

such dogs, when at rest, each stimulation of the esophageal stoma and resulting swallowing movement expelled a quantity of secretion which varied within the same limits whether the interval between stimulations was one minute, 5, 30, or 60 minutes. My conclusion is that either very little or no secretion at all was produced in the interval, and that the material obtained was secreted reflexly in response to the licking and swallowing movements alone.

Using these 8 dogs, I have also determined the approximate amounts secreted in response to weighed quantities of various materials placed in the mouth and collected through the esophageal fistula together with the secretions produced. It appears that hydrochloric acid is the most potent of the stimuli used, followed in diminishing effectiveness by magnesium sulphate, sodium chloride, and sucrose. Of the foods administered, raw meat induces relatively little secretion; dry meat, much more; and peptone powder, the most of the three. Dry bread crumbs are a much more efficient stimulus than moist bread. In their responses, therefore, the small oral and pharyngeal glands closely resemble the salivary glands.

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Iodobismitol in Experimental Syphilis.

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In a previous report,¹ it was shown that iodobismitol (N.N.R.) exerts prophylactic and curative effects on the experimental syphilis of rabbits. Since then, confirmations of the antisymphilitic action in rabbits have been made by Levaditi, Vaisman, Manin and Schoen² and by Strandberg and Sjögren,³ da Nova Gomes and de Oleveira,⁴ and Carrillo, Schujman and Campos⁵ in clinical syphilis, the latter authors agreeing with Mehrtens and Pouppirt.⁶ These reports also

¹ Johnson, Hanzlik, Marshall, and Mehrtens, *J. Pharm. Exp. Therap.*, 1932, **45**, 469.

² Levaditi, Vaisman, Manin, and Schoen, *Bull. de la Soc. Franc. de Dermat. et de Syphil.*, 1933, No. 5, p. 738.

³ Strandberg and Sjögren, *Acta Dermato-Venereologica*, 1933, **14**, 1; Strandberg, *Nord. Med. Tidssk.*, 1932, **4**, 834.

⁴ da Nova Gomes and de Oleveira (personal communication).

⁵ Carrillo, Schujman, and Campos, *La Semana Méd.*, 1933, No. 48, p. 1.

⁶ Mehrtens and Pouppirt, *Arch. Neurol. and Psychiatry*, 1931, **26**, 1220.

contain confirmation of other claims for iodobismitol, namely, electronegativity of iodobismuthite, rapid absorption, sustained excretion, low toxicity and positive cerebrospinal penetration. The chemotherapeutic tests begun in this laboratory 7 years ago have been continued and this report submits the final results on the curative effects of iodobismitol together with some interesting comparisons.

The procedure was the same as that used previously,¹ except that during the past 2 years curative treatment with iodobismitol was given in 3 divided doses within 1 week, instead of 1 single dose. Since 1 week of a rabbit's life (expectancy about 8 years) is equal to about 8 weeks of a man's life (expectancy about 60 years), the treatment-period was the equivalent of clinical medication for 2 months, which is a fairly common initial period in practice. The iodobismitol was injected intramuscularly in a range of doses to permit determination of the minimum effective dose and "therapeutic index", if possible. The virus was a strain of *treponema pallida* from a penile chancre, and, by this time, has had 37 passages through rabbits. Fully developed scrotal chancres containing treponema appeared in 3 to 4 weeks after inoculation of the virus. Lymph-node transfers were made 3 months after injection of the bismuth, using generally 3 rabbits, sometimes 4, for tests of lymph-node infectiousness. Virus infected but untreated rabbits were used as controls throughout. Examinations of all rabbits were made routinely in the usual manner. A total of 60 rabbits was used, at least 3 for each dose of iodobismitol. Inasmuch as the results with single and divided doses of the iodobismitol were the same, they were put together, and medians used for the curves in Fig. 1.

The curves in Fig. 1 indicate certain definite tendencies. Doses of less than 20 mg. Na_2BiI_5 (6.5 mg. Bi) per kg. were ineffective, since the duration-periods for chancres and treponemata were grouped around those for the untreated rabbits. There was some evidence of antisiphilitic action with 30 mg. Na_2BiI_5 (6.5 mg. Bi) per kg., but not of curative action since the lymph nodes remained unsterilized (positive). More definite antisiphilitic and curative actions occurred with doses of Na_2BiI_5 from 40 to 120 mg. (8.6 to 25.8 mg. Bi) per kg. The minimum curative dose, therefore, might be around 35 mg. Na_2BiI_5 per kg., although this was not actually tested. It seemed clear that rate of clearing and healing of chancres increased with increasing dosage of bismuth. The periods for treponema and chancre were 3 and 6 weeks, respectively, with the minimum effective dose, and about 1 and 5 weeks, respectively, with

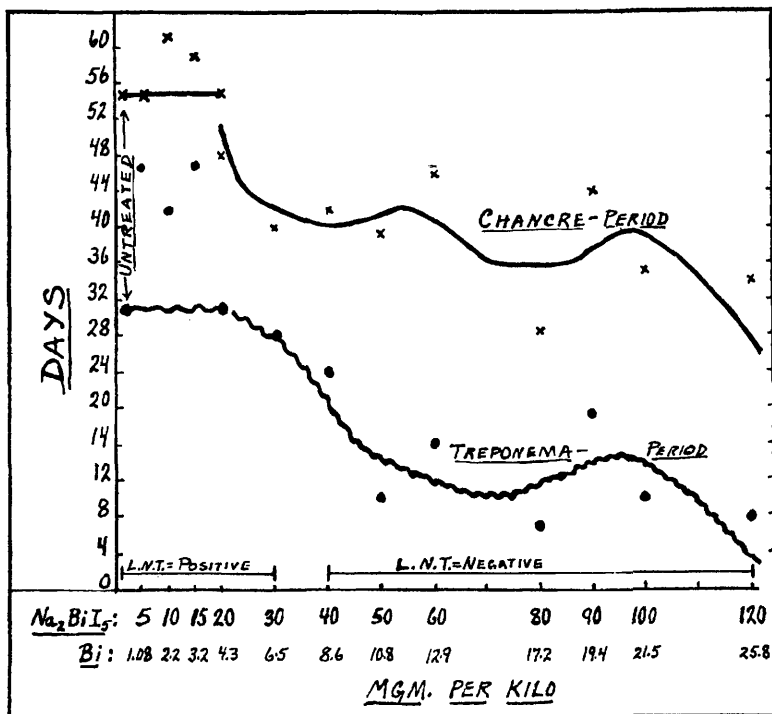


FIG. 1.

Curative Effects of Iodobismutol in Experimental Syphilis of Rabbits. Duration of chancres and *treponema pallida* are indicated by the curves. Iodobismutol (N.N.R.) contains: sodium iodobismuthite (Na_2BiI_5) 6% and sodium iodide, 12%, in ethylene glycol. L. N. T. = lymph node transfer.

the maximum dose used. Presumably, therefore, efficiency of the bismuth treatment was related to concentration of bismuth in blood and tissues. Such relationship, however, would indicate nothing of the fundamental nature of the chemotherapeutic mechanism.

The therapeutic index can be only approximately indicated, since toxicity tests⁷ of iodobismutol were made with single injections and curative tests chiefly with divided injections. The only justification for the comparison is that the results of curative tests with single and divided doses were similar. Since 120 mg. Na_2BiI_5 (in ethylene glycol) per kg. was the M.F.D. (70% mortality) for rabbits, and 40 mg. was the minimum curative dose, the therapeutic index was 3. The M.F.D. of iodobismutol prepared with propylene glycol was over 200 mg. Na_2BiI_5 per kg.,⁸ therefore the index might be over 5. For an antisymphilitic action, without complete sterilization of lymph

⁷ Hanzlik, Seidenfeld, and Johnson, *J. Pharm. Exp. Therap.*, 1932, **46**, 1.

⁸ Hanzlik, Mehrtens, and Spaulding, *J. Pharm. Exp. Therap.*, 1933, **49**, 300.

nodes, such as after 30 mg. Na_2BiI_5 per kg., the index might be from 4 to over 6. On the whole, the therapeutic index of iodobismitol compared favorably with that of other bismuth products.

If the results on rabbit syphilis be compared with those on clinical syphilis⁶ according to dosage per kilo body weight and period of medication in relation to life expectancy, and similar antisyphilitic actions be assumed for bismuth, in the 2 species, an interesting agreement is observed. Using 40 mg. Na_2BiI_5 per kg. as the minimum curative dose for experimental syphilis, and assuming 1 week of a rabbit's life is equal to about 8 weeks of a man's life, then for a 70 kilo adult the estimated total dose of iodobismuthite for definite antisyphilitic effects is 2.8 gm., or 0.35 gm. weekly in 3 divided doses of 0.12 gm. for 2 months. Actually, Mehrtens and Poupirt⁶ found that courses of medication consisting of 2 to 3 such doses of 0.12 gm., or a total of from 0.24 to 0.36 gm. weekly, for 2 to 3 months produced beneficial effects on advanced clinical syphilis in their report on 200 patients. This general agreement is about as good as might be expected, and probably not accidental, although comparisons with acute clinical syphilis might give different values. According to the criteria used, these chemotherapeutic tests on experimental syphilis would appear to be satisfactory for assessing the possible clinical antisyphilitic value of bismuth products.

Conclusions. Iodobismitol is definitely curative in experimental syphilis of rabbits. The minimum curative dose appears to be about 40 mg. Na_2BiI_5 (8.6 mg. Bi) per kilo body weight, which agrees with clinical tests according to certain criteria. The therapeutic index is about 3, or possibly 4 or over 6. Confirmations by others of antisyphilitic actions of iodobismitol in experimental and clinical syphilis are reported.