weight. Injections were usually repeated on subsequent days and occasionally twice a day. Thirty-one animals were treated and 39 served as controls.

Tryparsamide was given in doses of 0.05 gm. per kilo intravenously to 3 guinea pigs, intraperitoneally in 2, and subcutaneously in 1. A record of a guinea pig treated intravenously is shown in figure 1 A. Triphal was given in doses of 0.125 gm. to 6 animals intravenously. Germanin was given intravenously to 11 guinea pigs in doses of 0.2 gm. and metaphen in 1 cc. doses to 6 animals intravenously and to 2 subcutaneously.

To date we have observed the febrile reaction in 140 guinea pigs.

Results. In none of the animals thus treated could any effect of therapy be detected in the temperature curve. In all cases the temperature curve differed in no material respect from that of the untreated control animals.

Conclusion. Germanin, metaphen, triphal, and tryparsamide had no effect on the course of spotted fever in guinea pigs, when administered therapeutically.

6011

Penetration of Antipneumococcic Horse Serum into the Consolidated Lung in Lobar Pneumonia.

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In analyzing the action of antipneumococcic serum in the treatment of lobar pneumonia, the question of its penetration of the pneumonic lung is often raised. The clinical observation that specific therapy is effective early in the disease and ineffective late in the disease has sometimes been explained on the basis of the accessibility of the pneumonic area to circulating antibodies in the initial stages of consolidation and a lack of penetration after complete consolidation has taken place. Studies of the circulation in the pneumonic lung have usually supported this view. Mallory[1] believed from the study of pathological histology, that in the stage of gray hepatization the air sacs became distended and the capillaries compressed so that they no longer appear engorged. Kline and

Winternitz,[2] using vital staining methods with trypan blue, concluded that there is a marked impairment of circulation in the pneumonic lung, resulting from the wide distribution of capillary fibrin thrombi formed early in the consolidated area, and that this impairment of circulation in the pneumonic lung seriously interferes with the action of intravenous therapy upon the local lesion. Gross,[3] using injections of a barium sulphate emulsion in gelatine, noted that the consolidated lung of lobar pneumonia shows poor injection with compensatory injection in the non-consolidated lung. Coryllos and Birnbaum,[4] however, using iodized oil for arterial circulation and Ringers' solution and india ink for capillary circulation in the consolidated lung of the dog, concluded that "Only the capillary circulation was involved. Circulation in the pulmonary arterial tree is not affected. The capillary impairment is not complete."

It was felt that inability to inject the vascular bed in human pneumonic lungs was not conclusive evidence of marked impairment and the possibility remained that intravenously injected serum might penetrate into the consolidated area. The apparent maintenance of nutrition in the lung tissue, as evidenced by its quick return to normal after the crisis without abscess formation, suggests that no complete circulatory embarrassment occurs.

A number of workers have detected intravenously injected horse serum in the body fluids and organ extracts by means of specific precipitating antihorse sera. Hamburger and Moro,[5] Uhlenhuth and Weidanz,[6] Dean, Goldsworthy, and Ten Broeck,[7] among others, observed its presence in the blood serum. Menkin[8] studied the fixation of horse serum at the site of inflammation in the skin and peritoneum of the rabbit. He found the horse serum in greater concentration at the site of inflammation than in normal tissues.

In the present study the blood serum, and extracts of the consolidated and unaffected lung and of the liver, kidney, and spleen, all obtained at post mortem from patients with lobar pneumonia who

[1] Mallory, F. B., Principles of Pathological Histology. Philadelphia, W. B. Saunders Co., 1914, 472.

[2] Kline, B. S., and Winternitz, M. D., *J. Exp. Med.*, 1915, **21**, 311.

[3] Gross, L., *Canadian Med. Assn. J.*, 1919, **9**, 632.

[4] Coryllos, P. N., and Birnbaum, G. L., *Arch. Surg.*, 1929, **19**, 1346.

[5] Hamburger, F., and Moro, E., *Wien. Klin. Woch.*, 1903, **16**, 445.

[6] Uhlenhuth, P., and Weidanz, O., *Kraus and Levadittis Handbuch*, Jena, Fisher, 1909, **2**, 819.

[7] Dean, H. R., Goldsworthy, N. E., and Ten Broeck, C., *J. Immun.*, 1930, **18**, 95.

[8] Menkin, V., *J. Exp. Med.*, 1930, **52**, 201.

had received intravenous antipneumococcic serum therapy just previous to death, were examined for their content of horse serum. The 3 patients died 11, 4½, and 9½ days respectively following the onset of pneumonia.

Methods. 1. *Preparation of organ extracts.* Organs were removed at autopsy, 3 hours, 1½ hours, and 28 hours, respectively, after death. Contamination with tissue fluid and with pleural or peritoneal fluids was avoided, as far as possible. The organs were placed on clean dry towels and the surfaces wiped free of exuded blood and tissue fluid. They were then sectioned and blocks of centrally located tissue were selected. In the case of the lung, specimens of gray hepatization, red hepatization, and normal lung were taken. Blood from the heart was secured, in order to obtain serum. Forty grams of each of the selected tissues were ground with sand in a mortar, first dry and then with the addition of sterile normal salt solution until 20 cc. had been added. This mixture was centrifuged and the clear supernatant fluid was filtered through a Berkefeld V candle, under sterile conditions. These extracts were kept in cotton-stoppered test tubes at ice box temperature.

An antihorse rabbit serum was used to detect the presence of horse serum in the organ extracts. Rabbits were immunized with 6 doses of 0.5 cc. normal horse serum, subcutaneously, at weekly intervals, and bled 8 days after the last dose. The sera from several animals were pooled, passed through a Berkefeld filter and kept in sealed tubes. This serum gave a precipitate with normal horse serum in a dilution of 1:15,000 and with Felton's antipneumococcic serum in a dilution of 1:10,000. Two-tenths cc. of varying dilutions of the extracts were added to equal amounts of antihorse rabbit serum, incubated for 2 hours at 37°C., and read after over-night ice box storage. Pooled normal rabbit serum, obtained from the same rabbits before immunization, and normal salt solution were used as controls. Soluble specific substance was detected in the organ extracts in a similar manner, using Types I, II, and III antipneumococcic sera in each instance.

The titres of demonstrable horse serum in the post mortem sera and organ extracts are shown in the accompanying table. Liver extracts were unsatisfactory because of non-specific reactions in the normal saline controls. Tests with extracts of spleen were omitted from the table, as they gave nonspecific reactions with both normal serum and saline controls. A comparison between unaffected and consolidated portions of the same lung shows that in 2 cases the same amount of horse serum was present; in the third (Case III),

Case No. Age	Time of Treatment First dose	Time of Treatment Last dose	Amount Anti-pneumococcus Serum cc.	Autopsy Date Time	Autopsy Hours after Death	Organ	Culture At Autopsy	Tests for Horse Serum with Anti-Horse Rabbit Serum: Antihorse Rabbit Serum	Normal Rabbit Serum Control	Saline Control	Tests for S.S.S. with Specific Typing Sera Type I
						Post Mortem Serum	Pn. Type I	1:128	0	0	—
						Normal Lung	Negative	1:32	0	0	—
I-33	4/8 3:30 P.M.	4/13 1:00 A.M.	276	4/13 1:00 P.M.	3	Gray Hepatization L.L.L.	Pn. Type I	1:32	0	0	1:128†
						Kidney	——	1:32	0	0	0†
						Liver	——	1:4	0	1:16*	1:8†
						Post Mortem Serum	Negative	1:128	0	0	0†
						Normal Lung	Pn. Type I	1:16	0	0	1:8†
II-66	3/7 10:00 A.M.	3/7 1:00 P.M.	30	3/7 4:00 P.M.	1½	Gray Hepatization L.U.L.	Pn. Type I	1:16	0	0	1:64†
						Kidney	——	1:16	0	0	1:8†
						Liver	——	1:4	±	1:16*	1:8†
						Post Mortem Serum	Pn. Type I	1:256	0	0	0†
						Normal Lung	Negative	1:64	0	0	0†
III-45	2/16 12:00 P.M.	2/23 2:00 A.M.	295	2/24 4:00 P.M.	28	Gray Hepatization R.L.L.	Pn. Type I	1:32	0	0	1:8†
						Kidney	——	1:128	0	0	—
						Liver	——	1:16*	1:16*	1:16*	0†

* Nonspecific Reactions. † No reactions were obtained with Type II and Type III.

however, there was a slightly higher titer of precipitinogen in the non-consolidated portion. The concentration of horse serum in the kidney was the same as that in the unaffected lung in each case.

Type specific pneumococcic antigen was demonstrated in considerable concentration in all the consolidated lung extracts. It was also found in lower titer, once in normal lung extract, once in kidney extract, and twice in liver extract.

Discussion and summary. It has been shown that horse serum administered intravenously before death to patients with lobar pneumonia is present after death in the consolidated lung in a concentration similar to that in which it is found in unaffected organs. The short time elapsing between death and autopsy in 2 of these cases makes it seem likely that the post-mortem finding represents a condition present during life. No evidence was obtained as to the mode of penetration of the horse serum. Due to the lack of conclusive proof of circulatory occlusion in the pneumonic lung it is possible that the foreign serum entered and was contained wholly within the blood vessels. On the other hand, the foreign serum may have diffused through cellular membranes to such an extent as to penetrate a region in which little or no blood circulation was active. No increase in concentration was found in the consolidated lung which would correspond to the increase noted by Menkin[8] in local inflammatory areas, but this might be explained by the local impairment of circulation. In any case, the finding of the foreign serum within the consolidated lung, together with the penetration of foreign serum into pleural exudates, as shown by Finland,[9] suggests that therapeutic sera are active in lobar pneumonia at the site of the lesion.

Such penetration of therapeutic serum into the consolidated lung is of theoretical and practical significance. In the experiments above, the consolidated lung and other organs containing horse serum also contained type-specific precipitinogen, indicating that the latter was not completely neutralized. The relative lack of therapeutic effect of antipneumococcic sera late in the course of the disease may be due, not to the lack of penetration of antibodies, but to this accumulation of type-specific antigen. It seems possible that antibodies, if present in sufficient concentration, would neutralize all of the type-specific antigen. Whether or not the use of high concentrations of antibodies with a possible complete neutralization of the type-specific antigen would be effective in all advanced cases can not be judged without actual trial since other factors, such as antigens or

[9] Finland, Maxwell, *J. Exp. Med.*, In Press.

toxins not neutralized by the antiserum or irreparable toxic damage, may be present. A logical justification, however, for attempts to produce very potent antibodies is apparent.

6012

A Quantitative Relation Between the Chloride and Acid Concentrations in Gastric Juice.

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Examination of the literature on the chloride content of gastric juice shows that the usual method for the study of such data depends on their being plotted against the time which elapsed between stimulation and collection of the fluid. Correlation of total chloride and acidity is made by direct visual comparison of such time curves. Regarding the existence of a relation between these 2 variables, 3 different conclusions have been reached: (1) that the total chloride concentration is constant throughout any one experiment. (2) Significant variations do occur, but they are always smaller than the concomitant changes in acidity and bear no relation to the latter. (3) A parallelism exists between such acidity and chloride curves. In the present investigation, decisive evidence is offered for the existence of an exact quantitative relation between the concentrations of acid and total chloride, and an explanation is offered to account for the differing conclusions of other investigators.

Experiments with 5 Pavlov pouch dogs were performed in the usual way. In almost every instance, the chloride values fluctuated within such narrow limits that they gave a distinct impression of constancy. In only 2 of the 19 experiments was the total range greater than 10mM. When the 2 variables were each plotted against the time, an unmistakable parallelism of the 2 curves was noted in 12 of the experiments. In the remainder, the occurrence of such a parallel relation may have been hidden by the combined influences of high experimental errors and a small range in acidity values. These experiments, therefore, support the notion of a parallelism between the chloride and acid curves; they also suggest an explanation for the failure of other investigators to observe this relation.

Such a parallelism may be indicative of a quantitative relation