AXIOMS IN THE DIAGNOSIS AND TREATMENT OF LEUKEMIA

It is possible from the above discussion to formulate a few of the aforementioned principles as axioms:

1. The blood should be counted before, and at frequent intervals, during the active treatment of leukemia.

2. Do not treat a leukocytosis.

3. Cutaneous lesions are of diagnostic importance, since they are more common in Hodgkin's disease and lymphatic leukemia than in myelogenous leukemia.

4. Purpuric hemorrhages and petechiae suggest advanced stages of leukemia, in contrast to the sudden hemorrhages from the mucous membranes and oral cavity in acute leukemia.

5. The appearance of infiltration of the retinae, or of palpable lymph nodes, in the course of myeloid leukemia is decidedly unfavorable. It connotes a terminal stage of the disease.

6. The anemia in leukemia is due to the leukemia. It is usually alleviated in the course of treatment; if not, the prognosis is grave.

7. A high blast count is an unfavorable sign, especially when it occurs in the course of x-ray therapy.

8. An early death in the course of lymphatic leukemia is usually due to infection, because the myeloid cells (phagocytes) are depressed or absent.

9. Do not biopsy tissues unless it is absolutely necessary, because the leukemic processes at the site of the incision may become aggravated.

10. It is advisable to reserve irradiation for the treatment of mechanical disturbances arising in the course of leukemia.

11. Irradiation appears to hasten the fatal course of acute leukemia.

12. It is more valorous to be conservative in the treatment of acute leukemia. It is rarely benefited by any sort of treatment.

13. Our most hopeful therapeutic agents are, at best, only palliative measures.

14. As a rule it is advisable to irradiate the spleen and liver in myeloid leukemia, and the lymph nodes in lymphatic leukemia.

15. The bone marrow may be advantageously irradiated for the persistent anemia in the course of chronic lymphatic leukemia.

16. The lymph nodes appear to withstand more irradiation, without general constitutional reactions, than the spleen.

17. Massive doses of roentgen irradiation produce edema and swelling before decreasing the size of a leukemic tumor. This phenomenon may prove disastrous in the treatment of tumors around the delicate mediastinal structures.

CONCLUSIONS

1. There is no known method of cure of leukemia.

2. It is advisable to outline a conservative plan in the treatment of leukemia, and to attempt to understand the biologic reactions of the individual unit acting as a whole in his environment.

3. The goal of successful therapy in leukemia is the temporary restoration of the patient to a degree of efficiency, enabling him to live a useful though limited life.

4. At present, irradiation is the best single therapeutic agent in the treatment of leukemia.

5. Arsenic and radio-active elements offer a ray of hope in the chemotherapeusis of leukemia.

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SULFONAMIDE GROUP OF DRUGS: GENERAL PROPERTIES, USE AND DOSAGE*

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INTRODUCTION.—Almost five years have passed since the introduction of the sulfonamides into this country. They have been used on an unprecedented scale, and a tremendous wealth of material and reports has accumulated. Many drugs have been developed; only a few, however, have gained sufficient recognition to be included in our review. We shall concern ourselves with sulfanilamide, sulfapyridine, and sulfathiazole. Even this limitation will not make it possible to cover the field adequately. The following speakers will take up the applications in their respective fields, and Doctor Cutting, I hope, will stress in his discussion the pharmacologic principles. Therefore, I take the liberty to restrict my remarks to certain general principles which seem important at this time, and which constitute a present trend as it appears to us. The price for the required brevity of this presentation is a somewhat dogmatic character of my remarks, for which I want to apologize.

HISTORY

It is well known now that sulfanilamide was synthesized and described in 1908. Its chemotherapeutic properties, however, were not adequately appreciated until sufficient interest was awakened by the reports about prontosil as developed by the German workers around 1932-1934. In 1935, French investigators were able to demonstrate, in extensive animal experiments, that the chemotherapeutic results of prontosil could also be obtained with a simpler radical, contained in the complex prontosil molecule. This radical, sulfanilamide, reached the United States in 1936 at the same time as did prontosil. The latter was mainly used in conditions where sulfanilamide could not be given by mouth, while prontosil was available in a sterile stable solution.

In 1938, sulfapyridine was developed in England and gained rapid recognition as a potent agent against pneumococci and, to a lesser degree, against staphylococci. It proved, however, to be a much more toxic drug than sulfanilamide. It is for this reason that sulfathiazole, which was developed in this country in 1939, attained widespread popu-

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larity when it was shown that it was therapeutically equal to sulfapyridine, but much better tolerated.

ACTION

Briefly, the sulfonamide drugs are apparently bacteriostatic. It could be shown *in vitro* and *in vivo* that an inhibition of bacterial growth is produced, possibly by the interference with metabolic functions, although the nature of this mechanism is largely obscure. Under certain circumstances even bactericidal action—that is, killing of the organisms—may be obtained. Quite frequently, complete eradication of pathogenic organisms is not achieved even in the case of clinical recovery. It is necessary for the production of a satisfactory result that the drug reaches the bacteria, that they are susceptible to its action, that the concentration of the drug is adequate, and that the defense mechanism of the host is capable of taking care of the remaining organisms. In foci such as thrombi, which the drug does not penetrate, or abscesses where substances interfere with the action of the drug, no effect may be expected. It is in the tissue, which is affected by the infection, but not yet destroyed, where the drug exerts its optimal action. The drug prevents spreading and generalization of the infectious process and promotes localization. Therefore, surgical principles must be considered just as in the absence of chemotherapy. The same is true for bacteriologic studies, which should not be neglected in view of the relatively selective action of some of the compounds. For the demonstration of organisms by culture during the course of chemotherapy, media should be used to which para-amino-benzoic acid has been added. This substance will neutralize the bacteriostatic action of the drug contained in the specimen without interfering with the growth of any bacteria.

CHOICE OF DRUG

For a long time sulfanilamide was the drug of choice; sulfapyridine, and later sulfathiazole, were recommended in pneumococcus and staphylococcus infections and in all conditions in which the response to sulfanilamide had not been satisfactory. In this connection, I would like to point out certain misunderstandings commonly encountered. There is a widespread association between sulfanilamide and hemolytic streptococci, sulfapyridine and pneumococci, and sulfathiazole and staphylococci. This is due to their chronologic order, but it is quite misleading. In the development of prontosil and sulfanilamide it could be shown that they were active experimentally *in vitro* and *in vivo* against a variety of pathogenic organisms; in other instances, as in gonococcus infections, the clinical use preceded experimental investigations. When, later, other drugs were synthesized and tested, it was demonstrated that they were active not only against a variety of organisms, including those susceptible to prontosil and sulfanilamide, but also against others, as in the case of sulfapyridine against pneumococci. In the beginning, however, clinical studies were available only in those diseases where sulfanilamide had not been active or satisfactory. So there accumulated rapidly a literature about the use of sulfapyridine in pneumococcus, staphylococcus, and gonococcus infections; but at the same time no studies of larger groups were available in erysipelas and other hemolytic streptococcus infections.

This was largely accentuated by the fact that sulfapyridine was often producing most unpleasant subjective and objective reactions.

In the beginning of sulfathiazole medication it was mainly used as a substitute for sulfapyridine. Later, however, its use has become more and more extensive, until it now includes very frequently conditions in which, previously, sulfanilamide has been used exclusively.

The preceding remarks cover the initial choice of drug. It has become our practice to discontinue any of the drugs if some apparent effect cannot be demonstrated within two to three days. As it may be possible that we are dealing with a nonsusceptible or drug-fast strain which might be susceptible to one of the other drugs, those should be tried.

Considering the wide range of chemotherapeutic activity and the relatively low toxicity of sulfathiazole, I am personally inclined at the present time to recommend sulfathiazole as the drug of choice.

INDICATIONS

As the following speakers of this symposium will take up this problem in their respective fields, it should suffice to emphasize here that indications have become broader and broader, even including many conditions where the etiology has been by no means established. The fact that the drugs might possibly be of benefit is coming more and more into the foreground. Although we have to remember that all these drugs are potentially harmful and that their use presents a certain hazard, we have learned, on the other hand, to minimize this hazard by the recognition of danger signals which we shall discuss in the paragraph dealing with the toxic reactions.

It has become more and more a matter of judgment of the physician in the individual case, with careful consideration of the potential dangers of the underlying conditions weighed against the toxicity of the drugs; no hard-and-fast rule will relieve the physician from the burden of this decision.

CONTRAINDICATIONS

There is, strictly speaking, only one contraindication—intolerance to the drug. This might be inherent or more often acquired. In this respect it seems to be imperative that each patient should be carefully informed during or after the course of chemotherapy which drug he has received, how much of it, over what period of time, and whether he has shown toxic reactions indicating a possible intolerance. On the other hand, each patient should be questioned in detail about medication in the past, as the widespread use of these drugs makes it more and more likely that any patient might have experienced previous medication.

It seems wise to test these patients, if possible, with a small dose, and to give larger doses only if alarming toxic reactions do not occur.

TOXIC REACTIONS

The following reactions are grouped according to their severity and the corresponding recommendation of discontinuation:

Mild reactions: Medication may be continued, but watchfulness is necessary.

Malaise	Constipation
Headache	Moderate cyanosis
Giddiness	Chilliness
Muscular weakness	Palpitation
Loss of energy	Slight dyspnea
Nausea	Mild urticarial rashes
Anorexia	

Moderate reactions: Continuation is justified only if underlying conditions warrant it.

Vomiting	Extensive rashes
Diarrhea	Edema
Prostration	Marked cyanosis
Mental changes	pallor
Fever	dyspnea

Severe reactions: Medication to be discontinued, except in rare selected conditions:

Destructive blood changes	Toxic jaundice
Marked leukopenia	Toxic nephritis
Agranulocytosis	Hematuria
Hemolytic anemia	Anuria
Extensive purpuric rashes with high fever	Peripheral neuritis

Medical supervision during the course of chemotherapy should be mandatory. The control of blood and urine cannot be overemphasized, notwithstanding the recognition of economic difficulties in many instances. There is no doubt that patients experience less severe toxic reactions if they are confined to bed, or at least to their home and also kept from work. But here, as in so many phases of medicine, the physician has to reach a decision on the merits of the individual case. If chemotherapy seems indicated, it should not be lightly dismissed, because not all rules of precaution can be satisfied.

PROPHYLACTIC USE

Experimental work has shown again and again that the prophylactic and protective actions of these drugs are far superior to their therapeutic action. The reason becomes quite evident from the test-tube and animal experiments. Aside from the susceptibility of the respective bacterium, the action depends largely on the concentration of the drug and on the size of the inoculum. With a small number of bacteria, even bactericidal action is frequently obtained. It seems reasonable to assume (and this has been borne out in experimental work in animals) that few bacteria are easily controlled by concentrations which do not affect large numbers.

It is for this reason that we recommend the prophylactic use of these drugs in conditions where contamination of otherwise sterile tissues has occurred, or where pathogenic organisms are likely to develop their deleterious action.

LOCAL USE

This leads to the local use of the sulfonamide drugs. The same considerations are valid here as have been outlined in the preceding paragraph. The difference is that, with local application, we may obtain tremendous concentrations. We are confronted here with an entirely new phenomenon. While in the past germicidal drugs invariably damaged the tissue cells of the host, at least to some degree we have in the sulfonamides drugs which interfere, in some obscure manner, with the metabolism of some bacteria, preventing their multiplication, but which at the same time do not harm the tissue cells. This fact has been demonstrated again and again in tissue cultures, in animals, and in many clinical instances where healing per primam has been demonstrated quite frequently after the introduction of sulfanilamide crystals. The small number of bacteria is easily disposed of, and the drug is eliminated without giving rise to toxic reactions.

GENERAL PRINCIPLES OF MEDICATION

In case it has been decided that one of the drugs should be used, we suggest to start with high doses, to be decreased corresponding to clinical improvement, and continued for a short while after clinical recovery from infection. Severe toxic reactions do not occur in the beginning of medication more frequently with high than with small doses. On the other hand, sensitivity is frequently acquired, so that, after a prolonged use of small ineffectual amounts, it might not be possible any more to give later the desired large doses. The fluid intake should be regulated, so that a minimum of 1,000 cubic centimeters of urine excretion per day is obtained. Excess of fluid will promptly lower the level of the drug in the blood and tissue fluids. Medical supervision, with control of blood and urine, is essential. If alarming toxic symptoms appear, the drug should be discontinued and fluids forced.

Oral administration of the drugs is preferable to any other; if not possible, intravenous, subcutaneous, intramuscular, and rectal use are to be considered.

The doses of the various drugs cannot be stated categorically. In the case of sulfanilamide, one gram (15 grains) for each twenty pounds of body weight may be given per day, divided into fractions given every four hours to obtain a relatively constant level of the drug in the tissues. Children excrete the drug more rapidly, require and tolerate up to double doses and more, computed per body weight.

The common dosage of sulfapyridine and sulfathiazole in severe conditions is one gram every four hours after an initial dose of two to four grams.

FUTURE PROSPECT

The development during the past five years has shown beyond doubt that we are only in the beginning of bacterial chemotherapy. New drugs are appearing constantly and are received with great attention and confidence, as, for instance, sulfadiazine and sulfaguanidine. They do not have to wait any more for bold pioneers, as in the past, but they are readily tested on large series in acknowledged institutions. On the other hand, the medical profession is ready to discard any of the older preparations as soon as advantages of the newer drugs over the older ones become apparent. It is more than likely that newer drugs will be found which are more potent, less toxic and, perhaps, more selective than those discussed.

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