The division surgeon procured fifty ampules of amyl nitrite, containing 3 minims each. These were used in all doubtful cases. Of course the influence on the heart, as far as it concerns our experiment, is very similar to the effect of exercise. However, there is one great advantage: It is possible to listen to the heart during its period of increasing activity and acceleration, and there is no attending dyspnea as a disturbing factor. In other words, as the patient administers the drug to himself the observer listens at the apex of the heart until the desired effect of the drug is produced. In this way several phases of increasing cardiac activity are observed. A total of forty-eight cases has been examined, and it is the opinion of the observers that a very valuable aid in diagnosis has been obtained. In ten cases, the doubtful nature of the presystolic sound was intensified to such a degree as to admit of a positive diagnosis of mitral stenosis. In the balance of the cases, the suggestive presystolic sounds were eliminated. It might be said here that the greatest difficulty was experienced in the negro, for here the element of neurosis is clearly manifest, and this influence on the heart produces at times varied changes. Chief among these are a greatly accentuated pulmonic second and a very loud sound at the apex and a thrill at this area, the timing of which is frequently difficult. In such cases we have found recourse to these inhalations valuable.

Naturally a report of this nature partakes entirely of personal experience, as there is no definite way to publish the data. The chief object in presenting our observations is to corroborate thoroughly the findings of Morison, and to suggest the further use of this method.

TREATMENT OF INFLUENZAL PNEUMONIA BY THE USE OF CONVALESCENT HUMAN SERUM

SECOND REPORT

L. W. McGUIRE, M.D.
Lieutenant-Commander, M. C., U. S. Navy
AND
W. R. REDDEN, M.D. (BOSTON)
Lieutenant, M. C., U. S. Navy
CHELSEA, MASS.

In a preliminary report,[1] we presented the data of thirty-seven cases of bronchopneumonia, following the present epidemic of so-called influenza, treated with serum obtained from patients who had recovered from a similar pneumonia. Later, in an informal letter to THE JOURNAL, we[2] advised the discontinuance of the compatibility tests, and other modifications to simplify the preparation and administration of the serum.

The present report gives as complete data as were obtainable in 151 cases at the Naval Hospital, Chelsea. This represents all cases of the foregoing type admitted to our wards since the treatment was started. For convenience and completeness, this includes the original thirty-seven cases reported.

In our preliminary report, we also noted that the severity of the disease was on the wane. Naturally, we wished for an opportunity to carry on the work in a field in which the severity of the epidemic was unquestionably great. After several futile attempts to find such a place, there came to us a group of men from the U. S. S. *Yacona*. Here the incidence of the influenza, the complicating pneumonia and the severity of the infection appeared quite comparable with the situation at the beginning of the outbreak. Hence, for comparison, we have considered this group not only in the 151 total cases, but also separately. In addition to this *Yacona* group, it should be noted that eighty cases represent the latter part of the first epidemic, whereas the others represent those in the more recent recrudescence of the epidemic where the severity of the disease has undoubtedly been great, though somewhat less than during the first part of the epidemic. Furthermore, also for the sake of completeness, we are presenting the entire laboratory and clinical procedure.

TABLE 1.—DAY OF PNEUMONIA WHEN SERUM WAS FIRST GIVEN, AND NUMBER THUS RECEIVING IT

Day	No.
First	36
Second	59
Third	25
Fourth	14
Fifth	9
Sixth	1
Seventh	3
Eighth	2
Undetermined	2
Total	151

The accompanying tabulations represent in detail our findings in the cases treated.

The day of the pneumonia on which the serum was first given in the 151 cases tabulated is indicated in Table 1. It is evident that most of the patients received serum within the first four days of the pneumonia, and that the majority received it within the first forty-eight hours. In other words, although most of the patients were seriously ill, they received serum within a time most favorable for serum therapy.

The number of injections of serum each patient received is shown in Table 2. It will be seen that

TABLE 2.—NUMBER OF INJECTIONS OF SERUM EACH PATIENT RECEIVED

No. of Injections	No. of Patients
1	56
2	49
3	27
4	9
5	6
6	3
7	1
Total	151

The average amount given at each injection was 120 c.c.

three injections of serum were sufficient in 132 cases, and that more than two thirds required only two doses and that about one third required only one dose. It is noteworthy that the majority of the patients requiring more than one injection had advanced at least two days in their pneumonia.

IMMEDIATE RESULTS

A chill, as described below, may follow in thirty minutes after injection of the serum. In a few hours,

1. McGuire, L. W., and Redden, W. R.: Treatment of Influenzal Pneumonia by the Use of Convalescent Human Serum, J. A. M. A. **71**: 1311 (Oct. 19) 1918.
2. McGuire, L. W., and Redden, W. R.: Discontinuance of Compatibility Test in Serum Treatment, Correspondence, J. A. M. A. **71**: 1765 (Nov. 23) 1918.

the patient shows decided signs of improvement. The toxic symptoms subside, as indicated by cessation of nausea and vomiting, if present, and disappearance of vasomotor disturbances and headache. The anxious expression of a sick patient is transformed into that of a patient in convalescence; these patients say that they are decidedly better, and often that they are well. The temperature, pulse and respiration begin to fall,

TABLE 3.—PERSISTENCE OF FEVER AFTER FIRST INJECTION OF SERUM

	No.
Normal less than 24 hours	27
Normal in 24 hours	56
Normal in 2 days	38
Normal in 3 days	14
Normal in 4 days	8
Normal in 6 days	3
Normal in 9 days	1
Normal in 11 days	1
Total	148

the temperature and pulse reaching normal in advance of the respirations. The appetite returns. Signs of improvement or recovery may follow the first injection of serum, or in severe cases a gradual improvement may take place. Two or more injections may be necessary to produce these results, as indicated in the preceding tabulations.

Of 138 patients, eighty-three recovered by crisis and fifty-five by lysis. As crisis we have considered a drop of temperature to normal within twenty-four hours, accompanied by a corresponding general improvement. A more gradual decline in signs and symptoms we have called lysis.

A summary of the number of days the fever persisted after the first injection of serum is given in Table 3, which represents 148 patients who recovered from influenzal pneumonia. Three of this group later developed a hemolytic streptococcus bacteremia and empyema, followed by death. The other three necessary to make our group of 151 cases represent the deaths.

As indicated above, the greater number became normal within forty-eight hours after the first injection of serum.

TABLE 4.—FEBRILE PERIOD OF PNEUMONIA

Day of Termination	No.
First	9
Second	21
Third	42
Fourth	28
Fifth	19
Sixth	12
Seventh	5
Eighth	1
Ninth	1
Thirteenth	1
Undetermined	6
Total*	145

* There were six deaths.

The total febrile period of the pneumonia in this series of cases is given in Table 4. It will be noted that seventy-two, or 51.7 per cent., of this number ran a pneumonia course in three days, and that 119, or 85.6 per cent., were normal in five days. This is a decided shortening of the disease.

The length of time the lung signs persisted, after the temperature remained normal, varied as to the amount of lung involvement and the time in the pneumonic complication when serum was administered. Those cases in which serum was given early in the disease, before extensive consolidation occurred, cleared more readily, while in those treated later in the disease, the physical signs remained a week or ten days and in some cases beyond that period. A striking feature in many cases is the persistence of the signs of consolidation during convalescence.

In several cases that are not included in the 151 reported, serum was given before definite signs of consolidation appeared. That is, only râles were present, accompanied by a high temperature, following influenza. These patients promptly recovered and did not develop consolidation, and it is believed that pneumonia may have been prevented.

The data on white blood counts taken on the group are incomplete. We attempted to have such counts in all cases, but when we came to tabulate, we found that in the early part of the work a number had been missed. However, this group represents 130 cases (Table 5). It is quite evident from this table that the vast majority of our influenzal pneumonias have had either a normal white blood count or a leukopenia.

TABLE 5.—WHITE BLOOD COUNTS

Day of Pneumonia	White Blood Counts 10,000 or Under	Over 10,000
1	36	7
2	30	4
3	18	2
4	11	6
5	2	5
6	3	3
7	5	1
8	1	4
9	0	0
10	1	4
11	1	4
12	0	..
13	0	2
Total	108	42

The extra twenty counts represent additional counts in a number of the cases.

It is noteworthy that all cases that did not respond readily to serum treatment were included in the group having high white counts, although many with high counts did respond readily. The foregoing group of high counts also includes all who showed the hemolytic streptococcus complication. Our differential counts show some tendency toward an increase in lymphocytes and a corresponding decrease in polymorphonuclear leukocytes; but there is no constancy in the findings.

It has been our custom to consider all patients with physical signs of pneumonia and a white blood count of 10,000 or 12,000 or under, as presumptive influenzal bronchopneumonias, and to start convalescent serum treatment immediately, especially if the history of onset is suggestive. But, if the count is higher, typing of sputum is done. Even if the count is high and pneumococci of Group IV are present, the convalescent serum is given with the idea that the Group IV may represent only a part of the infection or even only a mouth organism.

Complications were infrequent. One patient developed acute otitis media. One had intense jaundice, lasting over a week. Three had pleurisy, one phlebitis and two an evident relapse after an apparent complete recovery. Since the recurrence of the epidemic, among the last cases, seven streptococcic infections followed;

these were similar to the streptococcic pneumonias and empyemas present last winter. Six of these patients developed a streptococcic empyema, three of whom died. A pure culture of streptococci was obtained from the blood of one of the other patients. These streptococcic infections followed when the patients were convalescing from influenzal pneumonia, a normal temperature of from two to four days being present in the interval. This accounted for three of our deaths.

OUTBREAK ON THE YACONA

The U. S. S. *Yacona* left Bermuda, November 5. Influenza was epidemic, but reported to be well in hand there at that time. Eight hospital corpsmen of the Navy came North aboard the *Yacona* as passengers, having been on duty in Bermuda, assisting in the epidemic of influenza. They were left at New York. The ship arrived in New York on the 11th; liberty was granted; coal and provisions were taken on, and the ship sailed on the 15th for New London, arriving the same day. The first case of influenza developed in New London on the 18th, another on the 19th, and the third on the 20th. The ship sailed for Halifax on the 21st; six cases developed that day and she put into Boston, arriving the 22d.

Fourteen cases of influenza were admitted to the Naval Hospital, Chelsea, November 22; eighteen on the 23d; nineteen the 24th; nineteen the 25th; five the 26th, and two the 29th, a total of seventy-seven, plus three at New London, making a total of eighty cases of influenza from a crew of ninety-six. Seventy-four men and six officers developed the disease, or 83.3 per cent.

It seems probable that the source of infection was at New London, as the first case appeared three days after arrival there; this was well within the incubation period.

This outbreak was virulent, resembling the cases admitted during the early part of the epidemic in Boston. The patients were admitted with high fever, prostration, headache, injected eyes, dusky skin, albuminuria and low white blood counts.

The severity is well illustrated by the one death that occurred three days after the initial symptoms of influenza. The patient died of a diffuse bronchopneumonia, living only twelve hours after admission to the pneumonia ward, he being then semiconscious, with temperature, pulse and respiration very high. This is the shortest course of the disease of which we have record in this hospital.

TABLE 6.—SUPPLEMENTARY REPORT OF CASES OCCURRING ON THE U. S. S. YACONA

	No.
Complement, men	87
Officers	9
Total	96
Influenza cases	80
Bronchopneumonias	20
Deaths	1

Of the seventy-seven patients in this hospital, twenty developed pneumonia. All pneumonia patients received convalescent human serum immediately when a diagnosis of bronchopneumonia was made. Every influenza patient was examined at least daily to detect a beginning pneumonia, and twice daily if the temperature remained high beyond the second day of the influenza. One patient had a complicating Type I pneumococcus for which the appropriate serum was given. Two patients, after a prompt subsidence of the influenzal pneumonia, developed a streptococcic lung infection; one was complicated with empyema. These secondary invaders follow in the path of the influenzal pneumonia and are to be expected.

We believe that the low mortality was directly due to the use of convalescent human serum, as the patients immediately improved and rapidly recovered after its use: the serum was efficacious in this group of severe cases.

METHOD OF FOLLOWING CASES

The diagnosis of pneumonia in every case was made by at least two clinicians, and, in the majority of the cases, the diagnosis was confirmed by Dr. F. Van Nüys, Lieutenant, junior grade, U. S. N. R. F., one of the senior members of our medical staff, who was called in as a disinterested observer. Daily notes were dictated to a Red Cross worker in every case till the patient was convalescent. From these notes, from the laboratory reports and from the temperature charts, we have collected our data. The following is a statement from Dr. Van Nüys:

> Up to October 9, I treated pneumonia patients according to regular methods, with good nursing, fresh air, hydrotherapy and symptomatically with drugs.
>
> On the above date, I took clinical charge of that ward wherein serum treatment was being used.
>
> The contrast between the results of the two methods of treatment was very striking.
>
> In a ward under the old treatment, the atmosphere was predominately tragic—many patients desperately sick, cyanotic, dyspneic, coughing and often in agony. The convalescents were subdued by suffering about them.
>
> In the serum ward the atmosphere was that of hope and cheerfulness. A few patients were quite sick, but usually comfortably so. The rest practically convalescent.
>
> These contrasting pictures are fixed indelibly in my mind.
>
> With the old treatment, my mortality figures were close to 28 per cent.—identical with those of another pneumonia ward under Dr. Joseph A. Meledy.
>
> With the serum treatment, mortality was practically nil, except in those pneumonias entering too late for early use of serum.

PROCEDURE

Routine Wassermann tests are done on all patients admitted with pneumonia so that by the time for bleeding there is no delay. In outside practice, blood is obtained at the time of the first injection of serum.

The amount of blood obtained from each donor totals about 1,000 c.c.; that is, about 500 c.c. are taken at two succeeding bleedings, at an interval of a day or two. No untoward symptoms aside from slight faintness in two or three have ever occurred in a series of over 500 donors, so we believe that 500 c.c. are well within the limits of safety in an adult weighing 120 pounds or more. Most patients seem to feel better after the bleeding, especially in the matter of an increased appetite.

The time of bleeding after temperature reaches normal has been set at about ten days. However, we have bled even earlier than this. For an upper limit, we have considered about six weeks. Naturally, this is arbitrary in the absence of any method of titrating the serum. However, at one time, we were short of serum and were compelled to use that obtained from men who had been well for from six to eight weeks. We were impressed with the lowered potency of this pooled serum.

The apparatus for obtaining blood, as shown in the accompanying illustration, is wrapped in cloth and autoclaved. Negative pressure is produced either by an assistant sucking on tube *E*, or by connecting an aspirating bottle to *E*, with

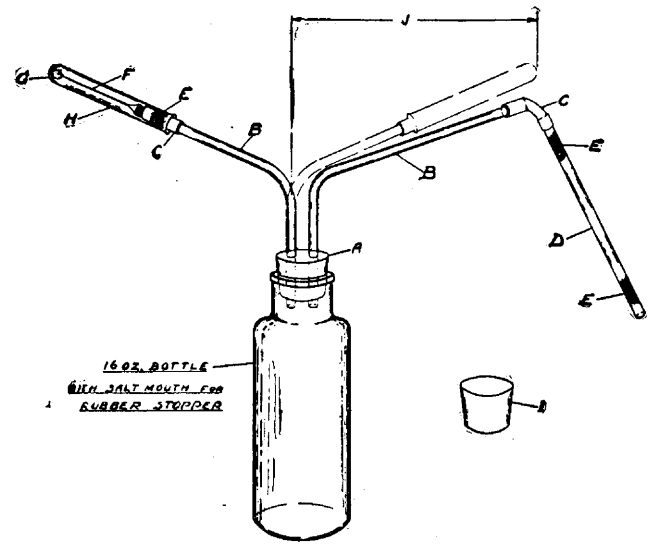
a tourniquet adjusted on the donor's arm so that the pulse is still palpable; there is usually no difficulty in getting the desired amount. At times, especially if the donor has not been up, there is a collapse of the vein over the end of the needle. This is due chiefly to an improper adjustment of the tourniquet or too much negative pressure or both. This can frequently be remedied by having the donor open and close the hand. In obtaining blood from men, there is usually not enough discomfort to require the use of a local anesthetic, but in women, it is advisable to inject a little 1 per cent. procain at the point of proposed puncture. An equipment should include about ten complete bleeding sets with a dozen extra bottles. For centrifugalizing, 50 c.c. or larger tubes are advisable.

Preparation of Serum.—The blood is allowed to remain in the incubator at body temperature for an hour shortly after it is collected. By this time, if one is pressed for serum, he can obtain about 100 c.c. from each 400 or 500 c.c. of blood; otherwise the blood is placed in the refrigerator for from five to six hours, or over night. Then the serum is decanted and centrifugalized to clear it of any bits of fibrin or red cells, etc., after which all the serum obtained is pooled. To this pooled serum are added 20 c.c. of 1.5 per cent. tricresol made up in physiologic sodium chlorid solution for every hundred c.c. of serum so that the tricresol content is about 0.3 per cent. The serum is then stored in 120 c.c. amounts. Serum prepared this way has been used with excellent results six weeks after storage. Frequently what appears to be fat accumulates on the surface of the serum; this goes into solution on heating to body temperature, and apparently is of no significance.

We formerly carefully took cultures of all serum before tricresolizing, but when we found no positive cultures of possible contaminating organisms in 200 serums, we considered the procedure sufficiently sterile to warrant the omission of cultures.

The amount of serum obtained from 500 c.c. of blood varies from 175 to 225 c.c. This seems to represent about the serum content of that amount of blood so that there is little, if any, waste of that part of the blood which contains all or most of the antibodies.

Administration of Serum.—We have found it convenient to give the intravenous injection of serum by means of a 120 c.c. glass syringe, or by the use of a 50 c.c. Lüer syringe connected to a three-way cock and proper tubing, as used in administering arsphenamin. Rarely does the procedure occupy more than ten minutes. The serum is first warmed to slightly above body temperature. We have given as high as 250 c.c. in one dose.



Bleeding apparatus: *A*, two hole rubber stopper K-33; *B*, glass tubing; *C*, rubber tubing; *D*, glass tubing for suction; *E*, cotton plugs; *F*, 18 gage needle; *G*, stylet; *H*, small test tube; *I*, blank rubber stopper K-33; *J*, the left tube turned for convenience in sterilizing.

SERUM REACTIONS

While we were doing compatibility tests, four patients had chills lasting from ten to thirty minutes, coming on about thirty minutes after the administration. These chills on the whole were less severe than those following horse serum. Since the discontinuance of the compatibility tests and the pooling of serum, the percentage of chills has been about the same or less. There is usually a rise in temperature, pulse and respiration, shortly after the injection, but never any sign of anaphylaxis. Never have we seen urticaria at any time after the use of human serum, or other signs or symptoms of serum sickness.

It has been our desire, from the beginning, to run parallel control groups without serum treatment, with treatment by use of "normal" human serum, and with treatment by use of serum from those having had influenza without lung complication. For obvious reasons, we were unable to allow patients with the pneumonia complication to go without serum treatment. However, it seemed justifiable to give some men one dose of serum from normal individuals, or from those recovering from influenza alone. Again, we were unable to complete the experiments but were able to get suggestive evidence. The patients chosen for the experiments were taken at random from the groups as they were admitted. The results are reported for what they may be worth.

Incomplete experiments were conducted with pooled serum from men who never had influenza, so far as we could find. Serum was obtained from ten so-called "normal" donors. This was pooled and tricresolized, and then 100 c.c. were given to five influenza patients admitted to the ward. At the same time, three other patients taken at random received 100 c.c. of the "anti-influenza-pneumonia" serum. The next day, all who had received the "normal" serum showed the same or a higher temperature, while the three receiving the same dosage of anti-influenza-pneumonia serum showed a drop of temperature to normal. Unfortunately for scientific accuracy, we were compelled to give the anti-influenza-pneumonia serum to the other five patients instead of continuing treatment with "normal" serum. The five showed normal temperatures after the first injection of the anti-influenza-pneumonia serum. We feel that this is suggestive, but not conclusive, though it corresponds with similar experiments earlier in the epidemic.

Incomplete experiments were conducted with pooled serum from men who had influenza and who never showed definite consolidation. Serums from five such patients were pooled and tricresolized, and a 100 c.c. dose was given to each of three patients sent to the pneumonia ward. Two others were given an equal dose of immune serum. Two of the first group showed slightly higher temperature the next morning; one showed a drop of 2 degrees. The two receiving the immune serum showed a normal temperature the next morning. On further examination, it was found that all had a definite area of consolidation except the man receiving "normal" serum, whose temperature fell 2 degrees. The first two showed a normal temperature sixteen hours after the injection of 100 c.c. of immune serum. Here again evidence is incomplete, but suggestive, as noted in the previous article.

In addition to the foregoing experiments, it was early noted by us, when serum from single patients was being used, that certain serums had no measurable

effect. On further investigation, it was invariably found that such serums came from men who had only a small lung involvement, or had only a small involvement and had recovered rapidly under serum treatment, or else had been obtained from individuals in whom the disease had run a long course with a swinging temperature and an increasingly high white count. Because of earlier findings in a few mild cases treated with serum, we were led to state that patients who had received serum did not yield potent serum. However, recent experience has demonstrated that serum from such patients has potency equal to that from untreated patients.

COMMENT

From the data presented, it is evident that a low white blood count is characteristic of the usual bronchopneumonia following influenza. Hence it is of prime importance before serum therapy is instituted. In our experience, a low respiration and low pulse rate, compared to the lung involvement and high temperature, aid in making a diagnosis of influenzal pneumonia.

At present, the only method of testing the potency of the convalescent serum is by its effect on the patients. In our observations here, it would seem that one of the first reactions is against toxic symptoms, such as nausea, vomiting, vasomotor disturbances and loss of appetite, so that it might be safe to say that the serum has some antitoxic action. Beyond this, we believe that discussion at the present time would be futile.

The method of obtaining and administering the serum has been reduced to its simplest form, so that little difficulty need be experienced in establishing the treatment, at least in centers. At the present time we would suggest the establishment of bronchopneumonia wards in various hospitals, with one man in charge of the serum treatment. Then by starting with four or five donors recently recovered from the disease, sufficient serum can be obtained to institute treatment. This, once started, can be continued, provided sufficient interest is taken in the procedure. We are convinced that the results will fully repay one for the effort.

That the tricresol is not an important factor in the results obtained is evidenced by the fact that no difference has been noted in the action of the preserved and unpreserved serum.

Influenza patients who have a continuous high temperature persisting over three days, or who have a secondary rise of temperature immediately following influenza, should be regarded as probably developing influenzal pneumonia. Signs of consolidation may not be present at this time, but patches of fine râles can usually be found. These signs, taken in conjunction with a persistent low white blood count and in the absence of other complications, almost invariably mean a beginning influenzal pneumonia. This is the most favorable time to start serum therapy. If serum is given at this early stage of pneumonia, favorable reaction is universal. If one depends on a rising pulse and respiration, as well as on the high temperature, he will frequently allow a patient to pass beyond the time most favorable for any kind of serum therapy.

SUMMARY

Out of 151 patients with bronchopneumonia following influenza treated by human convalescent serum, three have died without complications, and three have died after a complicating hemolytic streptococcus empyema, making a total of six deaths, or 4 per cent.

Most of the cases were treated early in the pneumonia complication, and hence were well suited for serum treatment.

Out of 151 patients, 132 received three doses of serum or less; about two thirds required only two doses, and over one third but one injection. Those who received more than one injection for the most part had advanced to at least two days in their pneumonia. The average dose used here is 120 c.c.

Out of the 138 patients, eighty-three recovered by crisis, and fifty-five by lysis.

In 148 cases, over half showed a normal temperature within forty-eight hours after the beginning of serum treatment.

The febrile period of the disease was decidedly shortened, though the lung signs persisted.

Several cases without definite signs were treated with serum. These are not included in the group reported. In some of these cases, it would seem that possibly a pneumonia was prevented.

Incomplete experiments with pooled "normal" serum and with pooled serum from uncomplicated influenza patients indicate a lack of curative power in such serums. Pooled serum from patients treated with immune serum seems to have about the same potency as that from the earlier untreated cases.

Over half the cases treated were received during the recent recrudescence of the epidemic, when there has been no doubt about the severity of the pneumonia complication. Complications have been infrequent.

There has been no increase in chills since the compatibility tests were discontinued. We have never seen urticaria or any other signs of serum sickness after the use of human serum.

Bronchopneumonias with a white blood count below 10,000 or 12,000 are most favorable for treatment with this serum, though a number with much higher counts responded readily.

CONCLUSIONS

Pooled serum from convalescent influenzal bronchopneumonia patients at this hospital has greatly reduced mortality, has shortened the course of the disease, and has proved almost a specific, not only during a waning epidemic but also during the more recent severe recrudescence.

U. S. Naval Hospital.

Treatment of Chronic Asthma.—Dr. M. Machado emphasizes the necessity for putting an end to the predisposition which brings on the attacks of true asthma. This constitutional predisposition is best combated, he has found in his experience, by iodid and emetin. "The iodid acts on the structure and functioning of the cells while the emetin regulates the apparatus of the internal secretions. The two combined break up the diathesis which is responsible for the asthma." He gives the emetin by injection of 0.04 gm., increasing by 0.01 gm. a day until the dose is 0.08 gm.—a total up to 0.30 or 0.38 gm. in the course of five or six injections. After this he gives a course of sodium iodid by intravenous injection of 20 c.c. daily or on alternate days, increasing by 10 c.c. each time until the 100 c.c. dose is reached. From twenty to thirty injections may be required to overcome the chronic tendency to asthma. It only gradually subsides. There has never been recurrence in any of his cases thus treated; in some the interval since has been three years. His communication appeared in the *Gazeta Medica da Bahia*, **50**:97 (September) 1918. No further details of the technic are mentioned.