

Comparative Tests of Glucosulfone Sodium (Promin), Thiocarlid (Isoxyl), and Two INH-Derivatives with Stefansky-Leprosy of the White Rat

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As long as the cultivation of *Mycobacterium leprae* on artificial culture media or in tissue culture is not possible with constant reliability, models of experiments have to be accepted in search for effective substances for the chemotherapy of leprosy. As human leprosy and leprosy of the rat show great similarities with respect to the pathogenic agent, as well as the clinical picture, leprosy of the rat presents itself as a suitable experimental model.

In 1903 leprosy of the rat was discovered by Stefansky in Odessa by finding 4-5 per cent of brown rats infected. The germ, *Mycobacterium lepraemurium*, shows the same features as *Mycobacterium leprae* in morphology, behavior toward dyes, and cultivation. Also the clinical picture with leprosy of the rat is similar to that of human lepra lepromatosa. After infection, nodules of the size of cherry stones up to that of pigeon eggs develop; these may break through the skin and then lead to ulceration lasting several months. Time of incubation also may take several months with this experimental model.

Advantages and disadvantages of this experiment are evident. The advantage is the similarity to leprosy caused by mycobacteria. The disadvantages lie in the long duration of the experiment, in the irregular and differing moments of death, even of the controls, and in the various sizes of the lepromas, which differ from animal to animal. Therefore exact interpretation of success or failure is very difficult, requiring much experience. The irregularities of the experiment must be compensated by a larger number of animals; strictly speaking the course of disease of each rat should be discussed.

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On the basis of long-term experience with this experiment, the following attempts to give a largely objective evaluation.

Method. A freshly excised nodule is homogenized in physiologic NaCl. Each rat gets an injection of 1 ml. of the homogenisate into the back. The intraperitoneal therapy begins when nodules become palpable under the skin. Treatment is given daily, on six consecutive days, then a break of one day. For each experiment 30 animals are infected: 10 of these serve as untreated controls. The duration of treatment can be extended up to 300 days: treatment is given for 100 days; then an interval of 90 days follows. During this time the animals are observed for the development of relapses; then another turn of treatment follows till the end of the experiment, when all animals are killed.

RESULTS

1. **Promin.** The therapy was started with doses of 5 mgm./kgm. daily intraperitoneally, applied nearly nine months after infection. Shortly after the beginning of the therapy most animals developed ulceration of the lepromas. The explanation for this lies in the degeneration of the mycobacteria caused by Promin. With increasing duration of the therapy the lepromas tend to diminish and the ulcers show significant tendencies to heal. This tendency to regression stays as long as the treatment is continued. Discontinuation of the therapy leads to relapse (Fig. 1).

2. **Thiocarlid (Isoxyl).** Therapy was started with 25 mgm./kgm intraperitoneally, applied four months after infection. Development of lepromas prevails even during the therapy; ulcers, resulting from decomposition of the lepromas, do not occur, in contrast to results after treatment with Promin.

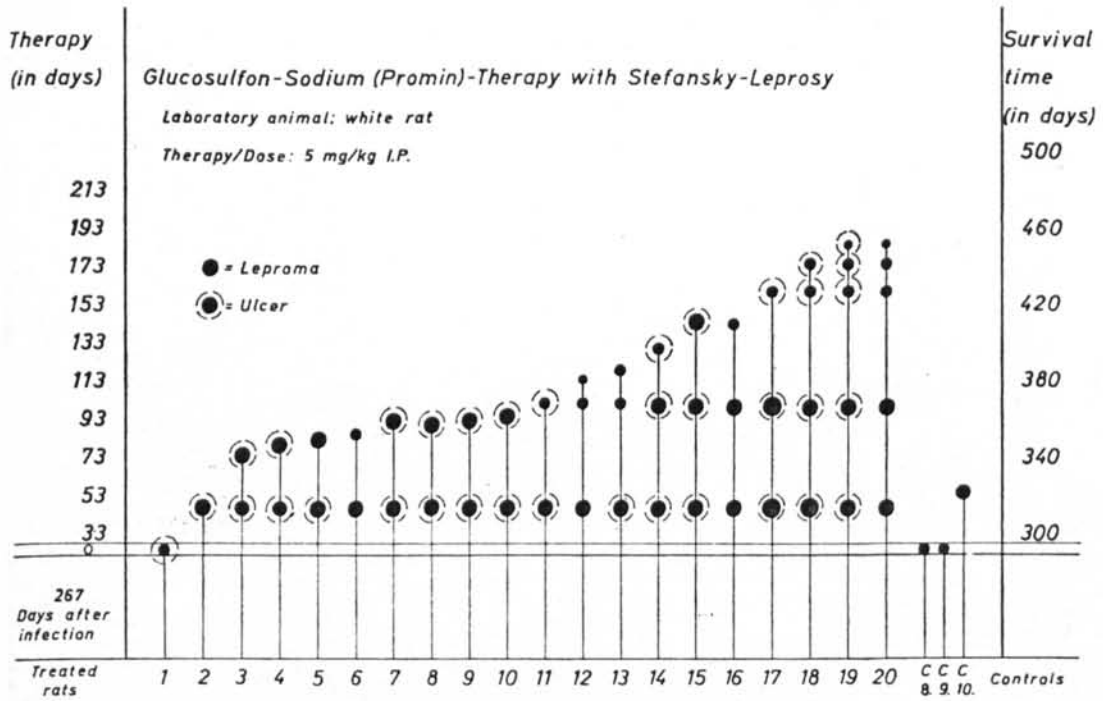


FIG. 1. Glucosulfone sodium (Promin) experiment.

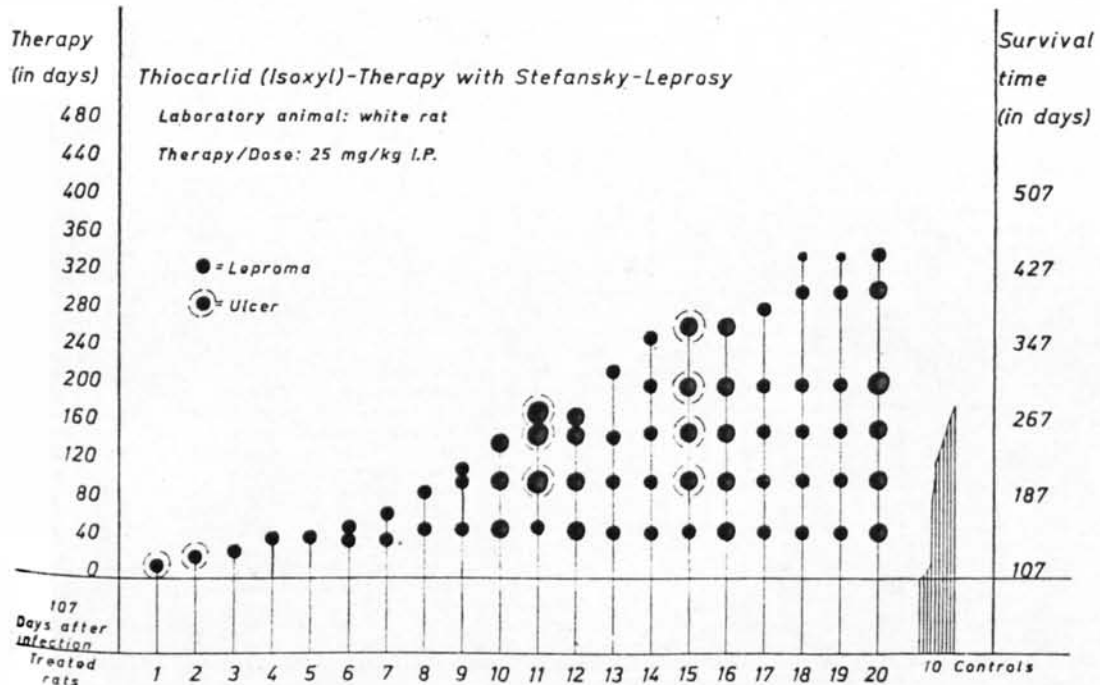


FIG. 3. Thiocarlid (Isoxyl) experiment.

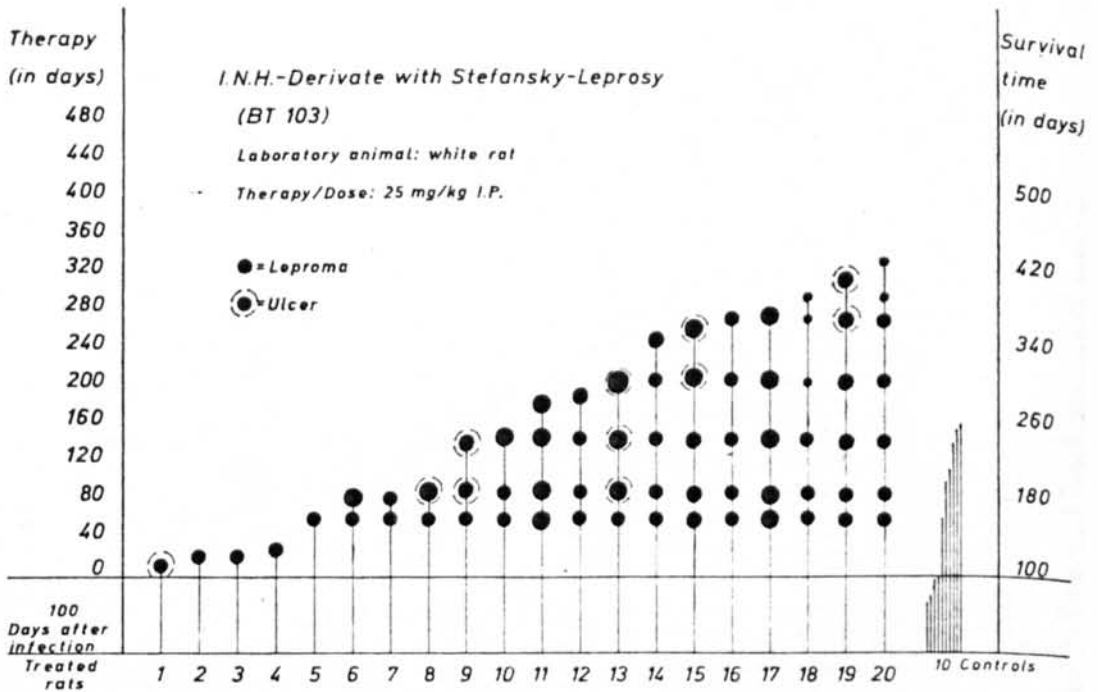


FIG. 3. INH derivative (BT 103) experiment.

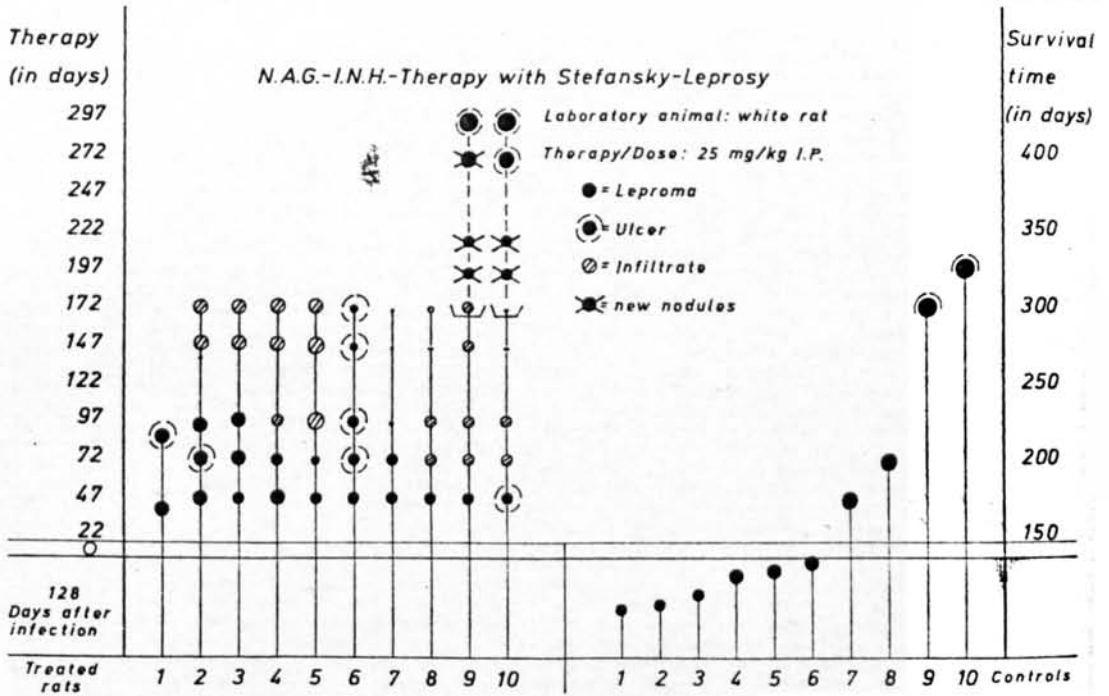


FIG. 4. NAG-INH experiment.

The reaction to Isoxyl differs and makes the evaluation difficult. A tendency of regression can be observed, however: about half of the animals outlive the untreated controls. Further experiments could prove that discontinuation of therapy will lead to relapse, as was the case noted above, with Promin, but much faster (Fig. 2).

3. β -methyl-mercaptopropionaldehyde-isonicotinic acid-hydrazone (BT 103). Therapy was started in the dosage of 25 ngm./kgm. intraperitoneally applied three months after infection. BT 103 brought about ulcerations of the lepromas more than did Isoxyl; these showed more distinct tendencies toward regression with increasing duration of the therapy than did the animals treated with Isoxyl. More than half the treated rats outlived the untreated controls. With respect to relapse, the same is true as for Promin and Isoxyl (Fig. 3).

4. N-acetyl-D-glucosaminy-isoniazid (NAG-INH). Four months after infection therapy was started with a dose of 25 mgm./kgm. applied intraperitoneally. NAG-INH led to regressions more distinctly than did Isoxyl or BT 103. The lepromas diminish and with continuation of the therapy can be perceived only as infiltrates (positive for mycobacteria), which lead, though, to relapse after discontinuation of the therapy.

The best of the four substances examined is Promin. NAG-INH, BT 103, and Isoxyl follow in that order. Complete healing without relapse of the Stefansky leprosy cannot be obtained with any of the substances examined in the dosage used and with the course and method of experiment (Fig 4).

SUMMARY

Three compounds with known tuberculostatic effect were examined, comparing their activity toward infection with *Mycobacterium lepraemurium* (Stefansky-leprosy of the rat) with the effect of Promin.

Promin is able to bring about regression of lepromas and ulcerations, but only as long as the treatment is continued. After discontinuation of the therapy relapse will occur, which will respond again to newly given doses of Promin. Complete healing could not be obtained.

Isoxyl shows only one implied but not significantly favorable effect on the chronic clinical picture. It is a remarkable fact that the effect—if any at all—shows only after 300 days of treatment, and only in the sense of stop in progression.

β -methyl-mercaptopropionaldehyde-isonicotinic acid-hydrazone (BT 103) in the dosage used leads to a regression of the lepromas and to partial granulation of the ulcerations, but only as long as the treatment is maintained. After discontinuation of the therapy a relapse will occur.

N-acetyl-D-glucosaminy-isoniazid in the three different dosages used is able to stop the Stefansky-leprosy in a manner similar to that with BT 103. A regression of the lepromas and a closure of the formed ulcers will take place. After discontinuation of the therapy a relapse will occur in this case, too.

Promin and two isoniazid derivatives show a depressant effect on Stefansky leprosy. Experimental courses show that it is a matter of bacteriostatic and not bactericidal effects.