in increasing the resistance to the massive dosage observed in the ten who escaped attacks in this group.

SUMMARY

An analysis of the data obtained during the past four years' observation on 796 children in our controlled study of pertussis prophylaxis strongly indicates that considerable immunity has been induced by Haemophilus pertussis phase I vaccine. The duration of this immunity, however, could not be definitely established, because observations over a longer period are necessary. The variability in the incidence of pertussis in a given community will influence the number of exposures that occur in children under observation. The variability in incidence also may play a role in altering the resistance to pertussis.

# TREATMENT OF CHRONIC ARTHRITIS

## RESULTS OF VACCINE THERAPY WITH SALINE INJECTIONS USED AS CONTROLS

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Despite years of experience in arthritis with vaccine therapy, given both subcutaneously and intravenously, difference of opinion still prevails regarding its value. This problem has been studied over a period of several years in the Arthritis Clinic of the Beth Israel Hospital. Our observations have been made in the past four years on a group of patients with chronic arthritis to whom vaccine therapy was given intravenously and physiologic solution of sodium chloride was given subcutaneously at weekly intervals.

Billings [1] in 1912 emphasized the frequent presence of foci of infection in patients with chronic arthritis; subsequent investigators [2] presented further evidence that chronic arthritis was due to a bacterial cause. Thus it has been reported that streptococci could be isolated from the blood, joints and distant foci of patients with chronic arthritis. Investigators [3] have also found streptococcus precipitins, agglutinins and increased antistreptolysin content of blood serum in patients with rheumatoid arthritis. Wainwright [4] has demonstrated positive cutaneous reactions to hemolytic streptococci in rheumatoid arthritis and thus has furthered the opinion that bacterial infection is of prime significance in the etiology of this disease. This bacteriologic evidence, coupled with the fact that the clinical picture in rheumatoid arthritis strongly suggests bacterial infection, led to the use of polyvalent streptococcus vaccine as an important therapeutic measure in this disease.

Occasionally striking benefit does result from vaccine therapy in chronic arthritis, but this is rare. Reports of clinical observations indicating that vaccine therapy is an effective agent in the treatment of chronic arthritis have unfortunately lacked proper controls for correct evaluation. Cecil [5] has reported improvement in the majority of patients treated with his polyvalent streptococcus vaccine; likewise Wetherby and Clawson [6] reported good results in patients treated with their polyvalent streptococcus vaccine. Crowe [7] in England has for a long time been an ardent devotee of vaccine in the treatment of both chronic rheumatoid arthritis and osteo-arthritis; he has used staphylococcus, streptococcus and mixed vaccines, all with much benefit.

However, quite an opposite point of view has been expressed by Stainsby and Nicholls,[8] who treated a large group of patients with various types of vaccine and found the results rather disappointing. They felt that the improvement noted in some cases might well represent natural remissions. Jordan [9] pointed out that caution should be exercised in interpreting the results obtained with vaccines until more adequate control studies were made. Similarly, Bauer [10] feels that vaccine therapy in arthritis has not proved to be of value in his experience.

## MATERIAL AND METHODS

The patients who formed the basis of this study were all ambulatory and made weekly visits to the Arthritis Clinic of the Beth Israel Hospital. With the exception of nine patients in the vaccine group who were followed for six months, only patients who were observed over a period of at least one year have been included; some patients were observed for four years. The diagnosis of arthritis was made by the usual criteria: history, clinical appearance, roentgenographic data and erythrocyte sedimentation determinations. Of the 122 patients who comprised this group, sixty-four had chronic osteo-arthritis and fifty-eight had chronic rheumatoid arthritis.

All the patients with chronic osteo-arthritis were treated with physiologic solution of sodium chloride subcutaneously as the only form of injection therapy. Twenty-five patients with chronic rheumatoid arthritis were treated with polyvalent streptococcus vaccine intravenously, while thirty-three received physiologic solution of sodium chloride subcutaneously. The polyvalent streptococcus vaccine was given intravenously in increasing amounts at weekly intervals, starting with 50,000 organisms and reaching a maximum of 10,000,000 organisms. The saline solution was given subcutaneously in the amount of 0.5 cc. at weekly intervals. The only other treatment employed for all the patients was the use of salicylates in approximately the same dosage for each one.

Erythrocyte sedimentation tests by the method of Rourke and Ernstene [11] were made at monthly intervals on all patients. The rates that obtained for the patients with rheumatoid arthritis were much higher in

From the Arthritis Clinic of the Beth Israel Hospital.
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9. Jordan, E. P.: Critical Evaluation of Vaccine Therapy in Rheumatism, J. A. M. A. **109**: 1444 (Oct. 30) 1937.
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11. Rourke, M. Dorothy, and Ernstene, A. Carlton: A Method for Correcting the Erythrocyte Sedimentation Rate for Variations in the Cell Volume Percentage of Blood, J. Clin. Investigation **8**: 545 (June) 1930.

general than those of the patients with osteo-arthritis; however, as noted by others, the rate of erythrocyte sedimentation was not infrequently entirely disproportionate to the clinical picture.

The following criteria were employed to determine improvement: first, the statement of the patient as to his feeling of well-being; second, the duration of the period of improvement; third, the ability of the patient to do an increased amount of work; fourth, a diminution in pain, stiffness, redness or swelling of joints as noted by the patient, and finally, objective improvement in the joints as noted by us. Each patient was observed independently by both of us, and only those patients who appeared definitely improved have been so considered in this series.

## RESULTS OF TREATMENT

Twenty-four (72 per cent) of the thirty-three patients with rheumatoid arthritis who were treated subcutaneously with saline solution benefited distinctly; seventeen (68 per cent) of the twenty-five patients treated intravenously with vaccine were likewise benefited. Most of the patients who showed improvement did so after the first several injections, a number of them after the first injection.

TABLE 1.—*Data on Ninety-Seven Patients with Chronic Arthritis Given Injections of Physiologic Solution of Sodium Chloride*

| | Rheumatoid Arthritis, 33 Patients | | | | | Osteo-Arthritis, 64 Patients | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Age, years | 20-30 | 30-40 | 40-50 | 50-60 | 60-75 | 20-30 | 30-40 | 40-50 | 50-60 | 60-75 |
| | 7 | 11 | 9 | 1 | 5 | 1 | 5 | 24 | 16 | 18 |
| Sex | Male | | | Female | | Male | | | Female | |
| | 14 | | | 19 | | 27 | | | 37 | |
| Sedimentation index | 0.1-0.4 | | 0.5-1.0 | | 1.0-2.5 | 0.1-0.4 | | 0.5-1.0 | | 1.0-2.5 |
| Before injection | 1 | | 9 | | 23 | 8 | | 49 | | 7 |
| After injection | 4 | | 15 | | 14 | 19 | | 41 | | 4 |
| Period of observation | 1-2 Yr. | | 2-3 Yr. | | 3-4 Yr. | 1-2 Yr. | | 2-3 Yr. | | 3-4 Yr. |
| | 10 | | 15 | | 8 | 17 | | 39 | | 8 |

Fifty-six (86 per cent) of the sixty-four patients with chronic osteo-arthritis, all of whom were treated with saline injections, showed definite improvement. Combining the two groups treated with saline solution, eighty (82 per cent) of the ninety-seven patients with chronic arthritis showed improvement while receiving injection therapy.

There was less correlation between the symptoms of the patient and the level of the erythrocyte sedimentation rate after injection therapy was instituted. Many patients who claimed marked improvement showed no reduction in their elevated sedimentation rates, while some patients who had a fall in the rate of erythrocyte sedimentation had no symptomatic improvement.

## COMMENT

Our study is an attempt to clarify the value of vaccine therapy in chronic arthritis. This group of 122 patients consisting of those with rheumatoid arthritis (fifty-eight patients) and osteo-arthritis (sixty-four patients) may serve as a fair cross section of the patients with chronic arthritis encountered in clinical and private practice. Also, the observation period of six months to four years seems sufficient to allow proper evaluation of results. Therapeutic benefit in any chronic ailment must be evaluated critically because of the many factors involved. Not the least of these is the psychologic factor, and the effect of enthusiastic administration must be taken into account as well as the agents employed. This is especially true in a prolonged, discouraging type of illness such as chronic arthritis, and any hope of relief is welcomed by the patient seeking some tangible method of help. Perhaps the various reports of successful treatment with vaccine injections in arthritis show a high percentage of improved patients more because of the psychologic effect of the needle puncture than of the substance injected.

TABLE 2.—*Data on Twenty-Five Patients with Rheumatoid Arthritis Given Polyvalent Streptococcus Vaccine Intravenously*

| | | | | | |
|---|---|---|---|---|---|
| Age, years | 20-30 | 30-40 | 40-50 | 50-60 | 60-70 |
| | 4 | 8 | 10 | 2 | 1 |
| Sex | Male | | Female | | |
| | 7 | | 18 | | |
| Sedimentation index | 0.1-0.4 | | 0.5-1.0 | 1.0-2.5 | |
| Before injection | 0 | | 16 | 9 | |
| After injection | 1 | | 14 | 10 | |
| Period of observation | 6-12 Mo. | | 12-15 Mo. | 15-18 Mo. | |
| | 9 | | 12 | 4 | |

Also one cannot neglect the element of natural remission in chronic arthritis. This is recognized by every one yet has been insufficiently stressed by many investigators who have employed therapeutic agents. The combination of anxiety on the part of the patient to have something done, with the incidence of natural remission, may explain the improvement in many cases.

Various workers from time to time have expressed the following views: First, bacteriologic and clinical evidence indicate that chronic arthritis is an infection that is frequently helped by the use of polyvalent streptococcus vaccine; second, chronic arthritis is a disease of frequent, natural remissions, which explain the benefit noted with vaccine therapy; third, no definite stand should be maintained as to vaccine therapy until adequate control studies are made; fourth, the psychologic effect of the injection itself must be evaluated. The evidence which we have been able to gather does not substantiate the idea that any specific substance is of value in injection therapy of arthritis. Many observers using various forms of injection therapy and using essentially the same criteria for improvement have obtained benefit in from 60 to 75 per cent of cases regardless of the agent employed, a percentage level somewhat lower than we found in our ninety-seven cases in which saline injections were administered. Striking beneficial results from vaccine therapy may occasionally occur, but as noted previously a number of our patients treated with saline solution claimed much improvement after the first few injections. There is no reason to believe that small amounts of physiologic

TABLE 3.—*Results of Injections in 122 Cases of Chronic Arthritis*

| | Rheumatoid Arthritis (Saline Injection) | Rheumatoid Arthritis (Vaccine Injection) | Osteo-Arthritis (Saline Injection) |
|---|---|---|---|
| Improved | 24 (72%) | 17 (68%) | 56 (86%) |
| Not improved | 9 (28%) | 8 (32%) | 8 (14%) |
| Total number of cases | 33 | 25 | 64 |

solution of sodium chloride given subcutaneously can produce a nonspecific protein-like effect, and therefore we must conclude that the injection itself rather than the substance injected must be credited with whatever improvement followed.

That weather changes, emotional strain and anything that induces lessened resistance will affect patients with chronic arthritis adversely is generally recognized, and of these various conditions that tend to reactivate or aggravate this disease we have been particularly impressed by the frequency with which the emotional factor is encountered. Perhaps it is less clearly recognized that improvement may be influenced when a physician shows interest in this discouraging chronic ailment and gives encouragement, especially when the interest takes a tangible form such as frequent needle injections.

The twenty-five patients treated with polyvalent streptococcus vaccine intravenously responded essentially in the same manner as the patients who were treated with saline solution. There is a close correlation between the results that we observed in these cases and the observations of other investigators who have used polyvalent streptococcus vaccine. We believe it fair to conclude that saline injection therapy is as effective in chronic arthritis as polyvalent streptococcus vaccine.

SUMMARY

One hundred and twenty-two patients with chronic arthritis were observed for from six months to four years; treatment consisted of weekly subcutaneous injections of 0.5 cc. of saline solution in ninety-seven cases and intravenous injections of polyvalent streptococcus vaccine in the remaining twenty-five.

Sixty-four of the patients had chronic osteo-arthritis, all of whom were treated by saline injections. Fifty-six, or 86 per cent, of these patients were improved.

Of fifty-eight patients with chronic rheumatoid arthritis, thirty-three were treated with saline injections and of these twenty-four, or 72 per cent, were improved; twenty-five were treated with polyvalent streptococcus vaccine intravenously and seventeen, or 68 per cent, were improved.

The psychologic effect of the injection itself rather than the substance injected seems important. This factor, plus the tendency to natural remission in chronic arthritis, may explain the high percentage of improvement.

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**Rancidity Destroys Vitamin E.**—The richest sources of vitamin E are green leaves and the embryos of seeds. Smaller amounts are found in many foods, the most important being the fat and muscle of animals and milk and eggs. The vitamin is very stable to heat, light, and being dried, but is rapidly destroyed by rancid fat. This is important, as rancid fat in the diet may destroy any vitamin E taken at the same time in other foods, and rancidity for instance in butter will, of course, destroy its own vitamin value even before it is eaten. . . . The diet of most people must be, at best, near the borderline of a vitamin E deficiency: a borderline which is easily passed if there is any difficulty in absorption from the bowel, or an unduly high consumption, for any reason, by the body. Only relatively small amounts of green vegetables are eaten. While dairy produce forms a large part of the food of the richer classes, there is the fact that the amount of vitamin E in milk and eggs depends on the diet of the cows and hens, a diet which itself is now often highly artificial and of low vitamin value.—Bicknell, Franklin: Vitamin E in General Medicine, *M. Press,* Feb. 28, 1940, p. 174.

# HISTAMINASE IN THE TREATMENT OF ALLERGY

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The theory that the liberation of histamine in the tissues is the immediate cause of the signs and symptoms of allergy has led to the use of its antagonist, the enzyme histaminase, for the prevention and alleviation of these phenomena. Elsewhere we [1] have discussed in more detail the theoretical considerations pro and con of this use of histaminase. Here we shall concern ourselves only with the report of the results of the clinical trial of histaminase as a therapeutic and prophylactic drug.

For a fairly complete review of the clinical experience of others, we refer to Laymon and Cumming's [2] recent publication of their presentation before the Society for Investigative Dermatology. This, together with the accompanying discussions of the other members of the society, leaves the impression that the clinical value of the use of histaminase is highly questionable. In view of this conclusion, our only reason for presenting this report is the fact that the manufacturers of histaminase have recently offered their product to the profession at large as an efficient remedy for a variety of clinical disturbances.[3]

Since June 1939 forty-two patients (twenty-eight with urticaria) were treated with histaminase.[4] The enzyme was administered in enteric coated capsules between meals and with from one to two glasses of water. In no case could it be stated unequivocally that histaminase was effective in alleviating or preventing symptoms, for reports of good results were open to several interpretations and their evaluation is difficult. If we use the criterion that the efficacy of the enzyme can be measured by the frequency with which patients requested more of the substance when their supply became exhausted, we find only four such requests, and these only by patients who prior to treatment suffered from intermittent urticaria, which of course made correlation with therapy difficult.

Another difficulty arose from the frequency with which patients first reported relief from urticaria only to have a persistent recurrence shortly thereafter, despite the administration of large doses of the enzyme over prolonged periods. This coincides with the oft repeated experience in the treatment of urticaria by whatever means undertaken.

The difficulties in judging the efficacy of a remedy in so capricious a disease as urticaria are obvious. It is notorious that urticaria has a high psychogenic factor in its inception, persistence and cure, so that attempts to evaluate the effectiveness of any therapeutic measure is hazardous. Witness the innumerable remedies to be found in medical literature. Being aware of this, we treated five patients suffering from chronic allergic

1. Miller, Hyman, and Piness, George: Histaminase in Allergy: A Study of Its Effect on Skin Reactivity to Histaminase and to Allergy, to be published.

2. Layman, C. W., and Cumming, H. A.: Histaminase in the Treatment of Urticaria and Atopic Dermatitis, J. Invest. Dermat. **2**: 301 (Dec.) 1939.

3. "Torantil: Treatment of Allergies by Detoxication of Histamine with Histaminase," Winthrop Chemical Company, Inc.

4. The histaminase was furnished by the Winthrop Chemical Company and identified by them first as product T. 360-K and later as T-360-KV. The enzyme, contained in enteric coated capsules, was described as being derived from hog's kidney and the unit of activity as "the amount which will inactivate 1 mg. of histamine hydrochloride during incubation at 37.5 C. for twenty-four hours." A preparation of a solution of histaminase in ampules was also provided and was said to assay at 0.75 unit to the ampule.