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SPREAD OF ANALGESIC SOLUTIONS IN THE EPIDURAL SPACE AND THEIR SITE OF ACTION: A STATISTICAL STUDY

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A number of variables determine how far neural blockade will spread after injection of an analgesic solution into the epidural space. Some of these are intrinsic to the patient, and some are extrinsic, depending on variations of technique and the drugs employed.

The intrinsic variables governing the spread of solutions in the epidural space are best understood if we consider the space as a more or less cylindrical reservoir, the volume of the reservoir being determined by such factors as the length and breadth of the cylinder, and the size of the structures normally contained in it. Draining the reservoir are certain conduits and escape routes, through which seepage and absorption of injected materials can take place. The rate of disappearance of solutions from the area will depend on the patency and efficiency of the escape routes. The most notable of these are the intervertebral foramina and the extradural venous plexuses, and any study of the spread of analgesic solutions must take account of the factors which affect these structures, for the extent of neural blockade will be governed in part by the speed at which nerves are blocked, in relation to the rate with which the analgesic solution is removed from their vicinity. If the speed of the latter is fast compared to the former, solutions may be removed so rapidly that there is no chance for them to spread and produce widespread blockade. Whereas if absorption is slow there will be an opportunity for more prolonged and intimate contact between solution and nerves, so that the extent and intensity of spread is likely to be greater.

Incomplete understanding and lack of quantitative information on these and other variables have given rise to the impression that epidural analgesia is haphazard and unpredictable. The purpose of this paper is to clarify some of the factors which affect epidural blockade, in the hope of increasing the accuracy of the method, and reducing the apparent anomalies of spread which are apt to arise from ignorance of underlying mechanisms. Some of these factors have been discussed elsewhere (Bromage, 1954a), but the accumulation of further data has made it necessary to revise and amplify certain conclusions reached at that time.

CLINICAL METHODS

Studies were made in 358 patients who received epidural analgesia for surgical, obstetrical, or therapeutic indications. Surgical patients with marked respiratory or cardiovascular disease, or with hepatic cirrhosis, were excluded from the series in case alterations in the haemodynamics of the extradural venous plexus accompanying these conditions should affect the spread of epidural solutions in an abnormal way. Careful records were kept of the exact volumes and concentrations of solutions injected into the epidural space, and the onset and spread of analgesia to pin-prick was charted in terms of dermatome levels at the upper and lower limits of analgesia, using a compromise between the dermatome maps of Foerster (1933) and Keegan (1947), as in a previous communication. (Bromage, 1958).

Epidural puncture was carried out at the second or third lumbar interspace, using the loss-of-resistance test. The exact volume of solution entering the epidural space from the test syringe was noted, and its quantity added to the volume of the subsequent main dose for purposes of calculation. Injection of the main dose of analgesic solution was made from 10-ml syringes, through a No. 16 or No. 17 Tuohy needle, with the orifice directed towards the head. The speed of injection

was kept as constant as possible in every patient at about 1 ml/sec. Dosage varied between 7 ml and 25 ml, according to the age and height of the patient, and never exceeded the latter amount.

Skin analgesia was tested with a No. 22 hypodermic needle, or by nipping the skin with thumb and finger-nails, and spread of blockade was considered to be complete when two identical dermatome levels were determined at intervals 5 minutes apart. In some cases difficulty was experienced in defining the exact margin between sensitive and analgesic skin, particularly when observations were hurried by the exigencies of a busy surgical schedule. If there was any serious doubt about completion of the spread, or the accuracy of the upper and lower limits of the block, the case was excluded from the series.

The resultant spread of analgesia was expressed numerically as a segmental dose, that is,

$$\frac{\text{Dose}}{\text{Spread}} = \frac{\text{Volume of analgesic solution injected (ml)}}{\text{Number of dermatomes blocked}}$$

or Millilitres per spinal segment

Segments were counted upwards from the 5th sacral segment, and the coccygeal segments were excluded, since they occupy such a small part of the spinal cord. Thus blockade of all dermatomes up to and including the second thoracic would be counted as 21 segments (5 sacral, 5 lumbar and 11 thoracic).

The spread of analgesia (in terms of ml/spinal segment) was plotted separately against age in years, and height in inches, as in a previous study (Bromage, 1954b). The data were then examined statistically and correlations were sought between dose and age and height. The influence of posture and of pregnancy at term were also considered. Early in the series it was noted that patients with arteriosclerotic gangrene seemed to require unexpectedly small doses of analgesic solution to block a given number of segments, and so these patients were treated as a small separate group to see if their spread differed significantly from normal patients.

Analgesic solutions

Two per cent concentrations of three xylidide derivatives, lignocaine (Xylocaine), mepivacaine (Carbocaine), and L67 (Astra) were used for the preliminary part of the series in approximately equal numbers of cases (table I). Later in the series 3 per cent solutions of L67 and lignocaine became available through the kindness of Astra Pharmaceutical Products, Inc., and it was then possible to investigate the influence of increased concentration on the spread of epidural blockade. Since L67 has a relatively low toxicity, little hesitation was felt in employing volumes as large as 20 to 25 ml of the 3 per cent solution in young fit subjects; this represents a dose of 600 to 750 mg of L67. However, lignocaine is known to have a higher toxicity, and the results of a previous study of blood concentrations of lignocaine discouraged the use of volumes in excess of 16 ml of the 3 per cent solution (i.e. 480 mg lignocaine). Doses up to this amount did not produce any toxic effects. In addition, six patients were given epidural injections with very small volumes of 4.5 per cent lignocaine.

In about one-half of the cases adrenaline 1/200,000 was added to the 2 per cent solutions, and this did not appear to affect spread to any marked extent. Adrenaline was not added to the 3 per cent solutions.

TABLE I

Supine position.

Relationship between age and dosage requirements for 2 per cent solutions of three xylidide derivatives.*

Drug (2% solution)	No. of cases	Mean age	Mean dose (ml/segment)	Regression coefficient (ml per year of age)
Lignocaine (Xylocaine)	54	49.62	1.1313	−0.01315
Mepivacaine (Carbocaine)	58	49.23	1.1101	−0.0123
L67	55	49.54	1.1405	−0.0122
Consolidated data for Lignocaine, Mepivacaine and L67	167	49.46	1.1273	−0.01255

* Limits of age 20 to 81 years.

RESULTS

Statistics.

The data from 358 patients were divided into the following categories:

(1) *Supine posture.*
- (*a*) 2 per cent lignocaine (Xylocaine).
- (*b*) 2 per cent mepivacaine (Carbocaine).
- (*c*) 2 per cent L67.

(2) *Sitting posture.*
   (*a*) 2 per cent solutions (as above).
   (*b*) 3 per cent solutions (lignocaine and L67).
(3) *Pregnant women at term* (sitting, 2 per cent solutions).
(4) *Patients with arteriosclerotic gangrene* (supine, 2 per cent solutions).

Supine Posture, 2 per cent Solutions.

The results from the first group were given a preliminary examination to see if the influence of age on segmental spread was the same for each of the three drugs used. Regression coefficients were calculated for age and dose (in terms of millilitres of solution per spinal segment), and the regression lines were found to be almost identical in position and slope for the age group between 20 and 80 years (table I). Therefore it appeared that the three drugs spread in a very similar manner, at any rate in the 2 per cent solution, and so from this point onwards they will be treated together as a single group for statistical convenience.

The age, height, and dosage requirements of each patient were recorded on IBM punch cards, and the mathematical relationships of dosage to age and height were calculated with the aid of a data processing computer (IBM 650).

Dose and age.

Figure 1 shows the individual data of dose requirements related to age in 174 patients between the ages of 8 and 81 years. The computer

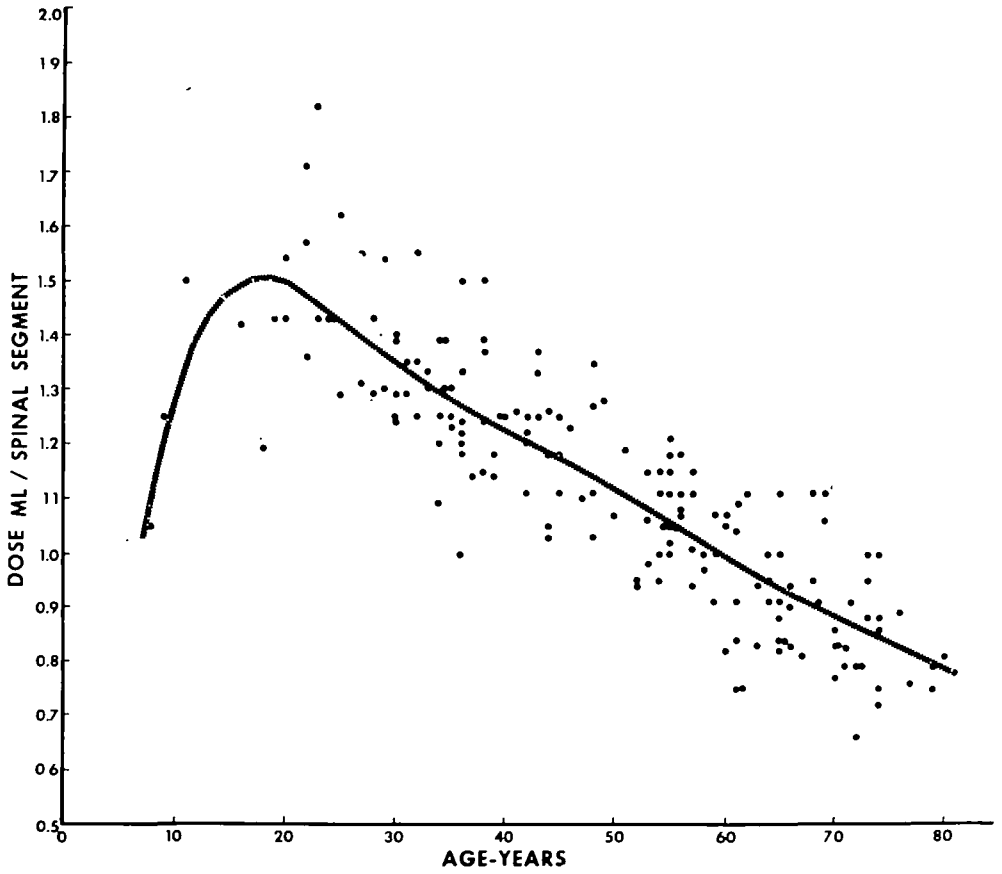

FIG. 1
Relationship of age and segmental dose for 2 per cent lignocaine, mepivacaine and L67 in the supine position in 174 patients aged between 8 and 81 years. The line is the mean of best polynomial fit from the data.

searched the data for the line of best polynomial fit of the form

$$y = a_0x^0 + a_1x^1 + a_2x^2 \ldots a_{25}x^{25}$$

and the best fitting equation was found to be:

$$y = -0.4329 + 0.3186x - 0.01964x^2 + 0.0005828x^3 - 0.000009213x^4 + 0.00000007415x^5 - 0.0000000002389x^6$$

The apex of the line occurs at about 16 to 19 years, but between 20 and 81 years the line is virtually straight. Figure 2 shows the regression line, with its 95 per cent fiducial limits (ABCD), after assuming a completely linear relationship of age and dose between 20 and 81 years. The regression equation for this straight line is:

$$y = 1.722 - 0.01204x$$

where y = dose in ml, and
x = age in years.

The lines EF and GH are drawn at twice the standard deviation on each side of the regression line, and 95 per cent of all data may be expected to fall within these limits. The correlation coefficient is -0.86, which indicates that dose requirements are very strongly associated with age.

Dose and height.

Figure 3 shows the individual dose requirements related to height in 155 patients between the ages of 20 and 81 years. The line of best fit is drawn through the plots, and the relationship is a linear one, with the equation:

$$y = -0.2378 + 0.02041x$$

where y = dose in ml and
x = height in inches.

The correlation coefficient (r) is 0.3434, which denotes a weak relationship between dose and

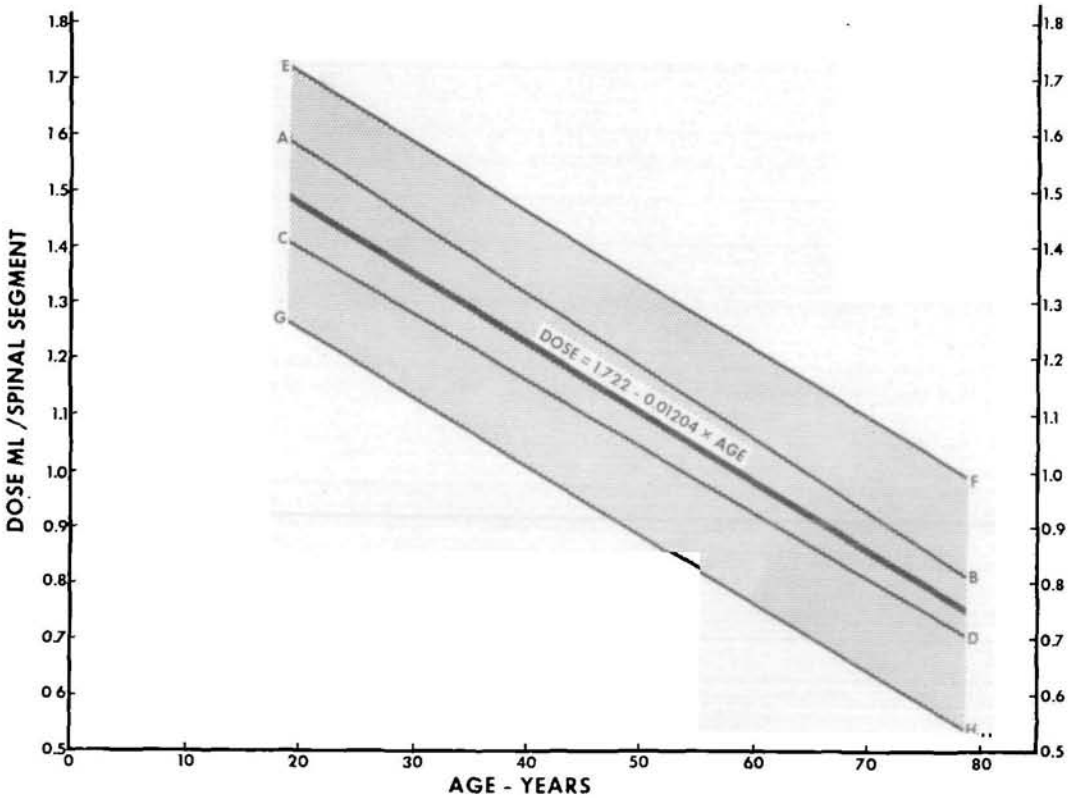

FIG. 2

95 per cent fiducial limits for the regression equation of dose on age in the 20 to 81 age group from figure 1, where $y = 1.722 - 0.01204x$. AB and CD are the 95 per cent confidence limits of the mean. 95 per cent of all patients fall within the limits EF and GH.

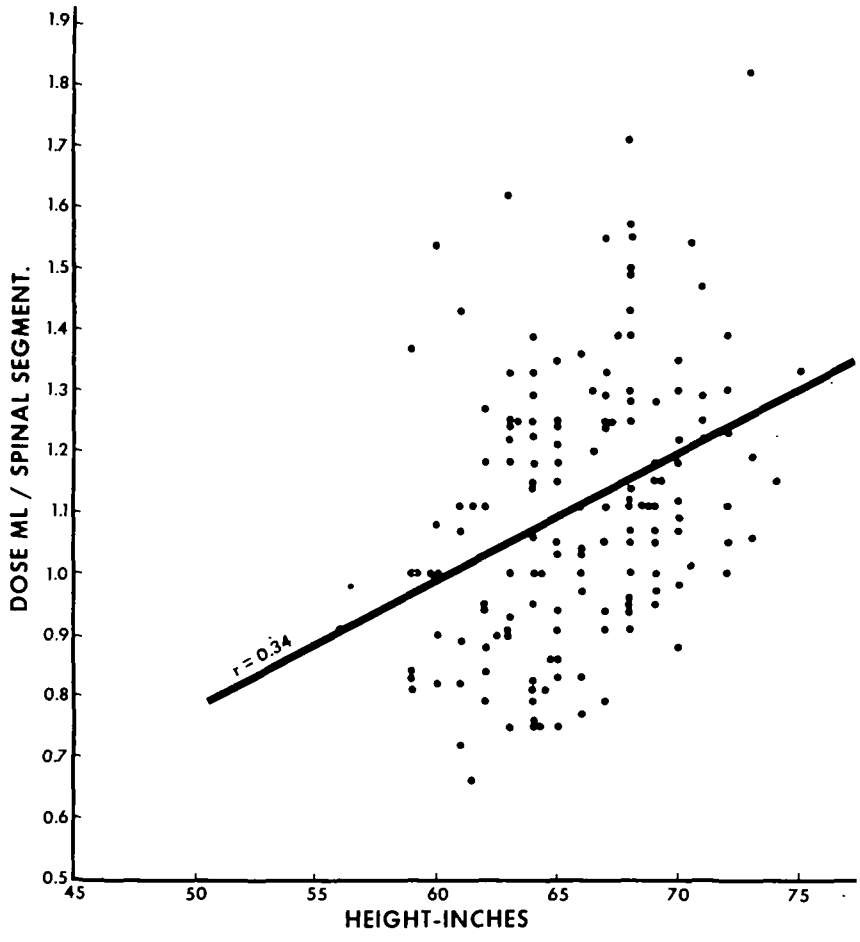

FIG. 3

Relationship of height and segmental dose for 2 per cent solutions in 155 normal patients between the ages of 20 and 81 years (supine position).

height, but a significant one in view of the large number of cases in the series.

Dose, age and height.

The multiple regression equation for dose in terms of both age and height was then calculated and found to be:

$$\text{Dose (ml/spinal segment)} = 1.714 - 0.0205A + 0.0000431H^2 + 0.00000136A^2H$$

where A = age in years, and H = height in inches.

Inspection of this equation shows that while stature has very little overall effect on dosage requirements, nevertheless height does tend to exert some influence with increasing age and increasing tallness. This equation provides the most accurate prediction of dose in terms of age and height. However, such an equation is clearly inappropriate for practical use, and so figure 4 has been constructed from it to show the various relationships of dose to age and height in graphic form.

It must be emphasized that this relationship is true only for the following conditions:

(1) Supine posture.
(2) 2 per cent solutions of the drugs tested (lignocaine, mepivacaine, and L67).
(3) Normal patients.

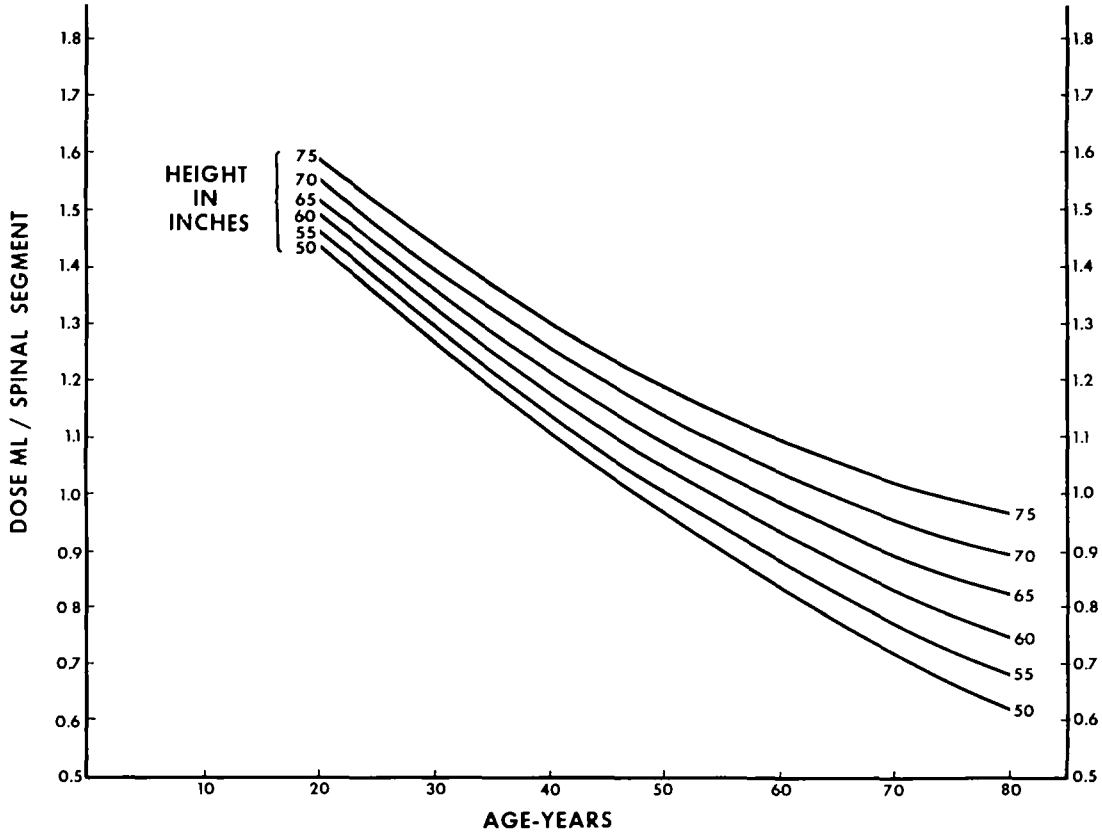

FIG. 4

Relationship of dose to age and height for 2 per cent solutions in normal patients between 20 and 81 years (supine position).

Sitting posture.

2 *per cent solutions.*

Figure 5 shows the individual data for dose in relation to age in eighty patients, after injection of 2 per cent solutions in the sitting position. Again, a linear relationship has been assumed between the limits of 20 and 80 years, and the regression line has been drawn through the plots. The broad confidence limits ABCD are twice the standard deviation on each side of the regression line, and 95 per cent of all normal patients given 2 per cent solutions in the sitting position may be expected to have dosage requirements within these limits.

The regression equation for the line is:

$$\text{Dose (ml)} = 2.0089 - 0.01269A$$

where A = age in years.

The correlation coefficient of dose and age in this group is −0.77 which shows that dose is again strongly associated with age, as in the supine position.

The regression line for patients in the supine posture has been drawn as a dotted line in figure 5 to show that the means of the two groups lie a significant distance apart ($P<0.001$). It can be seen that patients in the sitting posture will require larger doses than those in the supine position, the difference being about 0.25 ml per segment.

3 *per cent solutions.*

Figure 6 shows the individual data of dose requirements related to age in thirty-five patients who received epidural injections of 3 per cent L67 in the sitting position. The data from a further ten patients receiving 3 per cent lignocaine are

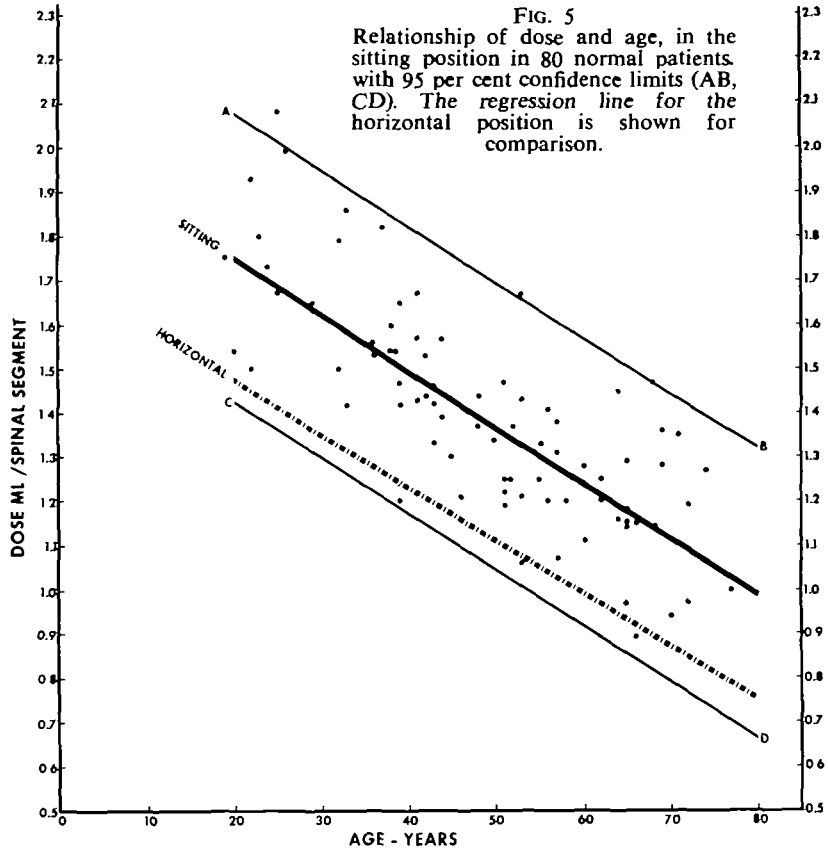

FIG. 5
Relationship of dose and age, in the sitting position in 80 normal patients with 95 per cent confidence limits (AB, CD). The regression line for the horizontal position is shown for comparison.

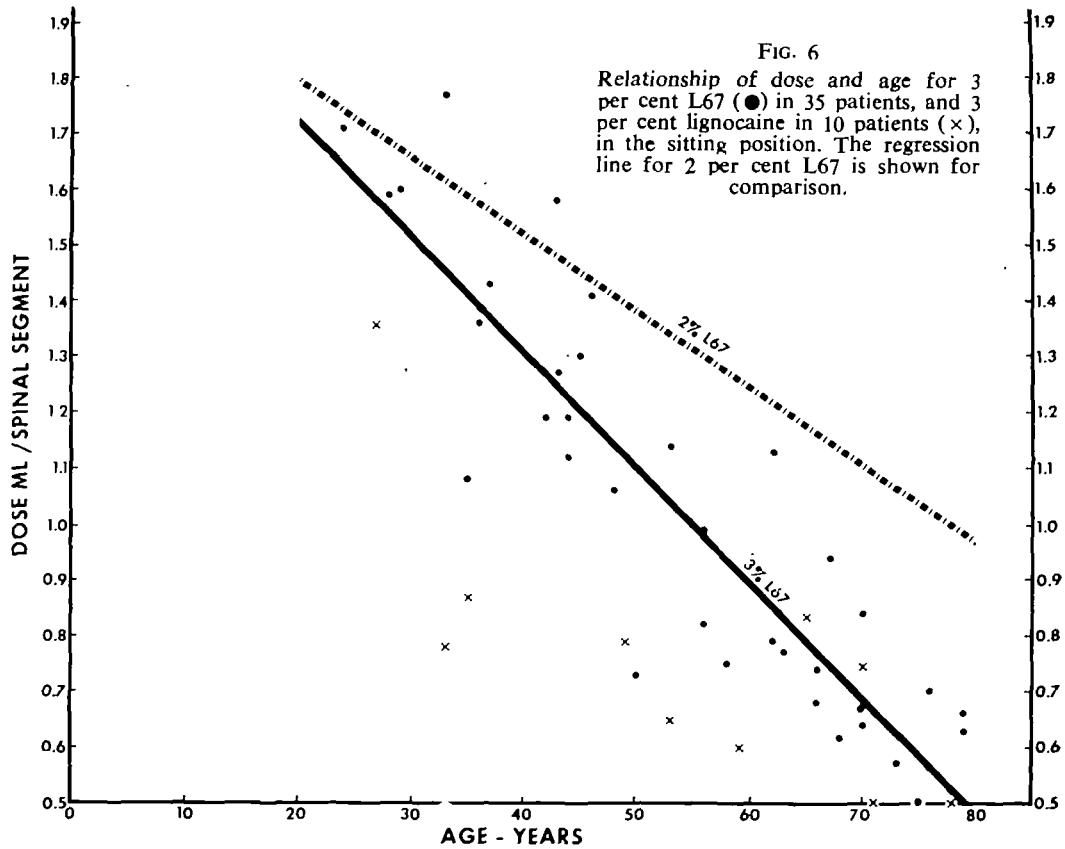

FIG. 6
Relationship of dose and age for 3 per cent L67 (●) in 35 patients, and 3 per cent lignocaine in 10 patients (×), in the sitting position. The regression line for 2 per cent L67 is shown for comparison.

also shown, but these 10 patients have not been included in the statistical analysis. The regression line for 3 per cent L67 is drawn through the plots, and the equation for this line is:

$$\text{Dose (ml)} = 2.137 - 0.02071A$$

where A = age in years,

$r = -0.89$, which again shows a very strong association of dose and age.

In this concentration blockade spreads very extensively, especially with advancing age, and the regression line slopes steeply downwards away from the 2 per cent line. The points for 3 per cent lignocaine lie even more steeply, but the number of cases with this concentration of the drug was not large enough to allow a statistical comparison to be made between 3 per cent lignocaine and 3 per cent L67. The 3 per cent plots deviate significantly from the 2 per cent line in both the upper and lower halves of the series on each side of the 50-years mark (29 to 50 years: $0.001 < P < 0.005$; 50 to 80 years: $P < 0.001$).

And so the stronger concentration may be said to produce enhanced spreading effects at all ages between 20 and 80 years, but the spreading effect is much increased by advancing age.

In the six patients receiving 4.5 per cent lignocaine the spread of analgesia was impressively extensive, considering the small volumes used. For example:

A 39-year-old man, 6 feet (1.8 m) tall, received 8 ml of 4.5 per cent lignocaine sitting up, at L2–L3. Analgesia extended from S5 to C7 after 10 minutes.

A healthy 70-year-old woman, 5 feet 1 inch (1.5 m) tall, was given 4 ml of 4.5 per cent lignocaine, sitting up, at L3–L4. Analgesia extended from S5 to T7 after 12 minutes.

This series of cases was too small to be treated statistically, but the results will be considered in the Discussion.

The effect of height on dosage requirements for 3 per cent L67 was also tested, but no positive relationship was found ($r = -0.041$), and so its influence can be neglected at this concentration.

Pregnant Women at Term.

Figure 7 shows the individual data points from forty women at term who received epidural injections of 2 per cent solutions in the sitting position. All except one point fell outside the lower 95 per cent confidence band for non-pregnant patients, and this shows an extremely significant difference between the two groups, dosage being reduced by about one-third below normal requirements in the patients at term.

Patients with Arteriosclerotic Gangrene.

Figure 8 shows the data points from thirteen elderly patients with severe arteriosclerosis who received epidural injections of 2 per cent solutions in the horizontal position. They had all had some degree of arteriosclerotic gangrene of the lower limbs, and nine of them had diabetes. It can be seen that all the points fall below the normal regression line, and eleven of the thirteen fall outside the lower 95 per cent data band, showing that these patients have very significantly reduced dosage requirements compared with normal patients of similar age.

DISCUSSION

The literature on epidural analgesia contains a confusingly wide range of recommended dose scales. Some authors suggest volumes as high as 60 ml. In a previous series where 1/600 cinchocaine was used, I advised doses between 15 and 50 ml, depending on the age and height of the patients, and about two-thirds these amounts if 1.2 per cent lignocaine was employed (table II).

At that time, when employing relatively weak solutions (1/600 cinchocaine or 1.2 per cent lignocaine), I made the statement, "It does not matter if an excess of solution is injected, carrying the block into the upper thoracic or even cervical region, for the concentrations of drugs are chosen to produce an autonomic and sensory block while allowing the motor fibres to escape, so that respiratory paralysis is impossible, however far the solution travels" (Bromage, 1954b).

More extensive experience and results with more powerful solutions have shown that this advice is not generally applicable, for, as will be seen later, increased intensity of analgesic action carries with it an increased tendency to spread, probably even across the dural barrier, so that with gross overdosage paralysis may not stop at the spinal nerves, but may extend even further to the cranial nerves as well.

Two per cent concentrations of lignocaine, and allied drugs, are now used more extensively for epidural analgesia than before, and it seemed appropriate to obtain more accurate information

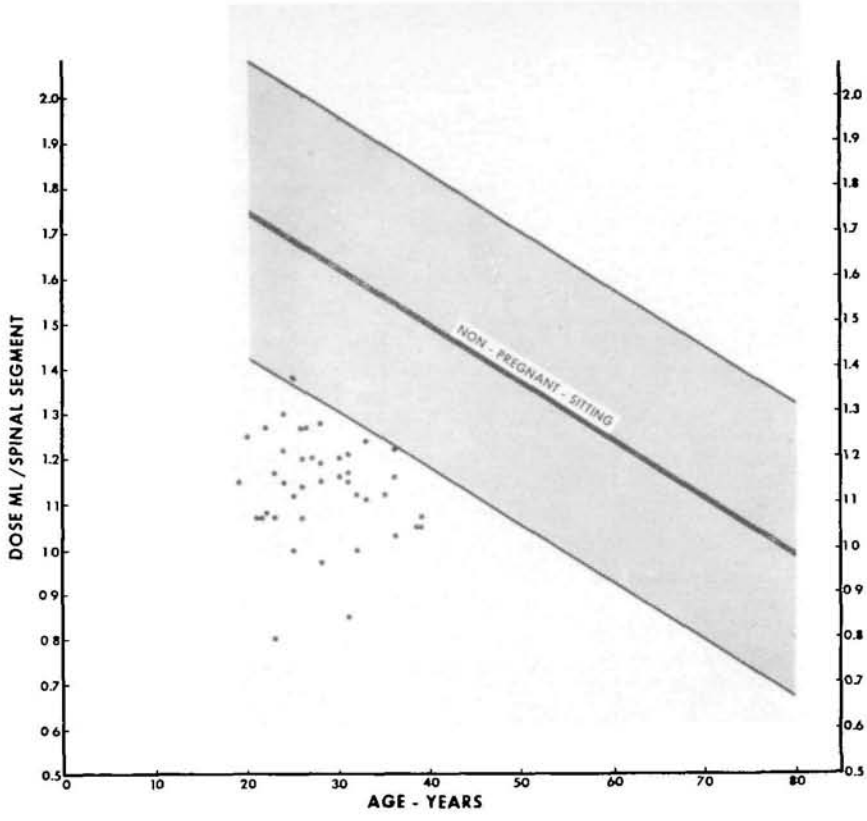

FIG. 7

Relationship between dose and age in 40 pregnant women at term, in the sitting position (●). The stippled area shows the 95 per cent confidence limits for dose requirements in non-pregnant patients.

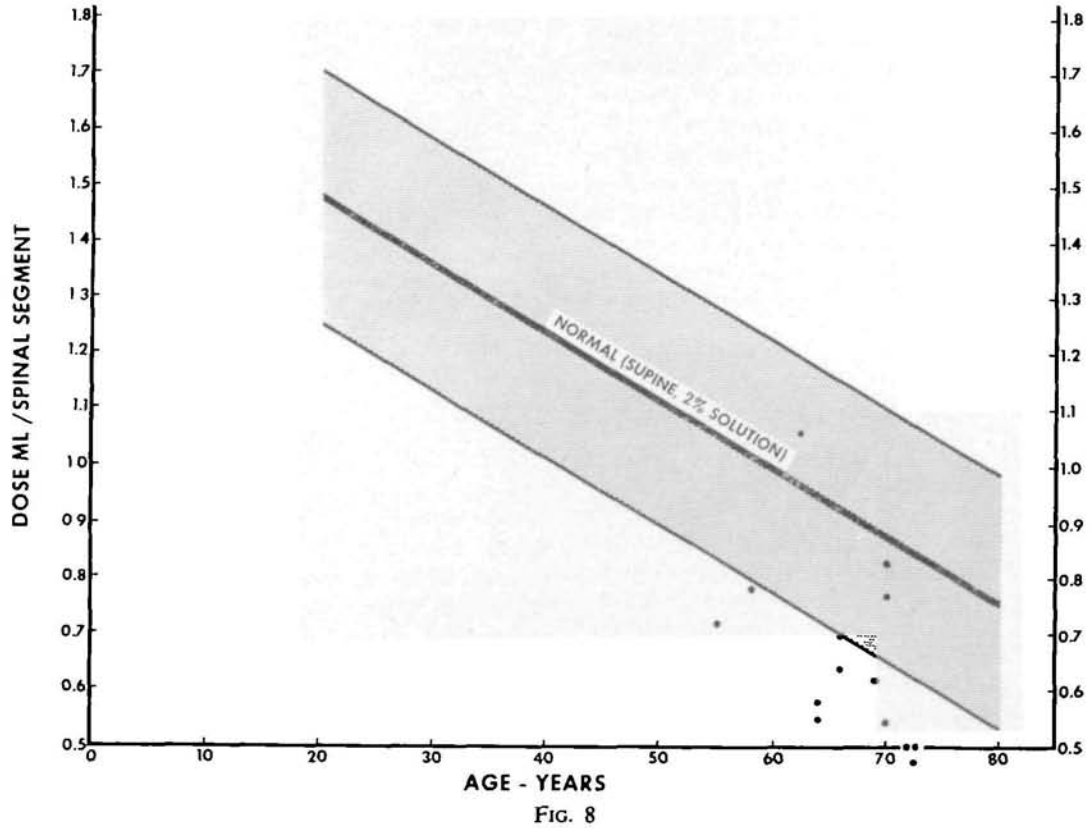

FIG. 8

Dose requirements in 13 patients with occlusive arterial disease in supine position (●). The stippled area shows the 95 per cent confidence limits for normal patients.

TABLE II

Some published recommendations for epidural dosage.

Author	Drug	Volume of solution (ml)
Pagés (1921)	2% procaine	20—25
Dogliotti (1939)	2–3% procaine	20—35*
Massey Dawkins (1954)	1.5% lignocaine	15—60
Bromage (1954)	(a) 1/600 cinchocaine	15—50
	(b) 1.2% lignocaine	10—30
Bonica et al. (1957)	2% lignocaine	5—25
Moore et al. (1958)	2% lignocaine	10—20
Lund, Cwik and Quinn (1958)	2% lignocaine	25—50

* In divided doses.

on the spreading characteristics of this concentration in normal patients, as well as in those conditions where clinical observations indicated that some measurable differences in dosage requirements were likely to be found. For with such a wide range of recommended dosage to choose from, it is probable that relative overdose and undesirably extensive segmental spread may occur in a fair proportion of subjects undergoing epidural analgesia, thus bringing unnecessary hazard to the patients, and the risk of discredit to an otherwise admirable technique.

In order to arrive at an understanding of the factors which govern the spread of solutions in the epidural space, let us first of all examine the intrinsic variables, that is those which are peculiar to the individual patient, rather than external conditions, such as alteration of posture or techniques which we may impose on him.

The epidural space may be considered as a reservoir surrounding the contents of the spinal canal. The space in this reservoir is taken up by:

(1) Spinal cord and nerves, and cerebrospinal fluid, contained in their meningeal wrappings.
(2) Fat and blood vessels, notably the extradural venous plexuses which adjust alterations in venous pressure throughout the body, and which can undergo considerable distension while doing so (Batson, 1940).

The reservoir also has a number of exits through which injected solutions can escape. These are:

(1) The intervertebral foramina.
(2) The blood vessels and lymphatics which absorb and remove drugs and fluids from the space. These vessels therefore have a dual role, functioning both as space-occupying structures, and as escape routes at the same time.
(3) Possibly the dura mater, which may act as a partially permeable membrane, at least in certain regions, allowing some passage of solutions into the c.s.f. (Frumin et al., 1953). The "ink-cuff" areas surrounding the spinal nerve trunks are particularly concerned here (Brierley and Field, 1948).
(4) Solution and diffusion in the epidural fat.

Solutions which are injected into the epidural space spread up and down within it to an extent determined by the opposing factors outlined above. The larger the space-occupying structures, the less space is left to be filled, and so the further a given volume will travel. On the other hand, if the escape routes are patent and efficient, solutions will pass out of these exits, as water through holes in a bucket, and relatively little spread will take place.

Age has two opposing influences on the mechanics of epidural spread, for it affects both the size of the space, and the patency of the escape routes. In childhood the capacity of the space is small, but it increases steadily with growth until full height and development are reached at about 16 to 20 years. At this point, in the flush of prime, the size of the space and the efficiency of the escape routes are both at their maximum. The neurovascular bundles pass loosely and freely through uncluttered intervertebral foramina, and venous and lymphatic drainage are in full spate with all the adjustments of venous pressure accompanying the violent activities and passions of youth. This point corresponds to the apex of the dose-age curve, calculated from clinical observations in figure 1.

Beyond this point in time the regression line slopes steadily downwards in an almost linear manner as ageing processes gradually crystallize about the space, like limestone deposits on a cavern wall. Blood flow becomes less brisk, and opercula of fibrous tissue obstruct the intervertebral foramina. The space slowly changes with the years from a busy corridor to a quiet cloister, where major adjustments of venous pressure are rare. The relationship between age and dose for this part of the line, between 20 and 80 years, is

very strong ($r=0.86$), indeed stronger than in a previous and similar series where the correlation coefficient equalled only 0.56 (Bromage, 1954c). As will be seen later, this increased dependency of dose on age is probably related to intensity of analgesia, for when the concentration of lignocaine is raised to 3 per cent, dose shows an even greater dependency on age (fig. 6).

Since height is a fair indication of length of back, and since the volume of the epidural space is proportional to its length, it might be expected that height would relate to epidural dosage more closely than was found to be the case. The poor correlation ($r=0.36$) is very close to that of the previous series for cinchocaine (where $r=0.33$), and this may merely confirm that height is a poor indication of length of back rather than that length of back is poorly related to epidural dosage. However, when height is combined with age in a multiple regression equation it is seen to gain significance with advancing age and increasing tallness. The graphic representation of this double relationship in figure 4 provides both a statistical confirmation that age and height are related to dosage requirements and a reasonably accurate guide to dosage in clinical practice. It should be noted that the data for this equation were obtained by using a constant site of puncture, at either the 2nd or 3rd lumbar interspace. It does not follow that the same relationships will hold exactly at other regions of the spine although clinical experience with high thoracic punctures suggests that if any difference does exist at other levels it is not very great.

The effects of gravity on epidural spread are well recognized by most anaesthetists, but not by all (Nishimura, Kitahara and Kusakabe, 1959), so it was necessary to demonstrate that posture does in fact influence spread, and hence the size of the dose that will be required. From figure 5 it can be seen that if the sitting instead of the horizontal position is adopted the dose must be increased by about 0.25 ml per segment in order to reach a given dermatome level, the extra volume being necessary to replace what has soaked downwards into the lower reaches of the epidural space. Once the initial injection has found its mark and created a solid area of analgesia, succeeding injections through an epidural catheter do not appear to be so dependent on gravity, for they seem to track along in the wake of the original path-finding dose, as if by capillary attraction, even in an uphill direction. For example, during a pelvic operation succeeding injections will continue to anaesthetize the sacral nerves despite a steep Trendelenburg position, providing the inducing injection was made with the patient sitting up. The upper limit of analgesia will certainly tend to creep higher in this position, but full sacral analgesia will usually be maintained by successive injections through the epidural catheter.

It is well recognized that spinal blockade has a tendency to spread widely during pregnancy, and that unless allowance is made for this, embarrassingly high levels of motor paralysis may follow injection of quite modest volumes of local analgesics into the subarachnoid space. Although Bonica and his colleagues (1957) have drawn attention to the fact, it is not so widely appreciated that the same tendency exists after epidural injections, at least at term and when labour has begun. Reference to figure 7 shows that the reduction in dosage requirements at term is very marked, being about one-third less than normal. For example, a woman aged 30 and 5 feet 5 inches (1.65 m) tall would normally require about 20 ml of 2 per cent lignocaine to ensure blockade up to the 10th thoracic segment after injection in the sitting position. At term, 14 ml of the same soluton is sufficient, and if the full 20 ml were given it would cause a block up to about the 4th or 5th thoracic segment, that is five or six segments more than necessary.

Much of the published work on epidural analgesia for obstetrics fails to take account of this increased tendency to spread, and doses as large as 20 ml of 2 per cent lignocaine in the lateral position are recommended by some authors. Now the best results from epidurals in obstetrics are only obtained by careful attention to detail and by planning the exact extent of segmental blockade required at each stage (Bromage, 1961); it is to be feared that technical results, in terms of analgesia and efficiency of labour, will fall short of the optimum, and the risk of hypotensive episodes will be increased, if arbitrary rather than realistic dose-scales are followed.

The reasons for these markedly decreased dose requirements at term still remain obscure. Several factors are probably involved. One of the most

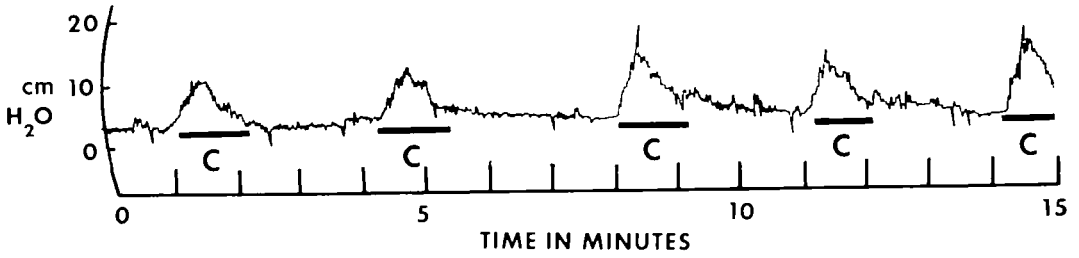

FIG. 9

Pressure tracing from epidural catheter at level of first lumbar vertebra during first stage of labour. C=uterine contractions.

important is the space-occupying and massaging effects of the distended extradural veins. The extradural plexuses, which receive a proportion of the venous return from the uterus with every uterine contraction, are dilated during pregnancy, and this engorgement is a recognized cause of cord compression and paraplegia in pregnancy from distension of pre-existing vertebral angiomas (Askenasy and Behmoaran, 1957; Newman, 1958). The pressure changes accompanying uterine contractions are transmitted to the epidural space, causing rhythmic pressure waves which tend to disperse solutions lying in their path. Figure 9 shows a recording of these pressure changes taken from a strain gauge attached to an epidural catheter during the first stage of labour. Extraneous pressure waves due to grunting and straining were prevented, since the mother was made comfortable and pain-free by a previous injection of local analgesic up the same catheter (Bromage, 1961).

Increased vascularity of the meninges and changes in the cerebrospinal fluid have been invoked as an additional explanation for the altered response to spinal analgesic drugs in pregnancy (Marx, Zemaitis and Orkin, 1961). It is quite possible that changes of this nature may contribute to the enhanced epidural spread, for, if the coverings of the nerve roots were more permeable than usual, analgesic solutions would have a greater opportunity to penetrate the nerves beyond. This possibility should be recalled when the effects of more concentrated solutions are discussed shortly, for the relation of concentration of solution on the one hand to nerve susceptibility on the other will vary somewhat from patient to patient, and the final outcome in terms of nerve blockade will depend on the balance between the two.

In the group of elderly arteriosclerotic patients the spread of analgesia is significantly greater than for normal patients of the same age, and although the difference is not nearly so striking as in the group of pregnant women, nevertheless the difference demands both an explanation and practical recognition. The cause may lie in one or more of three directions. Firstly, thickening of the arteriosclerotic vessels may encroach on the epidural space in the same way, but not the same degree, as the distended extradural veins of pregnancy. This does not seem a very likely possibility, for any thickening of the vessel wall will tend to occupy the lumen of the vessel rather than the space around it. Secondly, changes of permeability in meninges and perineurium may be involved, allowing greater penetration of nerve tissue. Or, lastly, the increased spread may be merely an expression of the exaggerated ageing processes which accompany severe arteriosclerosis, so that physiological age (and hence epidural spread) is advanced 15 to 20 years beyond the chronological span.

Hints of enhanced spread in arteriosclerotic patients have been dropped before, usually in the guise of reports on cases where anaesthetic difficulties followed inexplicably extensive neural blockade (Morrow, 1959; Mostert, 1960). A feature of these reports is not only an unexpectedly extensive spread, but a delayed one as well. However, in this present small series of arteriosclerotic patients no great delay has been encountered, and analgesia has extended to its full limits within a normal period of time. An example from the recent literature will serve to show that when compared alongside the present series these reports of extensive spread need not have been so unexpected after all.

Mostert (1960) quotes the case of a 70-year-old man, suffering from diabetes, hypertension, and gangrene of the toes, who received an epidural injection of 22 ml of 2 per cent lignocaine. This was followed by aphasia, apnoea, hypotension, and transient cardiac arrest. The height of the neural blockade is not reported, but if we assume that the patient fell within the dose-age distribution of the present series he would have required only about 0.6 ml of 2 per cent lignocaine for each dermatome (fig. 8). Under these circumstances a volume of 22 ml would be more than enough to block every spinal nerve up to the base of the skull, and possibly even beyond, if we accept the idea that transmeningeal spread is not impossible.

Clearly therefore there is a need for wide recognition of this peculiar susceptibility of severely arteriosclerotic patients. Adoption of appropriate dosage scales will then avoid this type of accident.

The effects of 3 per cent solutions of lignocaine and L67 and 4.5 per cent solution of lignocaine on epidural spread provide some of the most interesting, but at the same time most disturbing, results of this investigation, for the extensive analgesia caused by these solutions does not fit into the accepted schema of epidural blockade.

In the past, spread of blockade and the intensity of analgesia were considered to be two quite distinct and independent features, the number of segments anaesthetized being determined by the purely physical considerations of volume of solution in relation to the size and continence of the epidural space, together with the effects of gravity resulting from the posture of the patient at the time of injection (Bryce-Smith, 1954; Bromage, 1954b). On the other hand, intensity of analgesia was thought to be due mainly to the pharmacological potency and concentration of the drug used.

Indeed, considering the generally accepted site of action of epidural analgesia, it was difficult to see how things could be otherwise. For if epidural solutions act on spinal nerves at or beyond their point of emergence from the dura and the intervertebral foramina as many believe (Foldes, Colavincenzo and Birch, 1956; Bonica et al., 1957), then alterations of concentration should not affect the passage of solutions up and down the interstices of the space between the fat and extradural blood vessels.

Bonica and his co-workers (1957) have suggested that "the concentration and penetration of the local anaesthetic employed significantly affect the extent of the block". This assertion is confirmed by the parallel between extent of segmental spread and intensity of the analgesic solution, which has been demonstrated in this and a previous series, and which is summarized in figure 10. It should be possible to construct whole families of curves for dose and age, similar to those in figure 10, for different drugs and concentrations, with increasing dilutions requiring ever-increasing volumes to produce a given area of blockade.

What is the explanation of this increased spatial spread associated with increased concentration? Why, for example, should a volume as small as 7 ml of 3 per cent lignocaine in a 70-year-old man block as many segments as 14 ml of the 2 per cent solution? As Bonica has suggested, the difference must be referable in some way to heightened tissue penetration.

Increased diffusion across the meninges into the cerebrospinal fluid is one of the first possibilities that comes to mind, since it has been demonstrated that analgesic solute does reach the c.s.f. in appreciable quantities after epidural injection (Frumin et al., 1953). However, it seems extremely unlikely that this is the cause of the analgesia, for not only is diffusion through the c.s.f. very slow in the absence of extraneous forces such as barbotage or changes of baricity, which are normally employed to extend subarachnoid block, but analysis of the analgesic content of the c.s.f. after epidural injection shows that the rise and fall in concentration of analgesic solute is quite unrelated to the onset and disappearance of the block. Foldes, Colavincenzo and Birch (1956) demonstrated this very clearly, using 3 per cent 2-chloroprocaine as the analgesic drug. They took samples of cerebrospinal fluid at the onset of analgesia, and thereafter until the block disappeared. Their findings are summarized in figure 11, and it can be seen that there is wide dissociation in time between high concentrations of the drug and the presence of epidural analgesia. When the block had disappeared the c.s.f. concentration is three times as high as when the block was first fully developed. From these results Foldes, Colavincenzo and Birch concluded that the site of action of epidural analgesia is primarily outside the dura-arachnoid and

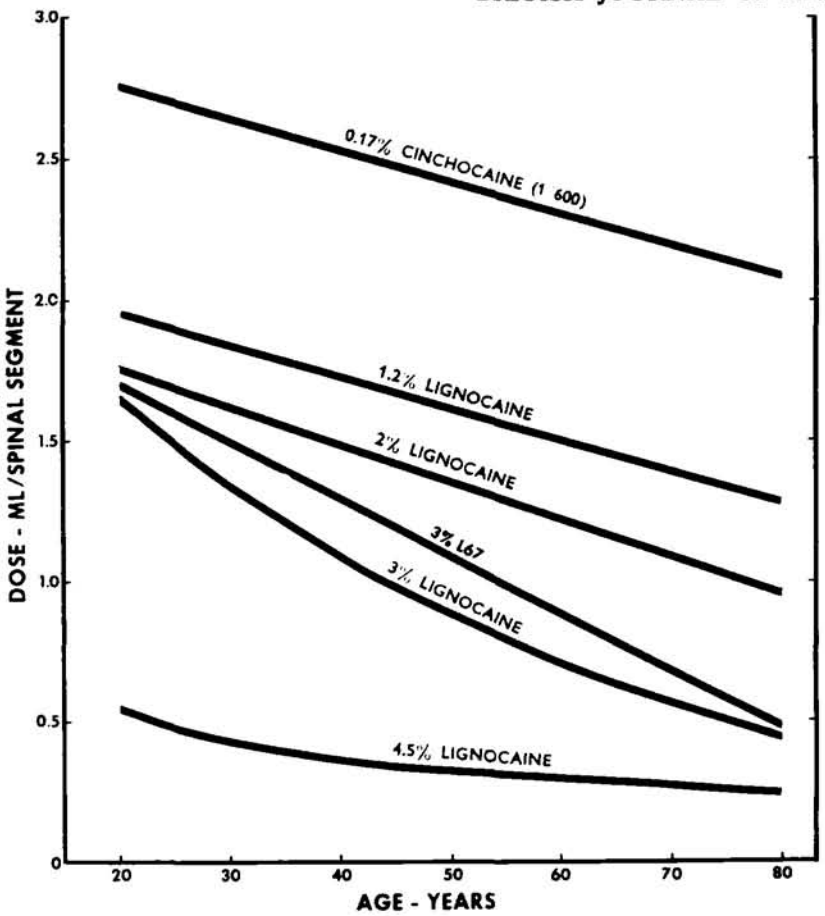

FIG. 10
Influence of potency and concentration on volume of epidural analgesic solution required to block each spinal segment (sitting position).

the spinal canal, involving the mixed nerves in the paravertebral spaces. However, the circumstantial evidence is strongly against such a conclusion. The volume of solution available for each paravertebral space after epidural injection is too small to account for the prolonged and effective block which follows, and studies with radio-opaque materials in geriatric patients suggest that the solution never reaches the paravertebral spaces in many instances (Bromage, 1954a).

In a previous study I concluded that the site of action lay in one or more of three possible situations (Bromage, 1954a):

(1) On subarachnoid nerve roots after diffusion across the dura into the cerebrospinal fluid.
(2) On dural-covered nerve roots within the epidural space after diffusion through the "ink-cuff" areas (Brierley and Field, 1948).
(3) On mixed spinal nerves in the paravertebral spaces after they have left the intervertebral foramina (this latter suggestion being regarded as rather improbable in view of the available evidence).

There is one remaining possibility which has been hinted at by several authors (Moore et al., 1954; Marx, Zemaitis and Orkin, 1961), but which has not until now been seriously advanced as an explanation for one of the main pathways and sites of action of epidural analgesia. This possibility appears to reconcile all the clinical and experimental evidence which is available at present.

Between 1948 and 1951, while investigating the passage of viruses into the central nervous system, Brierley and Field published a series of papers on the mechanism of spread of crystalloid solutions and particulate suspensions in and out of the sub-

arachnoid space and the neuraxis (Brierley and Field, 1948, 1949; Brierley, 1950; Field, 1951). They showed that the neighbourhood of the dural "ink-cuffs" where the dorsal and ventral roots fuse is permeable to quite large particles, 0.5 μ in size, and that material can diffuse readily between the sub-arachnoid, subdural, and epidural spaces in this region. Moreover, they showed that extremely small quantities of radioactive substances, introduced without pressure into the sub-perineural spaces of the sciatic nerve, could enter the spinal cord, brain stem, and even the basal ganglia, in significant amounts after a short time. On the other hand, passage into the cerebrospinal fluid was slow, and maximum concentrations were not reached until 50 to 60 minutes after injection, that is, about the same time that elapsed before maximum c.s.f. concentrations of chloroprocaine in the experiments of Foldes, Colavincenzo and Birch (fig. 11). The similarity of the time courses of c.s.f. concentrations in these two sets of data is very suggestive of an underlying mechanism common to both.

Moore and his colleagues (1954) also carried out some injection studies of peripheral nerves, using Efocaine and methylene blue in monkeys, and they too found very rapid spread from the peripheral nerves into the sub-pial spaces of the spinal cord.

Now this portal of entry into the neuraxis appears to be the key to the problem of unexpected variations in epidural spread. All previous discussion and tentative conclusions about the site of action of epidural analgesia has been dominated by the assumption that passage into the c.s.f. precedes neural fixation and blockade. If we abandon this assumption in favour of the idea that passage into the c.s.f. follows or accompanies neural involvement after sub-dural and sub-pial spread, then the pieces of the puzzle fall neatly into place. Analgesic solutions can reach the sub-perineural spaces by diffusion around the capillary and

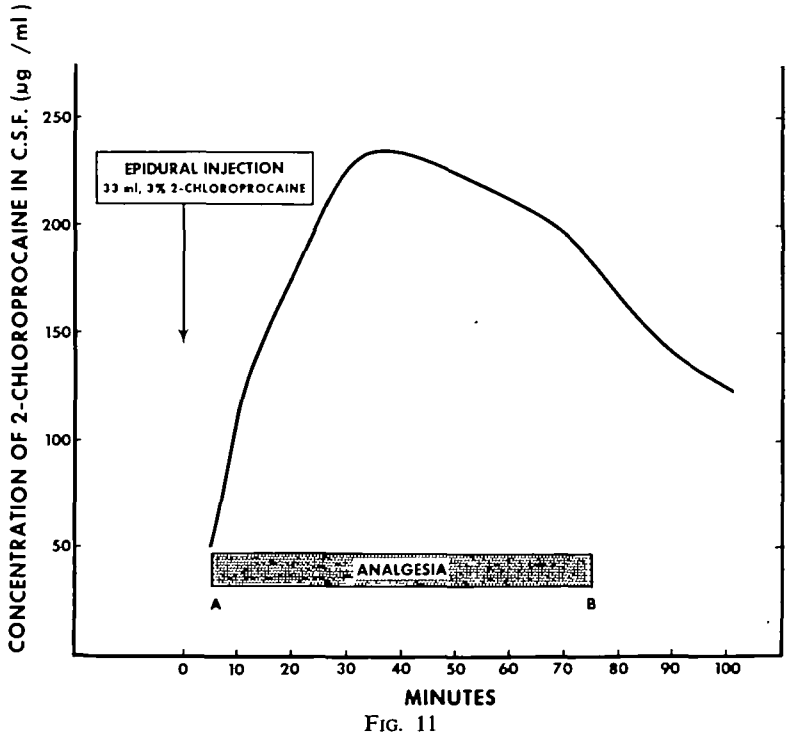

FIG. 11

Dissociation of epidural analgesia and concentration of analgesic solute in c.s.f. Analgesia commenced at A and wore off at B, when concentration of chloroprocaine in c.s.f. was 3 times as high as at A. (Modified from Foldes, Colavincenzo and Birch (1956). *Curr. Res. Anesth. Analg.*, **35**, 33)

lymphatic channels of the vasa nervorum, at and beyond the dural "ink-cuff" areas. Once inside the endoneural spaces, longitudinal capillary networks provide tissue interfaces along which solutions can track up the spinal roots and into the sub-pial spaces of the cord. From there the concentration gradient allows gradual diffusion out into the c.s.f. beyond, but only after neural blockade has already occurred.

Spread from an epidural injection therefore has two components:

(1) Spread within the epidural space itself. This is dependent on those conditions which have been discussed, such as, volume, speed of injection, posture, and so on.
(2) Sub-dural and sub-pial spread (fig. 12).

The amount of drug which reaches the sub-pial spaces around the cord, and which is available for spread along the neuraxis, will be proportional to the amount which is able to diffuse through the perineurium into the sub-perineural spaces. This in turn will be governed by the state of the neural coverings and those recognized physical laws which affect diffusion. The amount of solute traversing any membrane is proportional to (*a*) the diffusion coefficient, (*b*) the area of contact, (*c*) the concentration gradient, and (*d*) time of contact. The principal conditions which influence these factors are summarized in table III. It can be seen

TABLE III

Variable factors and influences determining degree of neuraxial diffusion after epidural injection.

Factors in neuroaxial diffusion	Influenced by
Diffusion coefficient	Potency of analgesic drug; ionic changes; state of neural coverings.
Area of contact	Volume of solution in relation to volume and continence of epidural space.
Concentration gradient	Concentration of analgesic solution; dilution by oedema, or pre-existing fluid in epidural space.
Time of contact	Rate of removal of analgesic drug via epidural escape routes (blood flow, etc.); viscous solutions (Bromage, 1954b).

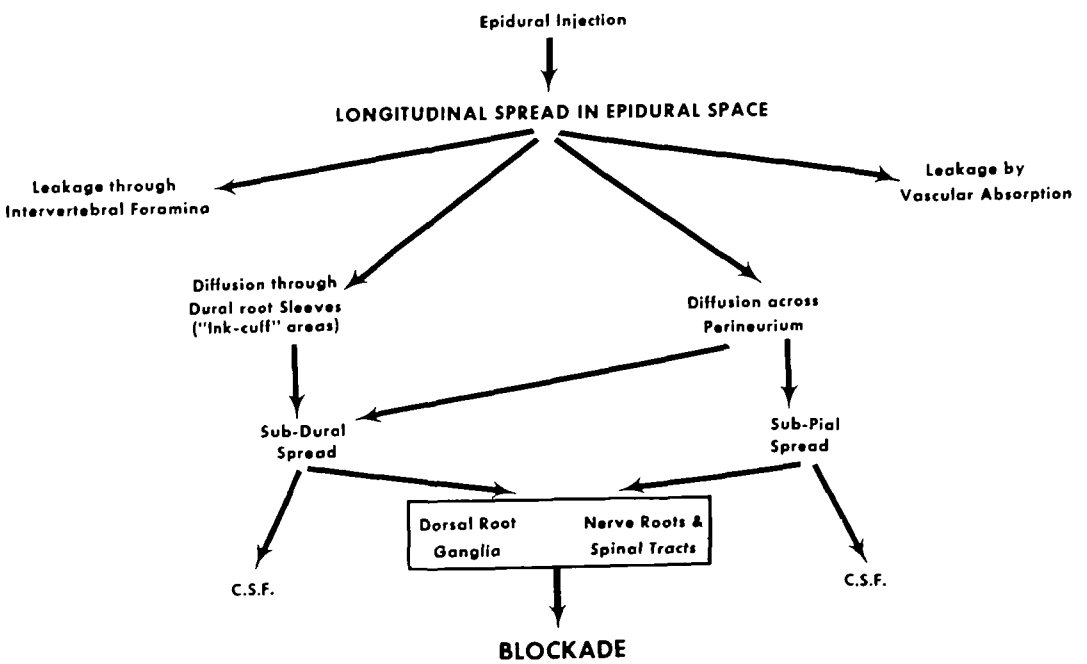

FIG. 12

The fate of an epidural injection.

that ultimately segmental spread is dependent on the mass of analgesic solute available for transneuronal diffusion in the epidural space. The appropriate mass of solute can be presented in the form of a large volume of weak solution, in which case it will travel widely in the epidural space and diffuse relatively poorly, or as a very small volume of concentrated material, as in the patients receiving 4.5 per cent lignocaine, where presumably epidural spread was limited by the small volumes used, but where neuraxial spread was extensive owing to the high concentration gradient of lignocaine.

Thus it can be appreciated that our ideas about epidural spread need to be more sophisticated than hitherto. The outcome of an epidural injection is the resultant of many different forces. If any one of these is unusually weak, or another particularly strong, we may expect that clinical results will deviate from normal, and the accuracy of our results will depend on our ability to choose the appropriate dose with intelligent anticipation.

SUMMARY

The segmental spread of epidural analgesia was measured in 358 patients, and the dose requirements in each case were expressed as the number of millilitres of analgesic solution necessary to block one spinal segment.

The effects of the following factors on dose requirements were then studied:

(1) Age.
(2) Height.
(3) Posture.
(4) Pregnancy.
(5) Occlusive arterial disease.
(6) Varying concentrations of analgesic solutions.

Tall people require larger doses than short ones.

Dose requirements are greatest at 16 to 20 years, and then decline steadily with age.

Dose requirements are reduced in pregnancy and in patients suffering from occlusive arterial disease.

The volume of epidural solution necessary to block a given number of segments is dependent upon the concentration and potency of the drug used.

The mode of spread and the site of action of epidural blockade is discussed in the light of these findings.

ACKNOWLEDGMENTS

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CORRESPONDENCE

COLOURING OF INTRAVENOUS INFUSIONS

Sir,—Faced with the recurrent problem of being asked to follow intravenous urea with trimetaphan, I have taken to tingeing the hypotensive with a few drops of methylene blue. This enables me, without using three drip sets for every patient, to see through the transparent plastic when the trimetaphan first reaches the vein and when it has been washed through subsequently.

Routine colouring of dangerous drip solutions might go some way towards preventing the occasional accident. I wonder if your readers would care to discuss these points.

P. H. BEVES
Maida Vale Hospital, London

ANTANALGESIA

Sir,—I am very interested in the series of papers on somatic pain by Dundee and his colleagues.

I rather carp at the word "antianalgesic" and would suggest "hyperaesthetic" as a happier one.

Normal physiological sleep induces a state of general hyperaesthesia and anything producing a normal physiological condition cannot be regarded as anti-anything.

The analgesics which overcome this state are the abnormals.

D. F. REES
Dewsbury, Yorkshire

HYPOTENSIVE ANAESTHESIA

Sir,—I have read with interest the article by Drs. Holloway, Holmes and Hider on "Guanethidine in hypotensive anaesthesia" (*Brit. J. Anaesth.*, 1961, **33**, 648. They make the statement that "copious bleeding continued, even after halothane had been administered in sufficient concentration to produce respiratory depression". Clearly the authors are endeavouring to maintain the Edinburgh tradition of preserving spontaneous breathing during hypotensive anaesthesia. I do not believe this is necessary provided the anaesthetist is prepared to exercise the necessary constant vigilance. For the past 3 to 4 years I have routinely produced hypotension for the microsurgery of the middle ear by the use of controlled respiration and halothane alone. Not once has resort to ganglionic blocking drugs proved necessary to provide a dry field. Patients are premedicated with pethidine, hyoscine and perphenazine given intramuscularly 1 hour before operation. Anaesthesia is induced with 2½ per cent thiopentone to which 5 mg of d-tubocurarine is added; intubation is carried out after the injection of suxamethonium and the blood pressure is reduced to 60–70 mm Hg at heart level by gradually increasing the concentration of halothane until this level of pressure is achieved. Hyperventilation with a soda lime canister in the circuit is used. The hypotension is associated with a bradycardia and the postoperative recovery phase is tranquil and uneventful.

Reference to this technique has been made elsewhere (Murtagh, 1960; Rollason, 1960).

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Royal Infirmary, Aberdeen

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