Theophylline is a valuable measure in the treatment of the cardiac failure of arteriosclerosis. The best results are obtained in the congestive type of failure. Experimental and clinical observations support the belief that the elimination of fluid is promoted by the favorable influence on the coronary circulation.

Theophylline in doses of 2 or 3 grains (0.13 or 0.2 Gm.) after meals has repeatedly been administered throughout the period of hospitalization and in some instances was continued after the patient returned home. There have been very few complaints of abdominal discomfort which could be attributed to the drug.

[EDITORIAL NOTE.—This paper, together with that of Drs. Spiro and Newman, which precedes it, and the papers of Drs. Bradley and Maxwell and Dr. Barr, to appear next week, constitutes a symposium on heart disease. The discussion will follow the papers to be published in our next issue.]

## CLINICAL RESULTS WITH MEASLES STREPTOCOCCUS TOXIN AND ANTITOXIN

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In March, 1926, Ferry and Fisher,[1] in a preliminary report, described the preparation of measles toxin and antitoxin from a green-producing streptococcus, which they called *Streptococcus morbilli,* isolated by them from blood in early cases of measles. In 1927, Ferry [2] described in detail later experiments with this organism and its toxin and antitoxin, on both man and the animal, and in a paper, soon to be published, Ferry and Noble [3] have compared this streptococcus with other green-producing micrococci by means of cultural and serologic reactions.

At this time a condensed report is presented of the clinical work recently conducted with measles antitoxin at the Children's Hospital and at Herman Kiefer Hospital, Detroit, and with measles toxin and antitoxin at the Children's Convalescent Home, Farmington and the Wayne County Training School, Northville.

It should be mentioned that, previous to the experiments included in this report, measles antitoxin was being clinically tested as a prophylactic measure in 5 cc. doses. While it was found that this amount of serum was not sufficient to protect against measles, it seemed evident that some of the treated cases were of a milder type than the untreated cases. This, however, may have been more apparent than real.

1. Ferry, N. S., and Fisher, L. W.: Measles Toxin: Its Preparation and Application as a Skin Test, as an Immunizing Agent, and for the Production of an Antitoxin, J. A. M. A. **86**: 932 (March 27) 1926.
2. Ferry, N. S.: Etiology of Measles, Am. J. Pub. Health **17**: 565 (June) 1927; Studies on the Etiology of Measles, J. Med. **8**: 191 (June) 1927; Recent Experimental Work on the Etiology of Measles, Nation's Health **9**: 51 (Dec.) 1927.
3. Ferry, N. S., and Noble, A.: Cultural and Serological Reactions with Green Producing Micrococci Isolated from Measles, to be published.

Without an attempt to determine the smallest amount of serum that would protect, but in an endeavor to establish the specific relationship of this serum to measles through its ability to prevent the disease, it was decided to resort to a much larger dose, and from 10 to 20 cc. was thereafter given, 10 cc. at Herman Kiefer Hospital and 20 cc. at the Children's Hospital and the Children's Convalescent Home. A goodly percentage of urticarias were encountered, as would be expected, similar to those following the use of any horse serum, and a few rather uncomfortable serum reactions of other types were noted, especially local reactions.

### TESTS CONDUCTED AT THE CHILDREN'S HOSPITAL

At the time the work was started at the Children's Hospital by Dr. Munro, an epidemic of measles was well under way and the children in every ward had been directly exposed to one or more active cases of measles. Histories, as definite as possible, were obtained at once. Half of the patients with negative histories to measles were immunized with 20 cc. of measles antitoxin, the remaining half being left untreated as controls. Fifty-two children, varying in ages from 3 to 12 years, were under observation (table 1). Twenty-six children with negative histories to measles were given prophylactic doses of measles antitoxin and twenty-six with negative histories were left as controls. The cases for treatment were picked according to their location in the wards and all children were as equally exposed as the usual hospital conditions with small wards would allow. In alternate negative cases, injections were made with the antitoxin and about the usual number with negative histories contracted the disease among the controls. It has been our experience and the experience of others in hospital practice that measles histories obtained from hospital patients in general are unreliable and that a larger number of children with negative histories have had the disease than would be expected. This, of course, necessitates, in a clinical test of this sort, at least an equal number of controls in the same wards and under like conditions receiving no treatment, in order to aid in determining the expectancy among the treated cases. If a proper control is not carried out the resulting figures are of no value whatever.

TABLE 1.—*Munro's Series at Children's Hospital (Dose, 20 Cc. of Measles Antitoxin)*

| Cases with negative histories..... 52 | |
|---|---|
| Received measles antitoxin..... 26 | Did not receive antitoxin.....26 |
| Contracted measles.... 1 ( 3.8%) | Contracted measles..... 8 (30.7%) |
| Remained well..... 25 (96.2%) | |
| Expectancy = 30.7% of 26 = 8 | |
| Real protection = 7 out of 8 = 88% | |

Of the twenty-six patients receiving the prophylactic dose of antitoxin, one (3.8 per cent) developed typical symptoms of the disease. All other treated patients (96.2 per cent) remained well. Of the twenty-six controls with negative histories to measles, receiving no antitoxin, eight (30.7 per cent) contracted the disease.

As 30.7 per cent of the controls contracted measles, it should be expected that 30.7 per cent of the treated patients were susceptible and, therefore, that eight instead of twenty-six should be considered the expectancy. In other words the corrected real protection afforded by the measles antitoxin was seven out of eight, or 88 per cent instead of twenty-five out of twenty-six (96.2 per cent).

EXPERIMENTS AT HERMAN KIEFER HOSPITAL

At Herman Kiefer Hospital the work was carried out by Dr. Gordon as a result of an impending measles epidemic among the patients in the scarlet fever wards and an excellent opportunity for carrying out a well controlled test was afforded.

Immunization with measles antitoxin was introduced following the exposure of all the children in the wards to two cases of measles which developed after the two children had been admitted with scarlet fever.

TABLE 2.—*Gordon's Series at Herman Kiefer Hospital (Dose, 10 Cc. of Measles Antitoxin and 5 Cc. of Measles Convalescent Serum)*

| Cases with negative histories..... 250 | |
|---|---|
| Received measles antitoxin..... 38 | Did not receive treatment..... 127 |
| Contracted measles..... 7 (20%) | Contracted measles.....40 (31.5%) |
| Remained well..... 31 (80%) | |
| Expectancy = 31.5% of 38 = 12 | Received measles convalescent serum ..... 85 |
| Real protection = 5 out of 12 = 42% | Contracted measles.... 22 (25.8%) |
| | Remained well..... 63 (74.2%) |
| | Expectancy = 31.5% of 85 = 27 |
| | Real protection = 5 out of 27 = 19% |

Thirty-eight patients with negative histories to measles were prophylactically immunized with 10 cc. of measles antitoxin, eighty-five were prophylactically immunized with 5 cc. of measles convalescent serum as the epidemic continued, and, as a control, 127 did not receive any serum (table 2).

These cases were divided as follows: In two small wards off the general wards, where the children were directly exposed, thirteen received measles antitoxin and five received measles convalescent serum. In the large wards where the children were indirectly exposed, twenty-five received measles antitoxin and eighty were immunized with measles convalescent serum after the children in these wards became directly exposed.

Among the 250 patients with negative histories under observation there developed sixty-nine cases of measles distributed as follows: Of the thirteen directly exposed who received measles antitoxin, three developed the disease, and of the twenty-five indirectly exposed four developed the disease; of the thirty-eight in all, therefore, treated with measles antitoxin, seven (20 per cent) contracted the disease; of the five directly exposed who received measles convalescent serum, none contracted the disease, and of the remaining eighty who received measles convalescent serum twenty-two contracted the disease; of the eighty-five in all immunized with measles convalescent serum twenty-two (26 per cent) contracted the disease; and of the 127 controls receiving no treatment, forty (31.5 per cent) developed the disease.

With the figure 31.5, which was the percentage of the controls contracting the disease, the expectancy among the patients treated could be determined, and it developed that twelve of the antitoxin treated patients, instead of thirty-eight, could be expected to develop the disease and twenty-six of those treated with convalescent serum, instead of eighty-five. The real protection afforded by the antitoxin, therefore, was five out of twelve, instead of thirty-one out of thirty-eight, or 42 per cent, and with the convalescent serum the real protection was five out of twenty-seven, or 19 per cent, instead of sixty-three out of eighty-five.

WORK AT THE CHILDREN'S CONVALESCENT HOME

Under the supervision of Dr. Munro, skin tests were made with measles toxin on 165 children. Of these cases forty-four (26.5 per cent) gave positive reactions, twenty-three (13.8 per cent) gave pseudoreactions, and ninety-nine (59.6 per cent) were negative (table 4). The pseudoreactors and negative cases occurred mostly in the children of school age who had previously been exposed and many of whom had had the disease. All skin tests were controlled with a mixture of toxin and dilute measles convalescent serum for the double purpose not only of controlling the reactions but also to show that measles convalescent serum will neutralize measles toxin obtained from *Streptococcus morbilli.*

In the infant ward, and this ward was used as it was small and all were exposed, where the ages ranged from 1 to 6 years, six of the twelve positive reactors were given measles antitoxin and the other six were allowed to remain untreated, as controls (table 3). In this instance the histories were discarded and only the skin reactions were used as criteria for susceptibility to measles. Of the six patients treated, one (16.6 per cent), who at the time of injection was suffering with coryza, cough and fever, developed a rash on the fourth day. The other five patients (83.4 per cent) remained well. Of the six patients untreated, three (50 per cent) contracted the disease.

In this instance the expectancy would be three, or 50 per cent, of the patients treated. This would give an estimated real protection of two cases out of three, or 67 per cent.

The average real protection at the Children's Hospital and the Children's Convalescent Home, where the dose of measles antitoxin was 20 cc., was 78 per cent. This is in contrast to the 42 per cent at Herman Kiefer Hospital, where only 10 cc. was given.

Of all the patients (forty-four in number) in this institution showing positive skin reactions to measles toxin, fourteen (31.8 per cent) developed measles. Of the twenty-three pseudoreactors to the toxin, five (21.7 per cent) developed measles, and of the ninety-nine negative reactors nine (9 per cent) also developed the disease (table 4).

Of the fourteen children who gave positive skin reactions to measles toxin and who later developed the disease, thirteen who were still in the hospital were retested two weeks after recovery. Ten of these, on this retest, gave negative skin reactions and three gave pseudoreactions (table 5). All thirteen, therefore, were rendered immune from the skin test with the toxin as a result of an infection with measles. As a control to this test, to determine the potency of the lot of toxin being used at the time, five other known positive reactors in the same institution, who had not contracted the disease, were retested at the same time and four gave positive reactions and one negative.

TABLE 3.—*Munro's Series at the Children's Convalescent Home (Dose, 20 Cc. of Measles Antitoxin)*

| Positive reactors to measles toxin in infant ward.... 12 | |
|---|---|
| Received measles antitoxin..... 6 | Did not receive antitoxin..... 6 |
| Contracted measles..... 1 (16.6%) | Contracted measles..... 3 (50%) |
| Remained well..... 5 (83.4%) | |
| Expectancy = 50% of 6 = 3 | |
| Real protection = 2 out of 3 = 67% | |

Another test was carried out in this institution for the added purpose of determining the antitoxic but not clinical value of measles antitoxin, as follows: Of the six positive reactors, which had been given prophylactic doses of measles antitoxin in the infant ward, the five

which did not develop the disease were retested with the toxin ten days after the injection of antitoxin and all five gave negative reactions on the retest, demonstrating pretty conclusively the neutralizing value of the antitoxin toward the toxin. As a control to this test, the one who had just recovered from the disease was retested at the same time and also gave a negative reaction.

### EXPERIMENTS AT THE WAYNE COUNTY TRAINING SCHOOL

Under the direction of Dr. Steele, all patients of the institution from 10 to 21 years of age were skin tested with measles toxin. Of these there were 142 (table 6). Twenty-five (17.6 per cent) showed positive reactions and seven showed pseudoreactions. One hundred and ten did not react. The high percentage of negative reactors in this instance is probably accounted for by the fact that the majority of the patients had had measles, having previously been transferred to this institution from the schools of Detroit.

In carrying out the skin tests at this institution, as well as on some of the children at the Children's Convalescent Home, not only were the tests controlled with the toxin neutralized with diluted measles convalescent serum, but a double check was placed on the test by a control with heated toxin. The results showed that the pseudoreactors could be selected from the positive reactors by means of neutralized toxin as well as

TABLE 4.—*Children's Skin Tested with Measles Toxin at Children's Convalescent Home and Those Contracting Measles*

| | | | |
|---|---|---|---|
| Number of children | 165 | Contracted measles | 28 |
| Positive reactors | 44 (26.5%) | | 14 (31.8%) |
| Pseudoreactors | 23 (13.8%) | | 5 (21.7%) |
| Negative reactors | 99 (59.6%) | | 9 ( 9.0%) |

by means of the heated toxin, again demonstrating the neutralizing value of measles convalescent serum toward measles toxin.

As there were no cases of measles at this institution, some of the positive reactors were utilized to standardize various lots of measles toxin and antitoxin.

The identical lot of measles antitoxin that was being used at the other institutions for immunization purposes was standardized at this time with the following results: Nine positive reactors were tested with neutral mixtures of toxin and antitoxin, diluted in such a manner that each 0.1 cc. of the mixture contained one skin test dose of toxin and $\frac{1}{5,000}$ and $\frac{1}{10,000}$ cc. of antitoxin, respectively. The test was controlled as usual with heated toxin and diluted serum. The results of the test showed that the $\frac{1}{10,000}$ mixture was neutralized on the majority of patients. In other words, the antitoxin contained 10,000 neutralizing units per cubic centimeter.

As it was desirable to know how measles convalescent serum compared with measles antitoxin in neutralizing power against measles toxin, a similar experiment was conducted with neutral mixtures of both the antitoxin and the measles convalescent serum, which was pooled from thirty convalescents. The results compared very favorably with the previous test and proved that the antitoxin and convalescent serum were about equal in neutralizing value toward measles toxin.

The one difficulty with the use of measles toxin for skin test purposes, which, up to this time, has not been satisfactorily overcome, lies in the fact that while the toxin is extremely heat stable it deteriorates very rapidly on standing, even at refrigerator temperature. This necessitates the use of fairly fresh toxin, which, until a means of obtaining a more stable product is worked out, militates against its use as a general diagnostic agent.

### SUMMARY AND COMMENT

At the Children's Hospital, where the treated patients were controlled with an equal number of untreated patients under the same conditions, the computed actual protection, following the use of 20 cc. measles streptococcus antitoxin, was 88 per cent.

TABLE 5.—*Action of Measles Toxin on Measles Susceptible and Immune Individuals*

| | |
|---|---|
| Retest of positive reactors at Children's Convalescent Home following infection with measles | |
| Reaction before measles | 13 positive reactors |
| Reaction after measles | 10 negative, 3 pseudoreactors |

At Herman Kiefer Hospital, where the patients treated with 10 cc. of measles streptococcus antitoxin were well controlled with a much larger number of untreated cases as well as a larger number of patients treated with 5 cc. measles convalescent serum, the computed actual protection afforded by the measles streptococcus antitoxin was 42 per cent, as compared with 19 per cent of those cases treated with measles convalescent serum.

At the Children's Convalescent Home, where the susceptible individuals were picked according to their reaction toward measles toxin, the positive skin reactors being considered susceptible, the computed actual protection, when the cases were controlled with an equal number of untreated patients, was 67 per cent.

The average computed actual protection shown in the three series of cases in the three institutions, therefore, was 66 per cent, and at the two institutions where the dose was 20 cc. the average protection was 78 per cent. This was apparently far superior to the computed actual protection afforded by the measles convalescent serum which was determined in the same series under the same conditions and controlled with the same untreated patients.

TABLE 6.—*Patients' Skin Tested with Measles Toxin at Wayne County Training School*

| | |
|---|---|
| Number of patients | 142 |
| Positive reactors | 25 (17.6%) |
| Pseudoreactors | 7 ( 4.9%) |
| Negative reactors | 110 (77.4%) |

In the Children's Convalescent Home it was shown in thirteen out of thirteen cases (100 per cent) that infection and recovery from measles changes a positive skin reactor to measles toxin to a negative reactor. This, together with the fact that diluted measles convalescent serum will neutralize measles toxin, speaks in favor of the proof of the specific relationship of measles toxin from *Streptococcus morbilli* to measles and argues in favor of the use of measles streptococcus antitoxin, prepared from this toxin, as a protective measure against the disease.

At the Wayne County Training School it was shown, in individuals susceptible to the skin test with measles toxin, that pooled measles convalescent serum, per cubic centimeter, was about equal in neutralizing value to the

lot of measles streptococcus antitoxin being used clinically and that it contained about 10,000 neutralizing units per cubic centimeter.

Had the measles convalescent serum been used in Herman Kiefer Hospital in amounts equal to those used with the measles antitoxin, the actual protection would in all probability have been more nearly equal to that afforded by the measles antitoxin; and had the dose of measles antitoxin at Herman Kiefer Hospital been as large as that used at the other institutions the percentage of protection would in all probability have been higher.

At none of the institutions under observation, except at Herman Kiefer Hospital at the outbreak of the epidemic, could an attempt be made to estimate the exact time of exposure of any of the cases. Some of the cases, therefore, were probably well on in the incubation stage before the measles antitoxin was given, especially at the Children's Hospital and the Children's Convalescent Home.

## THE CAUSES OF DEATH IN MASTOIDITIS *

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The first operation on an infected mastoid process was performed by Petit [1] in the early part of the eighteenth century. The operation was so incomplete (merely a drill hole through the cortex) and the results were so unfavorable that it soon fell into ill repute.

Like surgery elsewhere in the body, however, the operation attracted attention to the disease, and although the next step was still in the nature of trephining it did provide freer drainage with the larger opening, and more patients recovered.

Finally, in 1873, Schwartze [2] advocated and described a systematic method of removing the mastoid cortex and breaking down the infected cells. This laid the foundation of our present knowledge of mastoid surgery.

Since the development of this successful surgical attack on the infected mastoid, the anxiety aroused by this disease has been entirely out of proportion to the mortality rate. Kerrison [3] has stated that in any large series of patients operated on by competent aural surgeons the mortality rate does not exceed 1 or 2 per cent. This fact should be borne in mind if a balance that is necessary for the fair and honest treatment of all cases is to be maintained.

In addition to the three major complications of mastoiditis—meningitis, brain abscess and sigmoid sinus thrombosis—a rather startling additional complication has recently been attributed to this disease; namely, gastro-enteritis in infants. Marriott [4] says: "In our own experience over 85 per cent of all gastro-intestinal and nutritional disturbances in recent years have been due to infections of the ear, nose and throat."

Granted that this is true, is it fair to assume that operations on the mastoids of these infants is the proper treatment when Renaud [5] reports that he lost nine of the first ten, Lyman and Alden [6] had eight recoveries and seven deaths out of their first series, and eight deaths out of forty-two in a later series? They attribute their lower mortality rate in the last series to earlier operative intervention.

Coates,[7] in a recent discussion on infantile mastoiditis, makes the following concise statement: "That a bilateral mastoid operation should be performed by the otologist on apparently normal ears, on the simple demand of the pediatrist, as I have heard recommended in open meeting is, I think, dangerous to the reputations of both specialties, to say nothing of the welfare of the patients."

Jeans [8] has suggested that the climate of Iowa might be responsible for the apparently greater prevalence of ear infections there.

In an effort to determine the relation of this new complication to mastoiditis I have analyzed a series of cases, covering a period of five years, which comprise, in addition to my own cases, those of the other otologists on the staff of the St. Luke's, Kansas City General, Children's Mercy, and St. Margaret's hospitals and a series from the West Side Health Center Clinic. Since it is impossible to say when a patient has or has not mastoiditis, I have recorded only those coming to operation, stressing especially the deaths. There has been no attempt to present the laboratory or x-ray observations.

I regretfully admit that I have entered on this analysis with considerable prejudice and I am fully aware of the wide variations in the application of statistics.

TABLE 1.—*Mastoidectomy Deaths, 1923-1928, St. Luke's Hospital*

| Age | Predisposing Causes | Duration | Lived Following Operation | Complications | Causes of Death |
|---|---|---|---|---|---|
| 8 mo. | Influenza; measles | 42 days | 5 days | Septicemia | Septicemia |
| 10 yr. | Influenza; nephritis; uremia | ..... | ..... | Meningitis, streptococcic | Meningitis, streptococcic |
| 12 yr. | Unstated | 6 days | 10 days | Meningitis, streptococcic | Meningitis, streptococcic |
| 14 yr. | Infection from swimming | 6 days | 15 days | Abscess of brain; sigmoid sinus thrombosis | Abscess of brain; sigmoid sinus thrombosis |
| 20 yr. | Influenza | 49 days | 3 days | Meningitis, otitic, streptococcic | Meningitis, otitic, streptococcic |
| 31 yr. | Antrum infection from tooth extraction | 16 days | 29 days | Abscess of brain | Abscess of brain |
| 47 yr. | Severe cold | ..... | ..... | Meningitis, streptococcic | Meningitis, streptococcic |

In defense of this prejudice I wish to state that I believe that the operation itself, properly performed on the mastoid process, was never fatal to any patient. Particularly is this true of the minor procedure called antrotomy, which is used in infants. In recent years this comparative safety of operative procedure has, however, in my opinion, prompted the overzealous use of surgery out of all proportion to the benefits derived. Diagnostic skill and surgical judgment seem to be having trouble in keeping pace with the therapeutic demand and surgical technic.

* Read before the Section on Laryngology, Otology and Rhinology at the Seventy-Ninth Annual Session of the American Medical Association, Minneapolis, June 14, 1928.

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