INTERNATIONAL JOURNAL OF LEPROSY

OFFICIAL ORGAN OF THE INTERNATIONAL LEPROSY ASSOCIATION

PUBLISHED WITH THE AID OF THE
LEONARD WOOD MEMORIAL

Publication Office: School of Medicine, Tulane University,
1430 Tulane Avenue, New Orleans 12, Louisiana
Entered at the Post Office at New Orleans as second-class matter.

VOLUME 20, NUMBER 2 APRIL-JUNE, 1952

EDITORIALS

Editorials are written by members of the Editorial Board, and opinions expressed are those of the writers.

THE ISONICOTINIC HYDRAZINES IN TUBERCULOSIS

On February 21st, last, some five weeks before reports were to have appeared in a medical periodical, the conservative *New York Times* and other newspapers gave first-page place to a story of "startling" results that were being obtained at the Sea View Hospital, one of the municipal tuberculosis institutions of the City of New York, after only a few months trial of a new "wonder drug" which promised to be the most effective one yet known. This news immediately got world-wide distribution, and the play given it in many papers was sensational. The excitement aroused was without parallel.

The American news weekly *Time* ran a more informative story on March 3rd (overseas edition). The substances in use at Sea View were the hydrazide of isonicotinic acid, developed by Hoffmann-La Roche, Inc. and called Rimifon, and a related product called Marsilid (actually, the isopropyl derivative).[1] Simultaneously E. R. Squibb and Sons had also hit upon isonicotinic acid hydrazide, which they called Nydrazid, and had given it for clinical trial to physicians at the New York Hospital, where the laboratory facilities were superior.[2] Early in January these two manufacturers had gotten together to arrange jointly for further testing, and for requesting the Food and Drug Adminis-

[1] The first patients there were put under treatment on October 2, 1951.
[2] The work here was begun in November 1951.

tration to release the drug for general use. The probable cost, it was stated, would probably be $.75 for a day's dosage when large-scale production could be reached. For the present, it was pointed out, the sobering history of previous "wonder drugs" should be borne in mind.

The premature "breaking" of this news caused acute embarrassment. The medical director of the Squibbs company immediately addressed a statement to the medical profession, saying in part:

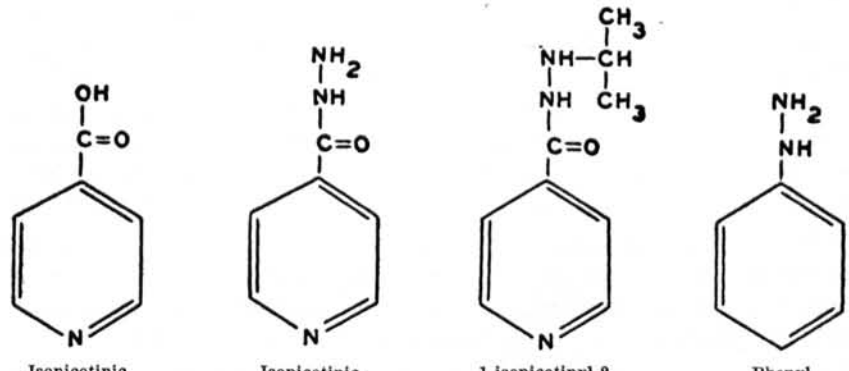
> "Under circumstances beyond our control news of a new anti-tuberculosis drug has found its way into the lay press before completion of clinical studies . . . and adequate scientific publication . . . . It has been on clinical trial for no more than a matter of months."

No estimate could be made, it was stated, of when the drug might become generally available, or of its ultimate cost to the patient.

The American Trudeau Society, the medical section of the National Tuberculosis Association, promptly got into action. Within two weeks, on March 5th, it issued a statement on the current status of isonicotinic acid hydrazide in the treatment of tuberculosis. This deals briefly with the chemical structure, activity *in vitro* and *in vivo*, toxicity and pharmacology, dosage, toxicity in man, and activity in man; and it points out deficiencies of existing knowledge, problems remaining to be solved, and precautions. Three paragraphs are quoted in part:

> 9. *Precautions:* At present there is no reason to believe that the fundamentals of therapy of tuberculosis should be altered in any way when isonicotinic acid hydrazide is employed. Patients receiving the drug should be hospitalized for careful observation . . . . Routine laboratory precautions should include frequent blood and urinalyses, neurologic examinations, and tests for renal and hepatic insufficiency.
>
> 10. *In General:* The introduction of a new drug in the therapy of tuberculosis is likely to raise more questions for a few years than it will answer. There is no knowledge at the present time that isonicotinic acid hydrazide or its isopropyl derivative will accomplish more than has been accomplished with streptomycin and PAS. It may prove to be an additional drug of great value. It may be years before its exact contribution to the therapy of tuberculosis can be assembled accurately . . . .
>
> 11. *Summary:* After a review of available data on the action of isonicotinic acid hydrazide and its isopropyl derivative upon the tubercle bacillus *in vitro*, and upon the course of experimental tuberculosis in animals and clinical tuberculosis in man, it may be stated that their demonstrated action, although highly encouraging, appears in no way to alter the basic principles of the treatment of tuberculosis as presently understood. Much more work will need to be done to ascertain the exact place of these drugs in the treatment of the disease . . . .

Certain of the several structural formulas accompanying this statement are reproduced here (the first three below):



Isonicotinic acid | Isonicotinic acid hydrazide | 1-isonicotinyl-2 isopropylhydrazide | Phenyl hydrazine

The definition of hydrazine in the New Gould medical dictionary first refers to a compound called diamine, $H_2N.NH_2$; then, generally, "one of a class of bodies derived from hydrazine by replacing one or more hydrogen atoms by a radical." That in Stedman calls hydrazine any member of the group $H_2N.NH_2$, from which phenylhydrazine and similar reduction products are derived. The formula of phenylhydrazine is given as $C_6H_5NH.NH_2$ (fourth formula above).

To whom credit should go for priority in the development of this new substance as an antituberculosis agent cannot be said from the information available to us; it seems likely that it will have to be shared. No official statement from Hoffmann-La Roche has been seen, but it has been reported that in their laboratories, beginning in 1947, Grunberg and Schnitzer tested almost 1,000 compounds before they got to the isonicotinic acid hydrazide in July 1950; the synthesis of that drug and various derivatives is credited to Dr. Herbert H. Fox. According to Grunberg *et al.*[3] some attention was paid for a time to compounds of the class of the thiosemicarbazone of isonicotinylaldehyde. Selikoff and Robitzek [3] have stated that isonicotinic acid hydrazine was used as an intermediate in the preparation of those substances.

The Squibb release referred to states that in an intensive research program which had been in progress "for many years," and in which approximately one and one-quarter million dollars had been invested, some 5,000 compounds had been tested for activity against tuberculosis. It was among the thiosemicarbazones and related compounds that the isonicotinic acid hydrazide

[3] Abstract in this issue.

was found; even the most closely related compounds had given no hint of its "spectacular effectiveness."

In Germany, work in this field has been carried on for several years by a Bayer group. From a recent article by Offe, Siefken and Domagk [3] it appears that, in 1946, Behnisch, Mietzsch, Schmidt and Domagk [4] reported that certain hydrazine derivatives had shown high tuberculostatic efficacy. References are given to subsequent articles in this field by Buu-Hoi (Paris, 1946, 1949), Levaditi and Giraud (Paris, 1950), and Fox (U. S., 1951). Offe was led to undertake a systematic study of the relationship between chemical structure and tuberculostatic effect, and he and Siefken at Leverkusen studied "some hundreds" (stated elsewhere to have been over 500) of hydrazine derivatives, while Domagk at Elberfeld investigated their tuberculostatic action *in vitro*, testing some of them *in vivo* in guinea-pigs and rabbits. They came to concentrate on isonicotinic acid hydrazide, to which the name "Neoteben" was given.[5] According to our Contributing Editor for Germany, Dr. E. Keil, a report on the subject was made by Domagk at the II Medical Congress in Nürnberg in the latter part of October 1951, and a publication appeared in *Aerztliche Praxis* **4** (1952), No. 5 (Feb. 2). More recently Domagk, Offe and Siefken [3] have reported on the laboratory phases of the matter, and on February 19 a paper was read by Klee on his clinical observations of 61 patients treated for from 6 weeks to 5 months.[3]

It appears that the hydrazide of isonicotinic acid was also discovered independently in Spain. Two weeks after its first story on the subject, *Time* magazine reported that that substance had been produced by a chemist, Juan Socias, in the Laboratorio Faes, in Bilboa, and that it—called FSR-3—had first been used for treating tuberculosis patients, on a small scale, a full year before. The experience there was similar to that reported in the United States, except that two patients proved allergic to the drug and had to be dropped. Spanish doctors, it was stated, were just as upset as their American colleagues over the pre-

---

[4] Domagk, G. Behnisch, R. Mietzsch, F. and Schmidt, H. Ueber eine neue, gegen Tuberkelbazillen in vitro wirksame Verbindungsklasse. Naturwissenschaften **33** (1946) 315. [The arrangement of the authors' names are as they appear in the Quarterly Cumulative Index Medicus, which differs from the reference given in the article mentioned.—EDITOR.]

[5] It appears from this report that F. L. Rose, of the Imperial Chemicals Industries, in England, has found a related compound (a l-pyrazolo-(4:3-d)-pyrimidin derivative) to be tuberculostatic.

mature publicity given the drug and the false hopes that might be aroused.

It appears that the hydrazide is easily made, not expensive and not patentable. How many pharmaceutical manufacturers are already making it cannot be said, but evidently they are many. The Nepera Chemical Company, of New York, has sent quantities of it, under the name "Pyricidin," to several Latin-American countries and the Philippines for trial. The Charles Pfizer Company, of Brooklyn, will put it out as "Cotinazin." The Abbott Laboratories, Parke, Davis & Co., and the Armour Laboratories have supplied it to the Leonard Wood Memorial for experimentation; also the Wellcome Research Institute of London. It also appears that the Maggioni Laboratories of Milan, Italy, are making it under the name of "Isobicin."

That the hydrazide can so readily be made on a large scale, at least in the United States, has been credited to the U. S. Army Ordnance Corps. There was no volume production of hydrazine until 1946, when its large-scale manufacture was sponsored by that Corps because it had shown promise as an improved rocket propellant. Deliveries of it have been deferred voluntarily so that more of it can be used in the production of the new antituberculosis drug.

It goes without saying that leprosy workers are also keenly interested in the potentialities of this new drug with respect to that disease, and it is already being tried out. In one of the earlier newspaper reports it was stated that Grunberg and Schnitzer had tried Rimifon with some success "on an animal form of leprosy." Hanks, of the Leonard Wood Memorial bacteriology laboratory at Harvard University, is reported as now cooperating with them. Y. T. Chang, a Leonard Wood Memorial fellow at the National Institutes of Health in Washington, D. C., is also testing the hydrazide on murine leprosy.

Regarding leprosy itself, the drug is said to be on trial at the U. S. Federal Leprosarium at Carville, and trials are known to be under way in Nigeria and Malaya. A supply from Germany has been promised for use at Culion. The medical director of the Leonard Wood Memorial has arranged for the trial of these drugs in the clinical evaluation units established in South Africa, the Philippines, and Japan, and also at the Tala leprosarium near Manila.

Because of the widespread interest in the matter, abstracts of all published articles of which we have learned appear in this issue. The first five, of articles in a special issue of *Quarterly Bulletin of the Sea*

View Hospital,[6] were promptly supplied by Dr. F. A. Johansen, our Contributing Editor for the United States. The next four, from the same group, were published in the April issue of *Diseases of the Chest;* a reprint of them was kindly supplied by the medical director of Hoffmann-La Roche. Those of six articles which appeared in the April issue of the *American Review of Tuberculosis* have been taken from a pamphlet distributed by the Pfizer company which deals with all American reports through April. Finally, abstracts and reprints of three German reports have been supplied by Dr. Keil. In view of the present thorough coverage,[7] we do not expect to make note of further articles dealing with tuberculosis unless they contain material of special significance.

ADDENDUM. The latest report seen, another signed story in the *New York Times,* May 10th, tells of discharges of Sea View Hospital patients. Several of the original group who had improved greatly had left the hospital at their own request; but one, put under treatment on October 2, 1951, after more than a year without improvement under other medicaments, had now been given an official discharge, and some others were expected to be discharged shortly. It is stated that there are indications that the isopropyl derivative, Marsilid, is proving more effective in clinical therapy than isonicotinic acid hydrazide itself, contrary to laboratory findings in which the latter had shown itself to be the more active.

After this note was sent to press, news reports emanating from Washington, D. C., on June 4th announced that the Food and Drug Administration had on that day authorized release of "isoniazid"—the short name for the hydrazide of isonicotinic acid—for general use. According to one report it would be "for use under close medical supervision"; another has it that the drug may be sold on any doctor's prescription, and that so great was the public demand for it that one of the largest New York department stores had advertised it in a newspaper.

---

[6] Apparently dated January 1952, but evidently not published until late in March.

[7] For much of the information which we have obtained appreciation is due to the efforts of Mr. H. L. Elias, executive secretary of the Leonard Wood Memorial.