute leukemia, the marrow may improve while the blood gets worse. She states that the white blood count may be carefully brought down to levels of 1,000 to 2,000. It should be remembered that some children with acute leukemia may have initial white blood counts lower than this. Initial therapy with prednisone is probably indicated in such children.

Ellison and Burchenal[15] state that therapy in acute leukemia can be continued in the presence of leukopenia as long as the marrow remains cellular. They also caution against a sudden drop in the white blood count.

Acute bone marrow depression is reversible by withdrawal of the drug. Delmonte and Jukes[1] mention the development of irreversible chronic bone marrow aplasia resulting from prolonged drug administration. It is characterized by severe chronic leukopenia with progressive anemia, and thrombocytopenia. However, they do not document this state of chronic aplasia. Death has resulted from bone marrow depression.

Lipsett[34] has concisely described the physiology of peripheral blood depression in relation to marrow depression. Lipsett[34] states that all elements of the marrow are affected by folic acid deficiency. The onset of marrow toxicity is rapid, but is not reflected in the peripheral blood until the cells circulating in the

blood stream have reached the end of their life span. For this reason, hemoglobin, white blood count, and platelet count may continue to fall for as long as a week after discontinuance of methotrexate.

Condit's[35] findings agree with this. He studied the acute toxicity of methotrexate in man, using single large doses. He found that reticulocytes decreased to minimum values in 4.6 days, leukocytes in 6.2 days, and platelets in 9.3 days. This, he felt, was essentially their life span. Incidentally, he noted that single intravenous doses of methotrexate as large as 16 mg/kg have been given intravenously without toxicity. This is because of the rapid excretion with brief duration of tissue contact. The same dosage given fractionated would be lethal.

Condit[35] stated that renal or marrow toxicity, or testosterone administration decreased tolerance to methotrexate. The effect of decreased renal function on methotrexate toxicity cannot be emphasized too strongly. Reduced dosage must be given if glomerular filtration rate is reduced. Vogeler et al[35a] also noted that androgen therapy decreased tolerance to methotrexate.

Other significant toxicity has occurred with methotrexate, but is rarely a limiting factor. Hepatic fibrosis has been the most important. At first there was some controversy as to whether the hepatic damage was due to the leukemia itself.[36] However, Lipsett[34] has noted hepatic fibrosis in treatment of patients with choriocarcinoma. Lipsett[34] has found that patients with preexisting hepatic disease are particularly susceptible to methotrexate-induced hepatic injury. He feels that patients with hepatic disease should not receive methotrexate "except under the most desperate circumstances." Hutter et al[37] state that before methotrexate was introduced, only 31% of their children with acute leukemia had hepatic fibrosis at autopsy and all but one case was mild. After methotrexate was introduced 80% had hepatic fibrosis and the degree was more severe. All adults they treated with prolonged methotrexate had hepatic fibrosis.

Hersh et al[38] describe some of the liver function test abnormalities occurring with methotrexate therapy. Liver biopsies in their series showed fatty metamorphosis.

I could find only one reported case of development of total anuria due to methotrexate treatment of acute leukemia.[39] However, it is a potential danger with methotrexate or other therapy in this condition.

Although anuria is extremely rare, Frei et al[40] reported 7 episodes of uric acid nephropathy in acute leukemia in 6 patients. Four of these episodes were associated with methotrexate therapy, and in 2 of these methotrexate-induced nephropathies, the blood urea nitrogen rose above 120. It is of interest that in Frei's[40] 7 episodes the peripheral white blood count was above 27,000 prior to therapy in 6, and above 100,000 in 4. Most patients with acute leukemia have normal or low total white blood counts. It should be noted that nephropathy occurred early in the course of therapy with methotrexate or other agents, and was associated with a rapid fall in white blood count. It is probably true that uric acid problems will usually occur in the patients with elevated white blood counts.

Rieselbach et al[41] have shown that many children with acute leukemia have elevated serum uric acid and decreased glomerular filtration rate. For this reason, all children with acute leukemia should receive adequate hydration. These authors have studied the pathology and physiology of uric acid nephropathy.[40,41] They outline a regimen for treatment of children with acute leukemia with elevated serum uric acid. This consists of 5% glucose and water intravenously, 3 liters/$m^2$ body surface area/24 hours. $NaHCO_3$ is given intravenously, 100 mEq/$m^2$/24 hours, along with acetazolamide (Diamox), 1 gm/$m^2$/24 hours. If the patient is oliguric, they suggest giving a mannitol infusion first. To prevent potassium depletion on this regimen, a supplement of 40-80 mEq KCL is given. On the above regimen the urinary pH is consistently over 7.0. Uric acid is far more soluble in neutral or alkaline urine than acid.

Additional toxicity has been: (1) Alopecia, which is frequent but usually mild and transient even on maintenance therapy; (2) brownish skin pigmentation; (3) skin rash, which most often takes the form of a perifolliculitis; (4) pleuritic type of chest pain.[34] This has been associated occasionally with a transient friction rub. (5) rare localized peritonitis which may be confused with appendicitis;[34] (6) rare middle ear hemorrhages leading to deafness.[1]

Brewer et al,[20] using the high dosages needed for choriocarcinoma, report a high incidence of neurotoxicity. In 28 patients, they report mental depression in 9, urinary bladder dysfunction in 8, loss of reflexes in 2, and paresthesias and localized neuropathy in 1 patient each.

Van Scott[34] and Lipsett[34] have given a good discussion of the skin toxicity of methotrexate.

The last form of toxicity of methotrexate to be presented must be discussed in some detail. This is the effect of methotrexate on the fetus. Sokol and Lessmann[42] have reviewed the literature on the effects of various cancer chemotherapeutic agents. In general, there has been little trouble with any agents except the antifolics. Most of this toxicity has been reported with aminopterin, because several groups used this agent to attempt to induce abortions.[43,44] There is little doubt that methotrexate is just as capable of producing congenital abnormalities. In Thiersch's[43] first series 12 pregnant women received aminopterin in the first trimester. Ten of these women had spontaneous delivery of the dead fetus soon thereafter. Two women required surgical removal of the fetus. These two fetuses had congenital abnormalities. Meltzer[44] and Warkany[45] each report the birth of a child with multiple congenital abnormalities to a mother who received aminopterin in the first trimester of pregnancy in an attempt to induce abortion. Sokol and Lessmann[42] in their review mention two mothers who received methotrexate after the first trimester, and had normal infants. A third mother received methotrexate and 6-mercaptopurine in the fourth month of pregnancy, and had a miscarriage in the sixth month. No congenital abnormalities were noted.

These data would indicate that methotrexate should not be used in the pregnant woman in the first trimester except in desperate circumstances. After this period, its use is probably without hazard to the fetus.

If an excess dose of methotrexate is given inadvertently, citrovorum factor (Leucovorin®, Lederle) given within four hours will reduce or prevent toxicity. Three to 6 mg is the recommended dose.

In summary, methotrexate is a highly useful agent in childhood acute leukemia and choriocarcinoma. In the latter disease, this agent alone or in conjunction with other potent drugs has completely controlled the tumor in over 75% of cases. Intrathecal methotrexate is standard therapy for central nervous system manifestations of acute leukemia. Methotrexate is highly effective in psoriasis, but it cannot be considered safe enough for standard therapy in this benign disease. The major toxicity of methotrexate is on the gastrointestinal tract, with oral ulceration and diarrhea

as early signs, and on the hematopoietic system. This agent is highly toxic to the fetus in the first trimester, and its use often leads to congenital abnormalities.

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## CHAPTER IV

# 6-MERCAPTOPURINE

The only purine antagonist which is commercially available for clinical use is 6-mercaptopurine. Other antipurines have been used experimentally in animals and in humans. 6-mercaptopurine is manufactured by Burroughs Wellcome and Co. as Purinethol®. Its only clinical use in neoplastic disease has been in acute leukemia and chronic granulocytic leukemia. It is being tried in a number of so-called "autoimmune" diseases, such as autoimmune hemolytic anemia[1] and lupoid hepatitis.[2]

6-mercaptopurine is indicated primarily for the treatment of acute leukemia. It is probably the single most effective drug in this condition. An extensive exposition of the use of this agent in both adult and childhood acute leukemia has appeared as a symposium in the *Annals of the New York Academy of Sciences,* Volume 60, December 1954. Although several excellent articles have appeared since this time,[3-6] very little has been added except for clarification of liver toxicity. The greatest advances have been in using 6-mercaptopurine as one of the agents in a planned cyclic alteration of therapy. This will be discussed in a later chapter (see Chapter XI).

Although some form of cyclic alteration of agents is now the treatment of choice for childhood acute leukemia, it is important to review the original use of 6-mercaptopurine. The data obtained from these studies will enable us to use the drug intelligently in the newer regimens. One of the clearest and most complete articles is that of Ellison et al.[6]

Bross[7] analyzed the larger series from the New York Academy of Sciences symposium. In 11 series, which included a total of 174 children, the remission rate with 6-mercaptopurine was 36%. This rate of 36% includes only essentially complete remissions.

Table I summarizes complete and partial remission rates from some of the larger series, not all of which are included in the symposium. A discussion of criteria for complete remission will be included in the chapter on specific diseases.

*TABLE I*

*Response of Childhood Acute Leukemia to 6-mercaptopurine*

| Author | Ref. # | No. of Children | % of Remissions | |
|---|---|---|---|---|
| | | | Complete | Partial |
| Bernard and Seligman | 10 | 42 | 26% | 12% |
| Sutow et al | 5 | 64 | 30% | 28% |
| Burchenal | 4 | 87 | 47% | 18% |
| Hyman, Gellhorn et al | 24 | 22 | 32% | 27% |

The onset of remission in childhood acute leukemia usually is within 4 to 5 weeks of starting therapy with 6-mercaptopurine, although it may occasionally take as long as 3 months. The median duration of remission is 8 to 16 weeks although occasionally patients have had much longer responses. There is some evidence that the effects of 6-mercaptopurine in prolonging steroid-induced remissions are greater than its effects in inducing remissions. The Acute Leukemia Group B[3] found that corticosteroid-induced remissions lasted a median duration of nine weeks, when a placebo was used for maintenance. When children with steroid-induced remissions were given 6-mercaptopurine for maintenance, the median duration of remission was 33 weeks and 100% of children were in remission at 10 weeks. When 6-mercaptopurine was given to the steroid nonresponders and the patients who had relapsed on placebo, the overall complete plus partial remission rate was 55%.

In this study (Acute Leukemia B),[3] the 24 additional weeks of remission with 6-mercaptopurine is longer than the median duration of remission achieved by any group that has used 6-mercaptopurine to induce and maintain remission.

6-mercaptopurine is apparently less effective in the uncom-

mon cases of childhood acute granulocytic leukemia, than it is in the more frequent cases of acute lymphocytic or acute undifferentiated childhood leukemia.[8]

In adult acute leukemia, the results with 6-mercaptopurine have been far poorer than in children. This is partially due to the fact that most adults have the poorly responsive acute granulocytic form. However age itself may play a role. Bethell and Thompson[9] found that responses in patients under age 35 were more likely to occur than in patients over this age. This series is far from conclusive, as only six patients were over 35. Ellison and Burchenal[6] felt there was no correlation between remission rate and the cell type of acute leukemia in adults. Certainly, no authors of large series have found the less common acute lymphocytic leukemia of adults to respond as frequently as this type in children.

Table II lists the remission rates for some of the larger series of adult leukemia treated with 6-mercaptopurine. In many of these series, the acute blastic crisis of chronic granulocytic leukemia is included.

*TABLE II*

*Response of Adult Acute Leukemia to 6-mercaptopurine*

| Author | Ref. # | No. of Adults | % of Remissions | |
|---|---|---|---|---|
| | | | Complete | Partial |
| Whittington | 25 | 25 | 4% | 24% |
| Ellison and Burchenal | 6 | 58 | 7% | 28% |
| Hayhoe | 26 | 15 | 13% | 33% |
| Hall | 27 | 24 | 17% | 38%[1] |
| Bross[2] | 7 | 113 | 15% | |
| Hyman and Gellhorn | 24 | 12 | 17% | 17% |

[1] partial and clinical only

[2] excluding acute monocytic leukemia

Bross[7] and Bethell and Thompson[9] found that acute monocytic leukemia was even less responsive than the other types of acute leukemia in adults. Apparently, blastic crisis of chronic granulocytic leukemia responds to the same extent as adult acute leukemia, when treated with 6-mercaptopurine.[9-11]

The only other use for 6-mercaptopurine in neoplastic disease is in chronic granulocytic leukemia. One long-term study[12] concluded that 6-mercaptopurine was equally as effective as busulfan, but that the degree of control fluctuated less with the latter drug. A shorter term study[13] showed 6-mercaptopurine to be more useful in the occasional patient whose platelet count was lowered too far by busulfan.

A review of the clinical effects of 6-mercaptopurine in tumors other than acute leukemia or chronic granulocytic leukemia has appeared.[14] The conclusions of the review were that there is little or no usefulness of this agent in other tumors. The use of 6-mercaptopurine in non-neoplastic conditions is beyond the scope of this book.

The generally accepted dosage for 6-mercaptopurine is 2.5 mg/kg/day given in one dose. If, after four weeks of treatment no response has occurred, many authors advocate increasing the dose to 5.0 mg/kg/day. In acute leukemic patients, peripheral white and platelet counts are followed closely for toxicity. However, initial counts may be low, and high blast counts may drop, before normal cells return. Therefore the peripheral white blood count and platelet count may not be a completely accurate guide for dosage.

When the white blood count is dropping in patients with acute leukemia on 6-mercaptopurine, it is sometimes difficult to decide whether the patient is having toxicity or a beneficial response. This problem arises in most patients, since some degree of leukopenia is almost inevitable before remission occurs. In addition, a significant percent of children with acute leukemia are leukopenic before therapy. Thrombocytopenia is also extremely common in adults and children with acute leukemia.

Some points are helpful in deciding if the low white blood count is a sign of toxicity. If the patient's initial white blood count is normal or low, it is rare for the drug to cause toxicity in the first two weeks. However, patients with initial white blood counts over 20,000/mm$^3$ may have a precipitous fall in this count within the first 5 to 6 days of therapy. These are the patients

who are in greatest danger of developing urate nephropathy with anuria. (This will be discussed later in this chapter.)

If the hemoglobin and platelet count rise, or the differential improves as the white blood count falls, this is against drug toxicity. The bone marrow aspiration is very helpful. If the marrow is very hypocellular, the drug should be stopped until the peripheral white blood count rises. However, if the marrow is cellular, therapy may be continued.

It may be helpful at this point to review the serial changes in microscopic appearance of the bone marrow aspirate noted by Ellison and Burchenal[6] in 6-mercaptopurine-treated adult acute leukemia. These authors noted the first change in patients showing a favorable response, to be decreased marrow cellularity and a decreased percentage of blast cells. They then noted a marked increase in nucleated red blood cells, up to as high as 50 to 60% of total marrow cells. Normal cellularity of the marrow was then noted. They noted that some degree of marrow hypocellularity occurred prior to remission in the majority of cases undergoing remission.

If there is still doubt, it is best to stop the 6-mercaptopurine for 7 to 10 days. If the drop in white blood count is due to toxicity, the white blood count will rise within a few days. If the disease is causing the drop, there will be no improvement.

Rapid drop of peripheral white blood count at any time in the course of 6-mercaptopurine therapy should be considered very suspicious of toxicity. It is best to stop the drug for 7 to 10 days if this occurs.

Toxicity of 6-mercaptopurine is almost entirely directed to the marrow. Depression of white blood count, platelet count, or red cells can occur. However, the major effect is on the granulocytes. Ellison and Burchenal[6] noted that a few patients with chronic granulocytic leukemia, who had been on 6-mercaptopurine for 6 to 18 months, had anemia and thrombocytopenia which cleared when the drug was stopped. They had not noted this in 58 adults with acute leukemia.

Impaired renal function may increase the toxicity of 6-mercaptopurine. However, this has not been conclusively demonstrated in humans. In any case, it is best to use smaller doses if the blood urea nitrogen is elevated.

Marrow toxicity of 6-mercaptopurine is rapidly reversible, with the toxic effects usually over within less than seven days

of stopping the drug. However, death from septicemia may occur during this period.

After bone marrow depression, the most important toxicity of 6-mercaptopurine is liver damage. Animal studies have clearly demonstrated that 6-mercaptopurine causes hepatic necrosis.[15] However, at first it was thought that liver toxicity in man was not caused by 6-mercaptopurine. This is because of the moderate incidence of hepatic damage due to leukemia itself, or from the transfusions or infections occurring during the course of the disease.

Einhorn and Davidsohn[16] studied this problem. They noted jaundice in 16 of 38 patients with acute leukemia while on 6-mercaptopurine, but only one case in 11 patients not on 6-mercaptopurine. Of the 16 patients, they attributed the jaundice to 6-mercaptopurine in 9. In 8 of these 9, the jaundice cleared within 5 to 14 days of stopping the 6-mercaptopurine. The 9th patient died of leukemia while still jaundiced. Two patients had 2 separate episodes of 6-mercaptopurine-induced jaundice, with prompt clearing of 3 of these 4 episodes on stopping the drug. The 4th episode occurred preterminally.

Einhorn and Davidsohn[16] also studied the liver function abnormalities in these patients. Seven of the 9 patients with 6-mercaptopurine-induced jaundice, had elevated levels of glutamic-oxaloacetic transaminase, but 6 of these had maximum levels below 300 units. Alkaline phosphatase was moderately elevated. In the two patients who were jaundiced at death, both had intrahepatic cholestasis at autopsy, and one of these had foci of hepatic necrosis.

These authors also noted that 5 of the 9 patients with jaundice that they attributed to 6-mercaptopurine, had oral lesions, and 6 had severe leukopenia. Three of the 9 had received doses higher than the recommended 2.5 mg/kg/day. They felt that these three factors (oral lesions, high dosage, and severe leukopenia) were more common in jaundiced patients.

McIlvanie and MacCarthy[17] reported four patients who developed hepato-toxicity after 2 to 5 months of therapy with 6-mercaptopurine. Three patients had prompt clearing of jaundice after stopping the drug. Two patients had liver biopsies while jaundiced, which showed bile stasis.

Clark et al[18] reported two patients with acute leukemia who died with hepatic necrosis and intestinal ulceration while on 6-mercaptopurine. One of these was also on methotrexate, which

is known to cause similar lesions. These authors mentioned liver tenderness as a useful sign for cessation of 6-mercaptopurine therapy.

It is therefore advised that patients receiving 6-mercaptopurine be observed for hepatic toxicity. If jaundice appears, the drug should be stopped. If the jaundice can be attributed to other causes, the decision may be difficult. However, it is best to stop the drug until the situation is clarified. Jaundice due to 6-mercaptopurine should clear within two weeks of stopping the drug. The drug may then be cautiously restarted, and the patient's liver status followed carefully. If jaundice reappears, it is best not to use 6-mercaptopurine again.

Liver tenderness is a useful early sign of liver toxicity. Frequent liver function tests are apparently not necessary, as jaundice is reversible, and it is sufficient to examine for clinical jaundice.

Other less important areas of toxicity have been mouth ulcers occurring in less than 20% of patients, occasional nausea and vomiting, and rare drug fever and skin rash.

Uric acid nephropathy is an ever present danger, when 6-mercaptopurine is used in acute leukemia. Very few cases have been reported.[19,20,21] This is because of the general awareness of the danger, and the precaution of administering adequate fluids to these patients. This problem is discussed in greater detail in the chapter on methotrexate, and the chapter on special toxicity.

The problem of safety of 6-mercaptopurine in the pregnant woman will also be discussed in a later chapter. It should be noted that fetal abnormalities were not noted in animals given 6-mercaptopurine in the same dosage by weight as the usual human dosage (2.5 mg/kg).[22] However, higher dosage did cause fetal abnormalities in mice. Fetal abnormalities have not been noted in the few babies born to mothers receiving 6-mercaptopurine in the first trimester of pregnancy. Diamond et al[23] did report a child born with fetal abnormalities to a mother who received 6-mercaptopurine and busulfan together in the first trimester of pregnancy.

In summary, 6-mercaptopurine is a useful drug in childhood acute leukemia. At present, it is being used in conjunction with other active antileukemic drugs in various regimens of cyclic therapy. These regimens have significantly prolonged survival in childhood acute leukemia. 6-mercaptopurine is less useful in

adult leukemia, but is still the drug of choice. Its major toxicity is bone marrow depression, with hepatotoxicity a somewhat less important danger.

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# CHAPTER V

## 5-FLUOROURACIL

5-fluorouracil (FU), commercially available as Fluorouracil® (Roche), is the only pyrimidine antagonist available for clinical use. 5-fluorouracil-2' deoxyuridine (FUdR) has had extensive clinical trials and seems to be more effective.[1-4] However, it is not yet available, because of limited supply.

These drugs have an extensive literature. Heidelberger[1] states that more than 250 papers were published in 1962 alone, dealing with these compounds. In 1963 he was able to summarize 27 reports of large series with a total experience of 2,375 patients who had received 5-fluorouracil in gastrointestinal, breast, and female genital cancer. The reason for this great interest is that the fluoridinated pyrimidines are the only compounds which can produce objective remissions in a significant percentage of patients with adenocarcinoma of the gastrointestinal tract.

Despite the large amount of literature, and great interest, 5-fluorouracil is a drug of only slight usefulness. C. Gordon Zubrod of the National Institutes of Health evaluated his and other authors' experiences with 5-fluorouracil in 1961.[5] He discussed the price in toxicity that must be paid for the relatively short remissions, and came to the conclusion that there was very small, if any, advantage in using the drug. As experience with the drug has increased, it is apparent that a small group of patients receive useful results, but that many patients with objective response are helped little if at all. (This whole question will be discussed in detail later in the chapter.)

5-fluorouracil has been used most extensively in adenocarcinoma of the gastrointestinal tract. Heidelberger,[1] in reviewing 25 reported series, found 308 patients with objective responses of 1,041 treated. Apparently, response rates are the same for stomach, pancreas, or colon and rectum carcinomas.[6] Most

authors report a 15 to 30% objective response rate. The criteria for improvement used by the Wisconsin group[7] have been more or less those used by other groups. These criteria are as follows: (a) Measurable reduction of at least 25% in the size of a measurable lesion; (b) subjective improvement; (c) leveling off or reversal of a downward weight curve; (d) improvement in the performance status; (e) presence of all of these criteria for not less than two months.

Ansfield et al[7] reported their results of five years' clinical experience with 5-fluorouracil in 1,091 patients given 1 to 54 courses. However, they reported results in only the 428 of these patients with measurable lesions. They felt the other patients could not be evaluated for objective response, because of the lack of measurable lesions.

Despite this great care in attempting to describe *objective* response, Zubrod[5] feels that it is a difficult task. He states that "in reaching the judgment that drug favorably influence cancer, one is in the case of gastrointestinal neoplasms largely dependent on tumor size. Unfortunately, because of the anatomical sites of these tumors, changes in tumor size are always difficult and often impossible to assess. In other words, the only available endpoint for decision about drug activity is rather indeterminate, and thus different physicians may reach different conclusions about the effectiveness of drugs in these diseases."

It is difficult to determine the duration of remissions produced by 5-fluorouracil from reviewing the literature. Ansfield[7] reported 91 patients with remissions in gastrointestinal, breast, and female genital carcinomas. Thirty-seven remissions lasted more than six months, and 13 patients were still in remission at less than six months. Moertel[4] reported 31 patients with gastrointestinal neoplasms who responded. Twenty-two of these had reactivated their disease after an average of 4½ months of remission. Nine patients were still in remission, with an average duration of remission of 11 months. Kennedy et al[8] treated various tumors. Eighteen of 31 remissions lasted more than 2 months, and only 12 lasted as long as 6 months. However, Ansfield[7] had several patients still in remission over 4 years after onset of therapy.

It would seem that the median duration of 5-fluorouracil-induced objective remission in gastrointestinal carcinoma is in the range of six months. Occasionally patients may have remissions lasting over a year.

In breast carcinoma, percentage and duration of remission are of the same order.[1,7-13] Most therapists have come to the conclusion that 5-fluorouracil is the preferred chemotherapeutic agent in breast carcinoma. However, endocrine therapy, because of its lesser toxicity, should be tried first. In centers where hypophysectomy and/or adrenalectomy are performed frequently, these procedures too, would be used generally before chemotherapy. Certainly reported results with 5-fluorouracil in breast cancer seem to be better than those with alkylating agents.

Especially impressive have been the results in a few patients with massive liver involvement.[13,14]

There have been fewer reports of the use of 5-fluorouracil in ovarian carcinoma. Heidelberger[1] in his review, notes 48 responses in 164 patients with "female genital cancer." However, this group is not further broken down. In view of the good results with alkylating agents, they would seem to be the drugs of choice.

Before discussing the dosage and administration of 5-fluorouracil, it is important to discuss selection of patients for therapy. Ansfield[3] and his group[7] have studied this problem most extensively. They felt that there was a group of patients who could not tolerate sufficient drug for a therapeutic response. They called this group the poor risk group, and did not treat most of these patients. Certain patients within this group could be treated with a lower dosage regimen. These authors classified patients as poor risk patients because of the presence of one or more of the following; (a) protein loss or impaired protein intake; (b) extensive liver metastases; (c) extensive pelvic irradiation at any time; (d) extensive pelvic bone metastases; (e) previous repeated use of alkylating agents; (f) previous adrenalectomy or hypophysectomy; (g) advanced physiologic age of 70 or older; (h) significant infection. Apparently, as their experience increased, they were able to treat a larger portion of these poor risk patients, but always using a lower dose than in the good risk patients. In their latest article[3] where they used a newer, less toxic regimen, most poor risk patients were able to receive the drug. However, even with the newer regimen, poor risk patients received less of the drug than the good risk patients.

In addition to the above precautions, it is inadvisable to treat with 5-fluorouracil within thirty days of a major surgical procedure. Jaundice when due to intra- or extrahepatic biliary obstruction is not a contraindication to therapy.

Most authors would agree that the severely ill patient in poor nutritional status is a poor candidate for 5-fluorouracil therapy, and would not treat any patient who could not maintain food intake, due to frequent vomiting. Certainly, marrow depression from previous radiotherapy, chemotherapy, or the disease itself is an absolute contraindication to 5-fluorouracil. Marrow recovery after previous chemotherapy or radiation would not contraindicate the drug, but should be the signal for lower than standard dosage until tolerance is determined.

5-fluorouracil is available as Fluorouracil in 10 cc ampuls as an aqueous solution containing 50 mg/cc of the compound buffered with sodium hydroxide. It is given directly intravenously without dilution. The package insert recommends use of a 25 gauge needle. Hospitalization is generally recommended for at least the first course.

Ansfield et al,[7] with the largest experience, used the following dosage regimen until recently: 15 mg/kg intravenously daily for 5 days, then 7.5 mg/kg every other day until slight toxicity. The maximum daily dose was one gram, and ideal weight rather than actual weight was used in the presence of obesity or fluid retention, such as ascites or edema. This dosage regimen was similar to that followed by most other authors, although some limited the total number of injections to 7 to 9, whether toxicity appeared or not. This was academic, as toxicity usually occurred by the 7th or 8th injection.

Ansfield and his group[7] felt that repeated courses had to be given approximately thirty days after completion of the last course. This was continued until relapse. Their experience was that if intervals between courses were prolonged beyond this period, the disease became unresponsive. Until recently, they insisted that each course be carried to slight toxicity. Most authors have followed these recommendations. Some have advised reducing dosage in later courses, in light of sensitivity to the first course. By this technique, they give slightly less of the drug than caused toxicity in the first course, and avoid toxicity with most of the later courses. Vaitkevicius et al[13] felt that the intervals between courses should be less than 3½ weeks, and in their latest patients retreated as soon as toxicity was gone and white blood count rose over 4,000.

There have been numerous other regimens proposed. Lemon et al[15] gave the drug by infusion in 5% glucose and water over

an 8 hour period. Toxicity was far less; and they claimed equally good therapeutic benefit. These results have not been confirmed by others.[10,16,17,18]

Several authors have experimented with weekly or biweekly maintenance therapy rather than repeated courses.[10,12,18-20] Variable results occurred, with several authors, especially Rochlin,[10] reporting equally good results with maintenance therapy.

Ansfield[3] has recently reported a modified regimen that avoids toxicity in one-third of good risk patients, yet seems to give results equally as good as their earlier regimen. This regimen is 12 mg/kg/day for 5 days; then 6 mg/kg/day every other day to slight toxicity, or for 11 such half doses, whichever occurs sooner. The poor risk patients received the same regimen, except that the 12 mg/kg/day was given for 4 instead of 5 days. Patients with extensive whole pelvis radiotherapy were not treated, and if food intake was more than moderately impaired, the therapy was stopped for 30 days. In all patients, subsequent courses of 5-fluorouracil were started 30 days after the last dose of the preceding course.

Until these various dosage regimens are tested further, I would suggest using the newer Ansfield regimen[3] of 12 mg/kg/day for 5 days, followed by 6 mg/kg every other day until slight toxicity, as described above. Subsequent courses should have dosage adjusted down about 10%, or be stopped earlier, if more than slight toxicity occurs in the first course. Thirty day intervals between finish of one course and start of next are recommended. Poor risk patients, if treated, should receive only 3 to 4 of the 12 mg/kg doses followed by 6 mg/kg every other day.

Slight toxicity is defined as visible stomatitis, or diarrhea of 3 to 4 or more liquid or semi-liquid stools per day. White blood counts below 3,500 or platelet counts below 150,000 should cause one to end the course.

Toxicity of 5-fluorouracil is apparently an almost inevitable accompaniment of therapeutic doses. The trick is to prevent moderate or severe toxicity. Much has been written about the toxicity of the drug. Degree and frequency of toxicity depend upon how aggressive the authors are in using the drug. Most authors report a 3% to 7% incidence of drug-induced deaths.

Gastrointestinal tract injury is the major toxicity of 5-fluorouracil. Stomatitis occurs in 48% to 75% of patients,[4,7,11] while nausea and vomiting occur in 30% to 64%, and esophago-pharyngitis

in 6% to 10%. The stomatitis most commonly takes the form of small shallow ulcerations on the inner surface of the lower lip. Sore mouth may precede stomatitis by one or more days. The mouth and lips of the patient should be carefully examined for early ulceration before each intravenous dose.

Rochlin et al[10] have emphasized the occurrence of dehydration and electrolyte imbalance as a result of drug-induced diarrhea. This was not always reversible, and in several series, it was a cause of death. Vomiting alone is not sufficient toxicity to stop the drug unless it is frequent enough to interfere with food intake.

Vaitkevicius et al[13] have recommended the routine administration of oral neomycin along with 5-fluorouracil. They feel that this will prevent absorption into the blood stream of potentially lethal gram-negative bacteria through denuded gastrointestinal mucosa. Several of their patients died from gram-negative septicemia prior to use of neomycin. They have had no deaths from 5-fluorouracil in their last ninety treated patients.

Bone marrow toxicity is extremely common, although usually occurring after gastrointestinal toxicity. For this reason, it is usually not the reason for ending a course. Rochlin et al[10] found leukopenia inevitable after the initial course of 5-fluorouracil, even when the drug was stopped because of mouth ulcers. However, most authors have noted only a moderate incidence of severe leukopenia. Ansfield et al[7] found leukopenia below 2000/mm$^3$ in 32% of patients, and minimum white blood counts between 2000/mm$^3$ and 3000/mm$^3$ in another 22%. Moertel et al[4] noted a minimum white blood count below 3000 in 56%, below 2000 in 39% and below 1000 in 12% of patients. Weiss et al[11] noted leukopenia below 3000 in only 24 of 108 patients.

Kennedy et al[8] noted the maximum granulocytopenia between the 11th and 22nd day after the first dose. The average day of maximum leukopenia was the 16th day and the white blood count depression lasted from a few to 10 days. These authors used the same dosage regimen as the Wisconsin group.[7]

Thrombocytopenia has been less of a problem although 2 of the 170 patients of Vaitkevicius et al[13] died from hemorrhage. Kennedy et al[8] noted thrombocytopenia in 83% of cases with the maximum drop between 7 and 17 days from the first dose. Recovery of thrombocytopenia was slower than that of the leukopenia. However, petechiae were rare, and only 2 of 118 had platelet counts below 50,000.

Anemia, mild in degree, has been observed.[8] It can be concluded that thrombocytopenia and anemia are rarely a clinical problem with 5-fluorouracil therapy. However, leukopenia is a major problem. Most drug-induced deaths occur when the white blood count is below 2000,[13] and many of the deaths can be directly attributed to infection during a period of leukopenia.

Other toxicity is fortunately of less significance. Alopecia has been reported by most authors to occur in 5 to 20% of patients.[4,7,11] Ivy[9] stated that marked hair loss invariably followed the first course of therapy, but that alopecia severe enough to require wearing of a wig occurred in only 5 of 22 patients. He noted that there was frequently some regrowth of hair even with repeated courses. These subsequent courses were somewhat smaller than the initial one, in an effort to modify other more serious toxicity.

Dermatitis has been quite frequent, but rarely serious. Vaitkevicius[13] noted extensive erythema in exposed skin areas. Ansfield[7] noted an 8% incidence of dermatitis, and Moertel[4] noted a 15% incidence. Ivy[8] noted an erythematous burning eruption on the face in 2 of 22 patients. Vaitkevicius[13] noted tanning and marked atrophy of the skin in his more intensively treated patients.

Neurotoxicity has been a complication described by several groups. Weiss[11] described one patient who had two episodes of optic neuritis associated with 5-fluorouracil therapy. Moertel et al[21] have reported a 5% incidence of cerebellar ataxia associated with 5-fluorouracil or 5-fluoro-2'-deoxyuridine therapy of gastrointestinal carcinoma. This complication was more frequent when the interval between onset of one course and onset of the next was 4 rather than 5 weeks. Eight of 18 patients, with this complication, had disappearance of the ataxia when therapy was continued at less frequent intervals. It should be noted that Moertel et al[21] use a much shorter interval between courses than Ansfield et al[7] and most other authors. Ansfield et al[7] waited four weeks from *end* of one course to onset of the next.

Much has been written about the combination of radiotherapy and 5-fluorouracil. Toxicity with this combination is much greater and there is no evidence of added therapeutic benefit.

Patients who have had adrenalectomy are much more sensitive to 5-fluorouracil. Tipton[22] reported three women who were well maintained on maintenance corticosteroids after adrenalectomy. All three died rather rapidly after start of 5-fluorouracil therapy.

Tipton advises quadruping the maintenance dose of cortisone before using 5-fluorouracil in adrenalectomized patients. He cites experiments in dogs to support this idea.

In summary, 5-fluorouracil is a potent antitumor agent of limited usefulness in adenocarcinoma of the gastrointestinal tract and advanced breast carcinoma. Severe gastrointestinal tract and moderately severe bone marrow toxicity preclude effective antitumor dosage in most patients. A small percentage (perhaps 10%) of patients achieve a useful clinical result.

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## CHAPTER VI

## VINCA ROSEA ALKALOIDS

The *Vinca rosea* alkaloids (vinblastine and vincristine) are the most important new group of cancer chemotherapeutic agents of this decade. Just how new they are is illustrated by this quotation from a review article published in 1962:[1] "It's (vinblastine) use is to be decried except as an experimental agent of potential lethal toxicity in hospitalized patients who are resistant to other forms of therapy." However, at this time, in July, 1966, vinblastine is considered to be a safer and equally effective agent in Hodgkin's disease as the alkylating agents. It is usually given on an outpatient basis. Vincristine, an even newer member of the group, has been released by the Food and Drug Administration for use in acute leukemia, and while not as effective as methotrexate and 6-mercaptopurine, it is producing remissions in acute stem cell leukemia of children in over 50% of the cases.

### Vinblastine (Velban)

Vinblastine® (Lilly & Co.) is probably the least toxic of all effective cancer chemotherapeutic agents. Unfortunately, its usefulness is limited to three diseases: Hodgkin's disease, choriocarcinoma, and probably breast carcinoma. In Hodgkin's disease, objective remissions occur in 50 to 90% of patients treated.[2-8] Remissions last for several weeks to over a year. The median duration of remission is in the range of 4 to 7 months. Because of the recent introduction of this agent, the maximum duration of remission cannot be predicted. Several authors reported patients still in remission after 12 months.[3,6] Although occasionally patients with Hodgkin's disease have had prolonged remissions after one course of therapy, there is general agreement that maintenance therapy is necessary. Patients refractory to alkylat-

ing agents seem to respond as well as those not so treated. Remissions in choriocarcinoma have been reported in methotrexate-resistant patients.[8,9] These authors reported 5 remissions in 12 treated patients. Until more data are accumulated, the exact place of vinblastine in choriocarcinoma treatment is uncertain. It is doubtful whether it will approach methotrexate in usefulness.

The effectiveness of vinblastine in breast cancer has been demonstrated by Armstrong[3] and Johnston[10] in approximately 50% of a small group of patients. Unfavorable results were reported in 23 patients by Goldenberg.[11] However, he treated his patients for only 4 weeks, while the other two groups noted remissions only after 2 or more months of treatment. It should be noted that responses are seen in patients with Hodgkin's disease as early as 1 to 2 weeks after the onset of treatment, and patients with choriocarcinoma will show a drop in gonadotropin titre within 2 to 3 weeks.

Isolated instances of remissions in patients with solid tumors,[2-5] monocytic leukemia,[4,7] and other leukemias have been reported.[3,7,12] However, the remissions were partial, and rarely lasted over two months. One amazing case of complete disappearance of an extensive rhabdomyosarcoma in an 8 month-old infant has been reported.[12] No other reports of this type are available. Use of vinblastine in these conditions is still experimental, and at present vinblastine is not really useful in any condition other than Hodgkin's disease.

Vinblastine is administered intravenously, although the oral route has been tried with some success.[13] However, the absorption from patient to patient was variable, with an average of 3.7 times the dose required orally. Gastrointestinal toxicity was greater with the use of the oral form. When vinblastine is administered intravenously, great care must be taken to prevent infiltration. If there is any doubt as to adequacy of the veins, vinblastine should be injected into the tubing of an intravenous infusion. The drug is given once every seven days, until remission or toxicity occurs. Maintenance therapy is then given every one to four weeks. The initial dose is usually 0.10 mg/kg intravenously. However, if the patient has had recent extensive radiotherapy, or recent cancer chemotherapy with another agent, the initial dose should be lower.

In this and following paragraphs, I will outline a regimen for vinblastine that I have found useful. It is almost identical with

the one in the current package insert for Velban®. However, until August, 1963, the package insert suggested a higher dosage regimen. This was changed because of excessive toxicity. Blood counts are taken at 4 days and 7 days after the initial dose of 0.1 mg/kg. If neither white blood count is below 3,500, the second dose is given one week after the first. This dose is 0.05 mg/kg larger than the first. The medication is then given weekly, increasing the dose by 0.05 mg/kg/week, until leukopenia below 3,500 or remission is produced. As with other agents given to the point of mild toxicity (such as anticoagulants, and digitalis glycosides), it is best to approach the limiting dosage gradually. As leukopenia is approached, weekly increments of less than 0.05 mg/kg are advisable. If remission occurs, the dosage is maintained at weekly, and then gradually increasing intervals. Most patients will have either a remission or leukopenia by the time the dosage reaches 0.3 mg/kg/week. If toxicity occurs before remission, smaller dosages may be tried at weekly intervals. However in Hodgkin's disease signs of remission such as drop in fever, subjective improvement, and increased appetite, will occur within two weeks of reaching effective dosage. In Hodgkin's disease, remission may occur at doses that do not produce leukopenia. It should be noted again that the Velban package insert prior to August, 1963, advocated a more aggressive regimen. I would strongly advise against this regimen, unless the physician has had considerable experience with vinblastine.

In breast cancer, need for continuing therapy at weekly intervals, in a dosage which will keep the white blood count below 4,000 to 5,000 may be necessary for as long as three months, before remission occurs.

More aggressive regimens have been tried, and are useful in patients where rapid response is necessary. They are best utilized by the physician with considerable experience in cancer chemotherapy. Frost et al[6] gave 0.3 to 0.6 mg/kg over a 3 day period as initial therapy to 12 patients with Hodgkin's disease. However, septicemia due to leukopenia occurred in four of these patients. He noted six objective remissions, with 2 patients still in remission at 12 months.

With the less aggressive regimens, irreversible leukopenia almost never occurs. Maximum leukopenia usually occurs within 4 to 7 days after injection, and white blood count rises rapidly thereafter. It is important that no dosage of vinblastine be given,

until the white blood count is determined that day. White blood counts must be done carefully by an experienced technician, for a difference of as small as 25%, may be significant in deciding on dosage.

The maintenance dosage should be that necessary to maintain remission. It is not always necessary to cause leukopenia to maintain remission. However, the patient who has had a vinblastine remission should not have the drug stopped because of relapse, until white blood counts below 3,000 have been achieved. If relapse is not reversed after several successive leukopenia-producing dosages of vinblastine, it may be concluded that the drug-induced remission is over.

At first, some investigators did not continue maintenance therapy after the initial remission. However, it is now recognized that remissions are considerably shorter without maintenance therapy.

Although vinblastine is one of the safest of all cancer chemotherapeutic agents, it can produce serious toxicity and even death. The major toxicity of vinblastine is on the granulocytes. In almost every patient, leukopenia is the limiting factor in dosage. Further drop in white blood count rarely occurs more than seven days after a single dose of vinblastine. According to the Lilly & Co. package insert, spreading the weekly dose over a seven day period does not decrease toxicity. This is confirmed by Frei[2] who found 0.05 mg/kg/day for seven days equally as toxic as 0.35 mg/kg given in one single dose.

Leukopenia is apparently almost always reversible. When death occurs it is usually from septicemia during a period of leukopenia.[6] The effect of vinblastine on the platelet count is far less than on the white blood count.[2,3,7,8] With the higher dosage regimen Frost[6] noted some drop in hemoglobin. However, it is not unusual for hemoglobin to rise, when an anemic patient with Hodgkin's disease undergoes a vinblastine-induced remission.

Nausea occurs in approximately one-fifth of patients, usually occurring transiently after the injection.[3] Alopecia which is dose dependent occurs in 5 to 10% of cases.[4,5,7] It is reversible, and hair regrowth may occur during maintenance therapy. Neurological complications are mild, but fairly frequent, especially at higher doses.[2] A feeling of depression is the most common neurological complication; the other neurotoxicity is less frequent. Johnston[10] noted a feeling of depression in her six patients, coincident with

the appearance of leukopenia. Frei,[2] using higher dosages, noted psychosis, mental depression and convulsions. Hill[5] noted mental confusion. Frost[6] mentions anxiety as a side effect.

Most authors describe paresthesias and loss of deep tendon reflexes in the lower extremities in less than 10% of cases. Phlebitis may occur in less than 10% of patients, and local infiltration causes severe pain. Because of the danger of phlebitis, vinblastine should not be injected into a vein with increased venous pressure, such as might occur in a superior mediastinal syndrome (superior vena cava syndrome). Diarrhea is mentioned as an uncommon side effect.

Vinblastine has been used for local arterial infusion or perfusion[4,14] in a few cases. The results have not been promising, although some slight objective response was obtained in 2 of 10 astrocytomas,[14] and 2 of 4 melanomas.[4]

In summary, vinblastine is a useful and safe drug for Hodgkin's disease, on the order of usefulness of the alkylating agents. It is also of some value in choriocarcinoma and breast cancer. It is given intravenously at weekly intervals, in a dosage sufficient to produce remission or leukopenia in the range of 3,000. Remissions in Hodgkin's disease have a median duration of approximately four to seven months. Leukopenia has been the major and limiting toxicity, although mild emotional depression has been a somewhat annoying accompaniment of higher dosages.

## Vincristine (Oncovin)

Vincristine (Oncovin®) formerly known as leurocristine is probably the safest of all cancer chemotherapeutic agents, yet one whose usefulness is severely limited by its toxicity. This apparent paradox is explained, when it is realized that the toxicity of vincristine is rarely if ever lethal. The limiting factor in vincristine dosage, in almost every case, is neurotoxicity. Fortunately, children under ten years of age are more resistant to this neurotoxicity, so that vincristine is a useful agent for treatment of childhood acute leukemia. It is still questionable whether vincristine will be of great use in any other neoplastic diseases.

At the present time, vincristine is commercially available as Oncovin® (Elli Lilly & Co.), and is approved by the F.D.A. for use in acute leukemia in children. All other uses must be considered experimental.

The Oncovin package insert summarizes responses to vincristine therapy of 104 children with acute leukemia from six centers (Children's Cancer Research Foundation in Boston, National Cancer Institute, Roswell Park Memorial Institute, Sloan Kettering Institute for Cancer Research, University of Chicago, and the Lilly Laboratory for Clinical Research).

Because of difficulty in classifying leukemia, and differences in criteria among different centers, it is difficult to determine response rates for different types of acute leukemia from the data presented. However, there were only 5 patients with "acute myelogenous leukemia" in this group of 104 patients. One of these had a complete response, one had a partial response, and three had no response. The remaining 99 children with acute leukemia had 36 complete and 28 partial remissions. Twenty-six had no response, and 9 had inadequate trial. There seemed to be no difference in remission rate between the different age groups from 1 to 15. Only one child in the entire group was over 15.

It took an average of 38 days of treatment before remission was attained. Vincristine was usually given once weekly. Although there were some patients still in remission over 100 days, 36 patients had cessation of remission in 3 to 116 days after its onset. From this and other data discussed below, it is apparent that few children with acute leukemia will have vincristine-induced remissions lasting more than four months. Eleven of the 104 children needed intrathecal methotrexate for leukemic meningitis while receiving vincristine.

Mathé et al[15] noted 7 remissions in 15 children, and 2 remissions in 10 adults with acute leukemia. Remission lasted only a few weeks, but repeat courses were sometimes effective.

Selawry et al[16] of Roswell Park, using a rather high dosage regimen, noted 6 complete and 2 partial remissions in 10 children with acute lymphatic leukemia. The median duration of remission was 76 days, and one patient was still in remission at 167 days.

Evans et al[17] from Children's Medical Center in Boston, treated 68 children 14 or younger with acute leukemia. Some of their patients, as well as Selawry's were undoubtedly included in the 104 children summarized in the Oncovin package insert. Of these 68 children, 52 were considered evaluable, and 45 of these 52 were diagnosed as having "stem cell leukemia." Of these 45 patients, 11 received steroids in addition to vincristine. Of the 34 patients receiving vincristine alone, 23 had remissions. The

median remission apparently was in the range of sixty days.

Karon et al[18] from the National Cancer Institute reported similar results. These and other series are summarized in an excellent review article on the *vinca rosea* alkaloids by Johnson[19] from the Lilly Institute.

Vincristine has been used in a large variety of solid tumors with varying results.[19-27] The best results have been in Hodgkin's disease and reticulum cell sarcoma.[22-26] Remissions apparently occur in approximately 50 to 70% of patients, but last for less than four months in most cases. However, prolonged remissions up to a year have been reported in Hodgkin's disease.[20,22,27] While many of the remissions in Hodgkin's disease have been complete, useful partial remissions have also occurred. Remissions have been seen often enough in patients resistant to vinblastine, to conclude that there is no cross resistance.[22,24] It would appear that a small percentage of patients with Hodgkin's disease have a tumor so sensitive to vincristine that useful remissions can occur with minimal toxicity. Because of its neurotoxicity, vincristine is less useful than the alkylating agents or vinblastine in Hodgkin's disease.

In lymphosarcoma and reticulum cell sarcoma, partial and relatively brief remissions have occurred in a large percentage of cases.[15,19,20,22,24,26] Shaw et al[26] reported remissions in all seven patients with reticulum cell sarcoma treated with vincristine. However, the longest remission was 14 weeks, and the median duration of remission was 4 weeks.

Single instances of remission have been reported by Costa[22] in carcinoma of the cervix, carcinoma of the prostate, testicular teratocarcinoma, and choriocarcinoma. However, it is far too early to judge usefulness in these malignancies. Mittelman et al[28] noted 7 objective responses in 32 patients with breast cancer treated with vincristine. However "objective responses in these patients were too brief and toxicity was too severe" to make the agent useful. Hreshchyshyn[29] noted objective responses in 9 patients out of 20 with advanced carcinoma of the uterine cervix. However, in this series it would again appear that length of remission was brief, and neurotoxicity was severe.

There is evidence that vincristine may be of some use in tumors of children other than acute leukemia. Tan et al,[30] using very high dosages, reported brief remission in 2 of 3 children with embryonal rhabdomyosarcoma, 1 of 2 with neuroblastoma, and

1 with embryonal adenocarcinoma. Selawry[16] also using high dosages, reported single responses in children with neuroblastoma, rhabdomyosarcoma, ovarian dysgerminoma, and Wilm's tumor. The Southwest Cancer Chemotherapy Group[31] treated 13 children with Wilm's tumor with vincristine. Nine of these children had responses. However, only 3 of these responses lasted over 8 weeks. The most impressive report was of a 7 year-old girl, in whom a large liver metastasis was removed after 5½ weeks of vincristine therapy had shrunk the mass sufficiently to make resection possible. The child was free of disease 8½ months after hepatic lobectomy and 4½ months after vincristine therapy had been discontinued. Recently a regimen using alternate cyclophosphamide and vincristine has been reported to be effective in neuroblastoma. (See Chapter 8.)

While objective remissions have occurred with vincristine in many different types of malignancy, this is not the same as clinical usefulness. At present, vincristine is useful only in acute leukemia in children. It is worth trying in Wilm's tumor resistant to actinomycin D, reticulum cell sarcoma, and Hodgkin's disease. In Hodgkin's disease, it should be reserved for the patient who is resistant to alkylating agents and vinblastine, and who needs systemic therapy. It is possible that further investigation may reveal other uses for vincristine.

It should be mentioned that intraarterial therapy with vincristine has produced some objective remission in patients with brain tumors.[19] However this type of therapy, with other agents, has been of little clinical usefulness in brain tumors, despite objective responses.

Despite experimental use of several different types of dosage schedules, it is best to stick to the recommended method. Vincristine is highly irritating to tissues and great care must be taken to avoid extravasation. It is best administered into the tubing of a running intravenous infusion.

Vincristine should be given once a week. The initial dosage in children with acute leukemia is 0.05 mg/kg. The second dosage is .075 mg/kg with weekly increments of .025 mg/kg to a maximum weekly dosage of 0.150 mg/kg. If remission occurs before this maximum dose is reached, further increments are unnecessary. Weekly maintenance dosage, if used, averages .05 to .075 mg/kg. A prophylactic laxative regimen is suggested in conjunction with vincristine therapy (see below).

The question of whether to administer maintenance therapy after remission occurs is not resolved. Evans[17] attempted to compare duration of remission in those patients with and without maintenance therapy. His groups were too small to permit definite conclusions. In 11 patients with stem cell leukemia untreated with other agents, the remissions averaged 125 days in those on maintenance therapy, and 57 days in those not so treated. However, in 12 patients previously treated with methotrexate and/or 6-mercaptopurine, the remissions averaged 60 days in the maintenance group, and 55 days in the group not on maintenance therapy. A larger cooperative controlled study of this problem is being carried out. Preliminary reports from this study[32] show that a weekly maintenance dosage of 2 mg/m$^2$ of body surface did not significantly prolong remissions.

There is some evidence that vincristine gives a higher rate of remission in children with acute leukemia if it is used as the first drug.[19] However, Evans et al[17] report data that suggest it may be unwise to use vincristine as the first drug in the treatment of acute leukemia. They found that in 12 children who had vincristine as initial therapy for acute leukemia, only 3 subsequently responded to methotrexate. This is less than would be expected; the usual methotrexate remission rate is over 50%. However, there are far too few data on these points. More recently, Selawry and Frei[33] reported a remission rate of 85% in childhood acute leukemia using a combination of prednisone and vincristine. Very satisfactory maintenance of remission was achieved with methotrexate. It may well be that vincristine with prednisone is the preferred method of inducing remission in childhood acute leukemia.

Approximately 20% of children who have a vincristine-induced remission of acute leukemia will have symptoms of leukemic meningitis. This phenomenon is well known in methotrexate and 6-mercaptopurine-induced remissions, and is due to failure of the drug to pass the blood-brain barrier. Intrathecal methotrexate can be used in conjunction with the systemic vincristine, and will control the meningeal leukemia.

The dosage schedule for vincristine in adults is different than that previously described for children with acute leukemia. There is no generally accepted schedule. One that I have found safe and useful is outlined below.

As in children, the drug is given intravenously at weekly in-

tervals. The initial dosage is .01 mg/kg. Weekly dosage is increased by .01 mg/kg until remission is obtained or severe toxicity occurs. Minor neurological toxicity such as paresthesias is almost inevitable. If remission has not occurred before severe toxicity appears, it is still possible to give vincristine a further trial. The therapy is stopped until severe neurotoxicity clears. The drug is then resumed in a lower dosage without further increments. Johnson[19] presents the opinion that .025 mg/kg/week may be the best dosage for treatment of adults. Shaw and Bruner[26] gave 0.025-0.05 mg/kg/week in lymphoma patients without neurotoxicity.

Most remissions in adults have occurred within one month of start of vincristine therapy, and many have occurred within two weeks. This is, of course, influenced by the rapidity with which the dose is increased. Certainly, many patients will have a response within one week of reaching effective dosage. However, there have not been sufficient studies using a subtoxic dosage for several months. This approach apparently has been successful using vincristine's close chemical relative, vinblastine, in breast cancer. (See discussion earlier in this chapter.)

In the solid tumors, including solid lymphomas, maintenance therapy is apparently advantageous.[19] However, further studies are needed to clarify this point, and to determine the optimal maintenance dosage. At present, I would recommend the smallest weekly dosage necessary to maintain remission, raising dosage at the initial signs of relapse. This dosage should be in the range of .025 mg/kg/week.

The major toxic effects of vincristine have been on the nervous system. Only two groups have had significant bone marrow toxicity.[25,30] These groups used vincristine more often than once a week. It is not recommended, at present, that the drug be administered at shorter than seven day intervals. Shaw and Bruner[26] did note severe leukopenia in two jaundiced patients who received vincristine. This suggests that dosage should be lower in patients with jaundice.

The most troublesome neurotoxicity has been in the form of peripheral neuropathy. The earliest signs are paresthesias and loss of deep tendon reflexes. These usually occur after a month. The rate of appearance depends somewhat on the dosage schedule. The 104 children summarized in the Oncovin package insert had a 24.1% incidence of loss of deep tendon reflexes, and only 6.7%

incidence of paresthesias. The incidence of these side effects in adults is far higher.[20,22]

More severe neurotoxicity in the form of neuritic pain, foot drop, wrist drop, and muscular atrophy are not uncommon. A slapping gait as a result of foot drop and muscle weakness has been described.[16,19] Hoarseness and vocal cord paresis occur occasionally.

Eye muscle weakness has been reported, but it is not certain whether this is a result of meningeal leukemia rather than the drug itself.[16,18]

Severe constipation has been a troublesome and frequent complication of vincristine therapy, and is thought to be a form of neurotoxicity. Its occurrence is so common, that some form of prophylactic laxative regimen is recommended in conjunction with the use of vincristine in children. The Oncovin package insert recommends the use of a feces wetting agent and a methylcellulose bulk laxative three times a day. Should the child fail to have a bowel movement by noon, milk of magnesia is recommended, and if no stool is produced by evening, an enema is suggested.

High fecal impaction, with no stool in the ampulla, has occurred as a manifestation of vincristine-induced bowel hypomotility. Abdominal cramps and vomiting also occur fairly frequently as a result of the bowel disorder. Diarrhea is much less common.

Hair loss occurs in almost half the patients, and is often total. However, regrowth occurs on cessation of the drug, or when a lower dose is used for maintenance.

Bone marrow toxicity has been no problem except in the high dosage regimens.[25,30] Platelet counts actually tend to rise on vincristine therapy.[18,29] Vincristine is the only cancer chemotherapeutic agent that one can use in leukopenic patients without hesitation. Many of the children with acute leukemia, who have had vincristine, had white blood counts below 2,000 prior to therapy. These patients did not manifest marrow toxicity, and white blood counts rose in those who had remissions. However, because of the potential bone marrow toxicity, it is best to check the white blood count before administering the weekly dosage. Any significant drop in white blood count should be investigated, and if not otherwise explained, should lead to delay of vincristine administration.

Weight loss has been reported by Selawry,[16] but he used a

dosage higher than now recommended. Jaw pain[18,31] and oral ulceration (Oncovin package insert) are uncommon toxic effects. One series reported patchy hepatic necrosis in 5 of 12 patients.[22] However, liver function tests were not affected, and the significance of this toxicity is not yet known.

As with any other effective agent in leukemia, urate nephropathy is a potential hazard. Adequate hydration and frequent checks of serum uric acid are necessary.

Infiltration of vincristine into the tissues surrounding the vein causes severe local pain which may last for over a week.

Milder neurotoxicity may lessen or disappear when dosage is reduced. However, sensory loss, paresthesias, and muscle weakness are not so readily controlled. When vincristine is stopped, the paresthesias may last as long as three months.[20] Fortunately, in childhood leukemia the neurotoxicity has been severe enough to cause cessation of therapy in only a small percentage of cases.

In summary, vincristine is of established usefulness only in acute leukemia in children, on a par with methotrexate and 6-mercaptopurine. It shows some promise in Hodgkin's disease, lymphosarcoma, and reticulum cell sarcoma, but should not be used until alkylating agents have been tried first, and in addition, Velban, in the case of Hodgkin's disease. Its use in tumors of children and other malignancies is experimental.

It is given intravenously at weekly intervals, and neurotoxicity has been the limiting factor in dosage. The chief interest in vincristine is that it represents a totally new agent, with no cross resistance to any other known cancer drug, and little danger of lethal toxicity. It is hoped that a more useful analogue devoid of neurotoxicity can be developed.

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## CHAPTER VII

# ACTINOMYCIN D

Actinomycin D or dactinomycin has been released recently by Merck Sharp and Dohme as Cosmegen®. It is a highly toxic agent, but one which can be used with reasonable safety. Dramatic results have been produced by this drug in Wilm's tumor and choriocarcinoma of the uterus.

The most extensive literature on actinomycin D has concerned its use in Wilm's tumor of children. An excellent summary of the present role of actinomycin D in this tumor was published recently.[1]

Before one can discuss the exact place of actinomycin D in Wilm's tumor, it is important to discuss therapy of this tumor prior to the introduction of actinomycin D. Farber et al[2] state that cure rates with surgery alone or surgery plus radiotherapy were 40 to 48%, with 80% cure rate for children under the age of one year. Radiotherapy alone for lung metastases was hazardous, because of development of pulmonary fibrosis and interference with rib growth. With the addition of actinomycin D therapy to surgery and radiotherapy, Koop et al[1] report 81% survival in children over the age of one.

Koop et al,[1] Farber et al,[2] and Tan[4] report prolonged survival in some children with lung metastases, treated with radiotherapy to the lung lesions plus systemic actinomycin D. Smaller dosages of radiotherapy can be given because of the additive effect of the chemotherapeutic agent. Farber et al[2] report 10 children of a group of 29 alive 4 to 33 months after treatment with radiotherapy plus actinomycin D for widespread metastatic disease.

It is far from settled when actinomycin D should be used in Wilm's tumor. Combined local radiotherapy and systemic actinomycin D seems to be the best therapy for lung metastases. Routine treatment with actinomycin D for all children over the age of one,

even in the absence of metastatic disease, seems established. Whether preoperative and postoperative radiotherapy are both needed, and the strategic time for these courses of actinomycin D is not settled. Reference to articles by Koop et al[1,3] and Farber et al[2] is suggested for a more complete discussion of this problem.

The results with actinomycin D in choriocarcinoma are equally spectacular. Apparent complete cures with this compound have been reported.[5,6] The word "cure" here seems justified, as almost no patient with choriocarcinoma treated with methotrexate, who remained free of disease for one year, has relapsed. It is too early to say whether this will hold for actinomycin D-induced complete remissions. Hertz[6] reported 3 complete remissions in 7 patients with choriocarcinoma who received actinomycin D as initial therapy; and 10 complete remissions in 17 patients who relapsed after, or did not respond to methotrexate. With this regimen for choriocarcinoma (initial methotrexate therapy, with transfer to actinomycin D in those not responsive) he now reports 75% cure rate in this disease. He suggests actinomycin D rather than methotrexate as initial therapy for choriocarcinoma, if there is any evidence of liver disease.

Some objective responses have been reported with actinomycin D in other tumors, mainly highly anaplastic tumors of children such as embryonal rhabdomyosarcoma.[4,7-10] Generally, results have been far better when the drug was combined with local radiotherapy. Whether this combined therapy is better than radiotherapy alone remains to be seen. In any case, results have been only temporary in all but a rare patient with these tumors.

Actinomycin D is an ingredient of the so-called "triple therapy" regimen first described by Li.[11] This regimen will be discussed in the next chapter.

Actinomycin D is supplied as Lyovac Cosmegen® (Merck Sharp & Dohme). Each ampul contains 0.5 mg (500 micrograms) of the dry lyophilized powder plus 20.0 mg of mannitol. This powder is reconstituted with 1 cc of sterile water for injection. No other diluent should be used, as it may cause precipitation. The solution is then administered into the rubber tubing of a running intravenous infusion.

Dosage regimen varies with the tumor being treated. For Wilm's tumor, a course consists of 0.015 mg (15 micrograms) kg/day for 5 days if toxicity does not occur first. Farber et al[2]

recommend lowering this to a total of 0.60 mg (60 micrograms) kg for the entire course, if combined with radiotherapy.

In children under the age of one, with Wilm's tumor localized to one kidney, and no metastatic spread, it is doubtful that actinomycin D should be used. Postoperative radiotherapy in moderate dosage is recommended. However, Koop et al[1] do recommend giving actinomycin D during the surgery and for four days thereafter.

For children over the age of one, this regimen of actinomycin D with and after surgery is recommended without hesitation. Postoperative radiotherapy to the tumor bed is then given. Koop et al recommend a second 5 day course six weeks after the first.[1]

The situation in the presence of metastatic disease is far different. Here, the use of repeated courses of actinomycin D is mandatory. After removal of the affected kidney, radiotherapy is given to the tumor bed and to areas of metastatic spread. The lung dosage is limited (approximately 1200 r tissue dose). Koop et al[1] recommend 5 day courses of actinomycin D every 6 weeks for 6 months, then every 3 months for 6 to 9 months.

Bilateral Wilm's tumor presents a very special problem. Koop et al[1] report two children alive and well 13 and 26 months after bilateral radiotherapy and repeated courses of actinomycin D for bilateral Wilm's tumor. Neither kidney was removed.

For the treatment of metastatic choriocarcinoma, Brewer et al[5] recommend 0.010 mg (10 micrograms) kg/day for five days. Repeat courses are given when all evidence of toxicity except alopecia has subsided. Courses are repeated until complete remission occurs. Complete remission is defined as: disappearance of all physical, endocrinologic, roentgenologic, and pathologic evidence of disease. Three consecutive normal chorionic gonadotropin titres at weekly intervals are required for remission. Frequent follow-up, with monthly gonadotropin determinations for one year are recommended, because immediate retreatment is necessary in case of a relapse. As relapse after one year of sustained remission is rare, less frequent follow-up is required after the first year. Brewer et al[5] recommend every 3 months for the next 2 years, and every 6 months thereafter.

Dosage regimens for other tumors are less standardized. Reference to the original articles is recommended.[4,7-10]

Toxicity of actinomycin D is potentially quite severe. Toxic manifestations usually do not occur until 2 to 4 days after com-

pletion of a course of actinomycin D, and may not be maximal until 1 to 2 weeks after completion of therapy.

The major toxicity of actinomycin D is on the bone marrow, with thrombocytopenia of equal if not greater importance than leukopenia. Farber et al[2] recommend stopping therapy if platelet count falls below 150,000/mm$^3$, Tan et al[4] noted thrombocytopenia in 35% of courses and low white blood count in 50%. The depression of the white blood count was usually to 2000/mm$^3$, and occasionally less than 1000/mm$^3$. Pinkel[7] in treating 13 children, noted marked leukopenia in 2 children, and marked thrombocytopenia in 2.

Tan et al[4] found that the usual dosage was hazardous in patients with neuroblastoma with bone marrow involvement. Marrow toxicity was more likely to occur in these children.

The second major area of toxicity is the gastrointestinal tract from the oral mucosa to the rectum. Vomiting often occurs 4 to 5 hours after each injection. Nausea and anorexia are common, with abdominal pain and diarrhea less common. Mouth ulcerations are common, Tan[4] reporting oral toxicity in 60% of courses. Redness and ulceration may occur on the tongue, buccal mucosa, or mucosa of the nasopharynx. Pinkel[7] reported changes in the oral mucous membrane in 9 of 13 children.

Skin reactions are common, usually occurring at the site of previous radiotherapy. The most vulnerable time is within the first three months after radiotherapy, although flare-up of skin reactions has occurred as long as 17 months after completion of radiotherapy.[4] The skin reaction at the site of previous radiotherapy resembles the usual radiation reaction in the skin (erythema or increased pigmentation).

The Merck Sharp & Dohme direction circular also mentions skin eruptions at non-irradiated sites and acne as possible skin reactions.

Alopecia is an annoying side effect. Tan et al[4] report this in 40% of children. This usually occurred 7 to 10 days after the course was completed, and continued for 2 to 4 weeks before hair growth returned.

In summary, actinomycin D is a valuable drug for the treatment of Wilm's tumor and choriocarcinoma. Its toxicity is similar to methotrexate, affecting bone marrow and gastrointestinal mucosa. It has a potentiating effect on radiotherapy and can cause skin reactions at sites of previous irradiation.

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## CHAPTER VIII

# MISCELLANEOUS AGENTS AND TECHNIQUES

Previous chapters have discussed the major groups of cancer chemotherapeutic agents. Many agents which have been used extensively by investigators in the cancer chemotherapy field will not be discussed in this book. However, there is one agent, mithramycin, which shows great promise in treating embryonal cell carcinoma of the testis, and there are several techniques and concepts of therapy which remain to be discussed briefly. These include: (1) Combined drug therapies; (2) triple therapy; (3) combined radiotherapy and drug therapy; and (4) infusion and perfusion of chemotherapeutic agents (regional chemotherapy).

### Mithramycin

Recently, several groups have reported good results in some patients with embryonal cell carcinoma of the testis, using a new agent, mithramycin. Brown and Kennedy[1] report 7 objective responses in 12 patients. Three of the 5 non-responders received inadequate therapy, because previous extensive radiotherapy had limited the dose of mithramycin. In a review of the literature, they found 12 objective responses in 24 patients with embryonal cell carcinoma of the testis.

Brown and Kennedy's[1] patients had remissions lasting 2½ to 16 months. Two patients were still free of the disease, at the time of the report. Not all remissions were complete.

For dosage recommendations it is advised that the original articles be reviewed.[1,2] Brown and Kennedy[1] originally gave monthly courses. The first course was 0.050 mg (50 micrograms) kg/day intravenously for 5 days. The subsequent courses usually had to be given in reduced dosage, due to toxicity. Prior radiotherapy markedly reduced tolerance to the drug, necessitating

lower dosage. More recently, they advise 8-hour infusions of 0.025 mg (25 micrograms) kg in 1000 cc of 5% glucose and water. These infusions are given daily until early signs of toxicity appear. These signs have been epistaxis, or elevation of serum glutamic-pyruvic transaminase above 600 pyruvate units. The course is repeated at monthly intervals. Total number of courses to be given is not yet known.

Toxicity of mithramycin is impressive, affecting almost every tissue of the body. Nausea occurs for several hours after each dose. Central nervous system symptoms have occurred, such as irritability and lethargy. Bleeding, due to thrombocytopenia, is the major danger. Liver toxicity is manifested by increased prothrombin time, alkaline phosphatase, serum glutamic-oxaloacetic transaminase, serum glutamic-pyruvic transaminase, and serum lactic dehydrogenase. Renal toxicity is manifested by proteinuria, elevated blood urea nitrogen, and decreased urine concentrating ability. Hypocalcemia and hypokalemia also occur, as do stomatitis, fever, and plethoric facies. Three of Brown and Kennedy's[1] 12 patients died of drug toxicity. These died of massive gastric hemorrhage.

Recovery from drug toxicity is rapid when therapy is discontinued. Further experience with this drug is necessary before its exact role in embryonal cell carcinoma of the testis and other tumors is determined.

## Combined Drug Therapies

The concept of combined therapy has seemed an intriguing one. The outstanding success of this concept in the treatment of tuberculosis, has been an impetus to its study in the therapy of cancer. The concept is, that if several active agents are used, development of resistance to one or all will be delayed. Unfortunately, the results with combined or sequential therapies have been disappointing. The best results are described in the section on treatment of acute leukemia, where sequential therapy seems to have produced somewhat longer remissions. A number of authors have reported good results with combined therapy for solid tumors, at the meetings of the American Association for Cancer Research.

Ezra Greenspan[3] has reported good results in breast carcinoma with massive liver metastases by using "sub-optimal"

dosages of 5-fluorouracil combined with an alkylating agent, methotrexate, testosterone, and prednisone. Korst[4] reported better results in solid tumors with combined cyclophosphamide, methotrexate, and 5-fluorouracil. These results, although interesting, require much more study, preferably with the techniques of the CCNSC group studies.

Very recently, James et al[5] have reported very excellent results in childhood neuroblastoma using a regimen of alternating vincristine and cyclophosphamide. The principle of this therapy was that both agents had produced some degree of remission when given alone for neuroblastoma. The limiting toxicity of vincristine is neurotoxicity, while that of cyclophosphamide is marrow depression. Therefore, it was hoped that an additive antitumor effect could be obtained without any additive toxicity (true potentiation).

This group treated 9 children, 5 of whom had marrow or bone involvement. All 9 had some remission. Seven were still alive at time of reporting, having lived over one year. Five had complete remissions, and 2 more had complete remissions after chemotherapy, followed by additional radiotherapy and surgery.

The regimen used was vincristine 1.5 mg/m$^2$ BSA i.v. every two weeks, with cyclophosphamide 300 mg/m$^2$ BSA i.v. every two weeks on alternate weeks.

While these results are extremely impressive, confirmatory studies are needed. The most impressive fact in this study was that 4 patients with marrow or bone involvement had complete remission. This type of spread is almost 100% lethal with other means of therapy.

### Triple Therapy

Outside of sequential therapy for acute leukemia, the most promising combined therapy has been so-called "triple-therapy." This was developed by Li et al[6] at Memorial Hospital. It was used in testicular tumors, and complete regression was reported in some patients. Follow-up studies on this group and additional patients were reported in 1962 by Whitmore.[7] Objective response was noted in 3 out of 3 seminomas, 17 out of 25 embryonal carcinomas, 11 out of 17 teratomas, and 7 out of 10 choriocarcinomas of the testis. Some of these patients had received combined regimens, differing somewhat from the triple therapy regimen.

At the time of reporting, 5 patients were still in complete remission. These were:

1. Choriocarcinoma of the testis with pulmonary metastases and a positive human chorionic gonadotropin titre, still in complete remission at 42 months after start of triple therapy;
2. Embryonal carcinoma of the testis with pulmonary and left supreclavicular node metastases, still in complete remission 9 months after start of triple therapy;
3. Embryonal carcinoma of the testis with lung metastases, still in complete remission 33 months after start of triple therapy;
4. Choriocarcinoma of the testis with pulmonary metastases, in complete remission 36 months after onset of actinomycin D plus chlorambucil therapy;
5. Teratocarcinoma of the testis, with the only manifestation of disease prior to therapy being a positive chorionic gonadotropin titre, in complete remission for 75 months after onset of 6-mercaptopurine plus 6-diazo-5-oxo-L-norleucine therapy.

Triple therapy has also been used with some success in choriocarcinoma of the uterus by Brewer et al[8] in patients resistant to methotrexate or actinomycin D.

The triple therapy regimen is administered as follows: Initially, methotrexate is given orally, 5 mg daily in one dose. Chlorambucil is given simultaneously, 10 mg daily, also in a single dose. This is continued for 16 to 25 days. During this time, three 5-day courses of actinomycin D are given. These are started on the 3rd, 12th and 21st day after start of oral methotrexate and chlorambucil. Each course of actinomycin D consists of 0.5 mg (500 micrograms), i.v. daily for 5 consecutive days.

The subsequent courses are different from the initial course. They consist of methotrexate 5 mg and chlorambucil 10 mg given orally as a single dose, daily for 7 days. On the third day of this course, a 5 day course of actinomycin D 0.5 mg (500 micrograms) i.v. daily, is started.

The first of these subsequent courses is started two weeks after the initial course. The third course is started after another two week rest, and subsequent courses of triple therapy are then given after three week rest, until all evidence of disease is gone. If all evidence of tumor disappears (including return to normal

of elevated human chorionic gonadotropin titre), a one week course of triple therapy is given every two months indefinitely.

Toxicity of triple therapy is that of its component parts. Stomatitis, diarrhea, and/or marrow depression are almost invariable accompaniments of this therapy. Recovery is fairly rapid, occurring in 7 to 14 days.

In summary, occasional patients with testicular tumors have good results with triple therapy. Toxicity of this form of therapy is severe, but usually can be managed.

## Combined Radiotherapy and Drug Therapy

A number of agents have been proposed as radiation potentiators. Actinomycin D is the outstanding example. Administration of this agent to patients who have had previous radiotherapy will often cause skin reactions at the site of previous radiotherapy. Other agents such as 5-fluorouracil, triethylene melamine, other alkylating agents, and methotrexate have been proposed for use in combination with radiotherapy.

Unfortunately, there has been little evidence of true potentiation of radiotherapy with these combinations. True potentiation implies additive therapeutic effect without additive toxicity, or with a greater therapeutic ratio than with either agent (radiotherapy or drug) given alone. A provocative editorial in *Lancet*[9] on this subject was published recently. It was the conclusion of the writer that there was little if any evidence of true potentiation. The results with actinomycin D plus radiotherapy in Wilm's tumor, and Reese's[10] results with triethylene melamine plus radiotherapy in retinoblastoma, seem to be two areas where useful clinical results have been obtained.

Studies comparing radiotherapy alone, with the same dose of irradiation plus 5-fluorouracil, for colonic carcinoma have shown variable results.[11,12] However, I am unaware of any studies comparing a given dose of radiotherapy plus 5-fluorouracil with a higher dose of radiotherapy. There has been increased toxicity with the combination therapy. Studies which attempt to show an additive effect of oral methotrexate, or regional infusion with methotrexate, on radiotherapy in head and neck cancer, have been equally poorly designed.

## Regional Chemotherapy

The concept of regional chemotherapy is an attractive one. The basic principle is to deliver a high concentration of the chemotherapeutic agent to the tumor, and spare as much as possible of the normal tissue. A variety of techniques has been investigated. Lawrence[13] has published an encyclopedic article which is required reading for anyone interested in this field. He reviews all techniques and drugs used in regional chemotherapy. His concluding paragraph is an excellent summary of the current status of this field.

"For clinical treatment of cancer, regional chemotherapy in its present state appears to be of very limited value. In my opinion, it remains an investigational technic, and further study of these methods should be limited to those institutions where the clinical material, laboratory facilities, and supporting staff will allow pursuit of the leads that have arisen. Eventually regional chemotherapy will probably find an established place, either as the principal therapy or, more likely as adjunctive therapy in a few specific neoplastic diseases. At the present state of development of regional chemotherapy, however, the patient who received well-administered, conventional therapy for his cancer is still receiving the best treatment that is available. Until further advances are realized from these studies of regional chemotherapy, the majority of patients, in my opinion, should still be treated by established techniques."

There are several reasons for this rather pessimistic view of the present clinical applications of regional chemotherapy. The main reason is that there are very few situations where greater antitumor effect has been produced. These will be mentioned below. The second problem is the high rate of complications with present techniques. Postoperative hemorrhage, local damage to arteries by the drug, arterial or venous thrombosis, skin and other tissue toxicity due to the drug, local infection, and air embolism are among the formidable list of major complications.

The most effective use of regional chemotherapy was discussed in the chapter on alkylating agents. This is the use of melphalan by perfusion for local recurrence of malignant melanoma. Any patient with local recurrence, or metastases confined to inguinal nodes, should be considered for referral to a center where perfusion is carried out.

A highly specialized use of regional chemotherapy is intra-arterial triethylene melamine plus betatron irradiation for retinoblastoma.[14,15] All patients with this rare tumor should be referred to one of the few centers which treat many of these tumors yearly. Doctor Algernon Reese of Columbia University College of Physicians and Surgeons has the largest experience with this tumor.

In summary, regional chemotherapy is still almost entirely a research technique. Its clinical applications may prove of great use in the future.

## Methylhydrazine Derivatives

A number of methylhydrazine derivatives have been tested for antitumor activity in animals and humans. So far, the most successful of these has been N-isopropyl-alpha-(2-methylhydrazine)-*p*-toluamide hydrochloride (RO4-6467/1, NSC-77213). It has been released for investigational use by Hoffmann-LaRoche as Natulan®. Since no generic name has been chosen, the drug will be referred to as methylhydrazine.

At present, methylhydrazine has established itself as a useful drug in Hodgkin's disease where it gives results equivalent to the alkylating agents and vinblastine.[16-21] The Memorial group[16] reported significant responses in 12 of 20 patients. Todd[17] reported 15 responses in 24 patients treated, and Falkson[18] reported 8 complete remissions in 13 patients. Martz[19] cited 25 responders out of 25; most were complete. Mathé[20] noted 14 complete and 25 incomplete remissions in 51 trials. Most authors noted best responses in early cases, but there was no cross resistance with alkylating agents or vinblastine.

One outstanding feature of methylhydrazine is that remissions can be induced in Hodgkin's disease, even in patients with severely depressed bone marrows. Lower dosage regimens are necessary, and this will be discussed later. We have induced remissions in patients whose platelet counts were as low as 60,000 prior to therapy. Duration of remissions average about four months. Maintenance therapy is considered helpful in prolonging remissions.

There is a suggestion that methylhydrazine may be useful in the treatment of disseminated malignant melanoma. Todd[17] noted one remission in 6 patients. Falkson[22] noted objective improvement lasting 2 to 16 months in 6 of 9 patients with melanoma

treated with combined radiotherapy and methylhydrazine. He concluded that methylhydrazine sensitizes tumor tissue to radiotherapy. This conclusion is not warranted from the data. One can conclude that in these six patients the remissions were due either to the drug alone, radiotherapy alone, or the combination. We have had one patient who had a complete remission of melanoma metastases to the pleura, and an enlarged epitrochlear node after treatment with methylhydrazine.

Results in lymphosarcoma have been variable, but the impression is that methylhydrazine is far less useful in this disease than in Hodgkin's disease. Martz[19] has reported the best results in lymphosarcoma with 6 responses in 6 patients treated. However, his report is the exception. Gerhartz[21] has reported 6 excellent responses in 9 patients with chronic granulocytic leukemia.

Methylhydrazine is supplied as 50 and 100 mg oral capsules. It is generally given in divided doses after meals. Original dosage recommendations in the literature were for as much as 7 mg/kg daily. However, this amount is undoubtedly too high. Because of delayed onset of toxicity, the drug dosage should be tapered at an arbitrary time, rather than waiting for toxicity.

At present, I would recommend the following dosage regimen for patients with normal or high white blood and platelet counts and good marrow reserve. A course of 4 mg/kg/day in divided doses should be given for 21 days. This 4 mg/kg dosage should be achieved after a preliminary period in which the dosage is built up at 50 mg increments. This is done to minimize nausea and vomiting.

In practice, this works out to one 50 mg capsule the first day, 50 mg twice a day the second day, and 100 mg after breakfast and 50 mg after supper the third day. Daily increments of 50 mg are continued until the 4 mg/kg dose is achieved.

Lower dosages are recommended if the marrow is compromised or the patient has had extensive radiotherapy to marrow areas. For patients with severe leukopenia and/or thrombocytopenia, we have given 50 mg the first day and then 100 mg/day for 14 days.

After the initial 14 to 21 day course, maintenance therapy is started. This should be between 50 mg daily and 50 mg every other day. During the initial period, twice weekly white blood and platelet counts should be obtained. Thereafter weekly checks are sufficient. Rarely, 100 mg daily is needed for maintenance.

Toxicity of methylhydrazine is chiefly bone marrow depression. White cells are affected somewhat more readily than platelets, but depression of either element may cause cessation of therapy.

Marrow depression may last from one to three weeks after stopping the drug. Mild hemolysis has been described. Anorexia and nausea are almost invariable. Vomiting is common, but is usually controlled by dividing doses and giving antiemetics. These effects are much less pronounced on the lower maintenance dosage.

Neurotoxicity is very common, but usually not severe. This includes restlessness, drowsiness, and rarely, psychosis. Potentiation of phenothiazines, and flushing after alcoholic drinks have been noted.

In summary, methylhydrazine is a useful agent in Hodgkin's disease. It may also be helpful in melanoma, lymphosarcoma, and chronic granulocytic leukemia. Its major toxicity is marrow depression. Nausea, vomiting, and mild neurotoxicity are common side effects.

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# CHAPTER IX

## HORMONE THERAPY

The subject of hormonal therapy in malignancy is a vast one. A complete discussion of this field with all its theoretical implications and practical considerations would occupy another book as large as this one. The purpose then, of this chapter, is to outline the present role of hormonal therapy in malignancy, emphasizing accepted uses and neglecting the controversial.

### Pharmacology

Any attempt to discuss the mechanism of action of hormones would involve us in the latest advances in molecular biology. Many of the physiological effects of the hormones can be explained by their stimulating the production of messenger RNA by DNA. An excellent discussion of this topic in a form easily understood by the non-chemist has been presented by Davidson.[1] A more complex discussion of steroid hormone actions with amplification of other theories has been presented by Williams-Ashman.[2]

At the level of tissue or organ response the manner in which hormones exert their antitumor action is even less well understood. Suffice it to say that the earlier concepts of hormone dependent and independent tumors are now considered too naive. For example, there is no evidence for a direct anti-estrogenic effect of androgens in breast cancer.

### Estrogens

The estrogens are the most useful agents in the therapy of metastatic breast carcinoma. Where comparative studies have been carried out, diethylstilbestrol consistently is superior to testosterone propionate.[3-5] Traditionally, estrogen therapy has

been reserved for the woman with disseminated breast cancer, more than five years after her menopause (natural or artificial). Although occasional responses occur in women who are less than five years' postmenopausal, they are far less common. In the prospective study of the Cooperative Breast Cancer Group,[3] the response rate to diethylstilbestrol of women less than five years' postmenopausal was 5%, while those treated when more than five years after the menopause, had a response rate of 24%. It is also feared, with some justification, that estrogens may exacerbate the carcinoma in premenopausal women, or those just past the menopause.

The figure of 24% just quoted is somewhat lower than the figures obtained in earlier studies. This is partly because criteria for remission have become more rigid. The nature of the cases treated may play a role, as patients with visceral metastases respond less well to estrogens than those with bone metastases or local or nodal recurrences. For example, the Committee on Research of the American Medical Association reports an incidence of response of 36.8% for estrogen therapy. In Kennedy's[5] series, 16 of 55 women (29.1%) responded to diethylstilbestrol. However, of the 38 women who were more than five years' postmenopausal, 15 had a response for a rate of 39.5%. Remissions apparently last an average of one year.

Until the AMA study was published in 1960, it was widely believed that androgens were superior for bone metastases. In this study, androgens were approximately equal in value to estrogens for bone metastases, but significantly less valuable in visceral metastases or local and nodal recurrences. The Cooperative Breast Group study[3] found similar results.

Estrogens are also effective therapy in a significant proportion of patients with prostatic carcinoma. Just how effective, is very hard to determine. The reason for this is that objective changes are hard to measure. Changes in alkaline or acid phosphatase are hard to interpret. Acid phosphatase values may remain depressed under estrogen therapy, even though there is progression of metastatic disease. Also, it is hard to interpret x-ray changes in osteoblastic metastases. Improvement of anemia, if present, is significant. Soft tissue metastases if present, may regress, and the primary tumor may shrink.

However, more often than not, the patient is judged to have a remission because he has had marked relief of bone pain. Along

with this relief of pain, improved appetite and weight gain may occur.

Although estrogens probably produce a remission in 25% to 50% of patients with metastatic prostate cancer, orchiectomy is the preferred treatment for this disease. Five year survivals are significantly better when orchiectomy is used.[6] Occasionally, estrogens will be useful in a patient who has relapsed after an orchiectomy-induced remission.

Carcinoma of the male breast is a rare disease. Orchiectomy and/or estrogens appear to be of definite value when metastases are present.

The dosage of diethylstilbestrol is 5 mg three times a day. This drug is preferred because it is the least expensive. If diethylstilbestrol is not well tolerated, ethinyl estradiol 0.2 mg three times a day will be equally as effective. Treatment must be continued for a minimum of three months in breast carcinoma, as it is unusual for a remission to occur in less than eight weeks.

For women, the major side effect of estrogens is nausea. The nausea usually disappears after several weeks, and occurs in less than one-third of patients. Nausea may be minimized by gradual increase of dosage until the required dose is achieved. Naturally, nausea also occurs in men. Nausea can also be controlled by shifting from diethylstilbestrol to ethinyl estradiol or even to parenteral estradiol.

Fluid retention is occasionally a problem, but may be counteracted by a low salt diet and/or diuretics. Some care must be used in patients with cardiac disease, but measures to prevent edema will almost always permit use of the drug.

Naturally, feminization is a universal problem in men who receive estrogens. Loss of libido, gynecomastia, pigmentation of areolae, and sometimes voice changes occur. Fortunately, most men with prostatic carcinoma are over 60, which somewhat minimizes the problem.

Hypercalcemia is an ever present danger of estrogen therapy in breast cancer. However, it occurs with no greater frequency in the estrogen-treated patient than in the untreated patient, except for a moderately higher incidence during the first few weeks of estrogen therapy. Naturally, if hypercalcemia occurs, the estrogen should be stopped immediately, and 3 to 4 liters of parenteral fluids should be given intravenously. Corticosteroids should also be given. (See section on corticosteroids later in this chapter.)

## Androgens

Androgens have two uses in the treatment of malignancy. The first is as a palliative agent in female breast cancer, and second as an anabolic agent, both to treat associated cachexia and for marrow stimulation.

As we have seen in the last section, androgens are inferior to estrogens for visceral metastases and local recurrence in women with breast cancer more than five years after the menopause. They appear to be equally as good for bone metastases in this group.

While androgens are considered safer than estrogens for the woman who is premenopausal or less than five years' postmenopausal, the results in this group are less than satisfactory. The Cooperative Breast Cancer Group[7] reported 25 remissions in 192 patients who were less than five years' postmenopausal when testosterone propionate was given. This is a rate of 13%. The response rate in 329 women more than five years' postmenopausal was 26.7%.

There is a widespread clinical impression that androgens are useful as anabolic agents in patients with malignancy, particularly as a bone marrow stimulant. However, such impressions are hard to substantiate. It is often difficult to tell if improvement in peripheral white blood count, platelet count and hematocrit are due to the androgens, or to other factors, such as improvement of the disease due to other therapy, or withdrawal of marrow-suppressive drugs or radiotherapy.

The Group at the National Institutes of Health[8] report improvement of white blood and platelet counts with androgen therapy in multiple myeloma. Kennedy[9] reports improvement in peripheral blood values (platelet count and hematocrit) in patients with chronic lymphatic leukemia who received androgens. He felt that concurrent corticosteroid therapy was needed. A number of groups, particularly in England, have claimed that patients with breast cancer tolerate higher doses of alkylating agents when given androgens concurrently. This combination is claimed to give improved results in treating the cancer.

Unfortunately, none of the above studies have been well designed controlled studies, and there is still doubt as to the usefulness of androgens as marrow stimulants. There is a possibility that androgens may actually decrease tolerance to methotrexate (see Chapter III).

The preferred androgen has been testosterone propionate, given 100 mg i.m. three times a week. Fluoxymethyltestosterone (Halotestin®-Squibb, Ultandren®-Ciba) has the advantage of oral administration. The usual dosage is 5 mg orally 4 times a day. Other androgens which are less masculinizing and possibly equally as effective are $\Delta'$-testololactone and 4,5 $\alpha$-dihydro-2$\alpha$-methyltestosterone propionate. These agents are administered parenterally. However these are still being tested.[3]

The side effects of androgens, like estrogens are more troublesome than dangerous. The occurrence of hypercalcemia in androgen-treated patients with breast cancer is not too common, with the greatest risk occurring during the period of induction of androgen therapy. If hypercalcemia occurs the drug should be stopped at once. During the first few weeks of hormone therapy in breast cancer, the serum calcium should be checked twice a week.

Fluid retention may be a problem with androgens, at the same severity as in estrogen-treated patients. Masculinization poses a serious psychological problem in female patients. This complication is almost unavoidable in patients treated for over three months. Hirsutism is particularly annoying, but increased libido, and deepening of the voice also occur.

## Progestins

Since 1960, when Kelly and Baker[10] first reported objective remissions in endometrial carcinoma with high dosage progesterone therapy, there have been a number of other reports of favorable results.[11-14] Kelly and Baker[14] summarized the results in 165 cases reported by 65 investigators. Overall response rates were 25 to 30%. These authors summarized the present status of progestational therapy for endometrial carcinoma as follows: "The type of patient demonstrating the most impressive response has been characterized by a long hiatus between the original treatment and the recurrence of endometrial cancer, a well-differentiated adenocarcinoma or adenoacanthoma histologically, and pulmonary metastases, with or without local recurrence in the pelvis. In favorable cases, pulmonary nodules have regressed within at least 2 months of the initiation of therapy, have disappeared within 4 to 6 months, and have remained in abeyance as long as 4.5 years. Pelvic recurrences have been much less impressive in their response, although decrease in disease for several months has occurred."

"It is an accepted fact that the progression of metastases in endometrial carcinoma may be very leisurely, even in the absence of therapy. In our series, however, patients failing to respond objectively to progestational therapy have succumbed to their disease within several months, in contrast to the responders, many of whom have enjoyed prolonged remissions of several months' to several years' duration."

The drugs used have been aqueous progesterone, progesterone in oil, 17-α-hydroxyprogesterone caproate (Delalutin®, Squibb), and medroxyprogesterone acetate (Depo-provera®, Upjohn).

Dosages are not standardized. Progesterone in oil has been largely discarded because of the large volumes needed with associated local discomfort. Kelly and Baker[14] suggest that 500 mg of 17-α-hydroxyprogesterone caproate intramuscularly twice a week is sufficient, but Kistner[13] advocates 3 to 5 grams i.m. once a week.

Medroxyprogesterone acetate has been used orally in a dose of 300 mg daily.[11] Kistner[13] recommends 3 grams a week orally for 5 to 6 weeks, then a maintenance dose of 400 mg monthly. This maintenance dose is given intramuscularly.

The only side effects are nausea with the oral preparation, and occasional sterile abscesses with the injections. Mild fluid retention may occur, but is not common.

## Corticosteroids and ACTH

In this section only corticosteroids will be discussed. ACTH is rarely used because of the necessity for daily intramuscular injection. However, ACTH would have the same effects as corticosteroids in the diseases discussed.

Corticosteroids are used so frequently in terminal cancer that they have been called "the last rites of the cancer patient." Actually, these agents have a specific antitumor effect in only three conditions: childhood acute leukemia, the chronic lymphatic leukemia-lymphosarcoma complex, and breast cancer. They are also effective in combatting the systemic effects of Hodgkin's disease, and may possibly cause some tumor shrinkage in this disease. Corticosteroids are also useful in the immune hemolytic anemia of the chronic lymphatic leukemia-lymphosarcoma complex, and may play some role in the treatment of gram-negative septicemia which is so common in the terminal cancer patient. Another

use is in the hemorrhagic complications of thrombocytopenia (drug or disease-induced), and corticosteroids may temporarily reduce the neurologic abnormalities produced by brain metastases. They are also useful in combating hypercalcemia of malignancy.

Corticosteroids alone, induce complete remissions in approximately 30 to 50% of children with acute leukemia. However, when given in conjunction with vincristine or 6-mercaptopurine they induce remissions in 80 to 90% of children.[15] (See Chapter XI.) Duration of corticosteroid-induced remissions is usually less than three months. For this reason, corticosteroids combined with another agent are used to induce remissions. After one month, the corticosteroid dosage is rapidly decreased to zero, and another agent or cyclic therapy is started (see Chapter XI). Second and even third remissions may be induced with corticosteroids.

Corticosteroids may have a temporary effect on the systemic symptoms and bleeding manifestations in adult acute leukemia. However, even these effects are short-lived.

Corticosteroids may produce impressive remissions in patients with chronic lymphocytic leukemia or lymphosarcoma (particularly when the basic cell type is the small mature lymphocyte). However, the use of corticosteroids in these disorders is quite hazardous. Galton[16] has emphasized this in a particularly complete and thorough manner. In my experience, patients with the so-called lymphoproliferative diseases (chronic lymphocytic leukemia and lymphosarcoma of the same cell type) more often die from infection than from any other cause. They usually do well, needing occasional local radiotherapy, until their gamma globulin levels decrease markedly. At this point, their disease often worsens, and they become subject to infections. Lung infections, furuncles, and fatal septicemia are distressingly common. Corticosteroids can only increase the danger of these infections.

Unfortunately, there are times when patients with lymphoproliferative disease are ill from their disease (anemia, thrombocytopenia, diffuse deposits of lymphocytes). If possible, local radiotherapy or chlorambucil is the preferred therapy. Often the disease is refractory to chlorambucil and radiotherapy may not be applicable because of diffuse disease. At these times, the use of corticosteroids may be necessary. There is no evidence that prophylactic antibiotics are helpful in preventing infection, and

they may be harmful. The concurrent use of gamma globulin in high dosages (20 cc i.m. every 3 weeks) may be of some help, but there is no proof for this.

Therefore, the use of corticosteroids in lymphoproliferative disease should be reserved for the ill patient who has not benefited by chlorambucil or radiotherapy. When corticosteroids are used, every infection should be looked on as potentially fatal. Actually this is also true for the patient not on corticosteroids. Other toxicity of corticosteroids such as gastrointestinal bleeding, iatrogenic Cushing's syndrome and eventual osteoporosis also make these agents hazardous for long-term therapy.

Attempts have been made to decrease the toxicity of corticosteroids by giving them intermittently.[17] This regimen will be discussed in a later section. Unfortunately, studies so far have not been controlled, at least when applied to the lymphoma patient. However, the intermittent regimens do seem to be superior in childhood nephrosis, and further studies are needed in the lymphomas.

Corticosteroids play a small but definite role in breast cancer therapy. Objective remissions occur in approximately 15% of patients with metastases.[5] Remissions tend to be short, on the order of several months, and are more common in women who have had previous responses to oophorectomy or sex hormone therapy. Corticosteroids are also excellent therapy for hypercalcemia in this disease. (This will be discussed shortly.) Corticosteroids in breast cancer are usually reserved for late in the course of the disease, and may substitute for adrenalectomy or hypophysectomy in the patient too ill for these procedures.

The controversy over the usefulness or lack of effectiveness of corticosteroids in gram-negative sepsis is beyond the scope of this book. In patients with thrombocytopenia, whether due to antitumor drugs or the disease, corticosteroids will help to prevent bleeding without increasing platelet counts. (In childhood acute leukemia or lymphoproliferative disease such as chronic lymphocytic leukemia, platelet counts may rise.) Unfortunately, these effects on vascular fragility are temporary, lasting for a few weeks to months.

Corticosteroids sometimes produce impressive effects on systemic toxicity of Hodgkin's disease. Fever is usually lowered, occasionally to normal. The patient often feels better, appetite may improve, and weight gain can occur. However, these effects

are transient. Some shrinkage of tumor deposits may occur, but these are usually minimal effects. Corticosteroids are reserved for the terminal phase of Hodgkin's disease or else given for short courses until other therapy has had a chance to be effective.

Corticosteroids may also produce dramatic improvement in the neurological findings in patients with brain metastases. Sensorium may clear, paralyses may improve, and headaches and other signs of increased intracranial pressure may disappear. These effects are considered due to decrease of edema surrounding the metastases.

It is commonly stated that corticosteroids will prevent radiation-induced edema when radiotherapy is given to brain or epidural metastases. I am not sure that this so-called radiation edema exists, and we have not routinely used corticosteroids in these situations. However, most patients who receive cerebral radiotherapy have already been placed on corticosteroids for their effects in decreasing the neurological abnormalities due to the metastases. Controlled studies are needed in this area.

The hypercalcemia of malignancy whether it is due to bone metastases, or a humoral factor produced by the tumor, usually responds well to corticosteroid therapy. Manheimer[18] has reported return to normal serum calcium in 46 of 59 episodes of hypercalcemia due to breast cancer. Results are not quite as good in most other types of malignancy.

Finally, in autoimmune hemolytic anemia (Coombs test positive) which occurs not infrequently in chronic lymphocytic leukemia and lymphosarcoma, corticosteroids are usually very effective.

The dosages of corticosteroids that must be used in most of the above conditions are quite high. Amounts on the order of 80 mg of prednisone daily are usually necessary. Exceptions will be discussed. All dosages will be expressed as prednisone. Other corticosteroids may be substituted in equivalent dosages.

Lemon[19] has reported 48% remissions in 31 patients with advanced breast cancer on a dosage of 30 mg daily of prednisone. However, he insists that for this to occur, the women must be castrated first unless they are over 65. These exact conditions have not been studied by other authors. In any case, dosages of prednisone in breast cancer are on the order of 30 to 40 mg daily.

The standard dosage for prednisone therapy in childhood acute leukemia is 40 mg/m$^2$ BSA daily. In the chronic lymphocytic leukemia-lymphosarcoma group, daily doses may vary from 40 to 100

mg initially. Once remission occurs, the dosage should be tapered as low as possible. However, the maintenance dosage can rarely be kept below 20 mg daily. Burningham et al[17] have suggested a regimen of 60 to 145 mg prednisone daily for one to five weeks. When a plateau of improvement was reached, the dose was tapered and then discontinued over a period of 4 to 5 days. Seven days after the last dosage, maintenance therapy of 100 to 150 mg of prednisone was started, either once a week, or on two successive days each week. These authors claimed good results with far less toxicity. Controlled studies are needed to prove this.

Hypercalcemia of malignancy usually needs a minimum of 60 mg of prednisone daily, and brain metastases requires 80 mg daily. Autoimmune hemolytic anemia may respond to as little as 30 mg of prednisone daily, or may need 80 to 100 mg.

The toxicity of corticosteroids is well covered in any textbook of pharmacology. For this reason, the toxicity will be presented in outline form only.

### Toxicity of Corticosteroids

A. Short- or Long-Term Therapy
   1. Gastrointestinal bleeding – usually due to corticosteroid-induced gastric ulcer.
   2. Perforated gastric ulcer.
   3. Increased risk of pyogenic infections, tuberculosis, or fungus infections.
   4. Corticosteroid-induced diabetes. This is usually well controlled by antidiabetic therapy.
   5. Possible increased incidence of thromboembolic disorders.
   6. Psychiatric changes and psychoses.
   7. Electrolyte disturbances.

B. Long-Term Therapy Only
   1. Osteoporosis with compression fractures of the vertebrae.
   2. Muscle wasting and muscle weakness.
   3. Cushing's syndrome.

Naturally the risks of therapy increase with the dosage, and osteoporosis may occur in a few months on high dosage therapy.

In summary, the corticosteroids are useful in many areas in the treatment of malignant disease, but their toxicity with long-term usage often prevents their continued administration.

## Thyroid Hormone

The use of thyroid hormone for the treatment of metastases from papillary carcinoma of the thyroid has been reported by Crile[20] to give excellent results. The hormone's antitumor action appears to be mediated through its ability to suppress pituitary thyrotropin production. Results in other histologic types of thyroid cancer are poor. Crile[20] gives references to several other studies confirming his favorable results. Three to 5 grains of thyroid extract daily are required.

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# CHAPTER X

## SPECIAL PROBLEMS IN TOXICITY

Although the mechanism of action in each of the various classes of cancer chemotherapeutic agents is quite different, there are a number of problems that are common to most of the drugs. The most important problems of bone marrow and gastrointestinal mucosa toxicity have been discussed with each agent in its appropriate chapter. It has been stressed that the depressed marrow, or marrow invaded by tumor, is more sensitive to the anticancer drugs. Special problems unique to each agent have been discussed when appropriate. Several problems remain. These are: (1) Administration of chemotherapeutic agents to pregnant women; (2) uric acid nephropathy; and (3) alopecia.

### Administration of Chemotherapeutic Agents to Pregnant Women

The treatment of malignant disease in the pregnant woman presents special problems. Two problems must be considered here: damage to the fetus, and producing a genetic change that may not show up until future generations. This second danger is a potential hazard with radiotherapy, and possibly with the alkylating agents. However, most authors have tended to disregard it. The first and greater problem, that of damage to the fetus by radiotherapy or chemotherapeutic agents, is a real one.

There are two aspects to the problem of fetal damage: (1) death of the fetus and (2) induction of fetal abnormalities insufficient to cause death. There have been several useful review articles on this subject.[1-4] Although there is little that is proven, several important facts have emerged. As discussed in the chapter on methotrexate, this agent is contraindicated in the first trimester of pregnancy. Fetal abnormalities and/or abortion are an almost inevitable result. This problem should not arise often, as metho-

trexate is ineffective in adults, except in rare cases of acute leukemia. Its use might be justified in the pregnant patient, desperately ill with acute leukemia, who is resistant to 6-mercaptopurine. Little is known of the effects of methotrexate after the first trimester of pregnancy.

6-mercaptopurine in dosage of 2.5 mg/kg/day given to pregnant rats had no effect on the fetus.[5] Higher dosages did cause fetal abnormalities, the 7th or 8th day of gestation being the time of greatest sensitivity. The usual dosage of 6-mercaptopurine in humans is 2.5 mg/kg/day. In a partial search of the literature, I could find 17 pregnancies where 6-mercaptopurine was given.[1-3,6-11] In nine of these, it was given during the first trimester, and in two, no information is given as to the stage of pregnancy in which the drug was administered.

In only 1 of the 17 pregnancies did fetal abnormalities occur, but this mother received 6-mercaptopurine plus busulfan in the first trimester.[6] She was on 6-mercaptopurine at the time of conception. In three others of the 17 pregnancies, the mother conceived while on 6-mercaptopurine.[2,3,7] It would seem that 6-mercaptopurine at a dosage of 2.5 mg/kg is relatively safe in the pregnant patient, although there is some potential hazard to the fetus, and dosage should be kept as low as possible.

Alkylating agents are potentially toxic to the fetus, and in animals they have produced congenital anomalies. A relatively small number of patients who have received alkylating agents during pregnancy are recorded.[1,2,10,13-15,17-22] Excluding the one previously mentioned infant with abnormalities who received busulfan and 6-mercaptopurine, two of the fetuses developed congenital abnormalities. One of the mothers received cyclophosphamide during the first trimester, and her infant was born with multiple congenital abnormalities.[22] Sholton et al[21] reported an infant with abnormalities when the mother received chlorambucil in the first trimester. However, fewer than 20 mothers who received alkylating agents in the first trimester of pregnancy are reported. Busulfan has been considered potentially somewhat more hazardous than other alkylating agents, because several patients on long term busulfan have developed bizarre large cells in many tissues.[16]

Recently, three patients have been reported[23-25] who received vinblastine (Velban) during pregnancy. Two of these mothers received the drug throughout the entire pregnancy, and the third

received it for eight weeks, starting in the seventh month. In all three cases, the children were normal. It should be noted that hamsters who received vinblastine 0.25 mg/kg or vincristine (Oncovin) on the eighth day of gestation, bore fetuses with various defects.[26] These dosages are in the range of the usual dose in humans. Therefore, the same hesitancy should be observed in administering *Vinca Rosea* alkaloids in the first trimester of pregnancy as with other agents.

Smith et al[2] reviewed the literature in 1958, and were able to find 54 patients with Hodgkin's disease who received radiotherapy during pregnancy. Naturally, the fetus was not in the irradiated field. No harm to the fetus was noted. Of course how much genetic damage occurred, which might show up in later generations, cannot be known.

In summary, antifolics (methotrexate) are contraindicated in the first trimester of pregnancy. Although a potential hazard exists with all anticancer drugs, and radiotherapy, even with the fetus shielded, very little harm has occurred. Unfortunately, there are very little human data available on the use of anticancer agents during pregnancy.

## Uric Acid Nephropathy

One serious complication of therapy of the lymphomas and leukemias is uric acid nephropathy. In this condition, uric acid crystals precipitate in the distal tubules and collecting ducts of the kidneys, leading to oliguria, and if untreated, anuria and death. A small number of cases of this complication have been reported, and will be discussed below. The few cases reported are a tribute to the general awareness of the dangers of uric acid nephropathy, and the care taken in prevention of this condition. As will be seen in the discussion that follows, many patients are likely subjects for this complication. Therefore, constant care must be taken in its prevention.

Sandberg et al[27] studied the urinary uric acid excretion in untreated patients with various leukemias, and did a few studies on the effects of treatment. Their results in untreated patients are summarized in Table I.

As can be seen, the patients with acute lymphocytic leukemia have the most striking increases in uric acid excretion. Those with acute and chronic myelogenous leukemia also have marked

increases, but all patients with chronic lymphocytic leukemia have normal uric acid excretions.

*TABLE I*

*Uric Acid*

| Diagnosis | Uric Acid Excretion mg/kg/24 hours | |
|---|---|---|
| | Mean | Range |
| Normals | 6.5 | 5.2-7.3 |
| Acute Lymphocytic Leukemia | 30.2 | 11.9-74.8 |
| Acute Myelogenous Leukemia | 13.0 | 6.2-20.5 |
| Chronic Myelogenous Leukemia | 13.5 | 12.8-14.1 |
| Chronic Lymphocytic Leukemia | 5.2 | 3.5-6.8 |

What is the cause of this elevated uric acid excretion (and by inference, increased production) in untreated leukemia? The marked turnover and increased production of nucleic acids, related to the large number and rapid growth of tumor cells, explains this increased uricosuria. The long life span of the lymphocyte (possibly as much as 200 days) means that the turnover of cells in chronic lymphocytic leukemia is not as great as in the other leukemias. This explains the normal uric acid excretion in this disease.

The effects of treatment further aggravate the uric acid load the kidneys must excrete, especially when large quantities of leukemic or lymphomatous cells are destroyed rapidly. Sandberg et al[27] studied the effect of therapy on total daily uric acid excretion in a few patients. They noted that when therapy lowered the white blood count in acute myelogenous or acute lymphocytic leukemia, the elevated uric acid excretion increased further. However, in one patient with chronic lymphocytic leukemia, and one with chronic granulocytic leukemia, there was no further increase in uric acid excretion with therapy.

Further substantiation of these data in acute leukemia come from the work of Frei et al.[28] They noted the following figures for maximum total 24 hour urine urate excretion in seven episodes of oliguria associated with therapy of acute leukemia: 22.8, 37, 37, 69, 100, 130, 338 mg/kg/24 hours. In all but one of these episodes, there was a rapid fall of the peripheral white blood count in less than six days. The significance of these values is highlighted, when they are compared with the figures for mean uric acid excretion in various leukemias (Table I). All but one of these figures is greater than the mean uric acid excretion in untreated acute lymphocytic leukemia as reported by Sandberg et al.[27] This condition is the one these authors found to have the highest uric acid excretion.

A further illustration of the fact that rapid drop in peripheral white blood count is the main cause of treatment-induced increase in urinary uric acid in acute leukemia, are the data of Holland et al.[29] These authors found a further increase in elevated urine uric acid in some treated patients with acute lymphocytic leukemia, but in none of the treated patients with acute myelogenous leukemia. None of the latter group had a marked or precipitous drop in peripheral white blood count.

A complete review of the literature on anuria due to uric acid nephropathy has not been attempted. Data from two recent review articles[30,31] and several individual reports,[32-34] not included in these reviews, is summarized below.

A total of 22 cases of leukemia or lymphoma are included in these articles. In all patients anuria developed as the result of treatment of the disease. Eight patients' conditions were diagnosed as chronic myelogenous leukemia, 8 as lymphosarcoma, 5 as chronic lymphocytic leukemia, and 1 as acute leukemia. All but one of these patients had very high white blood counts prior to therapy. Eight of 12 whose blood counts were reported, had white blood counts over 200,000, and the lowest white blood count prior to therapy was 89,650, except for one patient with chronic lymphatic leukemia with a white blood count of 14,000. The nephropathy in this patient developed after irradiation of a massively enlarged spleen.

The various treatments inducing anuria in these 22 patients were as follows: radiotherapy, 10, alkylating agents, 8, $P^{32}$, 1, 6-mercaptopurine, 1, and radiotherapy plus urethane, 1. Of the

8 patients receiving alkylating agents, 5 received the rapid acting agent, mechlorethamine (nitrogen mustard).

A similar search of the literature uncovered ten patients who suffered 11 episodes of uric acid nephropathy with oliguria, but who did not progress to total anuria.[28,33,35] Actually, the problem that these cases present is the same as in the anuric patients, and the alertness of the physicians in instituting therapy prevented progression to total anuria. Two of these ten patients had lymphosarcoma, one had acute granulocytic leukemia, and one had acute lymphocytic leukemia. Seven episodes occurred in six patients who were classified as acute leukemia. Radiotherapy was the treatment in one patient, methotrexate in five, corticosteroids in three, cortisone plus 6-mercaptopurine in one, and methotrexate plus 6-mercaptopurine in one.

Of the nine episodes occurring in leukemic patients, eight occurred in patients whose pretreatment white blood counts were over 25,000. It should not be inferred from the above two series, that urate nephropathy in acute leukemia is less likely to progress to total anuria. It is because the increasing awareness of the problem in recent years, coincided with the development of effective therapy for acute leukemia. Thus the nephropathy was treated effectively, before anuria developed.

Uric acid nephropathy occurs soon after treatment is instituted, usually within six days, and occasionally as soon as 48 hours. From the data discussed above, it is apparent that the greatest danger lies in patients with leukemia, with initially elevated white blood counts, who respond rapidly to therapy. Frei et al[28] state that patients with initially elevated serum and urine uric acid levels are more susceptible. No patient with leukemia, acute or chronic, myelocytic or lymphocytic is immune. Patients with lymphosarcoma, with rapid dissolution of tumor masses due to therapy, are also susceptible. No cases of Hodgkin's disease have been reported to develop uric acid nephropathy, although elevated serum uric acid is common in this disease. It should be pointed out that one of Frei's[28] cases of acute leukemia had a pretreatment white blood count of 11,000. Despite this, severe uric acid nephropathy developed.

Other factors which enhance the danger of uric acid nephropathy are fever and dehydration. It has been suggested that salicylates, thiazide diuretics, Staphcillin® and adrenal steroids could aggravate the dangers.[36]

It would appear, that any form of therapy which is effective can induce the syndrome in leukemia or lymphomas. Some idea of the incidence of this complication can be gained from the data of Frei et al.[28] These authors noted 6 patients, in whom severe uric acid nephropathy developed, in a group of 57 patients treated for acute leukemia. Ultmann[37] has suggested that carcinomas can produce the syndrome. He presents two patients with carcinoma, who at autopsy had urate crystals in the renal tubules. These patients had elevated serum uric acids. He was able to find a number of other carcinoma patients with elevated serum uric acids. He suggests that this problem may become more frequent as effective therapy is discovered for carcinomas. It is of interest, that he found a correlation of elevated serum uric acid with anaplastic nature of the carcinoma, and with the presence of liver and bone metastases.

The spontaneous appearance of uric acid nephropathy in leukemias before institution of therapy must be rare, as I could find only one such case.[38]

Before discussing prophylaxis and therapy of uric acid nephropathy, a discussion of pathogenesis is in order. An excellent discussion of the pathophysiology is presented in the article by Frei et al.[28] These authors point out, that at a urine pH of 5.4 one half of the urine uric acid is in the un-ionized, less soluble form. At the physiologic blood pH, over 99% is in the more soluble, ionized, urate form. The latter is not only more soluble, but also tends to remain in supersaturated solution when solubility is exceeded. The maximal urine acidity and concentration occurs in renal collecting ducts, and it is there, that these authors feel is the initial and major site of uric acid precipitation. They cite microdissection studies in rabbits infused with uric acid, to confirm this theory.[39] Pathologic studies in humans with uric acid nephropathy tend to confirm this.[30,40] When mechanical obstruction of enough tubules occurs, oliguria results, and when all tubules are obstructed anuria occurs.

These authors in a later article,[36] further characterized the changes in renal function occurring during the development of uric acid nephropathy. They found diminished inulin clearance, with minimal depression of paraaminohippurate clearance. They suggests that precipitation of uric acid crystals in the collecting tubules, led to partial obstruction of these tubules. This in turn, would lead to increased intraluminal pressure within the proximal

tubule, resulting in reduction of net glomerular filtration pressure and therefore decreased glomerular filtration rate (inulin clearance).

The above facts suggest that two factors important in prevention of uric acid nephropathy are urine volume and urine pH. The larger the urine volume, the greater the amount of uric acid that can be excreted. In addition, if the urine pH is kept over 7.0, the greater amount of uric acid will be kept in the more soluble urate form.

Certainly all lymphoma and leukemia patients who are under treatment should be kept adequately hydrated. Daily urine volumes should exceed 1,000 cc/$m^2$BSA. Alkalinization of the urine is advisable in the high risk group. Probably all patients with acute leukemia with initial white blood counts over 25,000 should receive alkali for the first week of therapy, if their cardiac or renal status can stand the sodium load. Fairly high doses of alkali are needed to elevate urine pH (at least 10 grams of $NaHCO_3$ daily in adults).

Rieselbach et al[36] advise the following prophylactic regimen for patients with uric acid nephropathy who are not yet severely oliguric, and for patients with elevated serum uric acid prior to therapy. This regimen includes 5% glucose and water, 3 liters/$m^2$/24 hours, $NaHCO_3$ 100 mEq/$m^2$/24 hours, and acetazolamide (Diamox®) 1 gm/$m^2$/24 hours. They also advise potassium chloride supplementation of 40 to 80 mEq/day. With this regimen, they have been able to consistently achieve urine pH over 7.0.

Several other regimens have been used to achieve alkaline urine in other situations, and could be used in leukemia and lymphoma patients who were not oliguric. Potassium Triplex® 100 mEq/day for an adult will usually produce an alkaline urine. Atsmon et al[41] have used an alkalinizing solution to successfully dissolve a large staghorn uric acid calculus. I have used this solution, with safety and effectiveness, in nonleukemic patients who form uric acid calculi.

The formula of this solution is:

| | |
|---|---|
| Citric acid | 40 grams |
| Sodium Citrate | 60 grams |
| Potassium Citrate | 66 grams |
| Extract aurantii | 6 grams |
| Syrup simplex ad | 600 cc. |

The daily dosage is 60 ml a day.

Closely allied to prophylaxis of uric acid nephropathy, is therapy of the advanced nephropathy with oliguria or anuria. The above prophylactic regimens become dangerous in the face of oliguria, and could lead to serious fluid overload. Until several years ago, the standard therapy was to catheterize both ureters and attempt to flush out the uric acid crystals. Since the primary site of uric acid deposition is in the collecting tubules of the kidneys, this approach does not have great theoretical justification. However, it apparently worked in some but not all patients with anuria.[30-32] Drastic methods such as peritoneal dialysis[33] or hemodialysis with the artificial kidney[35] have been suggested, and may be necessary, with some anuric patients. However, before these more heroic measures are used, a trial of mannitol should be given to attempt diuresis. This method has been used with great success in severely oliguric patients, with markedly elevated blood urea and uric acid levels, by Frei et al[28] and Barry.[33] Frei's[28] patients had acute leukemia, and Barry's two patients had acute leukemia and lymphoblastoma respectively. Once diuresis is achieved, the alkalinizing solutions and diamox can be used.

Frei et al[28] recommend administration of 25 grams of mannitol/$m^2$ over a 15 minute period to severely oliguric patients. If diuresis does not ensue, they recommend ureteropelvic lavage or extracorporeal hemodialysis.

Recently, another approach to the prevention of uric acid nephropathy has been suggested.[43,44] This is the routine use of allopurinol in patients who are prone to uric acid nephropathy, such as the leukemia or lymphoma patient at the start of a course of therapy.

Allopurinol (4-hydroxypyrazolo (3.4-d) pyrimidine) is available as an investigative agent from Burroughs Wellcome as Zyloprim®. Release of the agent commercially is probably not far off, as it is also effective therapy for gout,[45] and toxicity is minimal.

Allopurinol is a xanthine oxidase inhibitor. Xanthine oxidase is the enzyme responsible for the conversion of hypoxanthine to xanthine and xanthine to uric acid. When allopurinol is administered, there is a fall in serum and urine uric acid. Although there is some controversy (probably explainable by differences in methodology) all of this drop is apparently replaced by an increase in the oxypurines, xanthine and hypoxanthine in the urine. Although each of these compounds is about as soluble in urine

as uric acid, crystals do not form. This is because each of these oxypurines has its own solubility product. This is similar to the situation when triple sulfas are administered.

Krakoff and Meyer[43] reviewed their experience at Memorial Hospital. They are somewhat pessimistic about the value of alkalinization of the urine and fluid therapy. They state that although fluid therapy is often successful, too many failures occur. They would appear to advocate the use of allopurinol, and describe excellent results in 15 patients who received this drug while receiving antitumor therapy.

DeConti and Calabresi[44] are more cautious, although they report excellent results in 24 patients who received allopurinol while undergoing anticancer therapy with drugs or irradiation. They state: "Studies to determine the frequency of significant hyperuricemia after treatment, as well as comparisons of the relative efficacy of allopurinol with the traditional use of hydration and alkalinization of the urine, will be necessary to define the role of allopurinol in this situation."

Dosage of allopurinol varies from 200 to 800 mg daily in divided oral doses. The serum uric acid can be used to guide dosage. Maximum effects may take as long as a week, so the drug should be started several days before antitumor therapy is initiated.

Allopurinol is apparently a very safe drug. Diarrhea and mild abdominal pain, skin rash and mild fever have been reported. Mild liver function test abnormalities have occurred rarely, but were reversible. Rare instances of leukopenia have occurred. In patients with gout, allopurinol may precipitate acute attacks of gouty arthritis.

Because xanthine oxidase is important to the catabolism of 6-mercaptopurine, allopurinol interferes with the degradation of 6-mercaptopurine. For this reason, approximately one-quarter of the dosage of this antitumor agent is needed when allopurinol is given concurrently. Higher dosages of 6-mercaptopurine would be dangerous.

In summary, the best treatment of uric acid nephropathy is prophylaxis. An alkalinizing solution plus adequate fluid intake should ensure this in almost 100% of susceptible patients. If severe oliguria occurs, mannitol diuresis is recommended, followed by alkali therapy. If this should fail, peritoneal lavage should probably be tried.

## Alopecia

Normal hair roots of growing human scalp hair have a high metabolic and mitotic activity. Germinative tissue of the average hair root produces 0.35 mm of hair shaft every 24 hours, and each day reduplicates its entire cell population. It is this rapid cell turnover which makes the hair root so vulnerable.

Crounse and Van Scott[42] have carefully studied the effects of cancer chemotherapeutic drugs on scalp hair. They found that almost all chemotherapeutic agents inhibit hair growth. This was manifested by narrowing of the shaft of the scalp hair. When this atrophy was severe enough, hair loss occurred. They also found that the number of hairs in the growing stage was markedly decreased by anticancer agents.

Although all cancer chemotherapeutic agents would seem to be capable of producing alopecia, many of the drugs almost never do. The alkylating agents, with the notable exception of cyclophosphamide, rarely cause hair loss. Some idea of the incidence of alopecia for the various agents can be gained from the individual chapters on each agent in this book.

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## CHAPTER XI

# CHEMOTHERAPY OF SPECIFIC MALIGNANCIES

This final chapter attempts to give an overall view of the chemotherapy of each of the malignant tumors. Details of therapy are omitted, and the emphasis is on the agent or agents of choice. Those malignancies for which there is no effective chemotherapy are omitted.

Included in this chapter is a reference table which lists the agents of choice of the various tumors. The agents are divided into those which produce marked, moderate, or slight benefit.

### Childhood Acute Leukemia

The treatment of childhood acute leukemia is in a state of flux. The traditional method was to use the various effective agents (methotrexate, 6-mercaptopurine, cyclophosphamide, vincristine) sequentially, with corticosteroids and ACTH generally used for short periods in the acutely ill child. With these methods median survival of one year was the rule. This was considerably better than the median survival of three months, prior to 1946.[1]

In the last two years, the concept of cyclic therapy has arisen, and the results seem superior. One of the most impressive series has been that of Zuelzer's,[2,3] since he has used his regimen for over nine years. Initial therapy in his patients was prednisone 2-3 mg/kg/day, or 200 to 400 mg of cortisone per day. Concurrently with this, 6-mercaptopurine 2.5 mg/kg/day was given. The corticosteroids were continued in full dosage until a hematologic remission was apparent from the appearance of reticulocytosis, increased platelets, return of granulocytes to the blood, and disappearance of blasts from the peripheral blood. This usually took 3 to 4 weeks. At this point, the corticosteroids were gradually withdrawn. Clinical response occurred in 8 to 10 days, consider-

| Disease | Marked Benefit | Moderate Benefit | Slight Benefit |
|---|---|---|---|
| Childhood Acute Leukemia | 6-mercaptopurine<br>Methotrexate | Corticosteroids<br>Vincristine | Cyclophosphamide |
| Meningeal Leukemia | Intrathecal Methotrexate | | |
| Adult Acute Leukemia | | | 6-mercaptopurine<br>?Methotrexate<br>(divided dose regimen) |
| Chronic Myelogenous Leukemia | Busulfan | 6-mercaptopurine<br>Chlorambucil | |
| Chronic Lymphocytic Leukemia | | Chlorambucil<br>Cyclophosphamide | Corticosteroids |
| Lymphosarcoma | | Chlorambucil<br>Cyclophosphamide | Corticosteroids<br>Mechlorethamine |
| Reticulum Cell Sarcoma | | Cyclophosphamide | Mechlorethamine<br>Chlorambucil |
| Hodgkin's Disease | | Methylhydrazine<br>Mechlorethamine<br>Cyclophosphamide<br>Chlorambucil<br>Vinblastine | Vincristine |

*(Continued)*

| Disease | Marked Benefit | Moderate Benefit | Slight Benefit |
|---|---|---|---|
| Wilm's Tumor | Actinomycin D | | |
| Other Embryonal Tumors of Infants | | | Vincristine<br>Actinomycin D<br>Cyclophosphamide |
| Neuroblastoma | ?Combination Therapy with Vincristine and Cyclophosphamide | | Vincristine<br>Cyclophosphamide |
| Multiple Myeloma | | Melphalan<br>Cyclophosphamide | |
| Breast Carcinoma | | Androgens<br>Estrogens | Corticosteroids<br>Chlorambucil<br>Cyclophosphamide<br>Triethylene Thiophosphoramide<br>5-fluorouracil |
| Adenocarcinoma of the Gastrointestinal Tract | | | 5-fluorouracil |
| Choriocarcinoma | Methotrexate<br>Actinomycin D | | Vinblastine |

*(Continued)*

| Disease | Marked Benefit | Moderate Benefit | Slight Benefit |
|---|---|---|---|
| Prostatic Carcinoma | | Estrogens | |
| Endometrial Carcinoma | | Progesterones in very high dosage | |
| Seminoma of Testes | | | Alkylating Agents |
| Choriocarcinoma of the Testis | | | Triple Therapy |
| Embryonal Cell Carcinoma of the Testis | | Mithramycin | Triple Therapy |
| Oat Cell Carcinoma of the Lung | | | Mechlorethamine |

ably sooner than full hematologic response. In a series of 175 patients, there were 99.4% remissions in those surviving over thirty days.

The 6-mercaptopurine was continued for a total of three months. At this point, methotrexate in a dosage of 1.25 to 5.0 mg/day, depending on age, was started. This was continued for three months, and the patient was then switched back to 6-mercaptopurine. The two antimetabolites were then rotated at three month intervals, until relapse occurred. At this point, corticosteroids were restarted.

On this regimen median survival was 17.2 months, with 25% of children surviving over 27.5 months, and 10% surviving over 45.0 months. It should be noted that 6-mercaptopurine had to be stopped on occasions when anemia occured in the face of remission.

Almost equally impressive were the results obtained by Brubaker et al[4] in 135 children, 114 of whom were unresponsive to 6-mercaptopurine. These authors used a cyclic regimen, starting with prednisone 2.2 mg/kg/day. After six weeks, the patient was switched to methotrexate 0.2 mg/kg/day for six weeks, and then to 6-mercaptopurine 2.5 mg/kg/day for six weeks. The cycle was then repeated continuously until relapse. The agent being used at the time of relapse was dropped, and the cycle continued with the other two agents. At the next relapse, the agent being used was dropped, and the last agent continued, until relapse again occurred. Of the overall group of 135 patients, median duration of clinical control was 13 months. However, 19 had inadequate trials, and 5 patients represented protocol deviations.

Of the remaining 111 patients, mean duration of clinical control was 19 plus months, with a median of 14 months. Of the overall group of 135, 22% were controlled for over 2 years and 5% for 4 to 7 plus years.

An extended discussion of the treatment of the child with acute leukemia is beyond the scope of this book. Proper attention to supportive care (transfusions, treatment of infections, emotional support of child and parents, control of bleeding phenomena) is as important as specific chemotherapy. Some excellent references on the overall care and chemotherapy of childhood acute leukemia are available.[1,5,6]

The usual criteria for complete remission of childhood acute leukemia are: (1) marrow – absence of cells that can be identified

as leukemic, and reduction in number of blasts to less than 10%, with lymphs less than 20%. Essentially normal granulopoeisis, erythropoeisis, and thrombopoeisis should be present; (2) peripheral blood-return to normal, for greater than one month, of hemoglobin, white blood count, and platelet count; (3) physical findings-subsidence of all evidence of leukemic infiltration; (4) clinical – no symptoms due to leukemia.

These criteria are those of the Cancer Chemotherapy National Service Center and are published in the journal *Blood*, volume 11, page 676, 1956. Criteria for partial remission are included. Also, criteria for remission of adult acute leukemia are defined. The use of intrathecal methotrexate for the treatment of meningeal leukemia is discussed in the chapter on methotrexate.

### Adult Acute Leukemia

6-mercaptopurine had been the only drug which produced objective remission in adult acute leukemia. Remission occurred in about 15% of the cases and was rarely complete. Survival of the overall group of adults with acute leukemia has not been significantly prolonged by 6-mercaptopurine, although it is felt that patients who have remissions do gain some prolongation of life.

More recently, one author[7] has reported a good percentage of remissions with methotrexate in four times a day dosage. Even more recently, the NIH group[8] have reported impressive remissions in adult acute leukemia with a combination of vincristine, prednisone, methotrexate, and 6-mercaptopurine given concurrently.

### Chronic Myelogenous Leukemia

Busulfan (Myleran) has been extremely effective in producing almost complete remissions in as many as 90% of patients with chronic myelogenous leukemia. Equally good results have been obtained with radiotherapy to the spleen. Therefore, which modality is used for therapy depends on the experience of the treating physician and the availability of a suitable radiotherapy unit. There are occasions when either radiotherapy or busulfan must be discontinued for specific toxicity. Under these conditions, the other modality may usually be substituted. For example, a long-standing case of chronic myelogenous leukemia may have received the maximum tolerated dosage of splenic radiotherapy. Busulfan could then be substituted. Patients in whom the syndrome

resembling adrenal insufficiency develops during busulfan therapy should be treated with splenic radiotherapy when the leukemia relapses.

The question of maintenance busulfan vs. treatment with intermittent courses has not been settled.

Chlorambucil has been used in chronic myelogenous leukemia, but is apparently not so effective as busulfan. Its use has been suggested for patients whose platelet counts are depressed by busulfan.[9]

6-mercaptopurine produces objective remissions in a large percentage of patients with this disease. However, stability of control with this drug is less. 6-mercaptopurine is also the drug of choice when the patients enters the acute blastic phase of chronic myelogenous leukemia. Unfortunately, few patients respond to therapy in the acute blastic crisis.

### Chronic Lymphocytic Leukemia

Alkylating agents produce objective remission in a large percentage of patients with chronic lymphocytic leukemia. Chlorambucil is the drug of choice. However, it may well be that cyclophosphamide is equally effective. There are not enough studies to demonstrate this point. Mechlorethamine (nitrogen mustard) is somewhat hazardous, because of the more sensitive bone marrow in this disease. However, objective remissions can also be produced with this agent.

Unfortunately, alkylating agents do not produce a marked degree of benefit in most cases of chronic lymphatic leukemia. Complete remissions are rare. A more complete discussion of this point will be found in the section on chlorambucil in the chapter on alkylating agents.

Spaced total body irradiation is as effective as chlorambucil. Local radiotherapy is occasionally needed for treatment of unsightly lymph nodes, a large spleen that is causing discomfort, or other local tumor deposits that are symptomatic.

Corticosteroids also produce objective benefit in chronic lymphocytic leukemia. However, side effects make these agents somewhat more hazardous to use for prolonged treatment.[10] The major role of corticosteroids is for treatment of the Coombs positive hemolytic anemia seen rather frequently in this disease. Neither radiotherapy nor chlorambucil affect this type of hemolytic anemia. More recently, 6-mercaptopurine has been used for

Coombs positive hemolytic anemia both in lymphomas and non-malignant illnesses.

### Lymphosarcoma

The diagnosis of lymphosarcoma covers a wide spectrum of histologic diagnoses and clinical pictures. The closer the cell type in the tumor tissue resembles the normal small lymphocyte, the closer the clinical picture and response to therapy resemble that of chronic lymphocytic leukemia. The farther away the cell type from the small mature lymphocyte, the less likely the patient is to respond well to corticosteroids or alkylating agents. Lymphoblastic lymphosarcoma, and large cell lymphosarcoma, are some of the diagnoses that would be found in the less responsive group. In general, most patients with the histologic diagnosis of giant follicular lymphoblastoma are highly responsive to chemotherapy. However, these patients usually require localized radiotherapy alone, and do not often need chemotherapy.

The above are only useful working generalizations, and occasional patients with rather wild-looking lymphosarcoma cells will be very responsive to alkylating agents.

Lymphosarcoma patients are less likely to require systemic therapy, than patients with chronic lymphocytic leukemia. These patients usually require radiotherapy to large tumor deposits in peripheral, mediastinal, or retroperitoneal nodes, spleen, liver, or even lungs. Often the patients are asymptomatic, and do not require therapy, especially if peripheral nodes are the only site of involvement.

Many patients in the lymphosarcoma and chronic lymphocytic leukemia group have low gamma globulin levels in the serum, and poor resistance to infection. Pneumonia, septicemia, and other infections are probably the leading cause of death in this group. Radiotherapy, alkylating agents, and corticosteroid therapy rarely improve the patient's resistance to infection, and may even decrease it. Corticosteroids are especially dangerous in this regard.

### Reticulum Cell Sarcoma

The treatment of large cell and more anaplastic cell lymphosarcoma merges into that for reticulum cell sarcoma. Radiotherapy to local areas of tumor is the mainstay of treatment. Reticulum

cell sarcoma is less likely to respond favorably to alkylating agents, although occasional patients have prolonged good responses. Several experienced investigators,[11,12] have reported unusually good responses of reticulum cell sarcoma to cyclophosphamide (Cytoxan). I have seen several such responses. Further clinical studies are needed to prove this. However, at present cyclophosphamide is probably the drug of choice for reticulum cell sarcoma.

Vincristine has also been reported to give a high incidence of objective responses in reticulum cell sarcoma.[13,14] Unfortunately, in most patients remissions are too brief, or vincristine neurotoxicity is too severe, for the remissions to have much clinical benefit.

### Hodgkin's Disease

In the section on mechlorethamine in the chapter on alkylating agents, the treatment of Hodgkin's disease is discussed in some detail. The key place of radiotherapy is emphasized.

This book is not the place to discuss the question of radical radiotherapy in early Hodgkin's disease. Vera Peters[15] has advocated prophylactic therapy to uninvolved lymph drainage areas in Stage I and Stage II of Hodgkin's disease. Although her data are suggestive, the issue is far from settled.[16]

Although there may be some disagreement with the delayed use of systemic therapy advocated in this book (see section on mechlorethamine in alkylating agent chapter), there comes a time in most patients with Hodgkin's disease when chemotherapy becomes necessary. Mechlorethamine is still the drug of choice in most patients. This is primarily because of the extensive experience with this agent. Although chlorambucil may be as effective, its delayed onset of action is a disadvantage in most cases. The annoying alopecia seen with cyclophosphamide is not counterbalanced by any superiority of antitumor action in Hodgkin's disease.

Vinblastine is approximately as effective as mechlorethamine. It has a minor disadvantage of requiring weekly intravenous injections. I prefer to use mechlorethamine first, because vinblastine is less toxic to the marrow. When the patient becomes refractory to mechlorethamine, he is further along in his disease, and the marrow is more depressed. The relative marrow-sparing

action of vinblastine is an advantage at this time. If vinblastine is used first, the patient's marrow may be more depressed by the disease and additional radiotherapy which may have been required in the interim. Thus by the time mechlorethamine is needed, it may be too toxic an agent. Actually, there is no strong argument in favor of this approach, and some may prefer to use vinblastine before mechlorethamine.

Once the patient becomes refractory to alkylating agents and vinblastine, the situation is often grave. By this time, the disease is usually no longer controllable by localized radiotherapy. Unfortunately, the other chemotherapeutic agents are even less effective than mechlorethamine and vinblastine. Occasional patients will have a good response to vincristine for over a year with only mild toxicity. Corticosteroids play a supportive role in advanced Hodgkin's disease. Control of fever, and other systemic symptoms, may be achieved for several weeks to months. Methylhydrazine,[17-18] a newer agent, is apparently equally as useful as the alkylating agents and vinblastine. (See Chapter 8.)

### Wilm's Tumor

The treatment of Wilm's tumor has been reviewed recently.[19] Radiotherapy and surgery are the major weapons. The effectiveness of actinomycin D in causing temporary regression (often of prolonged duration) has opened up a number of new approaches. It is difficult to say at present what the role of this most interesting agent will be. A more complete discussion will be found in the chapter on actinomycin D. In view of recent advances in the treatment of Wilm's tumor, it is perhaps advisable to refer children with this tumor to a center which has a large experience with Wilm's tumor and its recent treatment. This is especially important, because a significant number of these children are curable.

### Other Embryonal Tumors of Children

This area is one where results are usually poor. However, occasional responses to some of the newer agents in children with rhabdomyosarcoma[20,21,22] and other embryonal tumors[22,23,24] make this area one of great interest. The rarity of these tumors prevents most centers from developing a large series. Children with these tumors are best referred to a large center. The three

agents which have produced occasional results in these malignancies are vincristine, actinomycin D, and cyclophosphamide.

Recently, impressive results have been reported in neuroblastoma using combination vincristine and cyclophosphamide therapy. (See Chapter 8.)

### Multiple Myeloma

In view of impressive evidence that cyclophosphamide prolongs life in multiple myeloma,[25] and the even better objective responses to melphalan, I believe all patients with multiple myeloma should receive therapy with one of these two agents. There is little choice between the two drugs. Melphalan seems to produce better objective response, at a slightly higher price in toxicity. Although there are no published statistical studies with melphalan which show prolongation of life, there is every reason to believe that it does increase survival. Osserman[26] states that his preliminary data indicate that melphalan prolongs survival in multiple myeloma. Both drugs are alkylating agents, and it would seem logical that the more effective agent, melphalan, should at least be equal to cyclophosphamide in prolonging life.

My personal preference is to use melphalan for most patients, reserving cyclophosphamide for the patient with initially depressed bone marrow. Cyclophosphamide, in the suggested dosage regimen, is less marrow-depressing.

Urethane has been practically discarded for the treatment of multiple myeloma. It is doubtful that it was ever effective in more than an occasional patient. The Group at the National Institutes of Health[27] has suggested that testosterone is effective in raising the low platelet and white blood counts in patients with multiple myeloma. Confirmation of this by other groups has not appeared. However, testosterone is a safe drug, and I would favor its use in those myeloma patients with low peripheral white blood and platelet counts.

### Breast Cancer

The palliative treatment of disseminated breast cancer is helpful in about 40 to 50% of patients. There are a large variety of measures that can be taken, so that it is important to know when to use which modality. For this purpose, patients with disseminated breast cancer are divided into three groups by men-

strual age. They are also divided into groups by predominant metastatic spread. This latter division is of less importance in choosing therapy.

The division by menstrual age is into: (1) Premenopausal (this includes those women who are less than one year postmenopausal); (2) postmenopausal – one to five years, and (3) postmenopausal more than five years. For this classification it does not matter whether the menopause is natural or induced. The predominant type of spread is either: (1)Advanced breast involvement, local recurrence, or nodal spread; (2) bone metastases; or (3) visceral metastases.

For the premenopausal woman, the first treatment is oophorectomy, preferably surgical. Remissions occur in approximately 25 to 40% of patients. Remissions average between 9 and 15 months. No good controlled study has been carried out comparing radiation castration with oophorectomy. Radiation castration has resulted in remissions of approximately the same frequency and duration as surgical castration. On theoretical grounds surgical oophorectomy is preferred, because the irradiated ovary is still capable of converting androgens to estrogens. Also, the administration of corticosteroids can result in elevated gonadotrophin levels that will stimulate a functional ovarian struma. Some authors have advocated oophorectomy in women up to age 65 if estrogen production can be demonstrated by the vaginal smear. It is their contention that the ovarian struma may continue to produce enough estrogen to influence the breast cancer even after periods have ceased. This approach is not generally accepted.

If the premenopausal woman fails to have a remission of breast cancer after oophorectomy, her chances of responding to further ablative procedures (adrenalectomy or hypophysectomy) or hormonal therapy are very small, probably less than 10%. For this reason, many therapists would advise treating such a patient with a chemotherapeutic agent. At present, 5-fluorouracil is the preferred drug. Corticosteroids can be used too.

For the woman who relapses after initial response to oophorectomy, many authors advise hypophysectomy. Response rates as high as 80% have been reported. However, 50% is closer to the accepted figure for response to hypophysectomy in oophorectomy responders. An alternate view is to utilize androgens, and then perform hypophysectomy when the patient again relapses or fails to respond to androgens.

In the group of women one to five years postmenopausal, androgens are the preferred initial therapy, with hypophysectomy or adrenalectomy being the next step. Chemotherapy is a last resort, but it is doubtful that women who have had either of these of these two surgical procedures should receive 5-fluorouracil. (See Chapter 5.) Corticosteroids may be the preferred subsequent therapy after adrenalectomy or hypophysectomy.

In the women over five years postmenopausal, estrogens are the first choice of therapy for disseminated disease. Results in this group approach 40% remission rates. If the patient responded to estrogens, androgens may be tried when the remission is over. If the patient fails to respond to estrogens, the chances of an androgen-induced remission are small. After additive hormonal therapy responses are over, adrenalectomy or hypophysectomy is the next step, with corticosteroids and/or chemotherapy the last resort.

A final word should be added: it is not always necessary to treat the patient with incurable breast carcinoma. The accepted criterion is the presence of progressive disease. If metastases are asymptomatic and not progressing, it may be wise to withhold therapy until the disease advances.

Although this book is a manual of chemotherapy, radiotherapy deserves mention because of its important role in breast cancer. Skin recurrences or painful bone metastases are often best treated by radiotherapy as is inoperable primary breast disease and nodal recurrences. Often, radiotherapy is combined with systemic therapy. Reference to any text on radiotherapy will reveal the numerous areas of usefulness of x-ray treatment in breast cancer.

### Adenocarcinoma of the Gastrointestinal Tract

There is only one group of agents that can produce remissions in these carcinomas. This is the group of fluorinated pyrimidines, of which 5-fluorouracil is the only commercially available member. Unfortunately, only 10% of patients receive significant clinical benefit without excessive toxicity. This is discussed in greater detail in the chapter on 5-fluorouracil.

### Choriocarcinoma

Treatment of this tumor is the outstanding achievement of cancer chemotherapy. Seventy-five to 90% of patients with this

malignancy can be cured by chemotherapy. Methotrexate is the agent of choice, with prompt change to actinomycin D in the unresponsive patient.

### Prostatic Carcinoma

No chemotherapy has been effective here, but estrogens produce remissions in over 25% of patients. Castration alone or castration plus estrogens is probably superior to estrogens alone as therapy for this tumor.[28]

### Carcinoma of the Endometrium

Several groups[29,30] have reported significant remissions in about 25% of patients with endometrial carcinoma by the use of high dosage progesterones. Synthetic progestins have been the agent used in most cases.

### Malignant Testicular Tumors

Occasional good results have been achieved with chemotherapy in these tumors. Seminomas are highly radiosensitive, and can often be cured by radiotherapy, even when they have spread to para-aortic nodes. For widespread metastatic seminomas, alkylating agents can produce some palliation.[31]

Recently, some highly impressive results have been reported with a new agent, mithramycin, in embryonal cell carcinoma of the testis.[32] This is discussed in the chapter on miscellaneous agents. Whitmore[33] has reported a few patients with this tumor, as well as a few patients with choriocarcinoma of the testis, who responded to triple therapy (see chapter on miscellaneous agents).

### Oat Cell Carcinoma of the Lung

Impressive objective remission (unfortunately lasting for only 2 to 6 weeks) can be produced in 25% of patients with this tumor, using mechlorethamine. The clinical usefulness of these brief remissions is minimal.

### Other Malignancies

There are only isolated reports of remissions with chemotherapy in tumors not discussed above.

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