Sir,—The recently introduced steroid anaesthetic agent Althesin has gained ready acceptance: smooth induction combined with rapid and complete recovery as measured by testing cortical function (Evans and Glennie Smith, in preparation) render it attractive, especially for outpatient anaesthesia. However, serious adverse reactions have occurred in this hospital group in the last 5 months.

Case Reports

Case 1

An 11-year-old girl, with no known allergic tendency and who had had many previous uneventful anaesthetics, was induced with Althesin 2 ml, intubated with the aid of suxamethonium, and the anaesthetic maintained with nitrous oxide, oxygen and tubocurarine: nothing untoward occurred. Ten days later, exactly the same technique was used. Some 10 seconds after the intravenous injection of Althesin 2 ml, she developed a crimson flush all over the face and upper trunk, and goose flesh appeared on the limbs. Thirty seconds after the injection, the crimson flush took on a mottled bluish-white appearance; peripheral and central cyanosis, unresponsive to ventilation with 100% oxygen, was present. There was tachycardia with consistent hypotension (unrecordable blood pressure). Bronchospasm was not displayed. Rapid fluid infusion resulted in prompt improvement, and neither hydrocorisone nor an antihistamine was given. However, it was noted that the peripheral circulation remained poor for some 30 minutes. Subsequently, full clinical recovery occurred, and there were no ill effects for the patient.

Skin testing was performed using a saline control, suxamethonium, and Althesin: there was no response to saline, an extensive weal and flare with suxamethonium (suxamethonium causes histamine release to a significant degree: Goodman and Gilman, 1970), and a moderate response to Althesin.

The features of this reaction strikingly resemble those seen in propanidid sensitivity (Johns, 1970; Evans, 1971). The vehicle used for both Althesin and propanidid is Cremophor EL, and it is obviously very tempting to blame this agent for the sensitivity reactions. Glaxo Laboratories have been kind enough to offer us samples of the pure steroid constituent and of Cremophor EL, and we hope to repeat skin testing on the girl: the results will be reported.

But, it should be noted that recent work in Germany seems to have exculpated Cremophor EL (Lorenz et al., 1972).

Suxamethonium has also been known to provoke an anaphylactic response (Jerums, Whittingham and Wilson, 1967), and to cause bronchospasm (Katz and Mulligan, 1972), and it produced a significant reaction to intradermal testing in this girl; on the other hand, suxamethonium had previously been administered to the patient without any trouble. Only a handful of cases of adverse reactions to suxamethonium has been reported over some 20 years, which contrasts markedly with this report of five cases in 5 months. Besides, in three of the cases reported below, suxamethonium was either not administered or only administered after an adverse reaction was obviously apparent; in the case where suxamethonium was not administered, the patient exhibited a marked skin reaction.

In Southampton, apart from the case reported above, Althesin has been strongly suspected of causing bronchospasm, as implied in the previous paragraph. With one patient this was relatively transient, responding to aminophylline; on another occasion the bronchospasm was more troublesome and was accompanied by a skin reaction; and, in the other two cases severe bronchoconstriction occurred, one patient dying despite treatment.

Case 2

Althesin 3 ml was used to induce anaesthesia in a fit woman of 23; she had no known allergic tendency. After the onset of anaesthesia, suxamethonium 70 mg was given intravenously to facilitate intubation. Upon application of the facepiece for oxygenation prior to intubation, the anaesthetist found the lungs very difficult to inflate and, assuming this to be due to airway obstruction, proceeded rapidly to intubation. Intubation was easy, with no laryngeal spasm or bronchospasm (this is a common allergic response here). After intubation, the patient was still very difficult to inflate and wheezing was heard on auscultation of the chest. There was no obvious skin reaction. The anaesthetist administered aminophylline slowly intravenously and, after 100 mg had been given (about 5 minutes after the recognition of bronchospasm), chest expansion gradually became easier. The patient had no untoward after-effects.

Case 3

A man of 50, who was said to suffer from chronic bronchitis and emphysema, was anaesthetized for a cataract extraction; preoperatively, there were scattered râles audible in both lungs. Five months previously he had received an anaesthetic for extraction of a cataract from his other eye. At that time, the sequence was thiopentone, suxamethonium and nitrous oxide-oxygen-halothane, the anaesthetic being uneventful.

Anaesthesia was induced with Althesin 4 ml, followed by alcuronium 20 mg. Immediately following these injections, the patient suddenly coughed and rapidly became cyanosed. When artificial ventilation was attempted, it was found to be impossible to ventilate the patient by facepiece even with a high inflation pressure. Endotracheal intubation was accomplished easily, the vocal cords being widely separated. Following intubation, it was still impossible to ventilate the lungs manually, even with high pressures. Total bronchospasm was diagnosed. After about 3 minutes it became possible to force some oxygen into the lungs and subsequently to ventilate the patient, although abnormally high inflation pressures were required. Intravenous aminophylline 250 mg produced no detectable improvement. Cardiac arrest did not occur. Since it was then possible to oxygenate the patient with an anaesthetic mixture of nitrous oxide, oxygen and halothane, it was then decided to proceed with the operation. Ventilation gradually became easier.

At the end of the operation—about 1 hour after the initial injections—the muscle relaxant was reversed with neostigmine 2.5 mg, preceded by atropine 1.2 mg: prompt return of adequate spontaneous ventilation occurred. When the towels covering the patient were removed it was noticed that an oval area of erythema and scattered weals some 10 cm in length were present around the site of the original intravenous injections, and extended centrally along the line of the vein. This swiftly diminished upon the administration of chlorpheniramine 5 mg intravenously, and 5 mg intramuscularly.

The patient awoke promptly when anaesthesia was discontinued, and had no unusual respiratory difficulty. He remained well until his discharge home.

Case 4

A nervous 49-year-old woman was to have a biopsy of an axillary lump under general anaesthesia. She had suffered from asthma and bronchitis for several years, and was controlled reasonably well with Intal Co. Spinacaps (sodium cromoglycate and isoprenaline sulphate) and a Ventolin inhaler (salbutamol). She displayed a pronounced and widespread allergic response to various animal proteins, and 1 month before the operation, a blood test showed her to have 17% eosinophils in her white cell count.

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On preoperative examination, she had inspiratory and expiratory rhonchi audible over both lungs with some expiratory wheezing. She was premedicated with papaveretum 20 mg intramuscularly.

When she was brought into the anaesthetic room, she was frankly wheezing, and had brought her inhaler with her. After atropine 0.3 mg had been given intravenously with no ill effect, the anaesthetist began the cautious intravenous administration of Althesin. Within seconds, and when only 1.0 ml of Althesin had been given, the patient suddenly took a deep breath, coughed with great violence, and collapsed back with gross bronchospasm and rapidly developing cyanosis. Suxamethonium 50 mg was given immediately, the patient intubated, and some degree of oxygenation achieved by means of high pressure insufflation of 100% oxygen: it was virtually impossible to inflate the lungs at this stage. The pulse remained of reasonable volume, and cardiac arrest never occurred. 8.4% sodium bicarbonate 50 m.equiv., hydrocortisone 100 mg, and aminophylline 25 mg were administered intravenously within 2 minutes from the onset of bronchospasm: the latter two drugs had a beneficial effect, bronchospasm lessening and some inflation being possible. Further doses of hydrocortisone 100 mg (once) and aminophylline 25 mg (four times) were given over the next 6 minutes, and halothane was added to the oxygen. Eight minutes after the onset of bronchospasm, inflation was much easier, and spontaneous ventilation had returned, although the anaesthetist assisted the patient's spontaneous efforts for a further 15 minutes. Further improvement was achieved by puffs from the patient's own Ventolin inhaler administered through the endotracheal tube during inspiration. The operation proceeded, the patient being given diazepam 7.5 mg and fentanyl 0.3 mg in divided doses. The electrocardiogram (attached after 3 minutes) remained in sinus rhythm except for occasional ventricular ectopics for a short time following the last dose of aminophylline. Forty-five minutes after the onset of bronchospasm, the patient was awake and coherent, and well oxygenated breathing air spontaneously; there were only minimal residual rhonchi to be heard at that time.

The remainder of her hospital stay was uneventful.

Case 5

A man aged 75 presented for biopsy of the prostate for possible malignancy. Peripheral blood films suggested either aleukaemic leukaemia or replacement of the bone marrow by secondaries; the platelet count was only 10,000 per cu.mm. Chest X-ray showed an opacity in the right upper zone which was also thought possibly to be malignant. Due to his initial anaemia (Hb=8.4 g/100 ml), he was transfused preoperatively: during this transfusion, when he was also being treated with ampicillin, he developed a generalized rash and a swelling of the upper lip which were considered to be an allergic reaction to the blood or to the ampicillin. He was said to have suffered from asthma in the past for which he took Theodrox (aminophylline) one tablet daily and as necessary for occasional asthmatic attacks. At the time of this incident he was being treated with Septrin and stilboestrol, and took quin-albarbitone at night. He had had no previous operation.

After premedication with papaveretum 10 mg and hyoscine 0.2 mg, anaesthesia was induced with Althesin 2 ml and maintained with nitrous oxide and oxygen via a face-piece. Upon raising the patient's legs into the lithotomy position his respiration became laboured and cyanosis unresponsive to 100% oxygen, ensued. Rapid intubation was achieved with the aid of suxamethonium 50 mg. Hydrocortisone 100 mg followed by a further 100 mg and aminophylline 500 mg were administered intravenously, which resulted in easier ventilation with reasonable chest movements: there was, however, no lessening of cyanosis. The situation deteriorated, the e.g.c. showing a progression to a slow idioventricular rate. Cardiac massage and intravenous sodium bicarbonate gained a temporary improvement, but ventricular fibrillation eventually ensued. The appropriate resuscitative measures were unsuccessful.

At autopsy examination, the small bronchi of the lungs appeared to be tightly constricted, and there were patchy areas of hyperinflation in both lungs; there was no mucus plugging. Histological examination showed extensive intra-alveolar haemorrhages, and muscular hypertrophy in the bronchial and bronchiolar walls, most being constricted. Many smaller bronchi were plugged with mucin and there was eosiinophilic infiltration of the tissues. An increase in the number of goblet cells and a gross thickening of the basement membrane of the epithelium of the small airways was seen. These changes were described by the pathologist concerned as typical of bronchial asthma, and he felt that severe bronchospasm was present at the time of death. Histology revealed that the lesion seen on the chest X-ray was benign, being an area of intra-alveolar fibrosis subsequent to organization of pneumonia.

Nothing abnormal was found in the pulmonary arteries, the myocardium, or the coronary arteries.

The prostatic pathology proved benign.

Microscopic examination of the bone marrow contradicted previous speculation: there was no tumour found, and the marrow was cellular with all cell types represented, although there was an unexplained reduction in the number of megakaryocytes.

This case was complex, and the pathology remained obscure. It does, however, seem fair to conclude that, due to some factor, bronchospasm swiftly followed induction of anaesthesia in this patient.

These five cases have occurred in four different hospitals within this group. After our initial suspicions, Glazo Laboratories replaced stocks of Althesin with early batch numbers in Southampton, substituting fresh stock. Case 4 occurred after this substitution.

We are presently trying to contact the patients described in Cases 1, 2, 3 and 4 for immunological testing. The results will be reported.

Because of the adverse reaction we report in Case 1, and because of our suspicions with regard to bronchospasm, we would urge especial caution in the administration of Althesin, particularly in known cases of asthma or allergy, or where the situation is that of a challenging second dose.

Acknowledgements. We should like to thank Drs B. A. Lovell, E. S. Machell, T. M. Moles and D. J. Pearce for affording us the details of their cases, and we also thank Dr R. H. Steele for the pathological findings.

A. F. AVERY
ANDREW EVANS
Southampton

Footnote. Since this letter was written, it has come to light that Dr M. B. Yorston has seen laryngospasm or bronchospasm develop in seven patients whilst using Althesin.

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Correspondence

Hester, J. B., and Grinstead, East Grinstead

Negative pressure of the epidural space

Sir,—We believe, and we are so teaching since 1969 in our
postgraduate courses, that negative pressure of the epidural
space is probably of the same nature as the subatmospheric
pressure that Gouton (1963, 1965) has shown in artificially
confined areas of the interstitial spaces of the body and
which could result from the interchange of protein and
fluids across the endothelium of the lymphatic vessels.
Would readers of this journal care to offer some enlighten-
ing comment on this matter?

Juan A. Nesi

Venezuela

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pressure based on pressures in implanted perforated

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Compatibility of drugs with blood

Sir.—Articles on side effects of anaesthetic drugs appear
regularly. The British Journal of Anaesthesia had 13 such
articles in the past year. One aspect of this problem, which
is usually not considered, is compatibility of drugs with
blood. Popular intravenous anaesthetic drugs are often
administered in a bolus, bringing a high concentration of
medication in contact with blood components. Any reaction
products may be filtered in pulmonary capillaries, causing
microscopic damage. This phenomenon has already been
described with transfused blood (Mosely and Dory, 1970).
We have previously noted that rapidly increasing blood
pH, at least 2 units with sodium bicarbonate, often pro-
duced detectable haemolysis (Trudnowski, 1971). To deter-
mine whether other drugs caused haemolysis, we made
a simple haemolysis test. The drugs tested were pento-
linitum, chlorziazepoxide, diazepam, diphenhydramine, doxa-
pram, tubocurarine, edrophonium, hydroxyzine, isoprena-
tline, pethidine, mephenetamine, metamizol, methotrim-
prazin, methoxyamine, morphine, neostigmine, phentyl-
prine, pentazocine, sodium thiopentone, and
suxamethonium.

One ml of drug was added to 9 ml of bank blood, un-
suitable for transfusion. After 30 sec, the specimen was
examined for haemolysis using a modification of the method
of Parpart and associates (1947). One hundred ml of treated
blood was added to 5 ml of buffered 0.85% saline. Five
ml of “complementary” solution was then added. The
mixture was centrifuged and the optical density of the
supernatant solution was read at 540 m
d on a Beckman
DU-2 spectrophotometer. The control supernatant was from
blood diluted with 0.9% sodium chloride and was set at 0.
One hundred ml of the blood diluted with 0.9% sodium
chloride was haemolysed in distilled water and its “comple-
mentary” solution to obtain the 100% haemolysis reading.
Drabkin’s solution was used to confirm the presence of
plasma haemoglobin in specimens showing haemolysis.
Haemolysis occurred with the following drugs under the
above conditions:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Percent haemolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlordiazepoxide (Librium)</td>
<td>98–100</td>
</tr>
<tr>
<td>Diazepam (Valium)</td>
<td>66</td>
</tr>
<tr>
<td>Doxapram (Dopram)</td>
<td>13</td>
</tr>
<tr>
<td>Hydroxyzine (Vistaril)</td>
<td>95–100</td>
</tr>
<tr>
<td>Methotrimeprazine (Levoprome)</td>
<td>95–98</td>
</tr>
</tbody>
</table>

The other drugs showed less than 2% haemolysis which is
within the error range of the method.

These results emphasize that care must be exercised if
these drugs are used. They should be injected very slowly
to minimize the amount of haemolysis which may occur.

Raymond J. Trudnowski

Buffalo, New York

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