RECENT THERAPEUTIC ADVANCES IN SURGERY.

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The elucidation of the problems connected with antiseptics and asepsis led to great advances in surgical technique and surgeons focussed their attention upon the art of surgery. Lord Moynihan, surveying what had been accomplished in the past and indicating the next phase in the development of surgery, summed the position up by stating that "modern aseptic surgery has made the operation safe for the patient. It is now the aim of surgery to make the patient safe for the operation." Surgical technique is capable of still greater development and operations are being conducted on organs which were once regarded as beyond their scope. The development of the surgery of the heart is an illustration of recent endeavour. It is necessary, however, that greater attention is devoted to physiology and to the changes which occur in bodily function when disease is present. A greater conception of pathologic physiology will certainly lead to advances in the management of a patient suffering from a disease in which surgical interference plays a part in the treatment, but the operation is merely an incident during the course of the treatment. It would appear that the art of surgery has progressed further than the science of surgery, but the deficiency is being repaired rapidly. The two components must not be separated from each other and it is essential that they march forward together.

The application of these principles in practice will undoubtedly lead to a great saving of life and the mortality from operation will be lowered. In many conditions surgical interference is not necessary immediately and the time and care expended during the pre-operative period will assuredly minimise the risks incurred in, and the length of, the post-operative period. The patient must come to the operating theatre in the best possible condition, both psychologically and physically. In the attainment of this ideal, recent researches in the physiological field have contributed knowledge of primary and practical importance. The object of this paper is to indicate certain advances which have been made.

Tissue Nutrition. Malnutrition of tissues is a commoner condition than has been supposed in the past and its effects are profound in their character. A better understanding of both the fluid and electrolytic requirements of patients has been an outstanding development in recent years.

Dehydration. In this condition there is a diminution in the volume of the water of the body and it is a common accompaniment of many surgical conditions. The loss of water occurs, in the first instance, at the expense of the interstitial fluid, and secondly from the blood plasma. Dehydration often results from surgical operations on account of vaporization, vomiting, hæmorrhage and other factors. It has been found that the usual loss of fluid during operation and the following four hours is of the order of 1000 cc. In some conditions no fluid is allowed by mouth following operation and thus the water in the body is still further depleted. If dehydration is allowed to persist the blood volume is diminished, the concentration of the blood increases and anoxæmia of the tissues with its ill-effects is brought about. A vicious circle may be established resulting in further losses of fluid from the circulating blood, a decline in blood-pressure and life may be threatened. It is advisable to give patients who can take fluids after the first day following an operation, 2000 cc. of normal saline by the rectal or subcutaneous routes. In patients who cannot take fluids by mouth, and in the presence of severe dehydration, seven litres of fluid should be given over a period until it is corrected, thereafter a smaller amount of fluid is required. A sufficient amount of fluid is given to ensure a daily output of urine amounting to 1500 cc.

Consideration must be given to the type of fluid which is given. In severe dehydration there is impaired renal function and glucose is required ; this is given as a 5 per cent. solution of dextrose in distilled water. If sodium chloride is required, a 5 per cent. solution of glucose-saline is administered. When severe acidosis exists, sodium bicarbonate is given in addition. Patients who are vomiting or losing gastro-intestinal secretions by other means require saline.

Coller and co-workers have devised a method to determine the amount of saline which these patients require. The plasma chlorides are estimated and for each 100 mg. per cent. the plasma chlorides require to be raised to reach the normal of 560 mg. per 100 cc., the patient should be given 0.5 gm. of sodium chloride per kilogram of body weight.

Care must be taken not to administer an excessive amount of fluid, especially by the intravenous route, owing to the risk of pulmonary oedema and cardio-vascular complications. Careful observations must be made of the balance between fluid intake, fluid output and the chloride content of the urine. In the presence of damaged capillary walls as in secondary shock the administration of solutions of crystalloids is contra-indicated, as the fluid quickly escapes into the tissue spaces causing oedema and it depletes the plasma proteins by carrying them with it into the tissues.

Acid-base disturbances. Acidosis may develop as the result of alkali deficiency brought about by the loss of alkaline fluids from the body, or it may be caused by excess in acid from the incomplete oxidation of fat. An example of the first condition is diarrhoea, and it is corrected by restoring the fluid and the base. If food and fluid are withheld from a patient for several days before and after operation, acidosis is very liable to follow. Treatment consists in the administration of fluid, base and glucose. If diabetes mellitus is present, insulin therapy will be required in addition. Children frequently develop acidosis following operation, and it is corrected by dextrose and sodium chloride solution.

Alkalosis occurs as the result of prolonged vomiting, biliary and duodenal fistulae, high intestinal obstruction, and sometimes after excessive alkali therapy for peptic ulceration. The treatment of alkalosis consists in the administration of sodium chloride solution, the correction of dehydration, and any abnormality present should be dealt with.

Hypoproteinaemia. The plasma proteins play an important part in the regulation of the water balance of the body. The blood proteins attract and hold fluid in the blood stream. They are reduced in conditions such as burns, injury to large masses of tissue, and malnutrition. If the intake of water and food is restricted in disease of the gastro-intestinal tract, hypoproteinaemia may develop. Many ill-effects result from this condition in surgical patients, and amongst these the following are mentioned—post-operative pulmonary complications, disruption of wounds, and oedema of the stomach wall leading to delay in emptying. Measures designed for the restitution of the blood proteins include the administration of blood, blood plasma, amino-acids and predigested food.

Vitamin Deficiency. Vitamins are of considerable interest and importance to the surgeon for they play a major rôle in many conditions which demand his attention. A considerable literature has developed in regard to this subject and no attempt is made to survey it in this place. An important aspect of the subject is the value of vitamins in combating infection and in the healing of wounds. Patients should be placed on a diet with high vitamin content for so long a period as possible before a major surgical operation is performed. This may also be supplemented by the administration of Multivite tablets.

Special mention is made of recent work which has been carried out in connection with vitamin K since the discovery was made in 1939 of the relationship of hæmorrhagic tendencies to vitamin K deficiency. This vitamin is intimately associated with plasma prothrombin and the mechanism for the coagulation of blood. It has been shown that fat-soluble vitamin K requires bile salts in the intestine for its absorption. Deficiency in bile salts occurs in disease of the liver and obstruction to the outflow of bile into the duodenum, and in these conditions abnormalities in the coagulation of blood may occur—the plasma prothrombin falls, the clotting time of blood increases and there is a tendency to hæmorrhage. The administration of vitamin K and bile salts increases the blood prothrombin and corrects the abnormal clotting time. Anderson and co-workers have treated a number of patients with a delayed prothrombin time by means of the oral administration of synthetic vitamin K. They recommend an initial dose of 6 mg. of the synthetic compound with 2 gm. of bile salts. The plasma prothrombin level is maintained with the daily administration of 3 to 6 mg. of vitamin K and 2 gm. of bile salts. They found that the amount of vitamin K necessary to maintain a normal percentage of clotting activity varies in different individuals and prothrombin determinations

are necessary as guides to maintenance dosage. It is stated that in biliary tract operations the prothrombin activity reaches dangerously low levels during the fourth to the seventh post-operative days.

The Use of Adrenal Cortical Extract. Recent work has been carried out with regard to the function of the adrenal cortex and it appears to play an important rôle in the regulation of water balance, the sodium-potassium ratio of the body and the blood-sugar level. It is of interest to note that the biochemical changes which occur in Addison's disease, adrenalectomized animals and secondary shock are very similar, in that there is a decrease of plasma in the blood stream, and increase in the non-protein nitrogen and a lowering of the sodium and chlorides in the blood. It has also been shown that the adrenal cortical hormone exerts a direct action upon the low blood pressure in experimental shock, and this pressor reaction appeared to be more or less independent of the electrolytes of the blood serum and associated blood volume changes. Selye and co-workers state that the adrenal cortex plays an important rôle during the response of the body to injury, and that it shows histological signs of increased activity. Weil and Browne found an increase in the amount of cortin in the urine reaching a maximum between the third and fifth post-operative day and then declining gradually to pre-operative levels. They suggest that an increased secretion of the adrenal cortical hormone forms part of the protective mechanism of the body against injury.

Reed has suggested the use of adrenal cortical extract in the prevention of shock as a sequela of operation. An intramuscular injection of from 1 to 2 cc. is given at an interval of from eight to eleven hours before operation and a second injection of from 1 to 2 cc. is given 1½ hours before operation. In the post-operative period doses of 0.1 cc. are given at intervals of from six to twelve hours during the early days. He states that as the result of this measure the blood pressure is stabilized during the operative and post-operative periods with a pulse-pressure at, or above, the normal level. In addition the body electrolytes are apparently maintained at a normal level.

Adrenal cortical extract has been used in the treatment of secondary shock and in burns. Rhoads and Wolff have found that this substance is of value in the treatment of the fluid shift occurring in a group of patients suffering from severe burns. When effective, it appears to act by reducing capillary permeability for plasma proteins as early as the eighteenth hour after injury. These observers state that the data does not indicate that this substance is capable of restoring the circulatory plasma volume unless adequate plasma is given by transfusion at the same time. They also found that marked chloride retention occurs in patients receiving adrenal cortical extract and they should not be given any sodium chloride unless this is indicated by chemical analysis of the blood. The preparation recommended is eschatin given intravenously in doses of 5 to 10 cc. at six-hourly intervals in adults.

It must be remembered that in cases of profound secondary shock the hormone by itself is not capable of raising the blood pressure. We have used the preparation in the treatment of secondary shock in conjunction with other methods of treatment such as transfusion and oxygen therapy, and the impression has been gained that it is of value. The preparation used is eucortone administered either intravenously or intramuscularly, depending upon the severity of the condition.

Chemotherapy with the Sulphonamides. The application of chemotherapy in the management of surgical infections has been a recent noteworthy advance. Colebrook published the first clinical report of statistical significance dealing with chemotherapy in puerperal sepsis in 1936. In this way the far-seeing view of Ehrlich that a drug would be found which is relatively non-toxic to man and animals and would prove bactericidal in vivo as well as in vitro was satisfied. The end result of the action of sulphonamides in vivo appears to be the setting up of bacteriostatic conditions in regions of infection, and the normal tissues are protected against bacterial invasion. Lockwood has pointed out that concentrates of sulphonamides in the tissues as low as 1 mg. per cent. (1 in 100000) will exert demonstrable chemotherapeutic effects. It is important also to note that concentrations up to the saturation level, 200 to 1500 mg. per cent. will produce little, if any, local injury to the tissues, and therefore there is no interference with the natural cellular mechanisms of phagocytosis and the repair of tissues. In this group of substances we possess potent drugs which will permeate all the cells and fluids of the body and render them unsuitable for the growth of many bacteria.

The Use of Heparin. The physiological anticoagulant substance postulated by Howell was investigated by a group of Swedish workers, notably Jorpes, who defined its chemical nature and made it available in pure form. The great problem was whether we have in this substance an agent which can be used in the management of thrombosis. This was investigated by Crafoord, who has shown that in heparin we possess an almost infallible measure against thrombo-embolism. He showed in a study of 500 cases that in no instance did post-operative thrombosis occur in patients treated regularly with heparin. The treatment begins a few hours after operation and continues without a break for five to ten days or longer and four intravenous injections are given daily. Unfortunately at present the cost of heparin is too great for its universal application as a prophylactic measure in surgical cases. The idea has been put forward that heparin therapy should begin in the earliest stage of thrombosis and the detection of this phase by phlebography is suggested by Bauer. He states that phlebography permits an earlier diagnosis to be made than is possible with any other method and with its aid the first manifestations of the disease in the lower part of the leg can be revealed. In the abortive treatment of thrombosis patients are given 100 mg. of heparin intravenously three times a day, and the total quantity employed is between 900 and 1300 mg. Treatment may cease as soon as the pulse rate has become normal and the temperature has dropped to within a few points of normal. This usually occurs within three to five days. In the treatment of later stages of thrombosis, heparin is continued over a longer period than in the early stage. Mention should also be made of the valuable work carried out by Murray in Toronto regarding the application of heparin therapy in the surgery of the blood vessels as a preventive against post-operative thrombosis.

Recently, Lyons of Boston has recorded his experiences in the treatment of two consecutive cases of staphylococcal cavernous sinus thrombophlebitis with heparin and chemotherapy. This condition has been so fatal in the past that the survival of these two patients, in the treatment of which recent advances were applied, is worthy of attention. Lyons summarises the salient features in these cases as follows. Both patients developed pulmonary infarcts while receiving heparin which healed uneventfully. The bacteraemia persisted for six and eight days respectively, and ten days of the treatment was necessary before marked improvement occurred. Intracranial infection persisted for many weeks after the external evidence of infection had subsided and this was controlled by chemotherapy. The paralysis of cranial nerves improved markedly during convalescence. Lyons states that there is reason for believing that staphylococcal bacteraemia usually arises from foci of septic thrombophlebitis in and around areas of suppuration and an attempt should be made to prevent the extension of septic thrombi as well as to kill the bacteria. The combination of heparin with chemotherapy is therefore indicated.

Oxygen Therapy. The subject of anoxia and its management is receiving increasing attention from the surgeon and its evil effects in the body are being recognised. Haldane has summed up the matter by stating the "anoxia not only stops the machine but wrecks the machinery." Chase in a recent review of the subject states that the effects of anoxia are variable and depend upon the degree of deficit and the rapidity of its induction. The effects upon the brain are both profound and destructive, the ganglionic nerve cells being more susceptible to oxygen deficiency than any other cells in the body. If anoxia continues over a period of eight to ten minutes the brain cells are irreparably damaged. The brain centres survive for a period of twenty to thirty minutes and the spinal cord centres from forty to sixty minutes. The myocardial conducting mechanism is very sensitive to oxygen lack and Krogh has stated that capillary stasis from oxygen deficiency is irreversible after fifteen minutes. The significance of anoxia in secondary shock is well known and it is probably the most important factor at work which maintains or deepens the condition and leads to death unless it is controlled.

In conditions where anoxia develops, or is likely to develop, oxygen therapy must be instituted as early as possible. In surgical work anoxia is frequently seen, especially in post-operative pulmonary complications, in secondary shock, and sometimes during general anaesthesia. Schnedorf and Orr carried out experimental work in nembutalized animals suffering from traumatic shock. They found that there was a decrease in the oxygen content and saturation of blood from the femoral artery and vein, but as the result of oxygen therapy

there was a significant increase in the oxygen content of both arterial and venous blood. The duration of life in animals with traumatic shock was increased by 70·3 per cent. as the result of oxygen therapy.

Chase has discussed the principles of oxygen therapy. There must be a "head" of oxygen in the pulmonary alveoli and an intact transport system enabling it to be delivered with adequate speed and pressure into the body tissues. He states that the free oxygen in physical solution in the blood is the final link of life, and the oxygen combined with hæmoglobin is only the reserve from which this supply of oxygen is being constantly replenished. In anoxia the tissue cells suffer, not so much from lack of oxygen, as from lowered tension, which interferes with the efficient delivery of oxygen. By the inhalation of from 95 to 100 per cent. oxygen the saturation of arterial blood is increased from 10 to 15 per cent.

In oxygen therapy an advance of importance is the introduction of the B.L.B. inhalation apparatus, which is capable of delivering concentrations of 100 per cent. oxygen, and the nursing and feeding of the patient who wears it are carried out easily. When oxygen therapy is employed it should not be continued for more than a period of forty-eight hours, an interval must then elapse before it is resumed if necessary. According to Chase the most reliable criterion of successful oxygen therapy is a gradual and steady decline in the pulse-rate.

The Use of Blood Plasma or Serum. There has been considerable discussion concerning the merits of plasma and serum, but from the therapeutic viewpoint there is no difference between these substances. Many authorities have called attention to their value in the treatment of secondary shock. Brennan has carried out important work emphasising the value of plasma transfusions. He reported the appreciable increase in size which occurs in the red blood corpuscles as a result of hæmorrhage and that considerable numbers become side-tracked in the body, probably in the capillaries of the muscles. As much as 20 per cent. of the total number of red corpuscles may be missing from the circulation. The restoration of these cells to the circulation corresponds to the number given by a blood transfusion of 1 litre. Brennan has shown in a series of cases that plasma transfusions will restore these missing red corpuscles to the circulation, thus acting as an auto-transfusion. After the transfusion the mean corpuscular volume returns to normal.

There is considerable evidence that plasma is an efficient substitute for blood in cases of secondary shock without hæmorrhage, in burns, and even in severe hæmorrhage if whole blood is not available. Plasma is prepared readily and may be stored for considerable periods of time. In a recent report by Mahoney and co-workers it is stated that the incidence of reactions to plasma transfusions is 3·5 per cent. and it may be given without regard to blood type. Compared with crystalloid solutions, plasma does not filter through the blood capillaries to the same extent because of the protein content and high colloidal osmotic pressure.

Dried serum and plasma have important advantages in that they are stable, can be stored in a small space and solutions of greater concentration than normal plasma can be prepared. Disadvantages are difficulties of solubility, especially with higher concentrations of plasma, and the care required to preserve sterility in solutions under emergency conditions.

Conclusion. The matters considered in this paper reveal the trend of modern surgery and indicate the lines along which the science is being developed. When we understand more clearly the intricacies of normal physiology and the complex nature of the biochemical changes constantly occurring in the body more progress will be made in surgery. We are beginning to appreciate the great developments which are occurring in the study of hormones, and it is safe to predict that we are on the threshold of great discoveries. The application of these discoveries will undoubtedly exert a tremendous influence on both our thought and practice.