THE PRESENT STATUS OF THE SULFONES IN THERAPY

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PROMIN

Synthesis of diaminodiphenyl sulfone was reported in 1908 by Fromm and Whittmann (1) during their researches in dye chemistry. Not until 1937 did Buttle (2) and his associates initiate interest in the compound by their chemotherapeutic studies against streptococcic infections in mice. They found the compound 100 per cent more effective than sulfanilamide.

On August 5 of the same year, Tuller made diaminodiphenyl sulfone in the research laboratories of Parke, Davis and Company, and the following day Tullitson made the compound soluble by converting it into promin. From that date to the present, chemical and laboratory work on sulfone compounds have continued without interruption.

Beginning in late 1937, laboratory and clinical studies of promin spread over the general field of infectious diseases. It proved to be of value in certain conditions such as streptococcic infections and certain types of pneumonia, and it also gave encouraging results in those conditions where it is necessary to give a chemotherapeutic agent intravenously.

A complete change occurred in the attitude and interest of the medical profession toward the sulfones following the work of Feldman and Hinshaw (30). They began working on experimental tuberculosis in guinea pigs in 1940, the same year that Rist, Block, and Harmon (13) reported the inhibitory effect of diaminodiphenyl sulfone upon tuberculosis in animals. Also this same year Bambas (55) made promizole.

The studies of Feldman and Hinshaw were enlarged and extended in this study of sulfone compounds, until an extensive number have been evaluated, and new compounds, as they are made, are placed on experimental trial.

1 Read at the Fifth International Leprosy Congress, Havana, on April 5, 1948. This paper is regarded as of special interest because of the bibliography of the sulfones.—Editor.
Promising results of promin in the treatment of animal tuberculosis stimulated Cowdry (17) to try the same drug for the treatment of rat leprosy. His results, published in October 1941, were encouraging but not as spectacular as those in the tuberculosis experiments. One observation in Cowdry's paper is significant. It is that the degree of granulation of the bacilli in the periphery of the nodules (i.e., in those nearest the circulating blood), appeared to be greater in the treated animals than in the untreated. This same change was first noticed by Eccles while making a microscopic study of biopsy specimens from treated leprosy patients at the U. S. National Leprosarium at Carville, Louisiana. Promin was first made available to Faget at Carville in January, 1941. In selecting cases for his study he chose lepromatous patients who were in an advanced stage of the disease. This fact made the beneficial results all the more spectacular to the observer, but was difficult to convey in the literature.

The first investigator among Faget's group to become convinced of the effectiveness of promin was Prejean (154), the dentist. Since oral and pharyngeal lesions are among the earliest to respond to sulfone treatment, Prejean had an opportunity to observe the first beneficial effects of the new drug.

Late in 1942, the first study of promin in treatment of Hansen's disease outside the United States was begun in the city of Trinidado, Bolivia. This study was conducted by Dr. Juan Jablonsky who, due to the exposures resulting from his work, contracted, pernicious malaria which resulted in his sudden death.

Faget (59) published his first report on the treatment of Hansen's disease with promin on November 26, 1943, three years after publication of the first tuberculosis study by Feldman and associates.

**TOXICITY OF PROMIN**

Due to the interest following Feldman and Hinshaw's announcement of the results of promin treatment in guinea pig tuberculosis, the manufacturer was deluged with requests for supplies of the compound. In order to discourage indiscriminate use, and to emphasize the need for care and control, the laboratory over-emphasized its toxic effects. It is now time that we re-evaluate our data on promin and determine its dangers in the light of present knowledge and experience.

Beginning in 1938, this drug has been used for treatment of
various human diseases. During this ten years of clinical study, thousands of patients have received it without a single death resulting from the effects of the drug. This record cannot be equaled by sulfanilamide or sulfadiazine, which are generally considered safe. The signs of promin toxicity are not hidden as is the case with those drugs; they are easily recognized, even by nonmedical individuals, in sufficient time for reduction of the dose or discontinuance of treatment long before grave symptoms develop. Recovery is thereafter always rapid.

**PROMIZOLE**

Promizole, first described by Bambas, is an isoster of 4,4'-diaminodiphenyl sulfone and has a 2-aminothiazolyl radical replacing one of the aminophenyl groups. Promizole is soluble in water to the extent of 0.08 per cent, but is highly soluble in dilute acids and some organic solvents. It is stable in dry form.

Dogs on a diet containing fresh horse meat received promizole in the amount of 0.1 gm. per kilogram of bodyweight for 40 days, and developed no symptoms of toxicity except occasional periods of slight incoordination and a moderate lowering of the red cell blood count. Autopsies revealed no gross or histologic pathology. After a period of 106 days' treatment there was a suggestion of hyperplastic change in the thyroid gland. Promizole concentration in the blood reaches a maximum in four to seven hours. It is slowly excreted. In the body the compound undergoes conjugation into more soluble products. Promizole enters the spinal fluid in demonstrable amounts.

In addition to the therapeutic effectiveness of promizole in treatment of Hansen's disease, it has been used successfully in the treatment of scleroderma by Wuerthele and of miliary tuberculosis and tuberculous meningitis by Lincoln and associates.

Present difficulty of manufacture increases the cost of promizole to a point which limits its use in therapy.

**PROMACETIN**

This compound is sodium-4,4'diaminodiphenyl sulfone-2-acetysulfonamide. It is a white crystalline compound which forms a 3 per cent solution in water at room temperature. Promaceatin does not break down into diaminodiphenyl sulfone, which perhaps explains its low toxicity. Dogs fed one gram per kilogram of bodyweight daily for seven days showed no complications.

In man the dose has varied from 4 to 12 grams per day over periods of one week without evidence of toxicity. Physiologic
studies indicate that, even with massive doses by mouth, the
blood level will seldom attain dangerous proportions. Blood
levels from a single dose, however, are maintained for at least
two days. This sustained blood level is not well understood
physiologically, but would be a great advantage should the drug
be used for mass treatment in large institutions.

Promacetin was found to be of value in certain cases of pneu­
monia, and presumptive trial at Carville by Faget and Johansen
indicated that it may be of value in Hansen’s disease.

**DISODIUM FORMALDEHYDE SULFOXYLATE**

**DIAMINOPHENYL SULFONE***

This compound was synthesized simultaneously and inde­
pendently by Raiziss, Clemence, and Freifelder (79,119) and by
Bauer and Rosenthal (4). Muir (109) initiated the clinical study
of this compound, and found it effective in controlling develop­
ment and causing a remission of symptoms and signs of
Hansen’s disease. Faget, Pogge, and Johansen (126) and Fern­
andez and Carboni (146) also reported favorable results from
their studies.

Intolerance to this compound has been reported in a wider
variety of reactions than in the case of promin.

**DICINNAMYL SODIUM SULFONATE DIAMINO DIPHENYL SULFONE***

This compound is bis (3"-phenylpropyl-1"-3"-disodium sul­
fonate) -4,4'-diaminodiphenyl sulfone. It has a molecular weight
of 892 and contains 27.8 per cent of 4,4'-diaminodiphenyl sul­
fone. It is very soluble in water, and readily decomposes in an
acid medium to give 4,4'-diaminodiphenyl sulfone.

Wharton (156) and Dharmendra and Chatterjee (159) have
used this drug in treatment of Hansen’s disease and report
satisfactory results from their preliminary studies.

**BENADRYL**

Benadryl gives promise of being of great value as an adjunct
in treatment of Hansen’s disease. Mom (153) and Wharton
(158) report it to be highly effective in controlling lepra reac­
tions. This will remove one of the annoying complications of
sulfone therapy, as well as furnish relief from one of the most
distressing syndromes of untreated Hansen’s disease.

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* Diasone (Abbott Laboratories), diamidin (Parke, Davis and Com­
pany).—Editor.

* Sulfetrone.—Editor.
PRESENT RESEARCH

Research in the field of the mycobacteria is divided into two stages. The first stage is being carried on in several laboratories which are actively screening numerous compounds both in vitro and in vivo. Therapeutic studies against animal tuberculosis are extensive. Those studying treatment of rat leprosy are more limited in numbers.

After a compound proves to be effective in the laboratory it is prepared for the second or clinical stage. This preparatory stage comprises exhaustive studies of tolerance and toxicity. Standards of purity must be determined, and methods of testing for blood and urine concentrations established. Testing tolerance and toxicity includes both animal studies and studies on human volunteers.

When the pharmacology and toxicology of a new compound are well understood it is ready for the clinician. Clinical evaluation of chemotherapeutic substances for Hansen's disease is a long and painstaking process. In the search for new drugs the factors involved are increased rapidity of action and greater tolerance. The Leonard Wood Memorial is the logical entity to facilitate these clinical studies and to aid in the interchange of information.

NEW COMPOUNDS

Certain sulfone compounds found to be effective in the laboratory have not as yet had clinical trials. These compounds have some chemical and physical characteristics which are of advantage.

**MONOPROPYL DIAMINODIPHENYL SULFONE**

The chemical name of this compound is 4-propylamino-4′ aminodiphenyl sulfone. It is a white crystalline solid which is only slightly soluble in dilute mineral acids and organic solvents. It has a molecular weight of 290 and contains the equivalent of 85.6 per cent of 4,4′-diaminodiphenyl sulfone. The side-chain cannot be readily split from the amino group.

**MONOALLYL DIAMINODIPHENYL SULFONE**

The chemical name of this compound is 4-allylamino-4′ amino diphenyl sulfone. It is a yellowish white crystalline product which turns yellow on prolonged exposure to light. It is slightly soluble in organic solvents. It differs from the above compound by having a double bond in the side chain. It has a molecular weight of 288 and contains the equivalent of 86.0 per cent of
4,4'-diamino diphenyl sulfone. The allyl group can not be readily split from the amino group.

**Acetyl Promizole**

This compound is a derivative of promizole, in which the acetyl group is attached to the amino group on the thiazole nucleus. Since promizole contains no 4,4'-diaminodiphenyl sulfone, this compound also contains none. It is quite insoluble in water and dilute mineral acids, soluble in dilute alkaline solutions. Its molecular weight is 297.

Clinical evaluation of these compounds cannot be determined until a carefully controlled comparative study is arranged with compounds of known efficacy. The time is rapidly approaching when such a study will be indicated.

**Control of Sulfone Drugs**

A suggestion has been made that the sulfone drugs be placed under some type of international control, in such a way that their use can be directed and their distribution limited for reasons of efficiency. We have seen that the use of the sulfones is not limited to the treatment of Hansen's disease. Their usefulness in general chemotherapy is recognized by many physicians. They are being used in treating various forms of tuberculosis, streptococcic infections, scleroderma and other conditions of less importance. Therefore this Congress would be encroaching on the field of general therapy should it advise any method of control.

Any political or economic crisis increases the ease with which bureaucratic power usurps the freedom of the individual. These are times when the medical profession must be on the alert to guard its ancient art and traditional freedom. Bureaucracy is a dark cloud attempting, in many lands, to smother the inherent liberties of the free practice of medicine, trying to reduce this ancient and respected art to the level of political decree. Let us be jealous of the liberties we still retain, and not encourage further smothering of our profession by governmental agencies.

I believe this Congress will agree that any governmental control of these drugs will increase the hardships of the individual physician in the pursuit of his profession. It will also directly or indirectly increase the cost of medication to the patient, or to the institution which has assumed his treatment and care.

Controlling the use of a drug by governmental decree requires...
the organization of a bureau consisting of numerous salaried personnel for the purpose of enforcing the control regulations. The salaries and other expenses of such a bureau are added directly or indirectly to the cost of the product. Often the personnel in such a bureau are not medical men, and as a result they lack sympathy or understanding of the medical problems involved. Such a program is the practice of medicine by decree, and if carried to its logical conclusion it would, in the end, result in slot-machine prescribing with no doctor being necessary.

When the Federal Government assumes the role of sole distributor of a drug the evils are still further multiplied. Not only is there great expense in such a program, but also the profession of medicine is subjected to the unnecessary delay and annoyance of the unavoidable red tape involved. Such a plan would limit use of the drugs to the extent that doctors living in the interior would not find them easily available, and the profession in general would be dependent upon political patronage for what is considered a traditional right and privilege. Would it not be easier, for all concerned, to limit the sale of these compounds by duly licensed pharmacies to or on the prescription of licensed physicians? Such a regulation would neither interfere with shipments or supplies of the drugs as would most other forms of regulation, nor would it add to the cost or inconvenience the patient or physician. This is the only control which would not interfere with the ethical practice of medicine, and at the same time it is the only control which would insure the prompt and adequate care and treatment of the sick in all communities. Such supervision would also afford the maximum amount of protection against the abuse and dangers of nonprofessional medication.

Let us be jealous of surrendering our professional liberty, because liberty and freedom once lost are difficult to regain.

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