INTRA-PERITONEAL THERAPY IN THE DISEASES OF CHILDREN

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The administration of fluids or drugs to infants and children may be a matter of difficulty. Vomiting or refusal to take fluids often hampers oral administration. Hypodermoclysis is painful and its possibilities are limited. Fluids administered by rectum are not retained, and the small veins make intra-venous injections impracticable except by exposure of the vein. Thrombosis usually follows and the limited number of veins available prevents frequent repetition of the procedure. Blackfan and Maxey¹ first advocated intra-peritoneal injections as a means of supplying fluid. Intra-peritoneal injection also furnishes a method of supplying food to the child and a route for therapy. The method of intra-peritoneal therapy is a practical one. Much larger amounts of fluid may be given intra-peritoneally than intra-venously or subcutaneously, and this procedure also throws less strain on the heart than does intra-venous injection.

A definite physiological basis for intra-peritoneal therapy has been shown by studies of absorption from the peritoneum. Buxton and Torrey² were able to recover nucleated blood cells from the mediastinal lymph nodes of guinea pigs, fifteen minutes after their intra-peritoneal injection. Bolton³ using lamp black and bacteria concluded that the drainage might be mechanical, the force being supplied by the respiratory movements. Cunningham⁴ in an exhaustive study of absorption from serous membranes, found that in cats a solution of washed nucleated blood cells, carbon particles and lamp black reached the anterior mediastinal lymph nodes in three minutes. The foreign cells were not phagocyted but moved freely into the surface cells of the diaphragm. It has thus been well established that materials injected into the peritoneal cavity are taken up by the body with extreme rapidity and without harm to the organism.

The route by which fluid and material injected into the peritoneal cavity reach the circulation has occasioned considerable interest. Poynter⁵, studying the absorption of colloids, bacteria and particulate matter, concluded that the venules of the omentum were the more important avenues because various colloidal particles have been recovered from the portal blood and the liver.

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Brown⁶ found in rabbits that the main path of absorption from the peritoneal cavity was by the thoracic duct, but that in dogs and cats this played a subsidiary part. Higgins and Graham⁷, studying the removal of bacteria and foreign substances from the peritoneal cavity, found that the pulmonary lymphatic routes were the most important avenues of absorption.

Injection of fluids.—In 1918 Blackfan and Maxcy reported the use of physiological sodium chloride solution intra-peritoneally in seven cases of vomiting and diarrhoea in infants. This method has been used widely since then with good results. Marriot⁸ pointed out that sodium chloride was possibly irritating to the organism that was dehydrated, and advocated the use of dextrose, this being non-irritating and a food as well. Six per cent. dextrose solution was used almost exclusively for the next two years. Beginning with Maches⁹ in 1921 various reports began to appear in the literature of glucose shock. This reaction varied from temperature and distension to cyanosis and death. These results almost led to the abandonment of dextrose solution for

TABLE 1.

RESULTS OF INTRA-PERITONEAL INJECTIONS OF DEXTROSE INTO INFANTS AND YOUNG CHILDREN.

Disease	Cases	Total injections	Deaths
Severe dehydrating diarrhoea	25	250	1
Decomposition	3	18	..
Lobar pneumonia	8	24	..
Broncho-pneumonia	14	56	4
Pyelitis	6	22	..
Tonsillitis	14	42	..
Post-operative : 3 intussusception, 1 peritonitis	4	12	1
Syphilis : dextrose, neoarsphenamine	2	8	1
Total	76	432	7

intra-peritoneal use. In 1922 Williams and Swett¹⁰ found that solutions of dextrose rapidly become acid on autoclaving, and for reducing this acidity, they advised buffering the solution. Solutions so buffered were used with success intra-venously by Stoddard¹¹. Sanford and Heitmeyer¹² in a study of the effect of dextrose solution on dogs found that reactions from intra-peritoneal injections increased in intensity with the length of time following sterilization of the solution. For example, a solution of dextrose which had been sterilized 3 hours before would show reactions following injection. These varied from simple distension to severe shock when specimens that had stood a longer time were used. They overcame this tendency to acid formation by autoclaving the dextrose dry and dissolving in distilled water. Either of these methods renders solutions of dextrose safe for intra-peritoneal injection. The varied uses of this form of therapy can best be illustrated by the table of Grulee and Sanford¹³ (see Table 1) of cases in which it was used.

The method of administering dextrose solution intra-peritoneally is usually by a 100 c.cm. Luer syringe. Small infants receive a correspondingly smaller

amount. The injections are made to cease just at the point of distention. Five per cent. dextrose solution is the best concentration as higher concentrations tend to draw the body fluids into the peritoneal cavity. Narat¹⁴ has confirmed this practical observation.

Intra-peritoneal injections of glucose should never be given in larger quantities at one injection than 100 c.cm., but as this amount is only about half the usual fluid intake of a child at one feeding, the injection, to be effective, must be repeated frequently. It is rather astonishing how rapidly the fluid is absorbed. In the series of cases given above, one child was given six intra-peritoneal injections of 100 c.cm. 5 per cent. dextrose solution daily for four days. The maximum number of injections in this series was 24, and the average number 6.

It may be said in summarizing the use of intra-peritoneal injections of fluid, that 5 per cent. dextrose solution is a useful method of providing food and fluid to the child. If the dextrose solution is buffered or dry sterilized no harmful reactions will take place. It is indicated in all dehydrating conditions, such as diarrhoeas, decomposition, and other nutritional disturbances, and at times in certain infections such as lobar and broncho-pneumonia, tonsillitis and pyelitis, and in post-operative conditions.

Injections of blood.—In 1923 Siperstein and Sansby¹⁵ reported their experiments and clinical results with the injection of citrated blood intra-peritoneally. Many authors have since substantiated these initial results, in particular Opitz and Metis¹⁶, McKhann¹⁷ and Ruh and McClelland¹⁸.

The method of carrying out intra-peritoneal blood transfusion is simple. It is possible that blood grouping is not necessary in this type of transfusion, but it is usually done. Cross-agglutination is the procedure of choice, but in an emergency there need be no hesitation in giving blood from a donor of the same group as the recipient or a universal type-four donor. Obviously, a Wassermann test should be made on all donors.

All that is necessary for an intra-peritoneal blood transfusion is a 100 c.cm. Luer syringe, two 18-gauge needles, an adapter with about 12 inches of rubber tubing, and some sterile 2·5 per cent. sodium citrate solution. Injections are best made as with dextrose solution, the amount depending on the size of the child, with 100 c.cm. of blood as a maximum, giving repeated injections as necessary. Approximately 0·5 c.cm. of sodium citrate solution should be used for each 10 c.cm. of blood. One of the needles is attached to the syringe and the calculated amount of citrate solution drawn into it. The plunger is withdrawn to its full extent and the citrate solution forced back through the syringe and into the needle again. The entire interior of the syringe is thus bathed in citrate solution and the needle bore is also full. The blood is then withdrawn aseptically from the donor, the needle changed to the one with the rubber holder and the blood is then injected into the surgically prepared abdomen.

There is little or no reaction from these injections. Moderate distension and abdominal distress are usually traceable to old citrate solution. We believe that reactions of any kind are due to a citrate reaction, and it is our practice to give intra-peritoneal injections of whole blood where possible. This

requires considerable speed and experience, and should not be attempted until the citrate method has been used many times to perfect technique.

The uses of intra-peritoneal blood transfusions are best shown by the excellent report of Cole and Montgomery¹⁹ who did 237 transfusions in 197 cases. In their series there were 5 cases of primary anæmia with 16 injections; 77 cases of secondary anæmia (27 being due to nutritional disorders and 50 associated with infections) with a total of 162 injections; 8 new-born and premature with a total of 15 injections; and 27 toxæmias, with a total of 44 injections.

The most spectacular results are obtained in secondary anæmias, where medicinal and dietary treatment is discouraging. The response to repeated small intra-peritoneal blood injections is very satisfactory. The hæmoglobin and red cells rise rapidly. In a case of secondary anæmia of nutritional origin, at the time of the first transfusion, the hæmoglobin was 30 per cent. (Dare); after 3 weeks following a total of three transfusions it was 65 per cent. (Dare) and the red cells had risen from 3,200,000 to 4,500,000. Excellent results are also obtained in toxæmias and septicæmias, in new-borns suffering from hæmorrhagic diseases or other debilitating conditions, and in the anæmia of prematures.

The contra-indications for intra-peritoneal transfusion are the same as for any other type of transfusion, with the addition that it should never be used when there is any intra-abdominal disease or when any abdominal distension might embarrass the respiration—as in severe cardiac disease or in the acute stages of a severe pneumonia—it cannot, of course, rapidly replace blood volume in shock or hæmorrhage. When it can be effected, intra-venous transfusion is unquestionably the method to be preferred, but the small veins in the child and the inadvisability of repeated transfusions make this method difficult. Intra-peritoneal blood transfusion of small amounts, frequently repeated, is safe, effective in comparison with intra-venous transfusions, shows fewer reactions, and above all is so simple of operation that its therapeutic usefulness is greatly extended.

Medication.—The ease of administering fluid and nourishment intra-peritoneally has led as a consequence to the use of various drugs in this way.

ANTI-SYPHILITIC DRUGS.—One of the best examples of this is in the treatment of congenital syphilis. The various forms of treatment of the child can be limited to the use of mercury inunctions or by mouth, potassium iodide, bismuth mixtures or the arsenical compounds. While many satisfactory results have been obtained with bismuth mixtures, it seems from present knowledge that the arsenical compounds will probably continue to give the most satisfactory results. Administration of the arsenical compounds to a child, however, is difficult. Intra-muscular injections are often accompanied by the formation of abscesses and the ideal procedure of giving intra-venous injections is hampered by the small size of the available veins in the infant and the resultant difficulty of injection.

Any method that will offer an easy means of administration, combining safety with rapidity of action, should be the procedure of choice. Rosenberg²⁰

was the first to report a case in which arsenic was injected intra-peritoneally. In 1925 Sanford²¹ reported the results of animal experiments and also the treatment of ten patients by this route. This work on animals was done to study particularly the absorption and irritation that might take place in the abdomen from neo-arsphenamine injection. It was found that a proper point of injection was essential. In dogs all injections into the upper quadrants of the abdomen caused permanent changes. These were adhesions of the omentum to itself, to the parietal peritoneum, to the intestine and to the mesentery. Injections into the lower quadrants did not cause local changes and were free from adhesions.

The method of administration of the neo-arsphenamine intra-peritoneally consisted of preparation of the abdomen with green soap and alcohol. The ideal site for entrance of the needle is located in the middle of the sheath of the left rectus, slightly below the level of the umbilicus. This spot was chosen because experiments on animals showed that it is necessary to go below any possible limit of the omentum. It must be remembered that a site too far below the umbilicus will endanger the bladder. For this reason, as in many children with syphilis the liver is at the level of the umbilicus on the right side, the middle of the sheath of the left rectus, slightly below the level of the umbilicus makes an ideal site for injection. A solution made up of 150 mgrm. of neo-arsphenamine dissolved in 15 c.cm. of warm sterile distilled water was used. The average child of 10 pounds (4.5 kgrm.) should receive 50 mgrm. of neo-arsphenamine or 5 c.cm. of the solution. It should be emphasized that the needle must be pushed well through the peritoneum and into the peritoneal cavity. The solution is then injected as fast as the plunger will fall in the syringe, and sprayed over the peritoneal contents.

Grulee, Sanford and Waldo²² reported 25 cases thus treated, and since that time 25 more cases have been added. The usual treatment consisted of four injections at three-day intervals followed by four injections at seven-day intervals, the same dose being used each time. This is usually sufficient to clear whatever clinical pathological condition due to syphilis exists, including the Wassermann reaction. The child is then turned over to the out-patient department for observation and returned to the hospital at the end of one month, when another Wassermann test is made and roentgenograms are taken. If there is any further evidence of syphilis at this time the children are rechecked at six months and again at one year.

Of the fifty patients thus treated, two were given neo-arsphenamine intra-peritoneally as provocative tests following anti-complementary and split Wassermann reactions. These reactions cleared up after one injection; of the remaining 48 patients, 35 (73 per cent.) were pronounced clinically cured, with negative Wassermann reactions, and negative roentgenograms. 6 patients (12 per cent.) showed distinct clinical improvement, but were removed from the hospital by their parents before treatment could be concluded. 7 children (15 per cent.) died during treatment; only one of these deaths could be attributed to the form of treatment.

This child had a severe case of syphilis and was in bad condition. She was 2 months old and weighed 5½ lb. (2.4 kgrm.). She received seven injections during which time she gained

2½ lb. (1.0 kgrm.). By mistake the eighth injection was given into the sheath of the rectus instead of into the abdomen. An abscess developed in three days and the child died eight days later. Autopsy showed an abscess 4.5 cm. by 2.5 cm. in the muscular layer of the abdominal wall, containing thick, grayish-green, fibro-purulent exudate, with lepto-meningitis of the entire surface of the brain. By cultural methods, *B. coli* and *streptococcus viridans* were isolated from the spinal fluid and the abdominal abscess. Whether the poor condition of the child resulted in a lowered resistance is uncertain.

A similar accident happened two years later. This child weighed 10 lb. (4.5 kgrm.) and was in much better condition. As much of the arsphenamine solution was sucked out of the rectal sheath as possible, and 10 c.cm. of 10 per cent. sodium thio-sulphate solution were injected back into the site of the former injection. No abscess formation occurred, nor did the child show any disturbance of any kind. It is clearly shown, however, that intra-peritoneal injections of neo-arsphenamine are not without danger if care is not taken in placing the needle in the abdomen.

The experience of four years has led us to conclude that intra-peritoneal injection of neo-arsphenamine is a rational therapeutic method for treating congenital syphilis. It is especially indicated in conditions in which rapidity of action is required, and the small veins of the child make intra-venous injection impossible.

The rapidity of action is best shown in two cases of hæmorrhagic syphilis in which this treatment was used.

The first patient was a child, aged 4 weeks, who had hæmorrhage from the cord, nose and anus, with a bleeding time of 1 hour and 50 minutes and a coagulation time of 17 minutes. This child did not improve when given whole blood intra-peritoneally and intra-muscularly. The bleeding time continued to be 1 hour and 20 minutes, with a coagulation time of 11 minutes. Two hours after neo-arsphenamine had been given intra-peritoneally the bleeding stopped, and the coagulation time fell to 6 minutes and the bleeding time to 40 minutes. After another injection, the bleeding time fell to 3 minutes and coagulation time to 5 minutes.

The second case was one of hæmorrhagic syphilis complicating lobar pneumonia. The coagulation time in this instance was 4½ minutes and the bleeding time 77 minutes. After 40 c.cm. of mother's whole blood was given, the coagulation time fell to 4 minutes and the bleeding time to 48 minutes; two hours after neo-arsphenamine was given intra-peritoneally, the coagulation time was 4 minutes, and the bleeding time 5 minutes.

We feel justified in saying from the experience with fifty cases that intra-peritoneal injection of arsphenamine is indicated in the treatment of children who have congenital syphilis, where rapidity of action is desired and the small veins make intra-venous injection impossible.

DIPHtheria ANTIToxIN. In 1917 Fonde²³ first reported giving diphtheria antitoxin intra-peritoneally in a case of malignant diphtheria. No particular attention appears to have been paid to this method until 1921, when Goehle and Dauer²⁴ used antitoxin mixed with saline solution intra-peritoneally in 5 cases. Platou²⁵ used a specially prepared globulin antitoxin in 12 cases. He advocated this method particularly because of its rapidity of absorption. To quote his own words, 'the striking difference in the two methods is manifest in the first seven hours, the time of greatest importance. Within an hour after intra-peritoneal injection the blood is appreciably antitoxic, and up to seven hours the absorption is about five times that of intra-muscular injection.' Toomey, Goehle and Dauer²⁶ used undiluted antitoxin just as received from commercial houses intra-peritoneally in 168 cases of diphtheria. They consider

that antitoxin given intra-peritoneally is a safe and simple method. It is the method of choice in cases complicated by toxic myocarditis, as there is no reaction to foreign protein. It is in this type of case that a reaction such as a chill, fever, and the like, can cause a shock to the damaged heart muscle that may be fatal. Beside the advantages of rapid absorption and absence of reaction, there was almost no pain following injection: for these reasons they believed that intra-peritoneal use of diphtheria antitoxin has a definite therapeutic value. We have had no experience of this form of therapy.

IRON. During the past year we have been carrying out experiments on animals as to the advisability of intra-peritoneal iron injections. In rabbits the paths of absorption of iron are two. A considerable amount is taken up by the lymph glands of the mesentery and passes into the thoracic duct. This iron is mostly eliminated through the kidneys and cæcum. Another part of the iron is taken up by the macrophages from the material in the peritoneal fluid, which is deposited on the mesentery and peritoneal organs. These macrophages eventually penetrate between the endothelial cells and enter the lymphatic vessels of the sub-serous tissue. The iron finally reaches the liver and is found in the Kupffer cells of the liver in about 45 days. There was no particular rise in the hæmoglobin of normal animals. Those made anæmic by bleeding did not regenerate any faster after intra-peritoneal iron injections than those who did not receive it. It appeared that any benefit to the organism must take place after at least one month.

This work is still in the experimental stage, but so far six children have received injections of intra-peritoneal iron. Our method is to give eight injections of 5 c.cm. of colloidal iron, or two injections a week for one month. This means 8 mgrm. of metallic iron in the colloidal state as $\text{Fe}(\text{OH})_3$. There will be no apparent change in the hæmoglobin for this entire period. At the end of this time there will begin to be a rise in the hæmoglobin of about 5 per cent. a week (Newcomer). There is also a slow increase in the red cells.

We believe that in secondary anæmias intra-peritoneal injections of colloidal iron are of benefit, but should not be relied upon entirely. Our plan at the present time is to give one or two intra-peritoneal injections of whole blood at once, and let the child receive the immediate effect of this. At about the time that the effects of this are beginning to decrease, the iron will begin to be utilized by the organism.

Conclusions.

1. The dangers of intra-peritoneal therapy may be grouped under three heads. (a) Infection: it is conceivable that infection may be introduced from improper, or rather insufficient, sterilization of the skin, instruments, or materials injected. Such certainly would seem to be remote possibilities if proper care is used. Peritonitis might result from puncture of the intestine or bladder. This has never happened to us, and seems a very remote possibility. On the other hand there is real danger of metastatic infection in the peritoneal cavity from infection elsewhere in the body, especially following an intra-peritoneal transfusion of blood.

- (b) Too large quantities may result in pressure on the diaphragm with resulting syncope, especially if there is abdominal distension present.

(c) Reaction of an untoward nature may follow injection, especially if care is not used in the preparation of the material to be injected. Such reactions usually consist only of slight rise in temperature and distension. The reaction at times, however, is much more serious, with collapse and in rare instances death.

2. The disadvantages are chiefly those of somewhat delayed absorption. This is especially evident in the case of red blood corpuscles. The material injected usually, however, is rapidly absorbed as is shown in the cases of syphilis cited above. The rate of absorption, of course, varies with the condition of the patient, but from all the evidence we have, it is quite rapid.

The greatest barrier to overcome is, however, the psychical one. Owing no doubt to early surgical training we fear the peritoneal cavity, and its use suggested above is inclined to startle us, even after the proof of its efficacy and relative harmlessness is shown.

3. The advantages seem quite obvious if the cases be properly chosen. Oral and rectal administration of fluids is often quite ineffective when their ingestion is most needed, and the supply that can be given subcutaneously or even intra-venously is entirely inadequate to meet the demands. In many cases of anæmia any therapy except transfusion of blood is of no avail, and where this has to be repeated often, as is frequently the case, the intra-venous route is impossible and the intra-peritoneal must be employed. Two facts stand out, however, as distinct advantages. The reactions are certainly fewer and slighter than in intra-venous injections, and the simplicity of the procedure is such as to make it applicable for almost universal use.

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