QUALITY OF EPIDURAL BLOCKADE

II: INFLUENCE OF PHYSICO-CHEMICAL FACTORS; HYALURONIDASE AND POTASSIUM

BY

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SUMMARY

A trial was made of hyaluronidase and potassium chloride as adjuvants for epidural analgesia in 137 patients. Lignocaine hydrochloride in 2 per cent concentration with adrenaline 1/200,000 was used as the control solution in 61 cases; hyaluronidase, 5 USP units/ml, was added in 26 cases, and 1 per cent potassium chloride was added in 50 cases. Hyaluronidase tended to impair the quality of sensory blockade rather than to enhance it, whereas 1 per cent potassium chloride gave rise to a shortened latency of spread and a more intense quality of sensory block, especially in the sacral segments. It is concluded that hyaluronidase has no place in epidural analgesia. Potassium chloride should be used with great caution because it produces undesirable effects if introduced into the subarachnoid space.

Spinal injections of local anaesthetics produce less effective neural blockade in the extradural space than in the subarachnoid space; thus, approximately five times more drug is required to block a given number of spinal segments by the epidural route than by subarachnoid injection, and onset and spread of analgesia is five to ten times slower with the former than with the latter. The delay is particularly marked in the lower lumbar and sacral segments, and this detracts from the practical value of epidural analgesia in operations involving the lower limb and perineum. Moreover, the intensity of epidural analgesia and motor paralysis is relatively slight and may be inadequate for some procedures.

The quality of epidural blockade can be enhanced by manipulating certain physical factors which increase neural uptake of local anaesthetic drugs from the epidural space; the effects of local anaesthetic concentration, regional vasoconstriction, and repeated injections were reported in a previous communication (Bromage et al., 1964). Even with the most favourable conjunction of physical circumstances, however, the quality of epidural analgesia still remains inferior to subarachnoid block, and in a proportion of cases it is frankly inadequate for clinical requirements.

A further step to improve the quality of blockade could be taken by altering the physico-chemical environment in the neighbourhood of the target nerves. Certain changes of ionic milieu are known to augment the effects of local anaesthetics, and there are a number of possibilities that might be exploited to suit this purpose. Thus, a low sodium concentration (Lorente de Nó, 1951; Krnjevic, 1954; Condouris, 1961; Nathan and Sears, 1962) or a high potassium concentration (Hoffmann and Kochmann, 1912; Krnjevic, 1954) or a high magnesium concentration (Coutinho, 1966) all intensify the effects of local anaesthetics.

The present paper and the one that follows are concerned with three of the many known agents that might be used to enhance the quality of epidural blockade.

THEORETICAL CONSIDERATIONS

Hyaluronidase.

The gel of intercellular cement imposes a barrier to the diffusion and spread of local anaesthetic solutions. Hyaluronic acid, an important constituent of this gel, can be structurally altered by the depolymerizing action of hyaluronidase, thus reducing the effectiveness of the cement as a tissue barrier. Hyaluronidase, which has been
widely used to increase vascular uptake from injection sites (Mushin, 1956), might also be expected to enhance neural uptake of drugs from the epidural space. Scott (1956), who investigated this possibility, reported that the onset of blockade was somewhat shortened when the enzyme was added to epidural solutions, although he did not comment on any heightened intensity of analgesia.

In the present study we investigated whether the shortened latency caused by hyaluronidase is associated with any improvement in the quality of sensory and motor blockade.

Potassium salts.

Conduction of a propagated wave in a single nerve fibre is an all-or-none affair. The outcome of local anaesthetic action on a single fibre depends on the concentration of the local anaesthetic and the length of fibre affected, as well as on the intensity of the propagated impulse, which in turn depends on the degree of polarization of the nerve membrane. When blockade is incomplete it is possible for a powerful excitation wave to jump short segments of inactive fibre in the “salt-bridges” around the nerve, or to pass through the narcotized area and continue beyond the site of partial blockade in undiminished intensity (Osterhout and Hill, 1930; Kato, 1936). Local anaesthetics do not lower membrane potential; instead they act by stabilizing the membrane, so that the inward sodium flux associated with excitation cannot occur (Shanes, 1955, 1958). Therefore, when a local anaesthetic blockade is barely sufficient or frankly inadequate to arrest a propagated impulse some advantage might be gained by lowering membrane potential and producing an enfeebled wave of excitation which would be more easily halted than the normal discharge of 120 mV.

The resting potential of excitable tissues depends mainly upon the thirty-fold preponderance of potassium inside the cell membrane, and the potential varies inversely with the logarithm of the extracellular potassium over a wide range of concentrations (Huxley and Stämpfli, 1951; Brock and Eccles, 1958). Thus, an increase in extracellular potassium will cause some degree of depolarization, depending upon the concentration (Caldwell, 1958), and this enfeeblement of membrane potential may be sufficient to prevent passage of a propagated impulse from a weakly narcotized area into a normal segment of nerve.

Potassium salts have been tried as adjuvants to local anaesthetics with varying success for many years (Hoffmann and Kochmann, 1912; Meeker, 1925). They have little or no effect when applied to mucosal membranes (Adriani et al., 1964) but appear to augment the potency of injected local anaesthetics (Lechat, Deleau and Griffié, 1964).

EXPERIMENTAL METHODS

Observations of sensory and motor blockade were made in 137 uncomplicated cases in which epidural blockade was induced pre-operatively. Pregnant women and patients with occlusive vascular disease were excluded as they respond atypically to epidural block (Bromage, 1962b).

Analgesic solutions.

(1) Lignocaine hydrochloride 2 per cent with adrenaline 1/200,000 freshly added immediately before injection: this was considered to be the control solution.

(2) Lignocaine hydrochloride 2 per cent with freshly added adrenaline 1/200,000 and lyophilized hyaluronidase (Wydase) in a concentration of 5 USP units/ml analgesic solution.

(3) Lignocaine hydrochloride 2 per cent with freshly added adrenaline 1/200,000 and potassium chloride to give a final concentration of 1 per cent KCl. This provides a K+ concentration of 128 m.equiv/1., which is approximately the same as the normal intracellular concentration of potassium.

The solutions were administered as shown in table I; pH was measured at 38°C by a Radiometer pH meter.

Epidural technique.

Epidural blockade was performed in a standard manner at the second lumbar interspace with the patient sitting up, as previously described (Bromage, 1962a). In most cases, loss of resistance was tested with an air-filled syringe to avoid errors in dosage resulting from the injection of an inexact amount of fluid at the time of entering the epidural space. Dosage requirements in relation to age were determined in each case by dividing
QUALITY OF EPIDURAL BLOCKADE—II

TABLE I

<table>
<thead>
<tr>
<th>Solution</th>
<th>pH</th>
<th>Mean age of patients (yr)</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 2% lignocaine hydrochloride plus adrenaline</td>
<td>6.49 ±0.01</td>
<td>48.6</td>
<td>61</td>
</tr>
<tr>
<td>2. 2% lignocaine hydrochloride plus adrenaline plus hyaluronidase</td>
<td>6.45</td>
<td>47.5</td>
<td>26</td>
</tr>
<tr>
<td>3. 2% lignocaine hydrochloride plus adrenaline plus 1% KCl</td>
<td>6.49</td>
<td>48.9</td>
<td>50</td>
</tr>
</tbody>
</table>

the dose (in millilitres of solution) by the number of segments rendered analgesic.

The method of measuring sensory and motor blockade was the same as described in a previous communication (Bromage, 1965). Analgesia was determined by pin-prick, and dermatome charts were constructed to show minute-by-minute spread of analgesia. These charts record a profile of the segmental spread of blockade and the mean profile of any test population can be used for comparison with that of others by the usual statistical methods. The dermatome data were transferred to punch-cards and statistical analysis carried out using an IBM 7044 computer. The degree of motor block in each leg was assessed 30 minutes after epidural injection, and was given a mathematical score, as previously described (Bromage et al., 1964; Bromage, 1965). Duration of action was taken as the time interval from the moment when analgesia had spread to its farthest limits until the upper limit of analgesia had receded two spinal dermatomes.

Experimental analgesia in dogs: toxicity study.

Five dogs were intubated under pentobarbitone anaesthesia (30 mg/kg), and ventilated with either 40 per cent oxygen in air by means of a Bird respirator or with air by a Harvard pump. Four ml of 1.1 per cent potassium chloride was injected under aseptic conditions into the subarachnoid space, in one case at the level of the second lumbar interspace and in four cases into the cisterna magna. In four of the five dogs, 2 per cent lignocaine hydrochloride was added to the KCl solution. The dogs were extubated on recovery from the subarachnoid blockade; they were examined daily for seven days for signs of any neurological damage and then were killed. The spinal cord, meninges, and brain were excised and placed in neutral formalin; they were sectioned and stained with haematoxylin and eosin and were examined microscopically.

RESULTS

Latency.

Profiles for onset and segmental spread of analgesia of a representative sample of each of the three groups are shown in figure 1. The data are confined to cases in which analgesia spread up to the eighth thoracic segment or beyond.

The characteristic pattern of epidural spread is well demonstrated by the mean profile of the control series. After an initial delay of 5–6 minutes analgesia appeared at the level of the twelfth thoracic and first lumbar segments, and then spread fairly smoothly upwards and downwards for a few segments. However, after descent to the fourth lumbar the block missed the next two segments and analgesia jumped to the second sacral, until, after an appreciable delay, it appeared finally at the levels of the fifth lumbar and first sacral and the fourth and fifth sacral segments. Complete spread occurred in 16 minutes.

With hyaluronidase added, initial onset was slightly faster (4.5 minutes) and analgesia made its first appearance one segment lower down, at the first and second lumbar segments. The pattern of spread appeared to be widely dispersed as shown by the scatter of dots in the second graph in figure 1: in some it was faster than in the control series. The resulting variation in the hyaluronidase data was very wide and therefore individual results were unpredictable. There was a general tendency for spread to be faster in the upper thoracic segments, and there was a significant shortening of waiting
time for the appearance of analgesia in the fifth lumbar and first sacral segments, but the rest of the mean profile is not significantly different from that of the control group.

The addition of 1 per cent potassium chloride gave rise to more significant changes in the latency profile. Again, sensory loss appeared faster, in a mean time of 4.6 minutes, but the most noticeable difference was apparent when analgesia had descended to the fourth lumbar level. At this point there was no great delay in the development of analgesia at the fifth lumbar-first sacral and fourth-fifth sacral levels, and analgesia rapidly became complete in the legs and perineum. This difference is highly significant for the first and fifth sacral segments (P<0.001).

Spread.

Figure 2 depicts dosage requirements plotted against age, as previously described (Bromage, 1962a); mean lines were drawn visually through the data. It can be seen that all three solutions have very similar dosage requirements at any given age.
Intensity of blockade.

The two adjuvants had different effects on the quality of sensory block. With hyaluronidase added, analgesia was less intense than in the control group and in three cases there was negligible loss of perineal sensation. On the other hand, the addition of potassium chloride produced a reliable and effective block that was relatively quick to develop in the sacral segments.

The scores for motor blockade of the legs are summarized in table II. Hyaluronidase impaired the effectiveness of the blockade and reduced the average score by more than half. On the other hand, the addition of 1 per cent potassium chloride did not produce any appreciable difference from the score of the control group.

Duration.

In the control group the average duration of action from the time of complete spread of analgesia until recession of the upper two analgesic dermatomes, was $97 \pm 19.2$ minutes. With 1 per cent potassium chloride added the duration was prolonged to $116 \pm 19.5$ minutes; this difference is just significant. In most cases the quality of analgesia with hyaluronidase was inadequate to allow patients to remain awake in comfort during surgical operations and so accurate data for duration of action were not obtained in this group.

### TABLE II

Comparison of intensity of motor blockade.

<table>
<thead>
<tr>
<th>Solution</th>
<th>No. of patients tested</th>
<th>No. of legs in each category</th>
<th>Average degree of motor block (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 2% lignocaine plus adrenaline</td>
<td>35</td>
<td>19</td>
<td>29</td>
</tr>
<tr>
<td>2. 2% lignocaine plus adrenaline plus hyaluronidase</td>
<td>12</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>3. 2% lignocaine plus adrenaline plus 1% KCl</td>
<td>44</td>
<td>16</td>
<td>49</td>
</tr>
</tbody>
</table>

N = No motor block (0%).
P = Partial motor block (33%).
AC = Almost complete motor block (66%).
C = Complete motor block (100%).
Experimentally induced analgesia.

The results of the experiments in which potassium chloride was injected into the subarachnoid space in five dogs are summarized in table III. Injection of 1 per cent KCl directly into the cisterna magna produced strong spasms and twitches which lasted more than 1 hour. The spasms were masked by the addition of local anaesthetic which, of course, produced flaccid paralysis throughout its period of action. On recovery from the local anaesthetic the dogs experienced spasms for a short period until vascular absorption reduced the potassium concentration. The animals showed no evidence of neurological damage after recovery from the general anaesthetic; they exercised, ate, and excreted normally during the subsequent seven days of observation. Histological examination of the spinal cord and brain stem revealed no sign of inflammation or cellular infiltration in the leptomeninges.

DISCUSSION

Several reasons may be advanced to explain the slow onset and spread of epidural analgesia and the relatively tenuous quality of its sensory and motor blockade. First, rapid vascular uptake from the extradural space removes a proportion of the injected drug (Bromage and Robson, 1961; Lund, 1965; Scott, 1965). Second, it takes some time to penetrate the thick integuments around the nerves. Third, some spinal roots are very much bigger than others, and it takes a relatively long time for the local anaesthetic to penetrate to the centre of the larger roots. Some lumbar and sacral nerve roots, especially those of the fifth lumbar and first sacral, combine bulk with thick coverings and this combination appears to be the most likely reason for their tardy blockade.

Several of the local anaesthetic drugs available today have high penetrating qualities and cause almost instantaneous analgesia when injected into the skin. A few of these, notably lignocaine, mepivacaine, and prilocaine, have virtually supplanted the longer-established agents such as cinchocaine and amethocaine, and their superiority in most forms of regional anaesthesia is unquestioned. Although the newer drugs have improved the quality of epidural blockade to a certain degree, however, the measurable extent of this improvement is disappointingly slight. For example, the results we have obtained with lignocaine and prilocaine show few major advantages when compared with three amethocaine solutions (table IV). Until the discovery of local anaesthetics that can effect the ultra-intensive penetration required to equate the efficiency of epidural blockade with that of subarachnoid analgesia, other means must be sought to weaken the defences of the target nerves or to impair their energetics in a reversible manner.

Hyaluronidase has been proposed as an aid to

### Table III

**Effects of subarachnoid injection of lignocaine and potassium chloride in dogs.**

<table>
<thead>
<tr>
<th>Dog</th>
<th>Solution</th>
<th>Volume (ml)</th>
<th>Site of injection</th>
<th>Immediate effects</th>
<th>Neurological changes</th>
<th>Histological changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>2% lignocaine plus 1% KCl</td>
<td>2.0</td>
<td>Lumbar</td>
<td>Flaccid paralysis for 45–50 minutes, followed by irregular twitches and spasms for 15 minutes</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>2.</td>
<td>2% lignocaine plus 1% KCl</td>
<td>4.0</td>
<td>Cisterna magna</td>
<td>Flaccid paralysis for 45–50 minutes, followed by irregular twitches and spasms for 15 minutes</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>3.</td>
<td>2% lignocaine plus 1% KCl</td>
<td>5.0</td>
<td>Cisterna magna</td>
<td>Flaccid paralysis for 45–50 minutes, followed by irregular twitches and spasms for 15 minutes</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>4.</td>
<td>2% lignocaine plus 1% KCl</td>
<td>5.5</td>
<td>Cisterna magna</td>
<td>Flaccid paralysis for 45–50 minutes, followed by irregular twitches and spasms for 15 minutes</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>5.</td>
<td>1% KCl in normal saline</td>
<td>4.0</td>
<td>Cisterna magna</td>
<td>Severe generalized tonic spasm for 2 minutes, followed by flaccid paralysis interspersed with irregular twitching and spasms for 1 hour</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>
### Table IV

**Efficiency and dosage requirements of amethocaine, lignocaine, and prilocaine for epidural analgesia.**

<table>
<thead>
<tr>
<th>Analgesia solution (with 1/200,000 adrenaline)</th>
<th>No. of patients</th>
<th>Latency (minutes)</th>
<th>Dosage requirements at 40 years (mg/spinal segment)</th>
<th>Average degree of motor block (%)</th>
<th>Duration to recession of 2 segments (minutes)</th>
<th>Approximate maximal safe dosage (one injection; mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amethocaine 0.2%</td>
<td>24</td>
<td>8.00</td>
<td>24.8</td>
<td>4.3</td>
<td>25.0*</td>
<td>135</td>
</tr>
<tr>
<td>Amethocaine 0.3%</td>
<td>22</td>
<td>6.75</td>
<td>19.5</td>
<td>4.5</td>
<td>21.6*</td>
<td>145</td>
</tr>
<tr>
<td>Amethocaine 0.4%</td>
<td>29</td>
<td>6.75</td>
<td>20.5</td>
<td>4.5</td>
<td>27.0*</td>
<td>135</td>
</tr>
<tr>
<td>Lignocaine 2.0%</td>
<td>61</td>
<td>5.50</td>
<td>16.0</td>
<td>27.0</td>
<td>37.5</td>
<td>97</td>
</tr>
<tr>
<td>Lignocaine 3.0%</td>
<td>30</td>
<td>4.80</td>
<td>14.0</td>
<td>26.0</td>
<td>35.2</td>
<td>98</td>
</tr>
<tr>
<td>Prilocaine 2.0%</td>
<td>40</td>
<td>7.30</td>
<td>19.5</td>
<td>27.0</td>
<td>36.3</td>
<td>97</td>
</tr>
<tr>
<td>Prilocaine 3.0%</td>
<td>45</td>
<td>5.10</td>
<td>16.5</td>
<td>27.0</td>
<td>34.6</td>
<td>99</td>
</tr>
</tbody>
</table>

*Motor block tested 40 minutes after epidural injection.*

Penetration and Scott (1956) reported that it shortened epidural latency appreciably, especially when injected caudally. His findings have been partially confirmed in the present small series but the difference in latency from the control group was not striking. Moreover, the general effect of hyaluronidase was disappointing, for the quality of epidural blockade was impaired rather than enhanced; it was for this reason that the series was terminated as soon as sufficient data had been collected to establish this fact. We draw the conclusion that hyaluronidase has no place in epidural analgesia.

Potassium salts have long been used as adjuvants to local anaesthetics (Hoffmann and Kochmann, 1912; Meeker, 1925). Lechat and his colleagues (1964) have recently revived interest in their use; they found that the duration of action of injected solutions of procaine was doubled and blocking activity was heightened when potassium chloride was added in concentrations of 135–150 mM, that is approximately the same strength as the normal intracellular concentration of potassium. Several mechanisms may be invoked to account for this heightened anaesthetic activity. The most obvious is a reduction in membrane potential from the altered Donnan equilibrium, where

$$E_m \propto \log \frac{[K^+]_i}{[K^+]_o}$$

The membrane potential, $E_m$, will decrease as the potassium concentration outside the cell $[K^+]_o$ increases. Also, inhibition of ion fluxes across the membrane may play a part. High concentrations of external potassium during excitation reduce potassium efflux from the cell and the altered ionic relationships may affect the orientation of lipoproteins in the cell membrane in such a way that the membrane lattice becomes less permeable to the influx of sodium, while at the same time becoming more permeable to lipid-soluble substances such as local anaesthetics (Wolman and Weiner, 1963). There are many other ions that might be employed to alter membrane permeability in a highly selective manner, and this aspect of local anaesthetic techniques should be a rewarding field of study (Lettvin et al., 1964).

In the present series the quality of epidural blockade was improved in three respects by the addition of 120 mM KCl (i.e. 1 per cent). Waiting time for complete spread was substantially reduced in the sacral segments: in the first and fifth sacrals this reduction amounted to 4½ minutes, or 28 per cent less time than in the control series. Also, the intensity of sensory block appeared to be greater, especially in the sacral segments, and the duration of action was somewhat prolonged. These are worthwhile improvements that might provide grounds for further clinical use of potassium in epidural solutions. However, the possibility of dural puncture and massive subarachnoid injection is very real in every epidural block. With care and experience this danger is remote but nevertheless its existence implies that all solutions injected epidurally must be as innocuous inside the dura as outside.

The results obtained in experiments in dogs in
which potassium chloride was injected into the subarachnoid space show that although the 1.1 per cent solution caused no permanent damage there could be objections to its use in clinical epidural analgesia. The depolarizing spasms caused by the presence of potassium in the cisterna magna are intense and dramatic. Although these motor phenomena are almost entirely masked by the simultaneous injection of a local anaesthetic, there is a short period in which the potassium effect outlasts the local anaesthetic, and during this time twitches and muscle cramps might be troublesome and painful in a conscious patient.

In the light of these findings the use of 1 per cent potassium chloride as an adjunct to epidural analgesia cannot be generally recommended. In expert hands, and when its accurate placement in the extradural space is assured, it gives rise to an enhanced blockade that is safe and reversible but injection into the subarachnoid space results in effects which, although harmless, might be temporarily painful and alarming.

ACKNOWLEDGEMENTS

This investigation was carried out with the aid of Grants No. MA1008 and MA1995 from the Medical Research Council of Canada. Thanks are due to Professor K. Krnjevic for constructive criticism.

REFERENCES


L’hyaluronidase et le chlorure de potassium ont été essayés comme adjuvants de l’analgésie epidurale chez 137 malades. Le chlorhydrate de lignocaine à une concentration de 2 pourcents avec l’adrénaline 1/200.000 a été utilisé comme solution contrôle dans 61 cas; l’hyaluronidase, 5 USP unités/ml a été ajoutée dans 26 cas et 1 pour cent de chlorure de potassium a été ajouté dans 50 cas. L’hyaluronidase parut inhiber l’effet de blocage sensitif plutôt que de l’augmenter, alors qu’un pour cent de chlorure de potassium provoqua une diminution du temps de latence de la dispersion et une augmentation d’intensité au bloc sensitif spécialement dans les segments sacraux. On en conclut que l’hyaluronidase n’a aucune place dans l’analgésie epidurale. Le chlorure de potassium devrait être utilisé avec une grande prudence parce qu’il produit des effets secondaires indésirables s’il est introduit dans l’espace sous-arachnoïdien.

DIE QUALITÄT DES EPIDURAL BLOCKS
II: EINFLUSS VON PHYSIKALISCH-CHIMISCHEN FAKTOREN: HYALORONIDASE UND KALIUM


NORTH OF ENGLAND SOCIETY OF ANAESTHETISTS
Programme for Session 1966–67

1966
FRIDAY, NOVEMBER 18.
PROFESSOR A. L. LATNER, Department of Clinical Biochemistry, Royal Victoria Infirmary.
"Possible Biochemical Mechanisms of Anaesthesia".

FRIDAY, DECEMBER 9.
PROFESSOR J. F. NUNN, Department of Anaesthetics, University of Leeds.
"Circulatory Factors in Oxygenation during Anaesthesia".

1967
WEDNESDAY, APRIL 19.
Joint meeting in the Royal Victoria Infirmary with the North of England Medico-legal Society. Details will be announced later.

FRIDAY, MAY 5.
MR. D. TACCHI, Princess Mary Maternity Hospital and DR. A. S. MACKENZIE, Royal Victoria Infirmary.
"Anaesthesia and Analgesia in Obstetric Practice".

There will not be an ordinary meeting of the Society in March but arrangements are in hand with the University Department of Anaesthetics for a one-day Symposium on "Interactions between drugs used in general practice, psychiatry, and anaesthesia". The provisional day is the third Saturday in March.

Meetings are held in The New Lecture Theatre, Royal Victoria Infirmary, Newcastle upon Tyne at 8 p.m. A buffet supper is served in the board room from 6.30 p.m. and coffee is available in the ante-room to the lecture theatre from 7.30 p.m. onwards.

All communications should be addressed to the Honorary Secretary:
DR. E. A. COOPER
Department of Anaesthetics, Royal Victoria Infirmary, Newcastle upon Tyne, 1.