As to technic, if there is deviation of the septum to the side of the diseased sac, the lacrimal operation should be preceded by a submucous resection of the septum. The easiest approach to the sac is through the thin bone of the anterior ethmoid region. The steps of the operation are as follows: The anterior end of the middle turbinate is removed and the slitting probe is introduced through the cut canaliculus into the sac and on through the nasal duct to the floor of the inferior meatus. Next, the anterior ethmoid cells are exenterated. Then a cut is made in the mucous membrane of the nose along the posterior edge of the ascending process of the superior maxilla, and the probe withdrawn to the upper margin of the inferior turbinate, and when clear of the turbinate the point is pressed upward and inward and made to break through the nasal duct into the nose. The tip of the probe is then slowly forced upward, all the while slitting the inner wall of the nasal duct. The upward excursion of the probe is finally stopped by the increased resistance of the superior part of the lacrimal bone. Experiments on the cadaver have shown that this manipulation opens not only the nasal duct, but the lower two-thirds of the inner wall of the lacrimal sac. Unless it is the purpose of the operator to exenterate the lacrimal sac intranasally, the operation is finished by inserting the silver style. This may be removed at intervals and cleaned. On evidence of closure of the duct the style must be reinserted.

DR. WILLIAM B. CHAMBERLIN, Cleveland: One point I did not have time to bring out in the paper is the subsequent closure. This is a difficulty in any endonasal operation. Three of my patients were operated on the second time; but the secondary operation is comparatively a simple thing. The probe is introduced through the sac again and at the point of stenosis you can see a slight bulging. It is a comparatively easy thing to resect this with the punch forceps. In the after-treatment, if one is careful in keeping down granulations, as in any other part, epidermization will not be retarded. In many cases a preliminary submucous resection, especially a resection as high up as we dare go, is absolutely essential. It is a sine qua non of the operation.

Another point Dr. Mosher brings out in the discussion is the resection of the posterior part of the ascending process of the superior maxilla, which makes a groove for the duct. This is dense, firm bone. It is for the resection of this ascending process that West has devised his chisels, and it is for the resection of this process that I have modified his chisels, making them very much thinner, and also putting on the handle, thus enabling one to see every step of the operation. The view is less obstructed than with the West chisels, and you can insert it under the bone, and if it does not make a clean cut the bone may be fractured by a twisting motion. The forceps are a modification of the familiar Gruenwald forceps for the ethmoid, and are quite as effective as the instrument which West has especially devised for the purpose.

Managing Atypical Children.—Atypical or backward children should not be coddled, but encouraged, and, like plants of slow growth, in some instances they may be "forced." This may be done by supplying favorable conditions for growth and development, and by directing their physical activities in the right channels. Comparatively poor health is not always a contraindication, but often a decided indication for this forcing process. Many a nervous child immediately begins to improve physically as well as mentally when well directed pressure is brought to bear upon him in psychophysical education.—G. Hudson-Makuen, M.D.

THE REACTION AFTER INTRAVENOUS INJECTIONS OF FOREIGN PROTEIN *

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During the last two years, intravenous injections of foreign proteins have been used as a therapeutic agent in various conditions. Satisfactory results have been reported in a variety of acute infections. In these reports the phenomena accompanying the injection are taken up as incidental to the presentation of the therapeutic results.

With the intravenous injection of a foreign protein, a certain reaction takes place which is fairly constant in all cases. For the purpose of observing the phenomena following the injections, careful records were made in the cases of acute articular rheumatism in which this treatment was employed. Observations were also made in a few cases of chronic arthritis and lobar pneumonia.

The foreign protein employed in these cases was typhoid vaccine. The vaccine was prepared from an active culture, grown twenty-four hours on agar slants, washed off with saline solution, killed by heating at

70 C. for two hours, and preserved by 0.5 per cent. phenol (carbolic acid). The vaccine was diluted so that each cubic centimeter contained 150,000,000; and injections of from 0.25 to 0.5 c.c. were used as the average dose.

Patients were taken as they entered the hospital with no selection except to exclude certain cases in which the vaccine was contraindicated, as will be shown later. Certain routine measures were taken

in the cases in which vaccine was given. The patient was allowed nothing to eat for at least one hour previous to the injection, so as to ward off nausea and vomiting. During the chill the patient was well covered with blankets. When the joints were acutely inflamed, from $\frac{1}{6}$ to $\frac{1}{4}$ grain of morphin was given to relieve the pain incident to the involuntary movements of the joints during the chill. The patient was kept in bed three days after all symptoms subsided. The vaccine was injected in the morning about three hours after breakfast, and the general symptoms, temperature, leukocytes and blood pressure were followed through the day and on the next morning.

THE GENERAL REACTION

Certain general symptoms were noted following the injection. For from half an hour to an hour there is no apparent change in the patient's condition. Then a chill occurs, which may become quite severe, and is accompanied with the usual symptoms of cyanosis and rapid pulse. With the onset of the chill the patient frequently complains of a dull temporal headache; nausea and even vomiting may be frequent at this time. The chill lasts from fifteen to thirty minutes and sub-

Chart 1.—Composite temperature curve following forty-seven intravenous injections of typhoid vaccine in twenty-five cases of acute articular rheumatism.

* From the medical clinic of Dr. Joseph L. Miller at Cook County Hospital.

sides gradually, the headache and nausea passing away with the chill. Following the chill there is a rise in temperature, and there are changes in the leukocyte count, in blood pressure and in the differential count, all of which will be more fully considered below. Following the chill there is profuse sweating. The sharp pains in the joints disappear shortly after the chill, though a feeling of soreness or stiffness may persist for a short time.

With large doses a more marked reaction was observed. In certain cases the average dose proved to be excessive, especially in those cases in which the patients were bedridden for some time. In these cases there was a severe rigor lasting one or two hours, and accompanied by marked cyanosis and a rapid, weak pulse. Following the chill the patient became very weak and showed signs of collapse. There seems to be a profound vasomotor disturbance, which may account for the sudden deaths that have been reported following intravenous vaccines.

Associated with severe reactions certain other symptoms were noted. Herpes occurred in three cases. The lesions were noted about the lips and inside the mouth. Prolonged headache occurred in several cases. Headache occurred in practically all cases during the chill; the headache was not constant in intensity, nor did the intensity seem to bear any relation to the severity of the reaction. Vomiting occurred in four cases with a severe reaction.

Temperature Curve.—Chart 1 shows a composite curve of forty-seven injections in twenty-five cases of acute articular rheumatism, and may be taken as a typical temperature curve. Little change is noted in the temperature until the chill occurred. Following the chill there is an abrupt rise until a maximum of 103.6 F. is reached four hours after the injection, after which there is a gradual fall to nearly normal in sixteen hours, and to normal at forty-eight hours. This curve corresponds closely to the curve obtained by Culver¹ in gonorrheal cases. Composite curves of primary and subsequent injections are similar, though the subsequent injections have a slightly lower curve. With the primary injections the maximum temperature of 103.8 was reached four hours after the injection. The highest individual maximum temperature observed was 106.6 three hours after the injection. The lowest individual maximum temperature was 102 three hours after the injection.

Leukocytes.—Chart 2 shows a composite curve of forty-three injections in twenty-four cases, and may be taken as a typical leukocytic curve. Following the injection and especially at the time of the chill there is a fall in the leukocyte count. The count may fall to normal or below, resulting in a leukopenia. This

will be noted in the chart, the count falling from 14,200 to 5,900. Toward the end of the first hour after the injection there is a gradual increase which continues until the highest count (39,900) is reached, about six hours after the injection. Following this there is a fairly rapid fall so that by the end of forty-eight hours the count is about the same as before the injection. This curve is similar to that obtained by Culver¹ in his cases.

Composite curves of primary and subsequent injections are similar, though the subsequent injections generally produce a slightly lower leukocytosis than the primary or preceding injection. The highest individual count was 77,200 six hours after the injection. The lowest maximal count was 13,600. Certain cases showed a persistent leukocytosis which did not seem to have any bearing on the severity of the infection or on the therapeutic result. The degree of leukocytosis did not seem to have any bearing on the results obtained, though cases with a marked reaction and a corresponding increase in leukocytes gave the best response to the treatment. With large doses the degree of leukocytosis was greater, counts of from 90,000 to 115,000 being noted.

Blood Pressure.—Chart 3 is a composite of thirty-eight injections in nineteen cases, and may be taken as a typical blood pressure curve. During the first hour after the injection, and especially at the time of the chill, there is a rise in blood pressure. This is not well shown on the chart, owing to fewer observations made, than at other points on the curve. This is due to the difficulty in taking the blood pressure while the patient is chilling, the twitching of the muscles making accurate readings difficult, and at times im-

Chart 2.—Composite leukocyte curve following forty-three injections in twenty-four cases of acute articular rheumatism.

possible. Probably during the height of the chill the rise is greater than shown by the readings which were made. After the chill there is a fall in blood pressure, reaching a maximal drop, 92 systolic and 60 diastolic, about six hours after the injection, and then coming up gradually to nearly normal in forty-eight hours. The systolic and diastolic pressures vary about equally at all times of the reaction. The composite curves of primary and subsequent injections are much alike, both diastolic and systolic, though in the subsequent injections the fall was not quite so great. The lowest single reading during the fall was 60 systolic and 40 diastolic six hours after the injection. With large doses a greater drop was noted. These patients show marked signs of shock.

Differential Blood Counts.—Considerable variation is noted in the differential count following the injection, as regards both the relative percentages and the absolute values.

Following the injection there is a steady rise in neutrophils from the first, reaching a maximum point two or three hours after the injection, and then falling gradually in forty-eight hours to a percentage

1. Culver, Harry: The Treatment of Gonorrheal Infections, THE JOURNAL A. M. A., Feb. 3, 1917, p. 362.

slightly lower than before the injection. The highest individual rise was to 94 per cent. from 60 per cent. In absolute values the neutrophils follow almost exactly the total leukocyte curve, showing that the increase in the leukocyte count is mainly due to an increase in neutrophils. During the chill there is a fall in the absolute value, followed by a sharp rise in six hours and then a fall to the same level as before the injection.

The large lymphocytes show a rapid fall following the injection, reaching the lowest point two or three hours after the injection and then rising to a percentage slightly higher than before. The most marked individual fall was from 23 to 3 per cent. In absolute values, there is also noted a fall during the chill, followed by a slight rise reaching its maximum in eight hours, and then falling to normal. While the percentage curve shows a steady rise after eight hours, the absolute value remains about the same, owing to the decreasing total leukocyte count.

The small lymphocytes show a slight rise during the chill followed by a fall two or three hours after the injection, then gradually rising to about the same percentage as before. The most marked individual fall was from 20 to 3 per cent. In absolute values there is a decrease during the chill, owing to the decreased total leukocyte count. With the increasing leukocyte count there is also an increase in small lymphocytes to about normal, where it remains constant.

The eosinophils show an absolute and relative decrease during the first six hours after the injection, followed by an absolute and relative increase. Simon² noted this variation in eosinophils following intraperitoneal injections of killed bacterial cultures. He found that subsequent injections were followed by a higher percentage of eosinophils than the preceding injection.

The basophils show a slight relative and absolute increase during the first eight hours, followed by a relative and absolute decrease.

The urine showed no marked change following the injection. At the end of twenty-four hours there was a slightly higher specific gravity due probably to the loss of fluids from the profuse sweating. No albumin appeared when none was found before the injection, nor was there any change when albumin was present before the injection.

Certain changes occur in the blood serum following the injection. Work by Jobling and Petersen,³ and later work by Petersen indicates a rise in ferments and a decrease in antiferments at the time of the reaction.

Four patients with chronic arthritis were also treated by intravenous vaccines with reactions similar to those in acute articular rheumatism. Three patients with lobar pneumonia also received the vaccine. Early

cases in the second or third day were chosen, and a similar reaction occurred, except that the temperature, instead of remaining low after the injection, gradually rose again in forty-eight hours to about the same level as before, where it continued until the natural crisis. No changes were noted in the physical findings following the injection.

Intravenous injections of vaccine are contraindicated in those cases in which the vasomotor system is weakened, and when the nervous system is unstable. In these cases collapse may occur, with a possibility of death resulting. Organic heart disease requires cautious treatment. In serious lesions the injection is absolutely contraindicated, as the heart becomes dilated and overworked, so that cardiac failure may result. In one case of this series with a mitral murmur, following the injection the heart dilated 2 cm. to the right, and 4.5 cm. to the left. Gradual recovery occurred, however, in twenty-four hours.

In acute infections, as lobar pneumonia, small doses are advisable because of the weakened cardiac musculature. Chronic alcoholism may be an absolute contraindication, as the shock of the vaccine reaction may precipitate an attack of delirium tremens, resulting in a prolonged or fatal course. In one case of acute articular rheumatism in a heavy alcoholic, the patient received the usual dose of vaccine and had a typical reaction following. Thirty-six hours afterward he became delirious and remained so fifty-two hours, when death occurred.

THERAPEUTIC RESULTS

In twenty-five cases of acute articular rheumatism treated with vaccine, the following results were obtained: Ten cases cleared up after a single injection. All were recent and uncomplicated cases. No recurrences were noted while under observation, nor did any of these patients return to the hospital. Three cases cleared up slowly, requiring two or three injections. The shoulders were the last joints to clear up, the stiffness and soreness seeming to remain longer than in the other joints. Two cases recurred ten days after clearing up nicely after the first injection. These patients remained well after a second injection. Four cases were complicated, two with endocarditis, one with pericardial effusion, and one with empyema. In these cases there was a continued high temperature, and the patients received only temporary improvement after the vaccines until placed on salicylates. Four other cases were resistant to vaccines and cleared up under intravenous injections of sodium iodid. The remaining two patients are the one developing delirium tremens with a fatal result as cited above, and the other leaving the hospital refusing further treatment.

SUMMARY

Following intravenous injections of a foreign protein, certain definite phenomena occur. A general reaction is first noted with a chill accompanied by headache and nausea, and followed by sweating and relief of joint pain.

Chart 3.—Composite blood pressure curve following thirty-eight injections in nineteen cases of acute articular rheumatism: A, systolic; B, diastolic.

2. Simon: Internat. Clin., 1906, 1, 166.

3. Jobling, J. W., and Petersen, William: The Nonspecific Factors in the Treatment of Disease, THE JOURNAL A. M. A., June 3, 1916, p. 1753.

Following the chill there is a rise in temperature reaching a maximum about three or four hours after the injection and falling to normal in forty-eight hours.

There is a fall in leukocytes followed by a marked increase reaching a maximum six hours after, and gradually falling to the same level as before the injection.

The blood pressure rises during the chill, then falls, remaining low for three or four hours, and rising gradually to normal.

There is considerable variation in the differential counts, but the main change is an absolute and relative increase in the neutrophils.

The urine shows no definite change following the reaction. Intravenous vaccines are contraindicated in marked cardiac lesions and chronic alcoholism.

Successful results were obtained in 40 per cent. of the cases of acute articular rheumatism after a single injection and in 52 per cent. after two or more injections.

TREATMENT OF PARESIS BY INJECTIONS OF SALVARSAN INTO THE LATERAL VENTRICLE

SECOND REPORT

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In our first report of this method of treatment of paresis,¹ only three patients had received any systematic treatment. Our first injection was given, Jan. 12, 1915. Since that time we have made injections in other cases, ten of which were treated at a sufficiently remote date to make a report now of value. Thus this article is based on the results obtained in the first thirteen consecutive cases, in all but two of which three injections were given, and in two, five injections each. A great deal of care has been taken in studying these cases both before and after treatment. We were particular to select for injection only those patients who undoubtedly had paresis, and in all cases the results of the examination of the spinal and ventricular fluids were carefully studied both before and after each injection. In none of these cases were there any symptoms of an alarming nature after the injections. Few patients showed even a slight rise in temperature, and none remained in bed longer than three days. Two of the thirteen, Patients 9 and 10, died, not from the effect of the operation but months after their final injection, dying in the terminal stage of paresis. Two other patients, one of whom received only one injection, were unimproved and have since been committed to asylums. The remaining nine have shown decided improvement, not simply in the serology, but from a clinical standpoint. They are much less emotional, their memories are better, they are

improved physically and mentally, and they are still improving.

In five of the nine (Cases 4, 5, 6, 7 and 8), there has been an exceptional improvement. These five patients have been able to return to their work and are now self supporting. They had been unable to work before coming to us for from three to eighteen months. Following injection and the period of several months' rest we advise after treatment, they have now been at their work for from five to eighteen months. Although two of these patients appear to be entirely normal and have been working steadily for more than a year, it is still too early to assert that any of them are cured. A period of three years, and possibly five years must elapse, without deterioration, before they can be considered free from danger of recurrence.

Our experiments on animals, as reported in the first paper, have shown that fluid introduced into the ventricle reaches all portions of the cortex of the brain and cord and has a much greater spread and diffusion than one introduced by any other method. It is only natural, therefore, that the improvement noted in these cases is such as has never before been obtained in any series of cases.

Not one of these thirteen could be termed an early case. The observed symptoms had existed for from six to twenty months. In several, however, the deterioration was but slight, and it is in these cases that we have obtained the maximum improvement.

In regard to the physical signs, naturally we have not been able to influence the Argyle Robertson pupil or to any extent the increased reflexes. However, we have seen the tremors of the face and tongue and dysarthria, if moderate, disappear after treatment.

Beginning with 0.6 mg. of salvarsan in the first case, we have gradually increased the strength of the serum until now we are giving double the initial dose. We do not know yet whether or not we have reached the maximum dose, or whether we are timing the injections so as to obtain the best results. It has been our custom to give the second injection a week or ten days after the first, and the third injection two weeks later. There is no positive reason for this, and it is purely tentative. Probably in the light of future experience, we may find it better to give it at different intervals. Probably we shall find it necessary to give more than three injections at first, and then, after several months, to give in some cases another series of injections. These are points that can be determined only by a wider experience and many more cases.

The harmlessness of the operation and the excellent results so far obtained lead us to urge that this form of treatment be universally adopted in the early stages of the disease. We have not found, and do not believe, that it has any effect in even retarding advanced cases. But it certainly seems to us that in the beginning of the disease, before serious changes have taken place in the cerebral structure, it holds out the best hope of improvement, and perhaps permanent stoppage of the disease, that we know of today.

SURGICAL ASPECTS

The operative technic which we are now using is the same as that described in the first paper. It is reasonably simple, has proved entirely safe, and we have seen no reasons for changing it. The time required for an intraventricular injection by this method varies from twenty to thirty-five minutes, the greater part of which is consumed in the gradual

1. Hammond, G. M., and Sharpe, Norman: The Treatment of Paresis by Injections of Neosalvarsan into the Lateral Ventricle, *THE JOURNAL A. M. A.*, Dec. 18, 1915, p. 2147.