USE OF ANTIPNEUMOCOCCIC REFINED SERUM IN LOBAR PNEUMONIA

DATA NECESSARY FOR A COMPARISON BETWEEN CASES TREATED WITH SERUM AND CASES NOT SO TREATED, AND THE IMPORTANCE OF A SIGNIFICANT CONTROL SERIES OF CASES *

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Practicing physicians have not as yet adopted the serum treatment for pneumonia. This has mainly been because the available serums have required relatively large intravenous injections, have been monovalent, and at times have occasioned severe reactions. Moreover, the beneficial effects have not been conclusively proved. In fact, the typing of pneumococci obtained from patients suffering from pneumonia has been abandoned in many hospitals, because it has been regarded as a procedure of little or no clinical value. But the results of treatment of type I patients by Avery and Cole and their co-workers, the recent studies of serums in experimental pneumonia in monkeys by Cecil, and the protection experiments on mice, all influenced Dr. Park to continue his efforts. We have used Felton's serum, refined in the cold, and made available through the Influenza Commission of the Metropolitan Life Insurance Company and Harvard University, and preparations of Dr. Banzhaf and of Dr. Sobotka of the Littauer Fund.

TABLE 1.—*Number of Pneumonia Cases Treated at Harlem Hospital from September, 1926, to October, 1927, by Type and Mode of Treatment*

Type	Total Cases		With Serum		Without Serum	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
All typed cases	365	100	169	100	196	100
Type I	112	31	58	34	54	28
Type II	69	19	30	18	39	20
Type III	43	12	25	15	18	9
Type IV	141	38	56	33	85	43

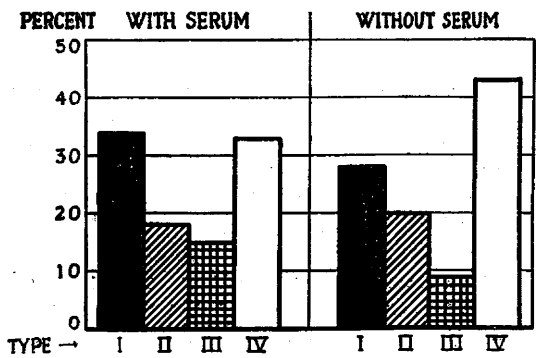

Chart 1.—Pneumonia cases treated at Harlem Hospital from September, 1926, to October, 1927, by type and by mode of treatment.

The evaluation of the effect of any therapeutic procedure in pneumonia is attended with certain inherent difficulties. Probably seven of every ten patients recover regardless of treatment, and therefore if one chances on a succession of favorable cases one is apt to attribute the benefit to the special treatment then in use. For example, we have encountered a series of thirty-one cases (not included in the present study), treated with and without serum, in which all the patients recovered. A short series of fatalities, unless carefully controlled and analyzed, may lead to a condemnation of what is really a very useful procedure.

Refined concentrated serums are desirable in order that the dose may be small and readily administered, without severe reactions. They must be polyvalent (several serums may be mixed) because the pneumonias resulting from pneumococci of different serologic types may be indistinguishable at the onset.

As the disease progresses, some patients must develop protection by their own mechanisms. Desperately ill patients may recover regardless of treatment, and critical termination may occur without warning. Invasion of the blood stream of patients with resulting bacteremia reveals definite lack of protection in the patient's blood. The results of protection tests or of blood culture studies, which might help reveal those patients in whom their own protective mechanisms have failed, are obtained too late for adequate guidance in administering serum. Because no one can foretell with certainty what patients may develop adequate protection in response to the pneumonic invasion, the benefit from treating patients is discovered only by comparing the results in a series of serum-treated cases with a similar series treated without serum.

Since we eliminated a chill reaction in the majority of our treated cases, we may conclude that the occurrence of a chill has small, if any, part in our result. For fair comparison, the influence of all other treatment must be balanced in two series.

ALTERNATION

There must be no selection of patients. At Harlem Hospital each alternate patient with pneumonia is placed in the serum series. Because of the structure and organization of our hospital, the male and female cases are conducted as separate units, with separate house staffs, but with the same visiting and resident physicians constantly in charge of all patients with pneumonia. It is not practicable to alternate the cases according to type on admission, as this might occasion a delay of many hours or days. The injection of a powerful polyvalent serum of types I and II, and soon of III also, assures prompt treatment of the cases selected for serum. Only the order of arrival in the ward determines whether a patient is to receive serum.

The delays in typing are occasioned by absence of sputum, by the time requisite for the growth of organisms in the peritoneum of a mouse, or for development of a subculture from its heart's blood. Sometimes a blood culture from the patient, or aspiration of a serous effusion or of the lung itself, furnishes the first information as to type.

REJECTION OF PATIENTS

We accept and retain as pneumonia patients those having pneumococcus infections of the lung with definite lobar involvement, as evidenced by unmistakable physical signs, fluoroscopy or roentgenography. We have been unable to separate with assurance the so-called confluent bronchopneumonias. If a patient dies of a surgical accident or complication, even though he has recovered from the pulmonary involvement, it is charged against the series. A patient is rejected from the series as not having pneumonia when it is discovered that he has not had a pneumococcus consolidation but such a condition as a tuberculous pneumonia with a high temperature. If the organisms recovered are not

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bile-soluble, the cases are rejected from the series. The patient's place is not filled, but the alternation continues as before in order to avoid selection. That there was no selection for either series is shown by comparing the number of patients of each type in the two series; they are approximately the same in the two. Patients came in early and late among the serum-treated and the controls, in about the same proportion. This is another test of the similarity of the series.

The time of the onset is dated from the occurrence of the chill or of sharp pain in the side, whichever came first.

TABLE 2.—*Time of Admission to Hospital After Onset of Disease*

Time of Admission	With Serum		Without Serum	
	Number	Per Cent	Number	Per Cent
Total cases	169	100	196	100
Admitted within:				
Less than four days	80	47	102	52
Four days and more	86	51	88	45
Time of onset unknown	3	2	6	3

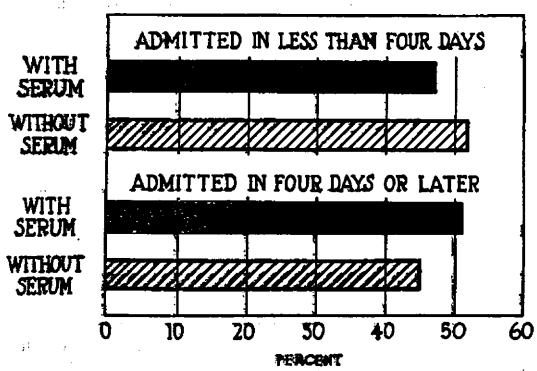

Chart 2.—Time of admission to hospital after onset of disease.

Except for the serum, all patients are given the same medical care in respect to drugs and nursing. Specific indications are treated in accordance with a definite standard plan. The house physicians are supplied with these instructions in writing and their work is constantly supervised, so that the standard treatment is followed. The method of administration of the serum and the dosage is described by Park and Cooper.[1]

SEVERITY RATING

To obtain an estimate of the severity of the illness for subsequent comparison of cases of like degree we have adopted the device of rating our patients in accordance with a definite plan. This avoids all reminiscing concerning the severity of the condition before treatment was begun. This rating has the advantage of not being confused by changes for better or worse in the course of the disease because it is given when the patient is first seen on rounds when all present agree to what have been chosen as obviously gross and readily appraisable objective departures from the normal (table 3).

The rating assumes 100 to be health, and for each of five categories a maximum of 20 may be subtracted. This rating expresses the percentage of health remaining, and indicates for us the reciprocal of the severity of the illness. It is not intended to indicate the chances for recovery, yet in a crude way it is prognostic (chart 3).

1. Park, W. H., and Cooper, Georgia: Antipneumococcus Serum in Lobar Pneumonia, this issue, page 1349.

For a portion of a lobe we subtract 3; for an entire lobe, 5; for an entire side, 10, and for the two lower lobes, 15. For pleurisy we subtract 5 for each side, and for respiratory rates above 34 subtract 5 and above 44 subtract 10.

TABLE 3.—*Severity Rating*

Health = 100. Each heading given equal importance: the maximum is always 20, excepting bacteremia, for which 20 is subtracted

	Subtract
Respiratory: Involvement: Portion of lobe	3
Entire lobe	5
One side	10
Both lowers	15
Rate: 35+	5
45+	10
Pleurisy: for each side	5
Nervous Condition: (headache, irritability, sleeplessness, delirium, apathy, coma) depending on severity up to	20
Circulatory Efficiency: Rate: 110+	5
120+	10
Cyanosis: depending on degree up to	10
Gastro-intestinal: Distention: depnding on severity up to	10
Vomiting: depending on severity up to	10
Complications and Special Factors: age 50+	5
age 60+	10
Obesity, depending on degree	5–10
Pregnancy, depending on the month	5–10
Tuberculosis, depending on involvement	5–10
Bacteriemia	20

Condition of the Nervous System.—For disturbances in the nervous system we subtract up to 20, depending on the degree of prostration or irritation.

Circulatory State.—For rates of 110 or more 5 is subtracted; for rates of 120 or more, 10, and for cyanosis, up to 10, depending on the degree.

Gastro-Intestinal Condition.—For distention, depending on the degree, we subtract up to 10; for vomiting, also, we subtract up to 10.

Complications and Special Factors.—When the age is more than 50, we subtract 5, and when more than 60 years, we subtract 10. The subtractions for obesity depend on the degree, and for pregnancy, on the month; for tuberculosis, depending on the involvement, we subtract up to 10, and for bacteremia we subtract 20.

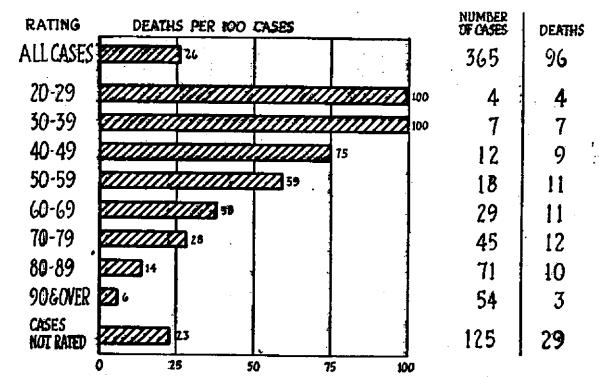

Chart 3.—Deaths per hundred pneumonia patients rated for degree of illness on admission.

To Dr. Louis I. Dublin and his staff of the Statistical Bureau, Metropolitan Life Insurance Company, we are indebted for the statistical study of our data. We have rejected the first 152 cases studied because of inadequate controls. In that series only early cases were treated (less than eighty-four hours) with serum. The mortality rate in the treated cases was apparently remarkably low. In our alternating series studied during the past year we had 401 cases of lobar pneumonia, of which twenty-eight were rejected because it was impossible to type them, and eight because of concur-

rent febrile diseases, such as scarlet fever and tuberculosis, or on account of an unreliable history of the onset. There remain 365 cases to be studied, 169 in the serum series and 196 in the controls; 220 were rated.

We were interested in determining the effect of the condition on admission on the mortality and whether

TABLE 4.—*Deaths per Hundred Cases of Type I Pneumonia Patients Treated with Serum and Without Serum, by Groups Rated for Degree of Illness on Admission*

	(a) With Serum			(b) Without Serum		
Rating*	Cases	Deaths	Deaths per 100 Cases	Cases	Deaths	Deaths per 100 Cases
Total.....	58	13	22 ± 5.4	54	19	35 ± 6.5
Poor.....	6	4	67 ± 19.2	4	4	100 ± —
Fair.....	6	2	33 ± 19.2	11	6	55 ± 15
Good.....	24	3	13 ± 6.9	20	1	5 ± 4.9
Not rated..	22	4	18 ± 8.2	19	8	42 ± 11.3

* Good, from 70 to 100; fair, from 50 to 69; poor, from 0 to 49.

we saved with serum very ill patients who might have died without it. From table 3 may be seen in a general way that the rating on admission indicated chances for recovery. The type I cases rated were sufficiently numerous to classify (table 4) as good (70 to 100), fair (50 to 69) and poor (below 50). Of six patients rated poor we saved two patients with serum, while we lost all treated without serum; of those rated fair, we saved four of six in the serum group against six among eleven without serum.

Many have maintained that the excellent results reported with serum treatment in hospitals have been due to the early hospitalization rather than to the serum. In type I, a group for which we had a strong serum and in which the cases treated and the controls

TABLE 5.—*Deaths per Hundred Patients of Those Admitted Within Three Days of Onset*

	(a) With Serum			(b) Without Serum			Ratio of
Type	Cases	Deaths	Deaths per 100 Cases	Cases	Deaths	Deaths per 100 Cases	Difference in Case Fatality (a — b)	Difference to Its Error
I	29	6	21 ± 7.6	28	10	36 ± 9.1	—15 ± 11.9	1.3
II	11	2	18 ± 11.6	21	6	29 ± 9.9	—11 ± 15.3	0.7
III	11	5	45 ± 15.0	9	5	56 ± 16.5	—11 ± 16.5	0.5
IV	29	2	7 ± 4.7	44	7	16 ± 5.5	— 9 ± 7.2	1.3

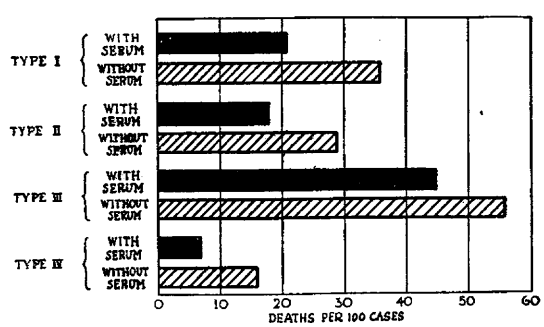

Chart 4.—Deaths per hundred patients of those admitted within three days of onset.

were sufficiently numerous, the mortality was 36 per cent among both early and late cases without serum; the benefit from treatment with serum was slightly greater in the early group, being 21 per cent in the early as against 24 per cent in the late. For the type II serum series the mortality among both early and late cases was less than for the controls (tables 5 and 6; charts 4 and 5).

Not only did the serum treatment reduce the number of deaths but it shortened the illness of those who recovered. If the number of days that elapsed (table 7; chart 6) between the onset of the disease and the return of the temperature to 100 F. are noted, it may be seen that in type I cases without bacteremia the period of illness was definitely shortened. Twenty-four per cent of the serum-treated cases and 9 per cent of the controls defervesced in less than five days; 68 per cent of the serum-treated cases and 52 per cent of the controls defervesced in less than ten days. After ten days only 8 per cent of the patients treated with serum continued to have a fever, as against 41 per cent of those not treated with serum. Certainly this was advantageous, as it meant a saving in hospital care and of subsequent invalidism. There were too few cases in which the blood culture was positive for type I to enable us to determine the average duration of illness. The short-

TABLE 6.—*Deaths per Hundred Patients of Those Admitted Four Days or More After Onset*

	(a) With Serum			(b) Without Serum			Ratio of
Type	Cases	Deaths	Deaths per 100 Cases	Cases	Deaths	Deaths per 100 Cases	Difference in Case Fatality (a — b)	Difference to Its Error
I	29	7	24 ± 7.9	25	9	36 ± 9.6	—12 ± 12.4	1.0
II	18	7	39 ± 11.5	16	7	44 ± 12.4	— 5 ± 16.9	0.3
III	14	7	50 ± 13.4	9	3	33 ± 15.7	+17 ± 20.6	0.6
IV	25	6	24 ± 8.5	38	2	5 ± 3.5	+19 ± 9.2	2.1

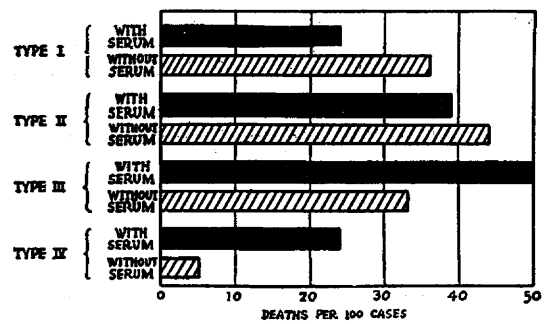

Chart 5.—Deaths per hundred patients of those admitted within four days after onset.

ening of illness, observed among the type IV cases, may have been due to mistaken classification or to an overlapping of antibody reactions.

This emphasizes again the advisability of administering polyvalent serum to all patients as early as possible without waiting for the result of typing. Serum not only saved more patients and shortened the illness of those who recovered, but apparently delayed death in those who perished, just as occurs in animal experiments. This gave them a better chance. We observed that of patients with the fatal type I pneumonia, 46 per cent lived for fifteen days or over in the series treated with serum, against 5 per cent who perished during that period among the controls, and 62 per cent survived ten days or more in the patients treated with serum, against 46 per cent among the controls. There were thirteen deaths in the series treated with serum and nineteen among the controls.

When all the cases early and late are grouped by types and the effect of the serum is studied it will be noted that those with type I and type II pneumonia for whom we had potent serum showed fewer deaths per hundred among those treated with serum (table 8; chart 7). The greater benefit from early treatment is revealed in the charts.

In spite of the fact that we were impressed, as the research proceeded, by the beneficial effects of the serum, the question arose as to whether there was conclusive proof that the serum is of value. What test can we apply to our data to see whether proof is adequate and how can we determine the number of cases necessary for a fair evaluation? This leads us into a brief digression concerning what difference in results is statistically significant, and the meaning of the standard error.

If we take a number of samples from a given material (such as a population of hospital patients with pneumonia) and measure these samples for any particular quality (such as case fatality), the measures obtained will vary somewhat, from sample to sample, and if plotted in a diagram will appear as a bell-shaped curve such as

TABLE 7.—*Number of Days Elapsed Between Onset of the Disease and Return of Temperature to 100**

Number of Days Elapsed	With Serum		Without Serum	
	Number	Per Cent	Number	Per Cent
Total cases	38	100	29	100
Less than five days	9	24	2	7
Five to nine days	26	68	15	52
Ten days or more	3	8	12	41

* Recovered pneumonia patients treated (a) with serum and (b) without serum; type I cases, without bacteremia.

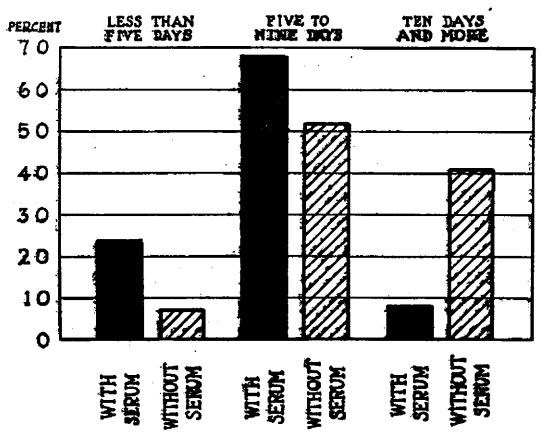

Chart 6.—Number of days elapsed between onset of the disease and return of temperature to 100; type I cases without bacteremia.

that shown in chart 8. If we do this for two separate materials, such as pneumonia patients treated with and those treated without serum, we shall obtain two separate bell-shaped curves. If the two separate materials are essentially different in their behavior as regards the quality measured, the peaks of the two curves will fall some distance apart, because the measure found most frequently in the one set will differ from the measure found most frequently in the other set. For example, the average case fatality in serum-treated patients is found to be different from the average case fatality in patients treated without serum. But if the difference is small, the peaks of the two curves will fall close together, and if the curves are rather flat, they will overlap and be practically indistinguishable.

The effect of using larger samples in such a case is to contract the two bell-shaped curves, making them high and narrow; the two separate peaks then become more clearly apparent, even though the distance between them remains the same.

This is the reason why it is necessary to have sufficiently large samples, for only thus can one detect with certainty relatively small differences in measurements obtained from two presumably different kinds of material.

TABLE 8.—*Deaths per Hundred Patients. (Deaths Within Twenty-Four Hours of Admission Excluded)*

Type	(a) With Serum			(b) Without Serum			Ratio of Difference Difference in Case Fatality (a — b)	to Its Error
	Cases	Deaths	Deaths per 100 Cases	Cases	Deaths	Deaths per 100 Cases		
I	55	10	18 ± 5.2	53	18	34 ± 6.5	−16 ± 8.3	1.9
II	26	6	23 ± 8.3	38	14	37 ± 7.8	−14 ± 11.4	1.2
III	24	11	46 ± 10.2	17	7	41 ± 11.9	5 ± 15.7	0.3
IV	54	7	13 ± 4.6	82	7	9 ± 3.2	4 ± 5.6	0.7

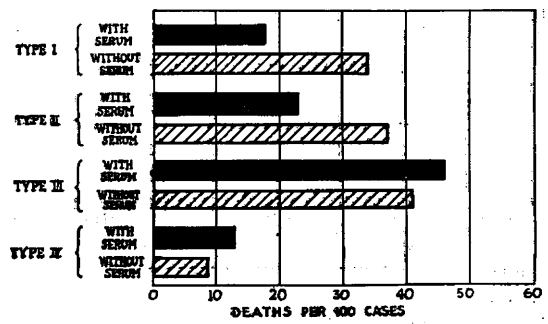

Chart 7.—Deaths per hundred patients (deaths within twenty-four hours of admission excluded).

Without going into technical details, I may explain that the relative spread or flatness of the curve is measured by what is called the standard error of the measurements, which is to the probable error as 3 to 2. In order that the difference between measurements in two separate materials shall be recognizable as definitely significant, the distance between the peaks of the two curves must satisfy a certain statistical test; namely, that the difference between the average measurements in the two cases shall be at least equal to twice the "standard error" of that difference.

In table 8 is a column giving the difference of case fatalities for serum-treated and for non-serum-treated patients. In this column there is appended to each entry a second figure, preceded by the sign ±. This figure is the "standard error" of the difference to which it is appended.

Finally, there is a column showing the ratio of the difference to its standard error. Whenever this ratio falls below 2, we are not in a position to judge whether any significant meaning is to be attached to the difference; that is to say, whether it is purely accidental or due to a real effect of the treatment. The further this ratio is below 2, the greater must be our doubt.

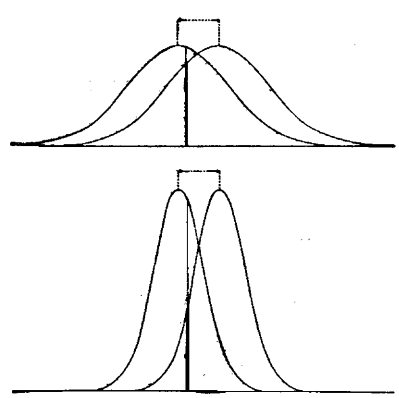

Chart 8.—Influence of size of sample on significance of difference between two rates.

In the type I cases we have practically obtained a result which is twice the standard error, 1.9. A greater difference in the percentage recovery of treated cases than those untreated may be accomplished by future

improvements in the serum, and by earlier administration. Even though the serum were to remain as it is, and the difference in the percentage of deaths the same as at present, 16 per cent, a greater number of cases would reduce the standard error and carry conviction of the value of serum treatment. In type II cases the difference is less significant. An effort must be made to make the serum more potent, larger doses may be needed, and more observations of its use must be accumulated. When for type I pneumonia the ratio of the difference in percentage fatality between serum-treated and non-serum-treated cases, to its standard error, becomes more than 2 or 3 it will be our duty to administer serum in all type I cases and to urge its administration on others.

We are aware that type III cases did not have sufficient treatment and that the antibody employed in type IV was negligible.

Finally, to evaluate the result of a treatment in pneumonia, there are required adequate comparable series with and without the treatment. We believe that we have obtained such series by the devices adopted of alternating patients and rating them on admission. The size of the series requisite is determined by a consideration of the standard error.

THE CHEMICAL OBLITERATION OF VARICOSE VEINS

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For the past fifteen years a number of European physicians have been treating varicose veins of the leg by the injection of various sclerosing solutions. Originated by Linser of Tübingen, Germany, in 1912, and later popularized in France by Sicard of Paris, the method is gradually replacing the operation of varicotomy in these two countries, as well as in Austria, Sweden and Denmark. Recently several papers on this method have appeared from England, and a few in the American literature. In each of these countries the method has slowly made headway in the face of considerable opposition on the part of conservative clinicians, who feared such complications as pulmonary embolism, sloughing of the tissues from perivenous injection, and toxic effects from some of the solutions used. All of these have been reported in the literature, but embolism has occurred so seldom as to be considered a negligible danger, toxic effects have been largely eliminated by the use of relatively harmless solutions, while local necroses occur chiefly in the hands of unskilled operators, as in connection with arsphenamine.

I first became interested in this treatment in 1922, and since then have treated more than 150 patients with very satisfactory results. At first the cases were carefully selected, but gradually the list of contraindications has narrowed down until now I feel that fully 95 per cent of patients can be successfully treated by this method. Some of these patients would be considered quite unsuitable for varicotomy by most surgeons, and at least half of the remaining 5 per cent would also be classed as inoperable.

While some of my patients were treated at the clinic, most of them were private patients. A few were treated at their homes at their own request, but the great majority were treated at the office. As a matter of fact, the greatest advantage of the injection method is its applicability to ambulatory patients, who usually pursue their occupations without interruption during the course of treatment. About twenty-five patients presented recurrences following a previous varicotomy, often as extensive as the original varicosities for which the operation had been done, and these invariably responded as well as the primary cases. Many had ulcers or eczema, which in no way interfered with the treatment, and which cleared up as rapidly as after operation. Various organic ailments, which would have made a general anesthetic very dangerous, did not seem to be aggravated by the injections. Nephritis and previous thrombosis of the deep veins are definite contraindications, of course, and should be ruled out first by the usual tests. Small sloughs have sometimes occurred, which separated and healed slowly, or required excision under local anesthesia. While this complication is annoying, it is never dangerous or incapacitating. No toxic reactions of any consequence have occurred, and of course no emboli. A transient edema of the foot and ankle is fairly common. The thrombosed veins are palpable and tender at first, but gradually absorb and disappear. Local recurrences are less common and less severe than after varicotomy, and are to be treated with additional injections. A thorough removal of all foci of infection, though often neglected, is the only really effective measure in the prevention of these recurrences.

For small veins I use the stock (1:500) solution of metaphen. This is a mercurial antiseptic of low toxicity, which has proved of considerable value in syphilis and septic infections when used intravenously. An injection is given every other day until all the veins are obliterated, the successive doses being 6, 9, and thereafter 12 cc. Saline cathartics are not to be used while metaphen is being given. The solution is painless and self-sterilizing. For larger veins I prefer a sterile 50 per cent solution of sodium salicylate, which I have had made up in 2 cc. ampules. Of this, from 2 to 4 cc. may safely be injected at one sitting, 1 cc. being used at each of several points. It is apt to cause burning and cramplike pain, lasting about one minute after each injection, but somewhat relieved by vigorous rubbing of the leg after the needle has been withdrawn. With either solution, a 10 cc. ampule of physiologic sodium chloride solution should be at hand, to be injected at once both into and under the skin in case of accidental extravasation. The prompt use of this simple precaution will prevent the sloughing that would otherwise be inevitable. An extra syringe and needle may be sterilized beforehand for this purpose.

The technic is important, and hence will be given in detail. It can be acquired only after long practice, and should not be attempted by those who find arsphenamine injections difficult, as the technical skill required to inject a tortuous, thin-walled, freely movable varicosity is often considerable. The patient sits upright on the table, with the legs horizontal. Two soft rubber tourniquets are applied, one about the ankle and one just above the knee, or higher if necessary. A 10 cc. eccentric tip Luer syringe and a 26 gage half inch needle are used. From two to four prominent points are selected and marked with ink, and the area is cleansed with 95 per cent alcohol rather than with iodine. The injections are made slowly, to allow time for distribution of the solution and for contraction of the veins. This forces out the contained blood and allows the solution to act in full concentration, thus completely destroying the intima of the vessel. A gauze sponge is pressed on each puncture site as the needle is withdrawn from it, and held long enough to prevent leakage.