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GENERAL ANAESTHESIA IN SHOCK

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Operations on seriously shocked patients are associated with a notoriously high mortality. This may be due to further loss of blood entailed during the operation, to the stimulus of the operative manipulations, or to the anaesthetic. In the present investigation an attempt has been made to evaluate the relative importance of these factors and to determine if any modifications of the methods in common use can lessen the mortality rate. It has become apparent that the most important single factor has been the anaesthetic, and an examination has therefore been made of the effect of different anaesthetics on the cardiovascular systems of patients with normal plasma volumes who have undergone various operations. These observations have enabled a clearer interpretation to be placed on the effect of these anaesthetics on shocked patients whose plasma volumes were below normal.

A series of 26 patients with normal plasma volumes were examined, of whom 19 underwent various major operations—the majority a partial gastrectomy—and 7 underwent minor operations. In all cases the pulse and respiration rates and the blood pressure were recorded at about three-minute intervals. Determinations of plasma volume (Crooke and Morris, 1942; Morris, 1944) were made and the dye-concentration curves followed at about 30-minute intervals until the end of the operation. The haemoglobin (Rimington, 1942) was also determined at the same intervals. Electrocardiographic records were made in nine cases which underwent major operations.

Changes in the blood pressure were not found to be related to any particular operative manipulation by the surgeon in any of these cases, but they could be produced by alterations in the depth or type of anaesthesia. The effect of increasing depth of different anaesthetics on blood pressure is summarized in the following table.

Anaesthetic	Blood Pressure				
	Rise	Rise, then Fall	Fall, then Rise	Fall	Constant
Nitrous oxide, oxygen, and ether	5	2	2	2	3
Cyclopropane	7	0	0	1	0
Spinal	0	0	0	4	0
Sodium pentothal ..	0	0	0	2	0

Fourteen patients who were given nitrous oxide, oxygen, and ether underwent major operations. At some period of the operation a large amount of ether was given in order to obtain very deep anaesthesia, but the effect on the blood pressure was very variable. Two examples are shown in Figs. 1 and 2. Eight patients were given cyclopropane, but two have already been included in the group who were given nitrous oxide, oxygen, and ether. In these two the anaesthetic was changed to cyclopropane towards the end of the operation. The blood pressure rose in proportion to the depth of the anaesthesia (Figs. 2 and 3), except in one of three patients who had only minor operations. In this case the blood pressure fell from an initial level of 195/100 mm. Hg to 145/90 mm. Hg. Two of the four patients who had spinal analgesics underwent major operations. The blood pressure fell in all of them, and in one the fall was very marked (Fig. 4). Two patients who had minor operations were given sodium pentothal, and the blood pressure fell in both.

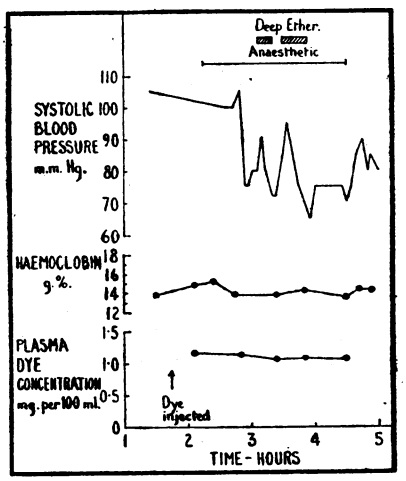

FIG. 1.—Effect of nitrous oxide, oxygen, and ether on blood pressure, haemoglobin, and dye concentration.

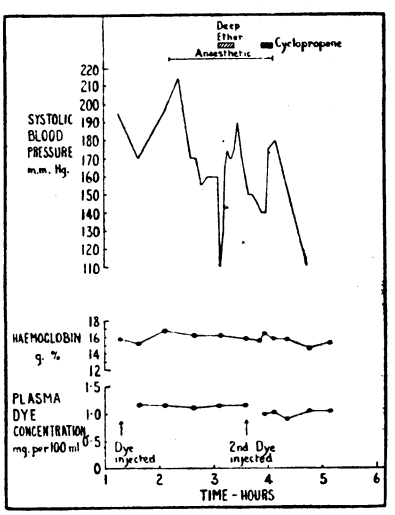

FIG. 2.—Effect of nitrous oxide, oxygen, and ether, followed by cyclopropane and oxygen, on blood pressure, haemoglobin, and dye concentration.

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These changes in the blood pressure did not appear to be effected through any changes in the plasma volume, since the dye-concentration curves and the haemoglobin level showed no significant alterations during the operation, as would have occurred if water had been lost from the blood stream into the surrounding tissues. The plasma volume was determined a second time at the end of all major operations in order to measure the haemorrhage. Anomalous dye-concentration curves were obtained in 10 patients, due to the previous injection of morphine or hyoscine (Bowler, Crooke, and Morris, 1944), but 9 patients had good second dye-concentration curves. Two of these showed an increase of plasma volume, three no change, and four a fall, but the changes were probably within the error of the method. In all these cases very great attention had been paid to haemostasis in order to eliminate haemorrhage as a factor affecting blood pressure, but haemorrhage occurring during an operation can be readily measured, as demonstrated by three other patients who underwent radical operations for carcinoma of the breast. Good dye-concentration curves were obtained, and the plasma volume fell from 3.31 to 2.47 l. in the first, from 2.47 to 2.0 l. in the second, and from 2.87 to 2.73 l. in the third.

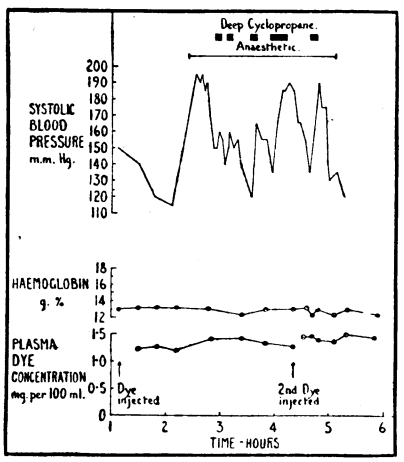

FIG. 3.—Effect of cyclopropane and oxygen on blood pressure, haemoglobin, and dye concentration.

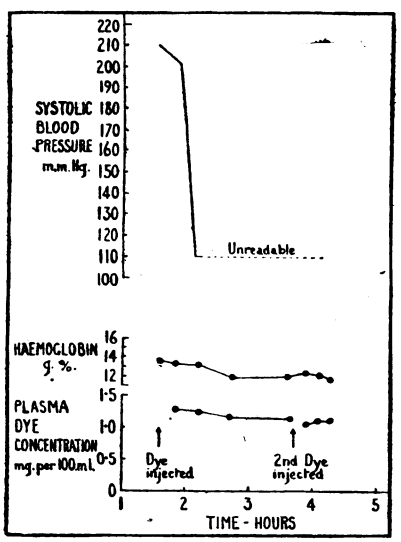

FIG. 4.—Effect of spinal analgesia on blood pressure, haemoglobin, and dye concentration.

The changes in the blood pressure were not effected through the heart, as judged by serial electrocardiograms which were taken in nine cases. Nitrous oxide, oxygen, and ether was given to five of the cases, nitrous oxide, oxygen, and ether followed by cyclopropane to two, cyclopropane and oxygen to two, and a spinal analgesic to one. The three limb leads were recorded in all cases before the operation, and Lead II was then taken at about 15-minute intervals during the operations and at other times when marked changes in the blood pressure occurred. Although cardiographic irregularities did take place they were never constant. When present they appeared to be related in no way to the changes in the blood pressure even when these were as marked as those shown in Fig. 4.

When these anaesthetics were given to patients with traumatic shock whose plasma volume was significantly reduced there was a greater tendency for the blood pressure to fall. Cyclopropane and oxygen generally caused an increase in blood pressure except in very severe cases, but even here the fall was less pronounced than with the other anaesthetics examined. Nitrous oxide and oxygen with a minimal amount of ether was the next most satisfactory, but an adequate amount of oxygen was essential. Deep ether or ether-and-chloroform anaesthesia caused a marked fall of blood pressure. In our series there are no records of shocked patients being given spinal analgesics, but several had sodium pentothal. Two of these had extensive burns, and the blood pressure fell from 145/80 mm. Hg to an unreadable figure in one and from 145/95 mm. Hg to 80/60 mm. Hg in the other. Induction was given to both patients by an expert anaesthetist, yet the former almost died on the operating table and the latter caused some anxiety. Examinations of plasma volume were attempted, but the dye-concentration curves were anomalous because the patients had received morphine shortly before injection of the dye.

Illustrative Cases

A number of examples are recorded to show the effect of various anaesthetics on shocked patients whose plasma volume had been determined.

Case 1.—A man aged 49 was injured by bomb splinters at 10.15 a.m., and was admitted to a small hospital together with a large number of casualties. He was probably not severely shocked on admission, because the surgeon had left him in order to deal with what he considered to be more serious cases. He had a compound fracture of the lower third of the right radius and ulna with much laceration of the tissues, a compound fracture of the left ankle involving mainly the astragalus with a metal foreign body retained subcutaneously, and a small deep puncture wound of the right forearm. He was given morphine gr. 1/4 at 11 a.m. At 4.15 p.m. he was conscious, quiet, and listless. His skin was ashen grey, cold, and moist. His pulse was 90 and blood pressure 50/45 mm. Hg. An electric blanket was placed over him. A rapid determination of plasma volume was begun at 4.32 p.m. Only two readings were taken, but they agreed closely, and gave a value of 2.54 l., or about 3.1% of body weight (about 13 st.). His haemoglobin was 10.5 g./100 c.cm. At 4.50 p.m. his condition appeared to be unchanged, but the blood pressure was unreadable An attempt was made to start a transfusion; but there was considerable delay in getting this working, and it was 5.30 p.m. before it began to run freely. At 6.5 p.m. he had already received 686 c.cm. of plasma, and blood was transfused instead. He was now warm, more restless, and in some pain. At 6.15 p.m. his pulse was 70 and blood pressure 65/40 mm. Hg. At 6.45 p.m. he was definitely better and more co-operative, even smiling at the doctors; his blood pressure was 60/40 mm. Hg. At 6.50 p.m. the transfusion was stopped and he was moved to the theatre. He had now received 924 c.cm. of blood, and at 6.56 p.m. his haemoglobin was 9.6 g./100 c.cm. A further reading of plasma volume based on the initial injection of dye gave a figure of 2.9 l., or about 4.7% of body weight. This showed an increase of 1,360 c.cm. in the plasma volume, and agrees fairly well with the estimated water content of the transfusion, which was 1,300 c.cm., for he had obviously been losing some blood from his injuries during this period. At the same time a second injection of dye was given, and induction with a mixture of ether and chloroform was begun by a practitioner. At 6.58 p.m. the blood pressure was 70/50 mm. Hg. It then fell rapidly, being 65/40 mm. Hg at 7 p.m., 60/40 mm. Hg at 7.3 p.m., and then unreadable. The puncture wound of the left forearm was cleaned and sutured, and the wound of the left ankle was cleaned and sutured and the ankle put in plaster. The right forearm was not touched, for the patient died at 7.10 p.m. A sample of blood taken at this time showed a haemoglobin of 9.6 g./100 c.cm. and a plasma volume of 3.9 l. based on the second injection of dye. This is identical with the reading taken at 6.56 p.m. based on the first injection of dye, and confirms the observation that his plasma volume was now within the lower limit of normal. A post-mortem examination made by Dr. Joan Ross on the following day revealed no other injuries than those already described.

Case 2.—A man aged 29 was injured by bomb splinters at 12.30 a.m. and was admitted to hospital at 1.45 a.m., when his condition was described as " pretty serious." He was conscious but

drowsy and ashen-coloured. His systolic blood pressure was 60 mm. Hg and pulse rate 130. He was immediately given morphine gr. 1/4, followed by gr. 1/6 soon after. There was no obvious haemorrhage, so he was left quiet till 4 a.m., when a fuller examination was made. His systolic pressure had now risen to 80 mm. Hg. He had a compound fracture of the middle third of the right radius and ulna, total destruction of the ulnar side of the right carpus, and amputation of the right index and middle fingers. There was a laceration on the dorsum of the left ring-finger, with removal of the nail and exposure of the terminal phalanx. There were superficial abrasions of the abdomen. A two-inch-long penetrating wound was present on the outer aspect of the lower third of the right thigh and several small wounds above it. There was a large T-shaped lacerating wound on the anterior surface of the upper third of the right leg, with several small perforating wounds below it. The arterial supply to the lower two-thirds of the right leg had failed. A blood transfusion was started at 6 a.m., when his systolic blood pressure had risen to 105 mm. Hg and the pulse rate had fallen to 100. At 8 a.m. two bottles of blood had been given. At 10 a.m. the systolic pressure had again fallen to 85 mm. Hg, and the pulse rate was 120. There was little change until 11 a.m., when a plasma transfusion was started, and at 11.20 a.m. morphine gr. 1/4 was given. At 12.45 p.m. an attempt was made to determine the plasma volume. Two readings of 2.58 and 2.68 l., or about 2.8% of body weight (about 15 st.), were obtained. These figures are not very reliable, because morphine had been given only 80 minutes before injection of the dye and a slow transfusion was being carried out at the time. The haemoglobin was 11.8 g./100 c.cm. At this time his blood pressure was 105/65 mm. Hg. Two bottles of plasma were then given, and at 4 p.m. his general condition had improved considerably, and the systolic pressure was 130 mm. Hg. At 8 p.m. the systolic pressure was 120 mm. Hg, and at 8.40 p.m. a second determination of plasma volume was begun. No more morphine was given until 8.48 p.m., when a reliable curve was obtained, giving a value of 3.6 l., or about 3.8% of body weight. The haemoglobin was 11.4 g./100 c.cm. Induction with nitrous-oxide-oxygen and a little ether was begun at 9.31 p.m. The blood pressure was 100/55 mm. Hg immediately before anaesthesia was started. It rose to 110/65 mm. Hg at 9.35 p.m., and then fell gradually to 80/50 mm. Hg at 9.59 p.m. Subsequently it was maintained at 85/50 mm. Hg until the operation ended at 10.20 p.m. No ether was given after 9.38 p.m. and no nitrous oxide after 9.52 p.m., but oxygen was continued until the end of the operation. During this time the wounds were cleaned, and dead tissue and a few small fragments of loose bone were removed. The affected limbs were covered with vaseline packs, the right arm up to the hand encased in plaster, and the right leg bandaged. At 10.55 p.m. the systolic blood pressure had risen to 100 mm. Hg, and it continued to rise gradually to 140 mm. Hg at 8 a.m. on the next day. He was too ill, however, to have his gangrenous leg amputated, and he died at 4.30 p.m.

Case 3.—A man aged 56 was admitted to hospital at 11.52 a.m. shortly after being injured by a falling chimneystack. He was alert and in considerable pain. His skin was warm, moist, and of fairly good colour. He had a compound fracture of the lower third of the left tibia and fibula, a haematoma of the scalp above the left eye, and pain in the chest, especially on antero-posterior compression. His pulse rate was 47 and his blood pressure 110/60 mm. Hg at 12.30 p.m., when he was given morphine gr. 1/4. At 1.50 p.m. a determination of plasma volume was begun. In spite of having had morphine recently, a flat curve was obtained over the next five hours. It showed a value of 3.3 l., or 4.3% of body weight (12 st.), and his haemoglobin was 12.2 g./100 c.cm. His general condition remained unchanged during the afternoon, and at 5 p.m. his pulse rate was 48 and his blood pressure 130/70 mm. Hg. At 5.10 p.m. anaesthesia with nitrous oxide, oxygen, and a minimum amount of ether was begun. His pulse rate increased to 96 and blood pressure to 170/75 mm. Hg at 5.20 p.m. The pressure then gradually fell to 140/75 mm. Hg at 5.45 p.m., and remained at about this level until the anaesthesia ended at 6.35 p.m. During this time the wound in his leg was cleaned and excised, pins put through the two fragments of the tibia, the fracture reduced, a dressing applied, and the leg and foot put in plaster-of-Paris. Subsequently he made a good recovery.

Case 4.—A woman aged 38 was admitted to hospital at 11 p.m. semiconscious and smelling strongly of beer, having been picked up in the street. No further history was obtainable, but she was found to have multiple lacerations of the scalp, and a laceration of the left ankle, with an oblique fracture of the left tibia just above the malleolus and involving the articular surface. She was drowsy but abusive if roused. Her skin was moderately pale and sweating; her pulse rate was 80 and her blood pressure 100/60 mm. Hg. A determination of plasma volume was begun at 11.31 p.m., and gave a figure of 2.1 l., or about 3.8% of body weight (about 8¼ st.). The haemoglobin was 14 g./100 c.cm. She was given morphine gr. 1/4 at 11.52 p.m. and anaesthesia was begun at 2.3 a.m. Cyclopropane was given first, and the blood pressure, which was 100/65 mm. Hg when anaesthesia started, was maintained at about 110/80 mm. Hg until 2.23 a.m. Ether was then gradually substituted and the blood pressure became erratic, eventually falling to 80/60 mm. Hg at 2.38 a.m. Ether was then withdrawn, and the blood pressure returned to 100/80 mm. Hg at 2.41 a.m. The patient was beginning to come round, and cyclopropane was given again from 2.42 to 2.47 a.m., the blood pressure being maintained at about 100/70 mm. Hg. During this time the wounds were cleaned and sutured, the fracture reduced, and the ankle put in plaster. Subsequently she made an uninterrupted recovery.

Case 5.—A man aged 67 was knocked down in the street by a lorry at 6.30 a.m. and sustained a comminuted fracture of the left femur and a right Colles fracture. On admission to hospital at 7 a.m. he was conscious and in considerable pain. His pulse rate was 45, with many extrasystoles, and his blood pressure 170/80 mm. Hg. At 9.20 a.m. his pulse rate had increased to 82 and his blood pressure had fallen to 110/60 mm. Hg. His skin was very pale, but warm and not sweating. A determination of plasma volume was begun at 9.30 a.m., and gave a figure of 3.05 l., or about 4.8% of body weight (about 10 st.). The haemoglobin was 8.8 g./100 c.cm. There was no appreciable change in his condition throughout the day. He was given morphine gr. 1/4 at 11.15 a.m. and omnopon gr. 1/3 and scopolamine gr. 1/150 at 4.28 p.m. A second determination of plasma volume was begun at 4.32 p.m., but gave an anomalous curve. He was taken to the operating theatre at 5 p.m. and intravenous pentothal was given at 5.22 p.m. There was a rapid fall in blood pressure from 110/70 mm. Hg, taken immediately before anaesthesia started, to 85/55 mm. Hg six minutes later. Thereafter the blood pressure was maintained at about 90/55 mm. Hg until the operation ended at 5.48 p.m. Altogether 0.5 g. of pentothal was used. A Kirschner wire was inserted through the upper end of the tibia and extension applied to the femur. The Colles fracture was reduced and a plaster applied. Subsequently he improved steadily, the blood pressure returning to the original level of 110/70 mm. Hg at 7 p.m. Unfortunately, he had to undergo a further operation four days later for malposition of his fractured femur, and afterwards he developed pneumonia and died.

Discussion

The effect of various anaesthetics on plasma volume and the cardiovascular system has been extensively studied. It has been claimed that some anaesthetics—notably ether—cause a reduction of plasma volume in the human subject (Bonnycastle, 1942). No significant changes were found, however, in the present series of cases even with prolonged anaesthesia for major abdominal operations unless there was appreciable haemorrhage such as occurred with radical operations for carcinoma of the breast.

That the anaesthetics affected cardiac action seems unlikely, because no significant changes were found in the electrocardiograms of patients showing such profound alterations of blood pressure as that revealed in Fig. 4.

It seems likely, therefore, that the main effect of anaesthetics on blood pressure is by the vasomotor system. Most anaesthetics lower the blood pressure, but nitrous oxide, oxygen, and ether may elevate it, and cyclopropane and oxygen nearly always elevate it. In shocked patients all anaesthetics tend to be more depressing, and in patients whose plasma volume is much reduced the effect of depressing anaesthetics may be disastrous. This may apply to severe cases even after the plasma volume has been restored to normal, because the vasomotor system is apparently unstable for some time afterwards. Case 1 is an example of this. A man was wounded in the peripheral parts of his limbs and the bleeding was not checked. His plasma volume fell in the next 6¼ hours to 3.1% of body weight, his haemoglobin to 10.5 g./100 c.cm., and his blood pressure became unreadable. A transfusion during the next 2½ hours restored his plasma volume to 4.7%, which is within the lower limit of normal; his haemoglobin was then 9.6 g./100 c.cm. There was considerable improvement in his general condition, but the blood pressure was still only 70/50 mm. Hg. An operation was undertaken 8¾ hours after the injury to clean the wounds and arrest further bleeding. So little was done surgically that it can have had only slight effect on the general condition; but the anaesthetic, a mixture of ether and chloroform, caused a rapid progressive fall in blood pressure and death in nine minutes.

The use of nitrous oxide and oxygen with a minimal amount of ether has a much less depressing effect, as demonstrated by a somewhat comparable patient (Case 2) who sustained severe wounds, chiefly to the peripheral parts of his limbs. Two bottles of blood were given between 5½ and 7½ hours after

the injury, and the plasma volume 12¼ hours after was about 2.8% of body weight. The haemoglobin was 11.8 g./100 c.cm. There was a temporary improvement after the first transfusion, but the blood pressure subsequently fell to 85/50 mm. Hg, and two bottles of plasma were given, therefore, between 10½ and 15½ hours after the injury. A second determination of plasma volume 19¼ hours after the injury gave a figure of about 3.8% of body weight; the haemoglobin was 11.4 g./100 c.cm. Anaesthesia was begun 21 hours after the injury, and the blood pressure rose from 100/55 to 110/65 mm. Hg in the first 4 minutes and then fell steadily to 80/50 mm. Hg in the next 15 minutes. Ether was stopped after the first 7 minutes. The blood pressure was then maintained at 85/50 mm. Hg until the operation ended 49 minutes after the anaesthetic began. During the next 12 hours the systolic pressure rose to 140 mm. Hg, although eventually the patient died with a gangrenous leg.

In less severe cases nitrous oxide and oxygen with a minimal amount of ether may cause the blood pressure to rise, as demonstrated by Case 3. This patient sustained a compound fracture of the left tibia and fibula. His blood pressure was 110/60 mm. Hg 40 minutes after the accident, and his plasma volume was 4.3% of body weight and haemoglobin 12.2 g./100 c.cm. two hours after. No transfusion was given. When anaesthesia was begun 5¼ hours after the accident his blood pressure was 130/70 mm. Hg. It rose to 170/75 mm. Hg in the first ten minutes and then fell gradually to 140/75 mm. Hg in the next 25 minutes, remaining there till the operation ended 50 minutes later.

The best anaesthetic used in our shocked patients was cyclopropane and oxygen. It was employed in Case 4. This patient, who had a crushed foot and lacerated scalp, had a plasma volume of 3.8% of body weight and haemoglobin of 14 g./100 c.cm. 30 minutes after the accident. The blood pressure was then 100/60 mm. Hg. Anaesthesia was begun three hours after the accident, and the blood pressure rose slightly to 110/80 mm. Hg, where it remained for the next 20 minutes. At this time the cyclopropane was gradually changed to ether for the purpose of comparison, and the blood pressure fell during the next 15 minutes to 80/60 mm. Hg. After withdrawal of ether the blood pressure recovered, and it was maintained at 100/70 mm. Hg during the last five minutes, when cyclopropane was given again.

In attempting to assess the depressing effects of anaesthetics on the cardiovascular systems of shocked patients it is necessary to emphasize that quite severe injuries can occur with little reduction of plasma volume. This may explain why the lowering of blood pressure by an anaesthetic is sometimes less than might be expected. It occurred in Case 5, a man who sustained a compound fracture of the left femur and a right Colles fracture. His plasma volume was within the lower limit of normal —about 4.8% of body weight—his haemoglobin was 8.8 g./100 c.cm., and his blood pressure was 110/60 mm. Hg three hours after the accident. During the next 11 hours his general condition remained about the same and his blood pressure was 110/70 mm. Hg when intravenous anaesthesia with sodium pentothal was begun. It then fell steadily to 85/55 mm. Hg in the next six minutes, and remained at about this level until the anaesthesia ended 25 minutes later.

The chief factors in anaesthetizing shocked patients seem, therefore, to be, first, the use of a minimal amount of anaesthetic—and it is often surprising how little these patients require; secondly, the choice of an anaesthetic which stimulates rather than depresses the cardiovascular system; and, thirdly, an adequate amount of oxygen. It is unfortunate that the two most satisfactory anaesthetics—cyclopropane and oxygen, and nitrous oxide, oxygen, and ether—both require somewhat elaborate apparatus. Fortunately, however, in modern war it is possible for the great majority of patients to be brought back for operations to base hospitals where such apparatus is available.

Summary

Plasma volume and haemoglobin concentration were measured repeatedly in 26 patients undergoing various operations under nitrous oxide, oxygen, and ether, cyclopropane and oxygen, sodium pentothal, and spinal analgesics. No significant changes were found, although marked alterations in blood pressure occurred.

Serial electrocardiograms examined in nine patients showed no constant changes even though a marked alteration in blood pressure had taken place.

It is concluded that anaesthetics affect blood pressure mainly through the vasomotor system.

Cyclopropane and oxygen tended to raise the blood pressure; nitrous oxide, oxygen, and ether had variable effects on it; sodium pentothal and spinal analgesics depressed it.

In patients whose plasma volume was reduced by trauma there was a greater tendency for these anaesthetics to depress blood pressure.

Cyclopropane and oxygen was the best and nitrous oxide with adequate oxygen and a minimal amount of ether was the next best anaesthetic for these cases.

We are indebted to Dr. Miles for access to clinical material and to Mr. Whittingham and Dr. Murdoch for their co-operation in the cases undergoing major operations at Oldchurch Hospital, Romford. Dr. William Evans kindly examined the electrocardiograms for us.

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THE USE OF PENICILLIN PASTILLES IN ORAL INFECTIONS

A PRELIMINARY REPORT

BY

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In July of this year it was decided to attempt to treat various types of oral infection with local penicillin. Previous experience had shown that the use of a spray was unsatisfactory in the treatment of acute tonsillitis, presumably owing to the transient action so exerted, and it was felt in consequence that, if any success were to be obtained, a means of maintaining an adequate concentration of penicillin in the mouth would be required.

It was therefore decided to try the effect of penicillin contained in a pastille. For this purpose a slow-melting medium unlikely to cause excessive salivation, approximately neutral in reaction, and not containing any penicillin inhibitor, was required. This was found in gelatin. To the gelatin base 0.1% nipagin was added in order to preserve the pastille, though whether this was necessary is doubtful, as pastilles kept over a period of three months do not appear to have deteriorated, apart from a slight hardening of the medium. In the preparation of the pastilles care was taken that the penicillin was not subjected to excessive heat; it was added to the gelatin base at 42° C. and stirred in just before the latter was about to set. Pastilles were cut to a standard size of approximately 3/8 in. square and 1/8 in. thick to facilitate insertion and retention in the buccal sulcus, and for trial purposes they were made in varying strengths from 1,000 units of penicillin to 100 units in each pastille.

With these pastilles experimental work was then carried out in order to determine: (1) that the penicillin derived from the pastille was present in effective concentration in the mouth, and that this concentration could be maintained; (2) that the incorporation of the penicillin in the pastille base would not interfere with its action, and that the pastille would keep and would remain active after its manufacture; (3) the effect of the pastille on the mouth and throat and their bacterial flora; (4) the required dose of penicillin in each pastille.

The results of these investigations were as follows:

1. A pastille containing 500 units of penicillin was allowed to melt in the buccal sulcus. After 15 minutes the pastille was removed and the penicillin content of the saliva was estimated by the standard technique. Further estimations at 15 and 30 minutes after removal