thyroid. He finally died of pneumonia and at autopsy a capsulated adrenal tumour, 6 cm. in diameter, of the chromaffinoma type was found, and a heart weighing 790 grm. His clinical symptoms were accounted for apparently by the presence of the tumour which showed no metastases. The thyroid gland was normal in size and in histological appearance.

Cases of death within 48 hours from slight injuries which become infected with streptococcus occur occasionally. In these cases, one finds a little pus around the wound, but no marked tissue reaction. Cultures at the site of injury usually show the presence of the organism, and occasionally it may be isolated from other parts of the body. These cases are sometimes hard to explain to lay juries. The problem of the balance between virulence and resistance is involved here and it may be that the question of allergy should also be given consideration.

The cases quoted above comprise a few of the more unusual findings in this series of autopsies, some of which have been reported in a previous paper.[1] Many of them are, no doubt, not unusual findings to those with a greater autopsy experience. The exchanging of experiences, however, helps to increase the sum total of our knowledge, and I think that most pathologists will agree that in autopsy work, one is apt always to encounter lesions just a little different, no matter how great one's experience.

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SPINAL ANÆSTHESIA*

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SPINAL anæsthesia was first advocated by Corning in 1885, but the method did not meet with much recognition by members of the medical profession until procaine was discovered in 1904. The method has had brief periods of popularity, but it was not until the use of ephedrine became general that spinal anæsthesia gained wide acceptance. During 1929 and 1930 the peak of the present wave of popularity was reached. The trend of opinion regarding the methods employed and results obtained has since become critical. Questions regarding the physiological changes produced by blocking the roots of spinal nerves have arisen, and unfortunately few of them can be satisfactorily answered. Conflicting theories have been evolved, and different methods of producing spinal anæsthesia based on these theories have been developed. Comment here will be limited to the method that is employed at The Mayo Clinic.

THE CHOICE OF CASES FOR SPINAL ANÆSTHESIA

Because many points regarding the physiology of subarachnoid block are not well understood it has remained for experience, based on large series of cases, to show that the method should not be used indiscriminately but should be reserved for certain types of cases. At The Mayo Clinic the use of spinal anæsthesia is limited to operations below the diaphragm. The method is indicated particularly for patients suffering from emphysema, advanced asthma, chronic bronchitis, bronchiectasis, and other respiratory diseases, for whom it is essential that reflexes be rapidly recovered and for whom a general anæsthetic given by inhalation is contraindicated. Patients suffering from diabetes may be operated on under spinal anæsthesia without remote untoward effect, provided the usual precautions are taken preoperatively and postoperatively to control the metabolism of carbohydrates. Because a few centigrams of the drug have so little effect on the general cellular metabolism, spinal anæsthesia is indicated in cases in which the kidneys are not functioning properly and in which a general anæsthetic, given by inhalation, is contraindicated. Patients suffering from intestinal obstruction may be operated on successfully after the administration of a spinal anæsthetic. Gastric lavage, followed by evacuation of the liquid

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content of the stomach immediately before the patient comes to the operating room, is advised. The likelihood of vomiting copious amounts of material is eliminated to a great extent, and aspiration of particles within the trachea and lungs is thus prevented. For patients suffering from intestinal obstruction, who are debilitated and dehydrated, abdominal block, supplemented by inhalation of ethylene and oxygen, rather than spinal anæsthesia, is advised. Aside from these conditions, the decision of whether to use spinal anæsthesia depends on the degree of relaxation considered necessary for successful completion of the operation. The method has been found useful for hysterectomy, the removal of tumours within the broad ligament, and removal of large ovarian cysts.

CONTRAINDICATIONS

1. The procedure is contraindicated in the presence of involvement of the central nervous system by a tumour of the spinal cord, syphilis, epilepsy, and intracranial or intraspinal hæmorrhage. Patients suffering from pernicious anæmia or subacute combined degeneration of the spinal cord should not be given a spinal anæsthetic. Subsequent involvement of the spinal cord, due to progress of the disease, might be attributed to the procedure.

2. Patients whose blood pressure is extremely high generally experience marked reactions following the induction of spinal anæsthesia, and for them the dose used must be conservative. Many persons have normally low blood pressure, and spinal anæsthesia in such cases does not entail greater risks than for patients who have a normal blood pressure. Patients with hypotension, (a systolic blood pressure of 100 mm. of mercury or less), who constitute poor operative risks, especially if decompensation is present and if cyanosis is evident, do not tolerate spinal anæsthesia well. For them the method should not be used for operations above the lower part of the abdomen, unless a general anæsthetic is contraindicated. In any case, the dose of procaine should be minimal. For patients whose systolic blood pressure is 90 mm. of mercury or less anæsthetic procedures other than subarachnoid block are advised.

3. Patients in a state of shock constitute poor risks for any form of anæsthesia. If the shock is not of hæmorrhagic origin spinal anæsthesia may be used and is satisfactory when the shock has been due to occurrence of intussusception or volvulus, or when an ovarian tumour becomes twisted on its pedicle. In some instances, due to the breaking of the reflex arc, shock may be partially controlled by the anæsthesia.

Burch, Harrison and Blalock[2] reported that hæmorrhage in association with spinal anæsthesia is much more likely to cause shock than the same loss of blood under ether. Under ether anæsthesia, withdrawal of blood equal to 3 or 4 per cent of the weight of the body produced marked decline in cardiac output and blood pressure of dogs, but the animals were not in grave danger of immediate death. Under spinal anæsthesia death was produced by removing an amount of blood which varied from 0.5 to 1.6 per cent of body weight, because the vasoconstrictor mechanism which normally compensates for hæmorrhage is disturbed. The method is contraindicated if patients have lost a large amount of blood, or if severe loss of blood during operation is anticipated.

4. For patients with diminished breathing capacity due to pleural effusions or intrathoracic tumours, combined with a lowered concentration of hæmoglobin, spinal anæsthesia is contraindicated.

5. Superficial infection over the area through which the spinal needle would be inserted precludes the use of the method. Patients suffering from septicæmia should not be given a spinal anæsthetic because infection might be carried within the dura.

PRELIMINARY MEDICATION

Administration by mouth of pentobarbital sodium, 1½ or 3 grains (0.1 or 0.2 g.), the evening previous to operation assures the patient of a night's rest. The patient's susceptibility to the action of the drug may be gauged, and decision regarding the preliminary medication to be given the morning of operation is thus facilitated. One hour before operation, 1½ or 3 grains of pentobarbital sodium may be given by mouth and morphine sulphate in a dose of 1-6 to 1-4 grain (0.01 to 0.016 g.) is given hypodermically. If it is intended that the spinal anæsthesia be supplemented by a general anæsthetic, atropine sulphate, grain 1-200 or 1-150 (0.003 or 0.004 g.), may be given with the morphine. If, however, the patient is suffering from abdominal distention, atropine is probably best omitted because it interferes with the function of the myoneural juncture of nerves which supply unstriated muscle fibres. The line of vagal

innervation is thus broken, and contraction of the intestines is rendered difficult even after the inhibitory sympathetic innervation is paralyzed following subarachnoid block.

Ephedrine.—Ockerblad and Dillon[8] were the first to advocate the use of ephedrine in spinal anæsthesia. The drug is now well recognized by many as a useful adjunct to spinal anæsthesia. Labat,[6] however, is of the opinion that "the injection of ephedrine or any other hypertensive drug is useless, occasionally harmful." Saklad[10] is of the opinion that a fall in blood pressure is of no serious consequence if the patient is kept in the Trendelenburg position. He maintains that ephedrine, by its power of accelerating the heart, places the patient in a condition approaching circulatory exhaustion. Chen and Schmidt[3] found that large doses depress the cardiac musculature and cause a fall in blood pressure. Burch and Harrison[1] showed by experiments on dogs that the initial change in spinal anæsthesia is reduction in arterial pressure. This vasodilatation may involve the unanæsthetized as well as the anæsthetized region. Venous return and cardiac output are affected secondarily. Since it is peripheral resistance that is primarily affected, it may be argued that vasoconstrictor drugs should be useful in maintaining blood pressure during spinal anæsthesia. At The Mayo Clinic evidence of circulatory injury attributable to ephedrine has not been noted when the dose is limited to that sufficient to maintain or restore the blood pressure to a normal level. The blood pressure may fall after administration of a spinal anæsthetic, in spite of ephedrine having been given, but it is felt that the reduction is not so great as it otherwise would be. The pressure is prevented from approaching the critical level at which circulation to vital organs becomes inadequate because of marked reduction in the cardiac output. In order to avoid any deleterious effect on cardiac action, the administration of ephedrine is limited to one dose, not exceeding 75 mg., either prior to introduction of the anæsthetic agent or immediately after. To patients who exhibit a decrease in blood pressure subsequently, epinephrine is given.

If the patient's blood pressure is normal, a hypodermic injection of 25 or 50 mg. (3-8 or 3-4 grain) of ephedrine is given ten minutes before the introduction of the anæsthetic agent. If the blood pressure is 160 mm. of mercury or higher it may be desirable to delay injection of ephedrine until the lumbar puncture needle has been inserted and the procaine injected. Thus, if it should appear that the procedure could not be successfully completed, one would be guarded against unduly raising the blood pressure. If the systolic blood pressure is less than 100 mm. of mercury, it is advisable to give 50 mg. of ephedrine twenty minutes before the spinal anæsthetic is introduced; unless there is some response to the hypertensive drug the dose of procaine should be minimal.

PROCAINE (NOVOCAINE, NEOCAINE ETC.)

The dosage of procaine depends on several factors. The patient's blood pressure, age, weight and height must be considered. An estimate of the patient's resistance in relation to his primary disease and in relation to any complicating disease from which he may suffer is made. These factors, together with the site and possible duration of the operation should guide in deciding on the dose of procaine. From 1 to 1.5 mg. of procaine for each pound of body weight, with a maximal dose of 200 mg., is a reliable guide. The smaller doses should be given to old and debilitated patients who are affected by hypotension, cardiovascular disease, recent extreme loss of weight, or lowered concentration of hæmoglobin with attendant decrease in the power of the blood to carry oxygen.

METHOD OF ADMINISTRATION

Formerly it was the practice at The Mayo Clinic to use crystals of procaine dissolved in spinal fluid. In order to simplify the method, procaine in 10 per cent solution (100 mg. in each c.c.) in physiological solution of sodium chloride has been used since October, 1931, with equally good results. The remainder of the bulk of liquid to be injected is composed of aspirated spinal fluid. It is recognized that there are many factors over which little control can be exerted that influence the final destination of a drug when introduced into the dural sac. Among these are the rate of circulation of the spinal fluid, the spinal fluid pressure, the presence of lordosis or scoliosis, the size of the nerve roots, and a possible partition effect of the dural sac in those cases in which the ligamentum denticulatum forms a fairly complete curtain.

There are, however, many factors over which control is possible and which may be varied in order to obtain anæsthesia of a desired level. At The Mayo Clinic all injections are given while the patient is lying on the side on a cart or operating table. Control of duration and of

extension cephalad of anæsthesia is achieved by varying the dose of procaine and the amount of spinal fluid with which it is diluted. The site of injection has been standardized for each operation. Barbotage is not practised and the rate of injection is kept uniform. For a given procedure, lumbar puncture needles of the same calibre are always used. Table I indicates the

TABLE I.

DOSAGE AND DILUTION OF PROCAINE IN SPINAL ANÆSTHESIA

Operation	*Injection between*	*Dose, mg.*	*Total physiological saline solution + spinal fluid, c.c.*
Perineal repair..	L_3 and L_4	80 to 120	2.5
Mayo vaginal hysterectomy..	L_2 and L_3	120 to 150	3.0
Herniorrhaphy..	L_2 and L_3	120 to 150	3.5
Appendectomy..	L_2 and L_3	120 to 150	4.0
Hysterectomy...	L_2 and L_3	150 to 200	4.5
Cholecystectomy	L_1 and L_2	150 to 200	5.0

Spinal needle, gauge 20-22; rate of injection, 0.5 c.c. per second.

dosage of procaine and the amount of liquid injected, the site and rate of injection, and the gauge of needle used for certain operations. For patients who constitute poor operative risks the dosage may be reduced 15 to 20 per cent without appreciably diminishing the duration of anæsthesia if injection is made one interspace higher than usual and if the dilution is decreased by 0.5 c.c. Two hundred milligrams of procaine are usually sufficient for operations on the gall bladder or stomach. Some pain, nausea, and vomiting may be induced, but rather than to increase the dose beyond safe limits it is preferable to administer nitrous oxide and oxygen or ethylene and oxygen.

COURSE OF ANÆSTHESIA

Following administration of the procaine the patient is turned on his back. A feeling of warmth followed by a feeling of numbness appears in the lower limbs. Motor paralysis develops, but with the smaller doses (120 mg.) loss of function may not become complete. The temperature of the surface of the feet increases to a maximum of 35°C. in the average case. Anæsthesia develops in three to seven minutes, and becomes stationary in ten minutes. During this period the extent cephalad of anæsthesia may be increased beyond the calculated level if the head of the table is lowered. After the drug has become fixed, the full Trendelenburg position may be employed if the surgeon desires it without further influencing the level of anæsthesia. All changes in position should be made slowly and gently to prevent nausea, vomiting, and respiratory embarrassment. When procaine is used, anæsthesia is maintained for from thirty to seventy minutes. For three to six hours after operation the patient is kept in the horizontal position and the head is not elevated. For patients who exhibit lowered blood pressure, the foot of the bed should be raised 6 to 10 inches.

ANÆSTHETIC AGENTS OTHER THAN PROCAINE

If one limits oneself to a maximal dose of 200 mg. of procaine, and in my opinion this should rarely be exceeded, the duration of anæsthesia for certain operations is frequently not sufficient. The nausea and vomiting sometimes encountered following the administration of procaine are distressing to the patient and may interfere with the work of the surgeon. Reduction in the systolic blood pressure may be accompanied by alarming symptoms. Occurrence of these difficulties has intensified the search for drugs which will not produce these untoward reactions. At The Mayo Clinic a number of newer drugs have been tested experimentally on animals and rejected as unsuitable for clinical use, either because they were too toxic or because they did not equal or surpass procaine in anæsthetic potency. Nupercain and pantocain have been used clinically.

Nupercain, the hydrochloride of *a*-butyloxycinchoninic acid diethylethylenediamide) is a quinoline derivative that is freely soluble in water, that is free from alkali. The drug was employed 327 times for production of spinal anæsthesia. It was found that when given in doses sufficient to produce uniformly satisfactory anæsthesia, its action was too prolonged, the incidence of pulmonary congestion was increased, and restoration of normal blood pressure was delayed and rendered difficult in the presence of surgical shock.

Pantocaine (butylaminobenzoic acid-β-dimethylamino-ethylester hydrochloride,) is a derivative of procaine. It differs from procaine chiefly by the attachment of a butyl group to the nitrogen of the aminobenzoic acid, and replacement of one diethyl group by one dimethyl group. The hydrochloride is a white crystalline substance, soluble in water and physiological solution of sodium chloride. A solution in a concentration of 1 per cent has a pH of 5.8 and a specific gravity of 1.006. Boiling does not reduce its efficiency, and sensitivity to alkali is not so marked as with nupercain. Füssganger and Schaumann[5] found that when injected intravenously in rabbits pantocaine is about nine times more toxic than procaine if 55 mg. per kilogram of body weight is considered the average lethal dose of procaine. The same authors found the drug three times more toxic than cocaine on the basis that 18 to 20 mg. per kilogram of body weight represents the lethal dose of cocaine. Wiedhopf[12] found pantocain two and a half to three times less toxic than nupercain when injected intravenously in dogs. Runge and Schmidt[9] found pantocaine to be six to seven and a half times as toxic as procaine on an absolute basis of milligrams per kilogram of body weight, but if effective concentrations, such as are used in practical anæsthesia were considered, pantocain was relatively slightly less toxic than procaine.

From February, 1931, to May 1, 1932, this drug has been used intradurally 628 times. Dosage is calculated on the basis of 1 mg. for each 20 pounds of body weight, with 5 mg. added. The maximal amount used for any operation is limited to 20 mg. A concentration of 1 per cent (10 mg. per c.c.) is employed, and, as with procaine, spinal fluid is used as diluent. The extent cephalad of anæsthesia is varied by varying the total amount of fluid injected. Details regarding the administration are outlined in Table II. For approximately 100 cases the dosage of pantocaine has been reduced by employing procaine in combination with it. It has been found by McCuskey,[7] and more recently by myself, that satisfactory anæsthesia can be obtained with 5 or 10 mg. of pantocaine, when combined with from 50 to 100 mg. of procaine (Table III.). The duration of anæsthesia is from one and a half to two times that obtained when a safe dose of procaine is employed for the same operation. If pantocaine alone, in an amount sufficient to produce anæsthesia to the desired extent cephalad, were substituted for the same operation, the anæsthetic effect would continue two to three times as long as when procaine was employed alone. For the majority of operations, a combination of pantocaine and procaine produces anæsthesia of satisfactory duration.

Pantocaine has not displaced procaine as the drug of choice. It has, however, displaced nupercain for operative procedures that are time-consuming. Because it fails to arrive at a fixed position in relation to the nerve roots to be attacked as rapidly as does procaine, and because it is exceedingly potent even when greatly diluted, employment of this comparatively new drug is reserved for operations below the umbilicus.

TABLE II.

USE OF PANTOCAIN IN SPINAL ANÆSTHESIA

Operation	*Injection between*	*Dose, mg.*	*Total physiological saline solution + spinal fluid, c.c.*
Mayo vaginal hysterectomy....	L_2 and L_3	10 to 12	2.5
Fulguration within urinary bladder..	L_2 and L_3	12 to 15	3.0
Transplantation of ureter.....	L_2 and L_3	12 to 15	3.5
Herniorrhaphy (bilateral).....	L_2 and L_3	12 to 15	3.5
Complete abdominal hysterectomy	L_2 and L_3	15 to 20	4.0

Spinal needle gauge, 20-22; rate of injection, 0.5 c.c. per second.

TABLE III.

USE OF PANTOCAIN AND PROCAINE COMBINED IN SPINAL ANÆSTHESIA

Operation	*Injection between*	*Combined dose, mg.*		*Total physiological saline solution + spinal fluid, c.c.*
		Pantocain-	*+Procaine*	
Mayo vaginal hysterectomy...	L_2 and L_3	5	50	2.5
Fulguration within urinary bladder	L_2 and L_3	10	50	3.0
Transplantation, ureter.....	L_2 and L_3	10	50	3.5
Herniorrhaphy (bilateral).....	L_2 and L_3	10	50	3.5
Hysterectomy, complete abdominal.....	L_2 and L_3	10	100	4.0

Spinal needle, gauge 20-22; rate of injection, 0.5 c.c. per second.

DESIRABLE AND UNDESIRABLE EFFECTS

Certain complications may occur during operation, and unfortunately knowledge of the physiological reaction involved is incomplete in many cases. Failure to obtain anæsthesia is regrettable, but is due usually to faulty technique rather than to anatomical anomalies. If anæsthesia is not effective twenty minutes following injection, a second injection may be made with comparative safety. Anæsthesia which does not extend as far cephalad as is desired is annoying and may necessitate administration of an anæsthetic by inhalation.

It is the reduction of blood pressure beyond anticipated limits which gives most concern. A fall in blood pressure of from 15 to 20 mm. of mercury in the first twenty minutes may be expected, but a continued drop creates a problem. It has been found clinically that inclination of the head downward is an essential factor in preventing excessive fall in blood pressure. This inclination may be increased to the full Trendelenburg position when it is necessary. If the depression of blood pressure continues beyond the limit anticipated in the average case the patient should be persuaded to breathe deeply. Administration of oxygen, 90 per cent, and carbon dioxide, 10 per cent, will increase the respiratory excursion; the blood flow to the heart is augmented and the blood pressure is raised. Epinephrine, 5 minims, may be given subcutaneously, and the dose repeated once or twice. If the drop in blood pressure occurs late in the operation, and is associated with surgical shock, intravenous administration of physiological solution of sodium chloride is frequently productive of

beneficial results. Epinephrine, 2 to 4 minims of a 1:1000 solution, may be injected with the first few cubic centimetres of the saline solution given.

With the decrease in blood pressure there may be pallor, nausea, retching and vomiting. Treatment of the drop in blood pressure ordinarily alleviated nausea of this type. Frequently the reaction is psychic and has no relation to blood pressure. Sufficient preliminary medication and an entertaining anæsthetist may eliminate this complication. Nausea may be due to a reflex stimulation initiated by insertion of intra-abdominal packs or by manipulation of the viscera, particularly of the upper part of the abdomen. The surgeon's cooperation is essential when these circumstances are present. In a percentage of cases the retching may be sufficiently annoying to the surgeon that supplementary anæsthesia with nitrous oxide and oxygen, or ethylene and oxygen, will be required.

Occasionally patients may complain of severe pain in the lower limbs, although anæsthesia and relaxation may extend to the costal margin. When this rather bizarre reaction occurs, supplementary anæsthesia with nitrous oxide and oxygen, or ethylene and oxygen, is indicated. One patient who complained of this pain also complained bitterly of pruritus. The area involved was a band two inches in width immediately cephalad to the level to which anæsthesia extended. This patient was not given a supplementary anæsthetic and his pain and pruritus persisted until the effects of the procaine disappeared. The post-operative course in any case in which these reactions have been exhibited has been uneventful.

Following operation, headache is the most common complication, but it does not occur more frequently following spinal anæsthesia than following lumbar puncture for diagnosis when from 6 to 7 c.c. of spinal fluid has been withdrawn. It has been reported that a retention enema of 180 c.c. (6 ounces) of 50 per cent solution of magnesium sulphate gives relief. Surgical pituitrin, 1 c.c., or ephedrine, 50 mg. (¾ grain), given hypodermically, produces improvement in some cases, but time is the essential factor influencing ultimate relief. Areas of numbness in the legs may persist for some time, but this numbness usually disappears without treatment. Foot-drop may develop occasionally, as it does following a general anæsthetic, and is likely due to pressure on a nerve trunk rather than to the anæsthetic agent or the method of administration.

In a series of more than 7,000 cases in which spinal anæsthesia was induced at The Mayo Clinic no permanent motor paralyses have been encountered. Ocular palsy, involving the lateral rectus muscles, is of rare occurrence. Strabismus may develop in the second week following operation, and the patient complains of double vision. Two cases have occurred in the series, and recovery without treatment took place. These complications occur rarely, but should be thought of as possibilities.

Properly induced spinal anæsthesia, using any of the approved methods, produces complete freedom from pain in the operative field, and absolute relaxation of the muscles. Operative exposure is facilitated. The dose of the drug is small, and is so placed that maximal anæsthesia is obtained with the least generalized toxicity. The maximal fall in blood pressure occurs early in the operation, when the patient is best able to withstand it. Mucous membranes are not irritated as with ether, and post-operative vomiting is minimal. The method may be used for patients requiring emergency surgical procedures but who have slight infection in the upper part of the respiratory tract. The incidence of post-operative pulmonary complications is not increased, and fluids can be administered earlier after operation than where general anæsthesia has been induced.

The method has its limitations. The patient is awake and may fail to cooperate. Faulty technique in administration is more obvious than with a general anæsthetic. Nausea and vomiting may necessitate the administration of supplementary general anæsthesia. With the use of procaine there is a definite limit to the duration of anæsthesia. For operations within the upper part of the abdomen, rather than increasing the dose of procaine, supplementary general anæsthesia is advised. For operative procedures below the level of the umbilicus that are time consuming pantocain, either alone or preferably combined with procaine (Table III), may be employed.

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