LEUCOPENIC EFFECTS OF PROLONGED NITROUS OXIDE TREATMENT
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SUMMARY
Studies of the leucopenic effects of nitrous oxide were made in rodents, with and without surgical wounds. The animals were exposed to one of the following atmospheres: (1) air; (2) 25 per cent nitrous oxide; (3) 60 per cent (rats) or 40 per cent (mice) nitrous oxide; the oxygen percentage was maintained at 21 per cent in each case. A leucopenic effect and suppression of the normal leucocytosis to trauma was seen with all concentrations of nitrous oxide after 2 days’ treatment. The effect of 60 per cent nitrous oxide was greater than 25 per cent nitrous oxide after 7 days but the difference was less pronounced in the first 4 days. The leucopenic effect was greater in animals with surgical wounds. Granulopenia was present after 3 days, but not after 1 day of nitrous oxide, and persisted for at least 3 days after completion of treatment. The safety of nitrous oxide therapy and its possible mechanisms of toxicity are discussed.

Long-term nitrous oxide therapy has been recommended for postoperative sedation and pain relief (Petrovsky and Yefuni, 1965; Pugachev and Kolygin, 1965), and also as an aid in prolonged hypothermia (Roth, 1963). In these reports the risks of leucopenia were minimized by frequent blood counts and were weighed against the excellent analgesia and sedation from nitrous oxide. The experimental studies to be described were made to investigate the leucopenic effect of the gas with a view to establishing the relative safety of continuous nitrous oxide therapy.

TECHNIQUE
Norwegian hooded rats were used as the experimental animal for these studies apart from one study in mice. The ventilation units described in the previous paper (Parbrook, 1967) were adjusted in each trial to provide the following atmospheres:
(1) air (controls);
(2) 25 per cent nitrous oxide, 21 per cent oxygen and 54 per cent nitrogen;
(3) 60 per cent nitrous oxide, 21 per cent oxygen and 19 per cent nitrogen.
In each trial, the animals were divided into three groups and each group was exposed to one of the above mixtures. In the case of mice, 40 per cent nitrous oxide was used in place of 60 per cent in group 3.

RESULTS
Fourteen days treatment with nitrous oxide.
In this trial 36 rats were divided into three groups of 12 and each group was exposed to one of the following mixtures: (1) air; (2) 25 per cent nitrous oxide; (3) 60 per cent nitrous oxide.
In 2 rats in each group a mild inflammatory reaction developed in the tail and prevented completion of serial readings. As the initial readings in these rats agreed closely with the mean for the group concerned it was considered justified to omit these incomplete results from the statistical analysis. The results in the three groups of 10 rats are given in the graph with 95 per cent confidence limits (fig. 1).
A leucocytosis was revealed in the control group and was attributed to inflammatory and stress.
response to the tail trauma. Both in the control group and in the 25 per cent nitrous oxide gas group, treatment was continued for 14 days; the results showed a significantly lower white cell count in the nitrous oxide group than in the controls in all tests, the earliest counts in this trial being made after 4 days of treatment.

The graph indicates the mean white cell counts and 95 per cent confidence limits for three comparable groups, each of 10 rats, exposed to air or to one of two concentrations of nitrous oxide. The leucocytosis in the control groups was attributed to tail trauma from repeated taking of blood samples.

The rats treated with 60 per cent nitrous oxide also had lower white cell counts than the controls on the 4th day, and on the 7th day the counts were significantly lower in the 60 per cent group than those in the rats treated with 25 per cent nitrous oxide (P<0.05). During treatment with 60 per cent nitrous oxide the animals remained in satisfactory health until the 7th day when 2 animals which had leucopenia appeared ill and a third died showing marked leucopenia (1,250 cells/cu.mm). It was not considered justified to prolong treatment in this group and the animals were destroyed.

White cell counts in the presence of a surgical wound.

In considering the use of nitrous oxide for postoperative pain relief it seemed wise to repeat these results in a comparable series of animals with incised surgical wounds. It appeared possible that in the presence of a wound the gas might prove more toxic to the bone marrow, since healing is associated with a leucocytosis. In view of the serious toxicity of nitrous oxide after 7 days' exposure as shown in the previous trial, the duration of treatment was restricted to 4 days using 24 rats in three groups of 8. Preliminary white cell counts were taken and a 4-cm-long incised wound was made during halothane and oxygen anaesthesia using anaesthetic apparatus described elsewhere (Parbrook, 1966); Michel clips were used to close the wound.

Because of variation in the total white cell counts between different rats, minor changes in counts can be assessed more satisfactorily using the changes in counts in the individual rats. The means of the changes in the white cell counts are given in table I, together with the comparable readings in the rats of the previous trial at 4 days. It is seen that the white cell counts have increased significantly in both the "wounded" and "non-wounded" controls but there is a significant lowering of the counts in all groups of treated rats. While there appeared to be a greater depression of the total white cell count with 60 per cent nitrous oxide than with 25 per cent, these differences were not significant (P>0.2 both in rats with and without wounds).

If all the rats treated with nitrous oxide were compared according to whether or not wounded, those with wounds showed significantly greater depression of the white cell counts. Further evidence of increased toxicity of nitrous oxide in the animals with wounds was indicated by the subsequent progress of these rats. In the case of rats with wounds there appeared to be a higher morbidity as 4 rats died or appeared ill and had to be destroyed within 2 days of completion of treatment. It was noted that all these animals had counts below 2,500/cu.mm whereas animals with counts above 2,500/cu.mm remained in satisfactory health.

Effects of nitrous oxide therapy of under 4 days duration.

Two further trials were conducted with rats with wounds to indicate the effects of nitrous oxide treatment over the first 3 days. In the first trial white cell counts were taken initially and after
**TABLE I**

*Mean changes in white cell counts (per cu.mm) after 4 days of inhaling air or nitrous oxide in 25 or 60 per cent concentration.*

<table>
<thead>
<tr>
<th>Controls (air)</th>
<th>25 per cent nitrous oxide</th>
<th>60 per cent nitrous oxide</th>
<th>Analysis of variance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>X</td>
<td>SE</td>
</tr>
<tr>
<td>Rats without wounds</td>
<td>10</td>
<td>+2,200†</td>
<td>969</td>
</tr>
<tr>
<td>Rats with wounds</td>
<td>7</td>
<td>+5,529*</td>
<td>1,869</td>
</tr>
</tbody>
</table>

X = mean of changes in white cell counts.  
N = number of animals in each group.  
SE = standard error.  
* Probability, P<0.05.  
† P<0.01.

Comparing all treated non-wounded with treated wounded animals, the increased depression of the count in the latter is significant (t<sub>s</sub>= 3.26; P<0.01).

**TABLE II**

*Mean changes in white cell counts (per cu.mm) after 1, 2, 3 and 4 days in rats with wounds.*

<table>
<thead>
<tr>
<th>Duration of treatment (days)</th>
<th>Controls (air)</th>
<th>25 per cent nitrous oxide</th>
<th>60 per cent nitrous oxide</th>
<th>Analysis of variance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>X</td>
<td>SE</td>
<td>N</td>
</tr>
<tr>
<td>1</td>
<td>6</td>
<td>+1,342</td>
<td>1,667</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>14</td>
<td>+929</td>
<td>719</td>
<td>14</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>+2,325</td>
<td>1,502</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>+5,529*</td>
<td>1,869</td>
<td>8</td>
</tr>
</tbody>
</table>

X = mean of changes in white cell counts.  
N = number of animals in each group.  
SE = standard error.  
* Probability, P<0.05.  
† P<0.01.

The rats at each day are different sets except for those which were assessed at 1 and 3 days after the start of the experiment. The counts were made 2 hours after treatment in the "1 day" results and 18 to 20 hours after removal from the atmospheres in the results of the 2, 3 and 4 days.

**Duration of treatment. Analysis of trend, in the 2-, 3- and 4-day results:**

- Controls: the increasing leucocytosis is significant; t<sub>s</sub>= 2.77; P<0.02.
- 25 per cent nitrous oxide: the increasing leucocytosis is significant; t<sub>s</sub>= 3.38; P<0.01.
- 60 per cent nitrous oxide: the increasing leucocytosis is significant; t<sub>s</sub>= 3.53; P<0.01.
1 and 3 days treatment; in the second trial the white cell counts were measured initially and after 2 days of nitrous oxide treatment. The composite results are shown, with those of the previous trial, in the histogram (fig. 2) and in table II.

The control rats showed increases of white cell counts which reached significance after 4 days. A significant depression of the counts was recorded after 2, 3, and 4 days with both 25 and 60 per cent nitrous oxide, and after 1 day in 25 per cent nitrous oxide treated rats.

The difference between rats treated with 25 and 60 per cent nitrous oxide is small compared to the marked differences in the response of the controls and treated animals. The histogram is suggestive of an overall tendency for 60 per cent nitrous oxide to be more toxic than the 25 per cent concentration between the 2nd and 4th days of treatment, but the difference between the two treatments is not significant at any individual day.

Comparison of the results of all four durations of treatment was not possible as the white cell counts after 1 day's treatment were taken about 2 hours after completion of exposure whereas the results after 2, 3 and 4 days' treatment were obtained 18 to 20 hours after removal of the animals from the ventilation units. In these 2-, 3- and 4-day results an increasing leucocytosis is seen in the controls, and an increasing leucopenia in both the 25 and 60 per cent nitrous oxide treated animals. On analysis, all these trends were significant (table II).

It seemed desirable to recheck the results after 24 hours treatment with nitrous oxide to see if the leucopenia persisted beyond the first 2 hours following the end of exposure. A similar trial was therefore conducted in which repeat counts were not taken until 24 hours after the completion of exposure to nitrous oxide. The 25 per cent nitrous oxide unit was not used on this occasion. A similar leucocytosis was seen in the controls and the animals treated with 60 per cent nitrous oxide; the mean rise of count in the 9 control rats was 4,528 cells/cu.mm, whereas that in the nitrous oxide group of 9 rats was 4,633 cells/cu.mm. It appeared that the leucopenia previously found after 1 day's nitrous oxide treatment was only a temporary effect.

Effects of nitrous oxide in mice.

Unfortunately it was not possible to repeat these investigations with rabbits or guineapigs as these animals appeared too susceptible to the sedative effect of the gas. A similar trial was, however, made with mice. The duration of treatment was 6 days, and 30 mice in three groups of 10 participated in the trial.

The results (table III) revealed a significant depression of total white cell counts both by 25 and 40 per cent nitrous oxide treatment.

Differential white cell counts.

Differential counts were made in rats and mice and changes were seen in the percentage polymorphonuclear count as indicated in table IV.

In rats differential counts made after 1 day's exposure to the atmospheres were similar in the three groups but counts after 3 days showed that a highly significant reduction of the polymorphonuclear percentage accompanied nitrous oxide treatment. The level in rats treated with 25 per cent nitrous oxide was significantly lower than the
LEUCOPENIC EFFECTS OF PROLONGED NITROUS OXIDE TREATMENT

### Table III

Mean changes in white cell counts in mice after 6 days' nitrous oxide.

<table>
<thead>
<tr>
<th></th>
<th>Controls (air)</th>
<th>25 per cent nitrous oxide</th>
<th>40 per cent nitrous oxide</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>X</td>
<td>SE</td>
</tr>
<tr>
<td>Change in count per cu.mm</td>
<td>10</td>
<td>-920</td>
<td>103</td>
</tr>
</tbody>
</table>

- \( \bar{X} \) = mean of changes in white cell counts.
- \( N \) = number of animals in each group.
- \( SE \) = standard error.
- \( * \) Probability, \( P < 0.05 \).
- \( t \) \( P < 0.01 \).

### Table IV

Percentage of polymorphonuclear leucocytes after nitrous oxide treatment.

<table>
<thead>
<tr>
<th>Animal</th>
<th>Duration of treatment (days)</th>
<th>Controls (air)</th>
<th>25 per cent nitrous oxide</th>
<th>60 per cent nitrous oxide</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>X</td>
<td>SE</td>
<td>N</td>
</tr>
<tr>
<td>Rats</td>
<td>1</td>
<td>6</td>
<td>24.3</td>
<td>2.9</td>
</tr>
<tr>
<td>Rats</td>
<td>3</td>
<td>12</td>
<td>30.6</td>
<td>2.4</td>
</tr>
<tr>
<td>Rats</td>
<td>14</td>
<td>10</td>
<td>26.5</td>
<td>3.1</td>
</tr>
<tr>
<td>Mice</td>
<td>6</td>
<td>10</td>
<td>23.2</td>
<td>2.0</td>
</tr>
</tbody>
</table>

- \( \bar{X} \) = mean of percentages of polymorphonuclears.
- \( N \) = number of animals in each group.
- \( SE \) = standard error.

The polymorphonuclear percentages in rats following exposure to the gases for 1 day are not significantly different in the treated and control animals. With longer durations of exposure in rats and mice the polymorphonuclear percentages are significantly lower in the treated animals \( (P < 0.01\) in every case).

### Table V

Percentage of polymorphonuclear leucocytes 3 days after completion of nitrous oxide treatment.

<table>
<thead>
<tr>
<th></th>
<th>Controls (air)</th>
<th>25 per cent nitrous oxide</th>
<th>60 per cent nitrous oxide</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>X</td>
<td>SE</td>
</tr>
<tr>
<td>Mean percentage polymorphs (rats)</td>
<td>7</td>
<td>38.3</td>
<td>3.6</td>
</tr>
</tbody>
</table>

- \( \bar{X} \) = mean of percentages of polymorphonuclears.
- \( N \) = number of animals in each group.
- \( SE \) = standard error.

The animals were treated with the atmospheres for 3 days and differential counts made 3 days later. The counts were taken by cardiac puncture under ether anaesthesia and are therefore not strictly comparable with those in table IV. The percentage of polymorphonuclears is significantly lower in the 60 per cent nitrous oxide group than in the controls \( (P < 0.001)\). The difference between the 25 per cent group and controls is not significant \( (P > 0.2)\).
controls, while the 60 per cent treated group showed an even greater depression than the 25 per cent group.

Differential counts taken from the rats treated for 14 days with 25 per cent nitrous oxide showed a similar depression of the polymorphonuclears in treated animals when compared with the controls.

The only other component of the differential count showing a change with treatment was the eosinophil count. In rats treated for 3 days with nitrous oxide the mean eosinophil percentage in the controls was 2.0 ± 0.4 per cent and this was significantly higher than that in the 25 per cent (mean 0.8 ± 0.3 per cent) or 60 per cent (mean 0.3 ± 0.1 per cent) nitrous oxide groups of animals.

A depression of the polymorphonuclear percentage was also seen in mice treated for 6 days with nitrous oxide (table IV). The percentages in nitrous oxide treated animals were significantly lower than in the controls.

Delayed recovery of differential count.

In a further series of rats treated for 3 days with nitrous oxide, white cell differential counts were not taken until 3 days after completion of treatment. These showed (table V) that there was still a significant difference between control animals and those treated with 60 per cent nitrous oxide though not between the controls and the 25 per cent nitrous oxide groups.

DISCUSSION

The results of studies in rodents and humans suggest that the effects of long-term nitrous oxide are closely similar in the two cases. Lassen and associates (1956) and Wilson, Martin and Last (1956) first described the granulopenia and leucopenia which was found in patients after about 4 days' exposure to nitrous oxide. This time interval agrees closely with a period of 4 days before significant depression of the white cell counts and altered differential counts were found by Green and Eastwood in their studies in albino rats (1963), and a period of 3 days for similar changes in studies in mice by Yefuni, Federmesser and Smertenko (1964). The latter group stressed the reversibility of the haematological changes and several recent workers (Roth, 1963; Petrovsky and Yefuni, 1965; Pugachev and Kolygin, 1965) regard several days continued sedation and analgesia with nitrous oxide as reasonably safe, provided regular blood checks are made.

While the present studies are in general agreement with those mentioned above they are more indicative of a serious toxicity of the gas, particularly in animals with surgical wounds. Thus a high morbidity and mortality followed 4 days' nitrous oxide treatment in rats with wounds, and the leucopenia appeared more severe than in a similar non-wounded series of animals. A significant leucopenia was present in animals with wounds after the 2nd day of treatment and a marked granulocytopenia was seen in addition after the 3rd day.

A similar prompt fall of leucocyte count was reported by Eastwood and his co-workers in leukaemia patients undergoing nitrous oxide therapy (1963). A review of the reports of leucopenia during nitrous oxide treatment for tetanus (Gormsen, 1955; Lassen et al., 1956; Wilson, Martin and Last, 1956; Last and Nicholas, 1956; Sando and Lawrence, 1958) indicated that the effect was well developed by the 4th or 5th day and that the fall in white cell counts started on the 2nd or 3rd day in some cases. In view of these studies and also the presence of histological changes in the marrow after 48 hours treatment with nitrous oxide in rats (Green and Eastwood, 1963), it appears that even 48 hours exposure to nitrous oxide may be associated with a leucopenic response in humans and a consequent risk of decreased resistance to infection. The depression of white cell count found after 1 day's treatment in these trials was not associated with an altered differential count, and could not be detected when a second 24 hours had elapsed after treatment. One cannot be certain whether this short-term leucopenic effect was due to a redistribution of leucocytes or whether it was an early sign of marrow toxicity.

Recovery from these effects of nitrous oxide has been reported after cessation of treatment (Green, 1964; Yefuni, Federmesser and Smertenko, 1964). It appears possible, however, that recovery may sometimes be delayed a day or two, as an altered differential count was still detected in the present studies several days after a 3-day period of
nitrous oxide treatment, and morbidity and mortality occurred in the 2 days following completion of 4 days' treatment, even though the animals had appeared in satisfactory health during exposure to the gas. A similar delay of over 3 days in recovery from nitrous oxide toxicity was reported by Lassen and associates (1956), by Last and Nicholas (1956), and by Sando and Lawrence (1958) in patients with tetanus; also by Lassen and Kristensen (1959) and Eastwood and associates (1963) after the use of nitrous oxide in patients with leukaemia. This delay in recovery from the leucopenic effects of the gas is in keeping with the toxicity of prolonged intermittent nitrous oxide therapy reported by Ablett (1956) and by Stead, Bush and Roth (1962).

If continuous nitrous oxide therapy is considered essential then regular white cell counts are advisable. Nevertheless, the presence of normal total white cell counts will not necessarily indicate absence of a nitrous oxide effect as it was shown in the first trial that long-term therapy with 25 per cent nitrous oxide could inhibit a leucocytosis which was seen in the control series in response to trauma.

**Mechanism of nitrous oxide toxicity.**

The mechanism of nitrous oxide toxicity is not fully understood. Studies of the bone marrow revealed a progressive hypoplasia (Green and Eastwood, 1963). The reported toxic effects of nitrous oxide on mitosis in embryonic myoblasts (Kieler, 1957) together with the decreased radiosensitivity of tissues caused by nitrous oxide (Evans and Orkin, 1962) both suggest that the gas may cause leucopenia by selectively inhibiting mitosis in some of the blood-forming elements in the marrow. Yefuni, Federmesser and Smertenko (1964), however, found no changes in chromosome structure in mice marrow cells after nitrous oxide treatment.

Higher oxides of nitrogen, nitric oxide and nitrogen dioxide, are possible contaminants of nitrous oxide. Leucopenia and granulocytopenia were reported in industrial workers exposed to these oxides in the form of "nitrous fumes" for prolonged periods (Pfenninger, 1943), and Vigdoritschik and associates (1937) also regarded leucopenia and granulocytopenia as probable symptoms of mild chronic poisoning with nitrogen oxides. A leucopenic effect of higher oxides of nitrogen is more understandable in view of their marked chemical activity than in the case of the chemically inert nitrous oxide. Consequently the presence of higher oxides in nitrous oxide is of considerable importance. The present accepted standards for intermittent exposure of industrial workers to nitric oxides during working hours are 10 p.p.m. (v/v) in Britain and 5 p.p.m. (v/v) in the U.S.A. In the U.S.S.R. the safety limit is set at a lower level (Riasanov, 1959). In the currently described studies the standard of purity of nitrous oxide was accepted as under 1 p.p.m. of higher oxides (A. Bracken, personal communication). Green and Eastwood reported the purity of their nitrous oxide as better than 10 p.p.m. of higher oxides. The exact level (in p.p.m.) at which the leucopenic effect of nitric oxides occurs is of added interest as appreciable quantities of the oxides are absorbed by smokers (Bokhoven and Niessen, 1961), and emitted in the exhausts of diesel vehicles (Gerhardson, 1963). In addition to the risk of contamination of nitrous oxide with higher oxides there is a possibility of traces of nitrous oxide being metabolized to chemically more active oxides in the marrow cells.

Pfenninger (1943) also described methaemoglobinemia in her patients suffering from "nitrous fumes". In the present studies, however, no evidence of methaemoglobinemia was found in the blood of 14 rats treated with nitrous oxide for 3 days, the blood being examined under the reversion spectroscope.

An alternative theory of the mechanism of nitrous oxide toxicity is that there may be a link between drugs producing anaesthesia and effects on mitosis and leucocytes. Thus the gases, nitrogen, xenon and argon, when used under hyperbaric conditions, are both anaesthetic and have analogous effects to those of nitrous oxide in reducing oxygen sensitivity of tissues to radiation (Ebert, Hornsey and Howard, 1958; Ebert and Hornsey, 1958). Pentobarbitone, too, has been shown to have a similar action (Evans and Orkin, 1962). Many anaesthetic agents other than nitrous oxide have also been shown to be toxic to leucocytes in patients (Tempo, 1965) and to have a leucopenic effect in animals (Smith et al., 1948; Graca and Garst, 1957; Usenik and Cronkite, 1965).
CONCLUSIONS

From the present studies and a review of the literature it is doubtful whether continuous nitrous oxide therapy can be recommended for routine postoperative sedation for periods of over 48 hours. There appears to be a risk that the nitrous oxide may inhibit a leucocytosis, in response to trauma and infection, and may lower patients’ resistance. The results should not necessarily be taken as indicating any toxicity for intermittent short-term administration of the gas in the course, for instance, of postoperative physiotherapy (Parbrook, 1965), in general anaesthesia, or for pain relief in labour.

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REFERENCES


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EFFETS LEUCOPENIQUES D'UN TRAITEMENT PROLONGE PAR LE PROTOXYDE D'AZOTE

SOMMAIRE

Chez des rongeurs avec ou sans plaies chirurgicales on a étudié les effets leucopeniques du protoxyde d'azote. Les animaux ont été exposés à l'une des atmosphères suivantes: (1) air; (2) 25 pour cent de protoxyde d'azote; (3) 60 pour cent de protoxyde d'azote (rats), 40 pour cent de protoxyde d'azote (souris); le pourcentage d'oxygène restant maintenu dans tous les cas à 21 pour cent. Un effet leucopénique et la suppression de la leucocytose posttraumitique non née ont été observés avec toutes les concentrations de protoxyde d'azote après deux jours de traitement. L'effet du protoxyde d'azote à 60 pour cent a été plus fort que celui du protoxyde d'azote à 25 pour cent après sept jours, mais la différence était moins nette au cours des quatre premiers jours. L'effet leucopénique était plus prononcé chez les animaux qui étaient atteints par des plaies chirurgicales. La granulopénie survint au troisième jour, mais non pas après un seul jour de traitement par le protoxyde d'azote, et persiste pendant trois jours au moins après la fin du traitement. La sécurité du traitement par le protoxyde d'azote et les différents mécanismes possibles pour l'explication de la toxicité sont discutés.

LEUKOPENISCHE WIRKUNGEN EINER AUSGEDEHNTEN LACHGASBEHANDLUNG

ZUSAMMENFASSUNG


SOUTH EAST METROPOLITAN REGIONAL SOCIETY OF ANAESTHETISTS

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on SATURDAY, MAY 20, 1967

The main subject for discussion will be "Pre-operative Assessment".

This meeting is open to junior anaesthetic staff of all grades and while it is intended primarily for those in the S.E. Metropolitan Region applicants from other Regions will be welcome.

Registration fee 5s. to include lunch, tea and refreshments, payable to the Secretary, Sussex Postgraduate Medical Centre, Brighton 7.