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THE PREPARATION AND USE OF DRIED PLASMA FOR TRANSFUSION

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The formation of blood banks has made available a considerable supply of plasma for therapeutic use. For many of the purposes for which a blood transfusion is given it is the plasma element that produces the desired effect; the red cells play a secondary part. The main constituent of plasma is the plasma proteins, and it is the administration of these, combined with fluid, which appears to be responsible for the resuscitative action in wound shock, post-operative shock, and burns. Further advantages of plasma are that it will keep indefinitely as compared with stored blood, which has a useful life of fourteen to twenty-eight days only, and that for the administration of plasma no grouping of the recipient is necessary.

Physiopathology of Plasma Proteins

Normal plasma contains 6.5 to 8.5 grammes of protein per 100 c.cm., and the three most important constituents are fibrinogen (0.3 gramme), serum globulin (2.7 grammes), and serum albumin (4.5 grammes). The molecular weight of these proteins is high. Fibrinogen is the highest (uncalculated), globulin next (100,000), and albumin the lowest (40,000). Consequently albumin diffuses out the more rapidly from the capillaries and the albumin/globulin ratio is higher in exudates than is normally found in the circulating blood. Fibrinogen is formed in the liver and is intimately connected with the clotting power of blood. The origin of the other two proteins is unknown. Their function appears to be entirely that of maintaining the osmotic pressure of the blood so that adequate interchanges between the plasma and the tissue fluids can be maintained in the capillary circulation. If the amount of protein in the plasma is experimentally lowered by replacing the plasma with Ringer's solution a condition is produced resembling very closely that of surgical shock, with collapse and fall of temperature (Whipple, Smith, and Belt, 1920).

The re-formation of albumin and globulin after any loss from the circulation is slow, and some days may pass before the normal level is regained. On the contrary, the re-formation of fibrinogen is rapid, normality after a severe haemorrhage being reached in six hours (Peters and van Slyke, 1931–2).

The Withdrawing of Plasma

Blood may be taken from donors for the express purpose of producing plasma, in which case the stored blood should be kept undisturbed for a period of three to four days to allow the maximum separation of plasma and red cells to occur. Up to the present most of our plasma has been obtained from bottles of citrated stored blood about fourteen days old. Such blood is starting to haemolyse and, although no definite change may be noted in the colour of the plasma, that part which is in contact with the red cells is certain to contain a considerable amount of haemoglobin. If these bottles have not been disturbed since the erythrocytes have settled the buffy coat forms a fairly effective barrier to the passage of haemoglobin into the supernatant plasma, and practically clear plasma can be withdrawn without any disturbance of the respective layers. A small amount of discoloration by haemoglobin is apparently of no disadvantage, however, and its administration seems to be reasonably innocuous. O'Shaughnessy, Mansell, and Slome (1939) have shown that a 5 per cent. solution of haemoglobin may be administered without serious deleterious effects provided that the urine is kept alkaline. The fractional amount which is present in the plasma has been shown, in our experience of the administration of over 600 bottles of stored blood, to produce no serious complication.

The standard blood bottle of the Merseyside War Blood Bank is a pint bottle containing glass shot (for use as a filter when inverted), fitted with a rubber diaphragm kept in place by a metal cap pierced by two holes. It is a modification of Boland, Craig, and Jacobs's (1939) apparatus. The plasma-withdrawal apparatus (Fig. 1) consists of a fine metal tube A fitted with a sharp point (unscrewable, for cleaning the tube) and a lateral hole. This tube is connected by a rubber tube, eighteen inches long, fitted with a glass sight tube C to a needle B, which is inserted through the diaphragm of a second bottle.

The metal tube A is thrust through the diaphragm of the blood bottle down to the plasma level and the needle B is pushed into the collecting bottle. An air inlet needle D is introduced into the blood bottle and an air outlet needle E into the collecting bottle. To this needle E are connected a rubber tube and a reversed Higginson syringe for suction. The plasma is withdrawn by gentle suction and the tube A is gradually lowered as the plasma level falls. In this way all but a few centimetres of the plasma can be removed. As soon as red blood cells are seen in the sight tube C the withdrawal is stopped, needles B and E are removed from the collecting bottle, and a viscose cap is placed over the metal cap. A full sterile technique is employed. From a pint of citrated blood 250 to 300 c.cm. of plasma is obtained.

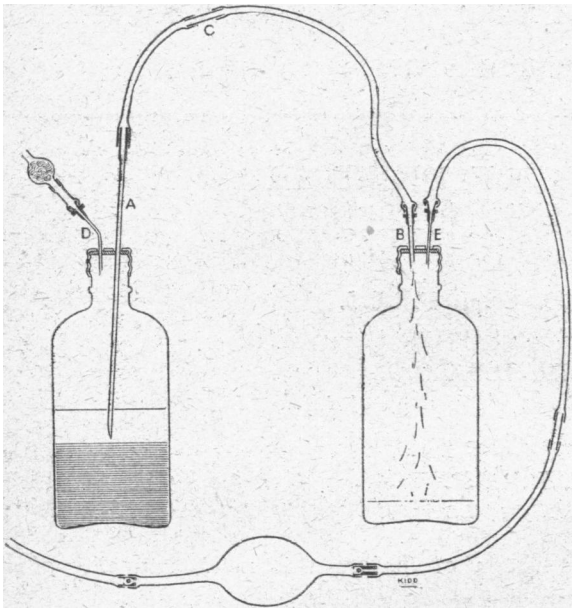

FIG. 1.—Method of removing plasma from bottles of stored blood.

Storage and Administration of Plasma

The plasma should be kept in a refrigerator at 4° C. with the stored blood: this is advisable to prevent any possible bacterial growth, but it appears to undergo no material change if kept for long periods at room temperature. On standing a slight precipitate which consists of fibrin slowly forms. This must be filtered off before administration, and accordingly the bottles used for the collection, storage, and administration of plasma are fitted with the rubber diaphragm and screw cap of the standard blood transfusion bottle and a layer of glass shot is included. The plasma will keep indefinitely: bottles of plasma two and three months old have been given without untoward reaction.

The plasma is warmed to 37° C. and given by the standard gravity method, using the bottle inverted, with an air inlet needle, an outflow needle connected to four feet of rubber tubing, and a small needle for entering the recipient's vein. Difficult veins may need a Kaufmann's syringe or a vein-seeker (Edwards, 1939).

Dried Plasma

Although the use and administration of pure plasma has been satisfactory, it was felt that if the product could be dried the question of storage and transportability would be greatly simplified and the possibility of bacterial growth greatly reduced. Flosdorf and Mudd (1935) have evolved an apparatus for drying plasma. The method, which consists in freezing the plasma in carbon dioxide snow and evaporating it under a very high vacuum, is expensive both in capital outlay and in running costs.

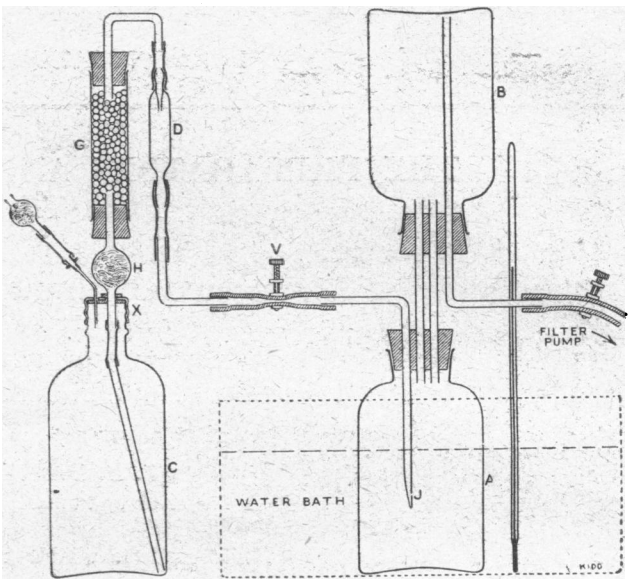

FIG. 2.—Continuous-flow plasma drier.

Plasma can, however, without detriment be heated to 37° C.—in fact, this is its normal temperature—and at this temperature the low vacuum produced by an ordinary standard filter pump will cause it to boil. It was found that if the filter pump was connected to the ordinary storage bottle of plasma a very marked degree of frothing occurred during ebullition and, although evaporation to dryness could be effected, the excessive frothing slowed the process considerably and there was a certain amount of wastage. The use of a continuous-feed plasma drier has prevented this, and the apparatus devised will deal with any number of bottles of plasma. The plasma is suctioned over in a thin stream into a special container and there dried. It is removed later under aseptic conditions and can be stored in ampoules.

Bottle A (Fig. 2), the plasma drier, is of 700 c.cm. capacity and is connected by two glass tubes to the trap bottle B of similar size. The plasma is fed into the drier from the standard bottle C, which is screwed into the cap X. The plasma is filtered through a layer of gauze H and a tower of glass beads G: it then passes through a drip D which serves to indicate the rate of flow, and then runs through the control valve V, which is a screw clamp on pressure-rubber tubing. It is finally sprayed into the drying bottle through a fine glass jet J. The bottle B acts as an efficient trap to any plasma that may escape out of A by frothing, and this trapped fluid eventually finds its way back into the drying bottle down one or other of the two connecting tubes. The whole apparatus is sterilized with a dummy bottle C in position. The bottle A is then put into a thermostatically controlled water bath kept at 37° C. The dummy bottle is removed and a bottle of plasma is screwed into the cap X. The flow is controlled by the valve and the rate so adjusted that a thin layer of plasma is maintained in the bottom of A. With the filter pump working continuously drying

takes place at the rate of about 100 c.cm. an hour, but the dried product is not produced until the last bottle has been attached at X and an extra hour's drying has been given to remove all traces of water. The drying bottle is then removed, and the product scraped out of the bottle under sterile conditions and stored in bulk or in ampoules (Fig. 3). Before doing this it is advisable to crush the product to a fine powder, as solution in water

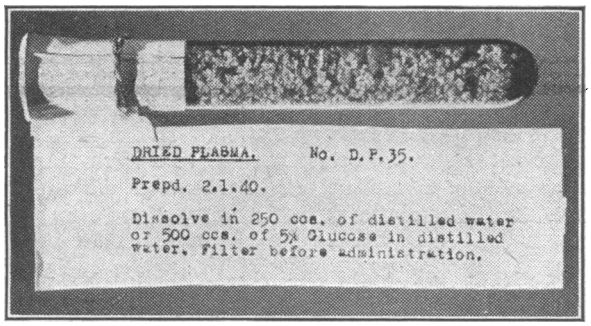

FIG 3.—Sterile dried plasma packed for transport.

is thereby rendered much easier. By enlarging or reduplicating the apparatus dried plasma in any quantity can be produced inexpensively.

Characteristics of Dried Plasma

100 c.cm. of citrated plasma gives about 8 grammes of the dried product, which is a pale yellow crystalline powder that dissolves readily in warm water. The colour of the powder depends upon the original colour of the plasma. A trace of haemoglobin will give the product an orange colour. To restore the constitution of the plasma it is dissolved in the ratio of 8 grammes to 100 c.cm. of warm distilled water: dissolving 20 grammes in 250 c.cm. of distilled water gives the plasma protein value of one pint of citrated blood. The administration of the dried plasma by dissolving it in double the quantity of 5 per cent. glucose solution in distilled water—that is, 20 grammes in 500 c.cm. of 5 per cent. glucose solution —so that the fluid factor is increased for cases of shock, has been tried and found to be satisfactory.

The reconstituted plasma is indistinguishable in appearance from the original product. The amounts of fibrinogen, serum globulin, and serum albumin in the original plasma and the reconstituted plasma have been estimated and found to be to all intents and purposes identical. No fundamental change appears to be produced in the individual proteins by the drying process and, in particular, it has been shown that they are not denatured. The protein value of the dried plasma was found to be unchanged after a period of two months, and there seems to be no reason why it should not remain stable permanently. It can be stored at room temperature, and its ease of transport is such as to make it the ideal for the surgeon's handbag and for military use, especially in advanced field stations, where it can be administered after solution and simple filtration by any intravenous saline apparatus.

Blood Groups in Plasma Transfusions

The following table shows the factors present in the cells and plasma of the different blood groups:

Group (Moss)	Cells Agglutinogen	Plasma Agglutinin
I	AB	None
II	A	β
III	B	α
IV	O	α and β

Group AB (I) plasma is therefore the ideal plasma for transfusions, as it contains neither of the agglutinins; while Group O (IV) plasma is the least suitable, as it has both α and β. Two to three pints of Group O (IV) blood can, however, be given to most patients without ill effects, and there is therefore no reason to suppose—nor in practice does it happen—that any deleterious effect arises from the administration of Group O (IV) plasma. The α and β factors are so diluted by the recipient's serum, or so quickly absorbed by the first few red cells with which they come in contact, that they produce no serious agglutinating effect upon the recipient's corpuscles. Groups A (II) and B (III) plasma come midway between Groups AB (I) and O (IV) in suitability for universal administration.

If the plasma has α or β, or both, in a very high titre then some reaction might occur in an unsuitable patient. Such cases, however, are rare, and in our admittedly limited experience no serious reaction has resulted. While the giving of plasma of the same group as that of the recipient is ideal, grouping may in general be regarded as unnecessary and the plasma of any group may be administered to any patient.

Under the blood bank system now in general use Group O (IV) blood is mainly if not solely used, and this leaves untouched a very high percentage of the donor volunteers, who are often deeply disappointed at their unsuitability for transfusion service. It is obvious that the extended employment of plasma transfusions in civilian and military medical practice will make it possible to use all volunteers, irrespective of their blood group. The supply of the ideal plasma from Group AB (I) donors is unfortunately limited by the small proportion (about 3 per cent.) of these, but an artificial Group AB plasma devoid of α or β agglutinins can readily be obtained by running equal quantities of Group A (II) and Group B (III) blood into the same collecting bottle. Our procedure has been to mark the pint bottle, containing 50 c.cm. of sodium citrate solution, at the 300 c.cm. and the 550 c.cm. levels. Two such bottles are used for a Group A (II) donor, 250 c.cm. of blood being run into each—that is, up to the 300 c.cm. mark. The two bottles are then filled to the 550 c.cm. mark from a Group B (III) donor and immediately removed to the refrigerator, where they are left undisturbed for three days. Under these conditions the α agglutinin of the Group B (III) plasma is absorbed on Group A (II) red blood corpuscles, and the β agglutinin of the Group A (II) plasma on the Group B (III) corpuscles. The resulting supernatant plasma is devoid of both agglutinins. No haemolysis of any importance has been observed in bloods so treated by us, and the plasma has all the advantages of natural Group AB (I) plasma. It is recognized that the technique described may fail if the Group A (II) blood used happens to be of the subgroup A_2, when the α_1 factor of the Group B (III) plasma will not be removed from the mixed plasma. We ourselves have up to the present ascertained beforehand that the Group A (II) donors used were of the subgroup A_1, but are considering a simple technique of dealing with pooled blood from such large numbers of Groups A (II) and B (III) donors as will ensure the removal of all α_1 and α_2 by A_1 and A_2 cells. In view of the earlier statements regarding the relative harmlessness of the α and β factors in plasma the above may appear to be an unnecessary refinement, but we are of the opinion that, because of the possible widespread use of plasma transfusions, every precaution aiming at the avoidance of agglutination accidents is worthy of trial.

Conditions in which Plasma Transfusions may be of Value

(A) WOUND SHOCK

In wound shock some change occurs in the capillaries which allows of exudation of fluid out of the circulation. This produces a diminished blood volume and a condition of haemoconcentration, as has been shown by Cannon, Fraser, and Hooper (1917), and since adequately confirmed by other workers. The concentration of plasma proteins does not rise in parallel with the red cell count, and thus it can be assumed that some proteins have been lost from the circulation into the tissues (White and Erlanger, 1920). The more severe the degree and the more prolonged the state of shock the greater is the outpouring of fluid and plasma proteins from the circulation. This develops into a vicious circle, as the osmotic pressure of the blood is being lowered continually and thus there is less chance of fluid being drawn back to re-establish the blood volume.

The primary requisite in the treatment of such cases of shock is the restoration of the circulatory volume and the reduction of the viscosity of the blood. The administration of intravenous salines in such cases produces a merely transitory beneficial effect. Although the circulatory volume may for a time be raised the plasma proteins are diluted; much of the salt passes into the tissues and tends to increase the flow of the fluid out of the circulation, so that the excess water enters the tissue spaces or is excreted by the kidneys. Hypertonic solutions similarly are only transient in action. Treatment by blood transfusion in these cases has hitherto been shown to give the most satisfactory result. Assuming the patient has not had a very severe haemorrhage, the need for red blood cells is not urgent. It is rare for a patient to lose more than three pints of blood, as the fall of blood pressure in such cases is so great that the haemorrhage ceases. This leaves him with 75 per cent. of his erythrocytes in some part of the circulation. Provided that the necessary amount of fluid can be introduced into the circulation—and made to stay in—his remaining red cells should be entirely adequate to maintain life. It is in such cases that the infusion of plasma protein should provide the necessary osmotic pressure to keep the fluid in the vessels.

Dried plasma, in the form of "lyophil serum" prepared by Flosdorf and Mudd's method, has been utilized in the treatment of experimental shock by Mahoney (1938) and Bond and Wright (1938). From a comparison of the results of plasma infusion with those of whole blood, saline, and gum acacia they considered plasma to be the most efficient therapeutic agent in restoring the normal blood pressure.

(B) POST-OPERATIVE SHOCK AND POST-OPERATIVE PULMONARY OEDEMA

Post-operative shock is similar in nature and effect to wound shock, although somewhat slower in onset. In a series of major post-operative cases Walther (1937) showed that a considerable fall occurred in the absolute plasma protein value of the blood in association with haemoconcentration in those cases which developed shock. Such cases are in the same need of plasma proteins as the cases of wound shock.

If the fall in protein value of the blood is treated by the administration of large amounts of saline pulmonary oedema tends to develop, and in fact it is the lung tissue which is the first area in shocked cases to give visible demonstration of the effect of the exudation of the fluid into the tissues from the capillaries. It is generally recognized that administration of sodium chloride in post-operative cases should be strictly limited, and, unless it can be controlled by blood chloride estimation, the amount should not exceed two pints of normal saline, given immediately after operation. The introduction of plasma proteins should reduce the tendency of fluid and salt to escape from the capillaries in these cases, and we would therefore suggest that plasma transfusions might be administered with advantage in cases of pulmonary oedema developing in the course of post-operative saline infusions.

(C) BURNS

Following burns the reaction in the skin and the tissues is the outpouring of a fluid rich in plasma proteins that produces the characteristic vesication. This factor, combined with the shock, again gives rise to a haemoconcentration, and the administration of plasma is indicated in such cases. The treatment of the shocked state in burns by administration of plasma has already been the subject of a communication by McClure (1939), and is being tried out in a number of centres throughout the country.

(D) OEDEMA

Oedema of nephritic origin is associated with a lowered plasma protein value, as has been shown by Moore and van Slyke (1930), who demonstrated that in such cases oedema supervened when the plasma protein value reached the critical level of approximately 5.5 grammes per cent. Such cases have been treated by giving a high protein diet, but the restoration of the normal plasma protein level is slow, particularly as regards the albumin factor. We have not as yet had the opportunity of testing the utility of introducing plasma proteins in cases of this kind, but it would appear possible that plasma transfusions might find an additional application of value in severe cases of renal oedema and possibly also in famine oedema, where a similar protein loss is operative (Knack and Neumann, 1917).

Amount of Plasma to be Administered

The maximum quantity of plasma we have given at one transfusion is 500 c.cm., and if Group O (IV) or pooled plasma is used it would seem advisable, in view of the presence of the α and β factors, not to exceed this dose, as the concentration of these agglutinins in the recipient may rise high enough to produce sufficient agglutination of the red cells to cause unwonted effects. Group AB (I) plasma or the artificial Group AB (I) plasma should, however, be administrable in any quantity.

Experience of the Use of Plasma Infusion

Our experience of the use of plasma transfusions, both of natural plasma and of the reconstituted solution from the dried product, is as yet not great enough to allow of full assessment of their value, but it may be said that the results so far fully maintain the claims put forward. The estimation of the value of any form of therapy in shock is not easy, as the different degrees and states of shock are difficult to estimate and compare, while the *post hoc sed non propter hoc* criticisms are not easy to contest. We do not propose to give detailed figures and an analysis of our results until we have studied the effect in a larger number of cases. At this stage we would merely state that our experience justifies the following observations: (1) The effects in cases suffering from wound shock and post-operative shock are certainly equal to those which experience would lead one to expect following a blood transfusion. (2) In the treatment of

severe burns and scalds our results confirm the already established claims of the efficiency of plasma infusions. (3) Previous testing of the blood groups of patients appears to be unnecessary in plasma transfusions.

Conclusion

We would point out that the chief aim of this article is to draw attention to the ease with which dried plasma may be prepared and to its obvious advantages over natural plasma in war surgery. In view of the possibilities of extensive demands being made on the resources of those who have to treat wound shock it is imperative that any line of treatment claiming to be of value should be tested as fully as possible and at the earliest opportunity. In the hope that the value of dried plasma will be submitted to this trial we have taken the step of publishing at this stage what is obviously an incomplete series of clinical observations.

Summary

The method of withdrawing, storage, and delivery of plasma is described.

Details of the continuous-feed plasma drier are given for the preparation of dried plasma. The production of dried plasma is cheap, and larger quantities may be prepared by reduplication or enlargement of the apparatus.

The ideal plasma for administration is Group AB (I) plasma, but the plasma of any group may be given to any patient up to 500 c.cm. Group AB (I) plasma can be administered in any amount.

Group AB (I) plasma may be prepared artificially by mixing Group A (II) and Group B (III) bloods and withdrawing the resultant plasma.

The dried plasma may be carried in ampoules and administered by any intravenous saline apparatus. It can be stored at room temperature, and will apparently remain effective indefinitely.

The rationale for the administration of plasma in wound shock, post-operative shock, and incipient pulmonary oedema, burns, nephritic oedema, and malnutritional oedemas is discussed.

Twenty grammes of dried plasma, dissolved in 250 c.cm. of distilled water or 500 c.cm. of 5 per cent. glucose in distilled water, is equivalent in plasma protein value to one pint of citrated blood.

Our experience of its use is not great enough fully to assess its value, but its anti-shock property appears to be comparable to that of whole blood. It seems to be ideal for use in emergency, where no supply of blood is easily available, and in war surgery.

We wish to express our grateful thanks to Professor O. Herbert Williams, professor of surgery, University of Liverpool, for much helpful advice and encouragement, and to Emeritus Professor Sir Robert Kelly for his keen interest. Our acknowledgments are due to the members of the staff of the Royal Liverpool United Hospital for allowing us to study the effect of plasma transfusions on their patients, and to the Merseyside War Blood Bank for supplies of plasma.

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TREATMENT AND PRIMARY SUTURE OF FACE WOUNDS

BY

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This paper has been written to emphasize the importance of the immediate treatment of wounds of the face by operation and primary suture. I treated a large number of these cases during the war of 1914–18 at a special hospital in London for injuries of the face and jaws, and also, later, at a casualty clearing station in France which was a centre for injuries of the head. Some of these cases have been followed up, particularly when the injury had involved the nose and nasal sinuses; and motor-car and flying accidents have also supplied a few sporadic cases in recent years.

During the early part of that war these patients arrived at the base hospital in this country in a septic condition: nothing had been done for them beyond the application of a large dressing. It is presumed that on account of the fear of cellulitis and severe sepsis there was no suturing. The torn cheek or lips or even eyelids were oedematous and hanging out of place. Secondary haemorrhages were common, and a large dressing soaked in saliva and discharge added to the patient's misery.

It was an entirely different picture when the patient had been operated on within twelve hours of being wounded. The lacerated edges were trimmed and the wound was thoroughly cleaned, loose fragments of bone were taken away, and foreign bodies, pieces of shrapnel, and bullets, if accessible, were removed along their track of entry. If a nasal sinus was involved free drainage was established into the nose. The soft tissues were loosely stitched by interrupted sutures, without tension of the skin, and the damage was repaired; when this was done within twelve hours, before any inflammatory reaction occurred, healing was satisfactory and rapid. If the wound was loosely sutured after inflammation had begun the stitches cut out; but even then haemorrhage had been controlled, the amount of sloughing reduced, and deformity diminished, though such a good result as is obtained with early suture must not be expected. Efficient drainage was of course essential. The wound was dusted with boric powder and no dressing was required; in fact, the patient was much better without it, and only needed a gauze mask to hide his injury from other patients.

Injuries to the Orbit and Nose

It is necessary to give a brief description of those cases of injury to the face which were seen at a casualty clearing station in order to indicate the details of the required operative technique, which varies according to the site and extent of the wound. The majority of the severe injuries in the region of the orbit or nose with penetration of the dura were fatal. At the post-mortem examinations extensive fractures of the anterior fossa of the skull, with fissure or comminuted fractures of the roofs of the orbits and nose, were discovered. The missiles had had a bursting effect, shattering the eggshell-like bone of the ethmoids and orbits. Specimens of these injuries are in the War Museum of the Royal College of Surgeons, and it is unfortunate at this time that the museum should be closed.

Fracture of the anterior fossa of the skull was accompanied by an extensive and diffuse intradural haemorrhage