

# INCOMPLETELY EXPLORED LEADS FOR THE TREATMENT OF LEPRO REACTION

## PROCAINE ADMINISTERED INTRAVENOUSLY

In a recent issue of THE JOURNAL, Horan <sup>1</sup> reported observations of the use of analgesic drugs in patients at the Kalaupapa Settlement in Hawaii. After discussing the effects of regional nerve blocking with pontocaine for acute neuritis, an unexpected

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<sup>1</sup> HORAN, J. S. Treatment of lepra reaction and acute neuritis and arthritis with nerve block and intravenous administration of procaine; preliminary report. THE JOURNAL 17 (1949) 211.

finding being rapid healing of chronic ulcers, he reported benefits derived from intravenous injection of procaine for a variety of complaints, many of which were relieved by it. Especially interesting are the effects seen in the various forms of lepra reaction, the usual treatment of which still leaves much to be desired.

In all but 3 of 11 cases with the erythema nodosum type of reaction there was marked improvement. Of 14 cases with other forms of reaction, 13 had subjective relief and in 6 there was definite objective improvement. In one case complicated with hepatitis, reported in detail, the results were dramatic.

This report recalls a much earlier one by Vishnevsky<sup>2</sup> of the use of procaine ["novocaine"] for lepra reaction and for modifying skin lesions and nerve manifestations. We have seen no evidence that that work was continued by him or taken up by anyone else, but that is not exactly surprising in view of the fact that one of the procedures employed was the rather drastic "lumbar blockade," which involves perirenal injection with the drug.

Horan reported his work as if intravenous administration of procaine were an established procedure, mentioning only two other articles which show that the drug so administered has an affinity for inflamed tissues and relieves pain in many conditions. An apparently comprehensive review of the considerable literature on the subject which has accumulated in the past few years has appeared in a recent issue of the house organ of one of the leading American manufacturers of pharmaceutical products,<sup>3</sup> and much of the following is taken from that publication.

The long-held idea that to introduce procaine accidentally into the vein would be followed by dire consequences was first challenged, it would seem, in 1935 by certain French workers who made such injections deliberately, and with success, to relieve intermittent claudication associated with vascular disease. There were occasional reports in the next decade, but most of them have appeared since 1945. The list of conditions for which that treatment, alone or in combination with other things, has been used with more or less marked success in very many cases

<sup>2</sup> VISHNEVSKY, A. A., JR. Novocaine blockage in the treatment of leprosy. *THE JOURNAL* 6 (1938) 477-490.

<sup>3</sup> *What's New*, published by the Abbott Laboratories, North Chicago, Illinois, issue for September 1949. We are informed by Dr. George R. Hazel, of the Medical Department of that firm, that reprints of the review referred to will be supplied on request.

is long and remarkable for its diversity. The following summary of it has been made to call attention to the possibilities of investigation of this procedure, which with due precautions regarding testing for sensitivity and the manner of administration seems not to be a hazardous one, at least in patients without inflammatory or degenerative cardiac lesions.

Outstanding is the relief of pain of many types, of both somatic and sympathetic origin: burns; traumatic conditions, including fractures, dislocations, sprains and other injuries; miscellaneous inflammatory conditions; gangrene and bedsores; postoperative conditions, for improved function as well as relief of pain; intercostal and cranial nerve neuralgia; arthritis of various kinds; and in obstetrics. Relief of pruritis associated with jaundice, with contact dermatitis, and with exfoliative dermatitis is claimed. The treatment has been used in peripheral vascular diseases and reflex sympathetic dystrophy, and particular emphasis is laid on the prevention of cardiac irregularities during surgery. Also included are the induction of vasodilatation in anterior poliomyelitis, the relief of spasms in spastic anterior poliomyelitis and the congenital spastic condition, and even the treatment of eclampsia and some cases of anuria.

Of particular interest, especially in connection with its use in lepra reaction, is the striking improvement said to be induced by it in certain allergic states. In this field it was apparently first used by State and Wangensteen<sup>4</sup> in cases of delayed serum sickness for the purpose of relieving the myalgia and arthralgia, but—quite unexpectedly—they found that all of the symptoms subsided almost immediately. It has also proved useful in asthma, in urticaria, and in the treatment of reactions to penicillin. "The mode of action of procaine in relieving the symptoms of sensitivity is not clear," it is stated, "but it seems probable that a clue may be found in the close chemical relationship between procaine and the antihistaminic drugs which has recently been established."

Other reports in the field of allergy which have been found in a limited search are the following:

Applebaum and associates<sup>5</sup> recorded another case of serum sickness with high fever and arthropathy, which responded dramatically to two injections of 1 gm. each on successive days. Rosellini and Van Rooy<sup>6</sup> used

<sup>4</sup> STATE, D. & WANGENSTEEN, O. H. Procaine intravenously in treatment of serum sickness. *J. American Med. Assoc.* **130** (1946) 990-995.

<sup>5</sup> APPLEBAUM, E., ABRAHAM, A. & SINTON, W. A case of serum sickness treated with procaine intravenously. *J. American Med. Assoc.* **131** (1946) 1274-1275.

<sup>6</sup> ROSELLINI, L. J. & VAN ROOY, C. W. Delayed allergic reaction to penicillin in oil and wax treated with procaine intravenously. *Northwest Med.* **45** (1946) 849 (abstract in *J. A. M. A.* **133** (1947) 204).

this treatment in a case of delayed allergic reaction to penicillin, with subjective improvement even before the end of the two-hour infusion period. Dressler and Dwork<sup>7</sup> reported another such case treated with gratifying results; relief of arthralgic pain, which had not been effected by benadryl, began within 10 minutes after the infusion was started. Durieu and associates<sup>8</sup> used small doses daily in 25 asthmatic patients for symptomatic relief, noting that neither the allergic state nor the neurovegetative disturbance is influenced. Morhouse<sup>9</sup> saw almost instant and lasting relief in a soldier on the verge of shock due to hypersensitivity to ant bite, in whom epinephrine and pyribenzamine had given relief of only short duration.

#### ANTIHISTAMINIC AGENTS IN LEPROSIS REACTION

Since antihistaminic agents have been found useful in alleviating various kinds of disorders of allergic nature or substrate, a matter thoroughly reviewed to 1946 by Feinberg,<sup>10</sup> such drugs have been tried out by various workers for leprosis reaction. The Havana Congress stated<sup>11</sup> that if the claims that these drugs may control and even abort reactions, one of the most serious obstacles to sulfone therapy would be overcome. As yet only three special reports of favorable results have been seen, by Mom, Mom and Basombrio, and Box.

Mom<sup>12</sup> treated 6 lepromatous cases in reaction with benadryl, 150-200 mgm. daily for six to ten days, with excellent results in four of them. To 3 other lepromatous patients with marked sensitivity to the sulfones manifested by severe cutaneous eruptions, benadryl was given in doses of 150-250 mgm. daily and after the second day the sulfone treatment was resumed with no subsequent trouble. The benadryl could be suspended after ten days with two of the patients, while the third continued to receive 50 mgm. doses a half hour before the promin injections with satisfactory results.

<sup>7</sup> DRESSLER, S. & DWORK, R. E. Reaction to penicillin. Procaine intravenously in the treatment of reactions similar to serum sickness. *J. American Med. Assoc.* **133** (1947) 849.

<sup>8</sup> DURIEU, H. Treatment of asthma with intravenous administration of procaine hydrochloride. *Acta Clin. Belgica* **1** (1946) 150 (*abstract in J. A. M. A.* **133** (1947) 729).

<sup>9</sup> MORHOUSE, C. H. Unusual reaction to ant bites. *J. American Med. Assoc.* **141** (1949) 193-194.

<sup>10</sup> FEINBERG, S. M. Histamine and antihistaminic agents. *J. American Med. Assoc.* **132** (1946) 702-713 (a Council report).

<sup>11</sup> [HAVANA CONGRESS] Technical Resolutions of the Congress; Therapy. *THE JOURNAL* **16** (1948) 209 *et seq.*; *Memorias*, p. 66 *et seq.*

<sup>12</sup> MOM, A. M. Benadryl en la reacción leprosa lepromatosa y en la sensibilización sulfónica. *Rev. Argentina Dermatosis.* **31** (1947) 188-192.

Later, Mom and Basombrio<sup>13</sup> reported briefly that various other symptoms of intolerance to diasone, among them nausea, headache and arthralgia, were relieved in most of the affected patients by one capsule of benadryl before meals, the diasone being taken after the meals. Furthermore, this medication enabled patients who could take only 1 or 2 tablets of diasone to tolerate quite well the desired therapeutic doses of 4 to 6 tablets.

Box<sup>14</sup> reported that 3 cases with spontaneous acute lepra reactions appeared to respond favorably to benadryl, as did 4 with reactions precipitated by promin treatment, whereas in 2 cases of major tuberculoid reactions the results were equivocal except that the patients were made more comfortable. The average dosage was 50 mgm. three times a day, given for a few days to several weeks depending on the length of the reaction.

Some writers, however, exhibit no great enthusiasm for this treatment of reactions. Two examples come readily to hand.

Wolcott,<sup>15</sup> in presenting his results with foudadin in the treatment of erythema nodosum reactions, gave mere mention to benadryl among "a host of remedies" used for the purpose. "All regimens produced some improvement in some cases," he wrote, "but there always remained a number of patients whose antileprous treatment was being withheld while they were suffering from prolonged febrile episodes of erythema nodosum."

Brenes and Romero<sup>16</sup> used benadryl in comparison with several other forms of medication for lepra reaction, giving details of the effects seen in 14 cases. That drug is not included among those which they found to have the most favorable effects.

To digress a bit, it appears that a curious effect of local injection of benadryl with lepromin has been observed by Mom. First, however, some pertinent observations regarding the effects of such drugs on the histamine flare may be noted.

In 1946 Elias and McGavin,<sup>17</sup> working with nonallergic patients, found that benadryl given by mouth in doses of 100 mgm. daily for three

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<sup>13</sup> MOM, A. A. & BASOMBRIO, G. Benadryl e intolerancia para la diasone. (Report to the Havana Congress, presented in abstract only.) *THE JOURNAL* **16** (1948) 268 (abstract).

<sup>14</sup> BOX, L. A. Benadryl in acute lepra reactions. *Hawaii Med. J.* **7** (1948) 303-304.

<sup>15</sup> WOLCOTT, R. R. Erythema nodosum in leprosy. *THE JOURNAL* **15** (1947) 380-388.

<sup>16</sup> BRENES IBARRA, A. A. & ROMERO, A. Terapeutica de la reaccion lepromatosa. *Rev. Med. Costa Rica* **15** (1948) 278-285.

<sup>17</sup> ELIAS, H. & MCGAVIN, H. Influence of benadryl upon histamine flare reactions. *Proc. Soc. Exper. Biol. & Med.* **61** (1946) 133 (cited by Freidman & Silverman).

days caused definite diminution of the flare. Arbesman and associates<sup>18</sup> got similar results in skin tests with histamine, and also with allergens such as ragweed and timothy, 45 minutes after giving 50 to 100 mgm. of pyribenzamine by mouth. In the next year Leavitt and Code<sup>19</sup> found that injection of benadryl diluted 1:1,000 into the skin reduced the size of the histamine flare by 62 per cent, this effect not dependent upon the local anesthetic property of benadryl, and that intravenous injection of 150 mgm. of the substance reduced it by 52 per cent; oral administration of the same amount caused only a 33 per cent reduction.

In the discussion of the paper by Mom referred to,<sup>12</sup> Guillot remarked that if the skin is pricked through a drop of 5 per cent benadryl there is notable diminution of the histamine flare to simple pinprick (the Bechelli test). Mom then spoke briefly of preliminary experiences with benadryl and lepromin. The drug given by mouth had no effect on either the early (Fernandez) or late (Mitsuda) reaction, nor was there any effect when 0.1 cc. of 5 per cent benadryl in saline was injected two or three hours after the lepromin was introduced. But when equal amounts of lepromin and the benadryl solution were injected simultaneously there was an extraordinary effect, much greater than in the controls. No description of what happened was given beyond the statement that in one case there was edema of the whole arm.

A question which has been debated of late is whether or not antihistaminic agents are capable of interfering with the allergic reactivity of the skin, particularly with respect to the tuberculin test. The matter remains in doubt, but those who hold for the affirmative have arguments which seem worthy of consideration.

Boquet<sup>20</sup> and Kreis<sup>21</sup> are said to have gotten negative results in tuberculous guinea-pigs, but Sarber,<sup>22</sup> mentioning only the former's experiments, criticized them on the ground that the tests were usually performed immediately after the administration of a single dose of the drug, and that a concentrated (1:10) dilution of old tuberculin was used. On the other hand Breton<sup>23</sup> reported—without details, it is said—definite blocking or reduction of intensity by an agent called "antergen."

<sup>18</sup> ARBESMAN, C. E., KOEPF, G. E. & MILLER, G. E. Some antianaphylactic and antihistamine properties of pyribenzamine. *J. Allergy* **17** (1946) 203 (cited by Freidman & Silverman).

<sup>19</sup> LEAVITT, M. D., JR. & CODE, C. F. A study of the action of beta-dimethylaminoethyl benzhydryl ether hydrochloride (benadryl) in the skin of human beings. *J. Lab. & Clin. Med.* **32** (1947) 334.

<sup>20</sup> BOQUET, A. Substances antihistaminiques et réactions tuberculini-ques. *Ann. Inst. Pasteur* **69** (1943) 55 (cited).

<sup>21</sup> KREIS, B. Action d'un antihistaminique de synthèse sur l'allergie tuberculeuse du cobaye. *Ann. Inst. Pasteur* **72** (1946) 308-313 (cited).

<sup>22</sup> SARBER, R. W. Effect of benadryl hydrochloride on the tuberculin reaction in guinea pigs. *American Rev. Tuberc.* **57** (1948) 504-510.

<sup>23</sup> BRETON, A. Cuti-réactions à la tuberculine sur papules intradermiques de 239RP, antihistaminique de synthèse. *Compt. rend. Soc. Biol.* **137** (1943) 254 (cited by Sarber).



Sarber himself saw definite and statistically significant depression of tuberculin reactivity in tuberculous guinea-pigs under the conditions of his experiments. He injected subcutaneously 50 mgm./kgm. of benadryl daily in two divided doses for two days before the skin tests were made and for the subsequent two days until the 48-hour readings were made, and the tuberculins (PPD and OT) were administered in three doses beginning with threshold ones. With the smallest doses many reactions failed entirely to appear, and the diminution of reactions with the higher doses included a marked reduction in the incidence of necrosis.

The consensus, however, is indicated by the statement of a consultant of the American Medical Association<sup>24</sup> that, although there is a difference of opinion, trustworthy reports indicate that antihistaminic drugs are ineffective in this matter. He speaks of unpublished experiments in which tuberculous guinea-pigs were given large injections of antihistamine without any inhibitory effect.

Experimentation in man seems to have been very limited as yet. Only two references have been found.

Freidman and Silverman<sup>25</sup> tested the effects of pyribenzamine on the tuberculin reaction in 43 highly reactive children, aged 5 to 11 years, given 60 mgm. of the drug for two days before testing and for a further two days afterward. The tuberculin dose was near the threshold limit, 0.001 mgm. of OT. No inhibiting effect was seen then, nor later when 10 of the same children were given 240 mgm. of the drug on the same schedule. They pointed out that histamine probably does not play an important role in the tuberculin reaction, contrary to the case in the immediate or anaphylactic type of reaction.

Henderson,<sup>26</sup> referring to a slightly earlier report of his own,<sup>27</sup> has criticized the conclusions of Freidman and Silverman. He studied the effects of antihistaminics on the Mantoux test and on the tuberculous lesions themselves in cases of tuberculosis of various kinds. When 500 mgm. of the drugs were given for six months, definite effects were seen; in 24 of 30 cases the skin reaction was gradually converted to negative, and it usually remained negative until after the medication was discontinued. Interesting effects on pulmonary lesions, "some quite dramatic," were also seen. He emphasized the necessity of giving adequate doses for sufficiently long periods of time, and also the observation that the therapeutic effects of the various antihistaminics are not all alike. When one of them is ineffective another may bring about a change in the Mantoux

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<sup>24</sup>[ANONYMOUS] Tuberculin reaction and antihistaminics. *J. American Med. Assoc.* **140** (1949) 1377 (Queries and Minor Notes).

<sup>25</sup>FREIDMAN, E. & SILVERMAN, I. The effect of antihistamine medication on the tuberculin reaction in children. *American Rev. Tuberc.* **60** (1949) 353-358.

<sup>26</sup>HENDERSON, A. R. The effect of antihistamine medication on the tuberculin reaction. *American Rev. Tuberc.* **60** (1949) 811 (correspondence).

<sup>27</sup>JUDD, A. R. & HENDERSON, A. R. The use of antihistaminic drugs in human tuberculosis. A preliminary report. *Ann. Allergy* **7** (1949) 306 (cited).

reaction or the tuberculous lesion. Furthermore, patients may after a time become refractory to one drug but not to another.

No evidence has been seen that any of the factors emphasized by Henderson have been considered by those who have experimented with antihistaminic drugs in the treatment of lepra reaction. It would seem, *a priori*, that in refractory reaction cases such drugs should be tried out in larger dosage and over longer periods of time than usual, perhaps shifting from one of the agents to another when indicated. If patients, who become so sensitive to antileprosy drugs that treatment has to be maintained at a low level or to be discontinued entirely, could be made tolerant by such means, as the brief statement of Mom and Basombrio suggests may be the case, it would render their prospects less discouraging.

In any such experimentation it would be well to distinguish, as a few have done, between "ordinary lepromatous," erythema nodosum, and tuberculoid reactions, for although the precise mechanism of none of them is known the circumstances suggest that there may be essential differences between them and consequently there may be differences of response to any particular form of medication.

—H. W. Wade