ACUTE HAEMODYNAMIC EFFECTS OF MEPHENTERMINE IN MAN

N. Ty Smith

SUMMARY

The circulatory effects of single intravenous injections of 0.75 mg/kg mephentermine were investigated in five healthy volunteer subjects. Ninety min after the first injection, atropine 1–2 mg was administered i.v. and the injection of mephentermine repeated. Cardiac output was measured beat-by-beat with an analogue computer-ballistocardiograph system, validated by dye-dilution cardiac outputs. The first injection of mephentermine increased mean arterial pressure, systemic vascular resistance, and left ventricular minute work, with no change in the other variables. The injection of atropine produced a sudden marked increase in heart rate, cardiac output, arterial pressure, and left ventricular work, and a fall in stroke volume. The repeat injection of mephentermine caused considerably smaller changes in the circulation than either previous injection. Atropine thus unmasked the beta-adrenergic stimulating effects of mephentermine, as well as a surprisingly prolonged action of the agent. It is suggested that the combination of atropine plus mephentermine be investigated as an approach to improved pressor therapy. Mephentermine is relatively slow in onset, with prolonged peak effects. For a given increase in arterial pressure, it produces much less drastic changes in other cardiovascular variables than does methoxamine.

Mephentermine (Mephine) is customarily administered in single intravenous injections. However, because of the limitations of conventional techniques for measuring cardiac output, its effects have been studied during or immediately after continuous intravenous infusion. By the time steady-state conditions necessary for measurement of cardiac output have occurred, circulatory homeostatic mechanisms may have considerably altered the drug effects. A new non-invasive method for beat-to-beat computation of stroke volume (Smith, Fleischli and Corbascio, 1966) has enabled the investigation of the haemodynamic effects of mephentermine produced by a single intravenous injection of mephentermine in man. Previous investigations of methoxamine using this technique (Smith and Whitcher, 1967a) revealed an initial circulatory depression, which would have been missed by conventional methods.

METHODS

Five healthy conscious male volunteers, age 21–24 were investigated. A detailed informed consent was obtained. Studies were performed in the morning, with the subjects unpremedicated and in a fasting state. Three catheters were inserted percutaneously: a No. 1514R (61 cm) Intracath into the superior vena cava via an antecubital vein, a No. 1617R Intracath into a forearm vein for the injection of drugs, and a No. 18BD teflon catheter into a brachial artery. After a 30 min rest period, each subject received mephentermine 0.75 mg/kg intravenously over 20 sec; 90 min later, atropine 1–2 mg was injected intravenously; 10–15 min after the administration of atropine, the injection of mephentermine was repeated.

Lead 2 of the electrocardiogram was recorded. A Beckman No. 9857 heart rate coupler calculated heart rate from the e.c.g. Arterial pressure was transduced with a Statham P23Gb strain gauge. Mean arterial pressure was obtained by passive low-pass filtering. Each subject lay on an undamped pendulum ultra-low frequency ballistocardiograph (b.c.g.) bed (f₀=0.3 Hz, mass=2 kg) suspended from eight 3-metre wires to allow head-foot motion only. Acceleration was transduced in this axis with a variable capacitance accelerometer. The data were simultaneously recorded on an Offner oscillograph and an Ampex FR1300 magnetic tape recorder.
Heart rate, mean arterial pressure, right atrial pressure, the e.c.g., and the b.c.g. were played back from the tape recorder into a general purpose analogue computer. The computer was programmed to calculate stroke volume from the b.c.g. using the Starr formula (Smith, Fleischli and Corbascio, 1966):

\[ SV = k \sqrt{\left( 2 \int J dt + J dt \right)} C \]

where \( SV \) = stroke volume;
\( k \) = a factor programmed into the computer;* 
\( C \) = cardiac cycle (R-R interval);
\( \int dt \) = area under the I wave;
\( \int J dt \) = area under the J wave.

The computer program uses operational relay logic to select the I and J waves of the b.c.g. The desired operations of integration, addition, multiplication, and square root extraction are simultaneously performed beat-by-beat. The R wave of the e.c.g. resets the computer and begins a new calculation. Stroke volume, rather than flow, is obtained by this method. The computer was programmed further to compute cardiac output from heart rate and stroke volume, as well as left ventricular minute work and systemic vascular resistance from mean arterial pressure, right atrial pressure, and cardiac output (Smith and Whitcher, 1967b). All of these variables were recorded from the computer on to a Brush rectilinear oscillograph (fig. 1).

In order to validate the data on stroke volume and other variables obtained from the b.c.g.-computer system, cardiac output was determined 15-20 times in each subject during steady-state periods by the indicator-dilution method, using indocyanine green dye (Smith et al., 1968). Manual and computer calculations were done with the same formulae. Stroke volume was obtained by dividing cardiac output by heart rate. Systemic vascular resistance was calculated by the formula:

\[ SVR (\text{dyne-sec-cm}^{-5}) = 1332 \times \left( \frac{AP - RAP}{CO (\text{ml/sec})} \right) \]

where \( AP \) = mean arterial pressure;
\( RAP \) = mean right atrial pressure;
\( CO \) = cardiac output.

Left ventricular minute work was calculated by the relation:

\[ LVW (\text{kg-m}) = 0.0135 \times CO (\text{1./min}) \times AP \]

Student's \( t \) test for paired data was used to evaluate the results. The 0.05 level was selected as significant.

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* The value of \( K \) depends upon several factors. The original Starr ballistocardiographic stroke volume formula was derived for a force system. Since we measured acceleration, \( K \) includes the mass of the subject plus the bed (force = mass \times acceleration). In \( K \) are also included Starr's original calibration factor, the calibration of our accelerometer, the amplifications of the tape recorder and oscillographs, and the scaling factors in the computer itself.

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**Fig. 1.** Output of the analogue computer as recorded on an oscillograph, giving data obtained from a single subject. From the bottom row up, the variables are stroke volume (SV), cardiac output (CO), heart rate (HR), left ventricular minute work (LVW), arterial pressure (AP), and systemic vascular resistance (SVR). The sharp depression in mean arterial pressure and the corresponding changes in left ventricular minute work and systemic vascular resistance are due to inflation of a blood pressure cuff proximal to the arterial catheter. From left to right, mephentermine (MEPH), atropine (ATR), and mephentermine were injected intravenously. The intervals between injections were 90 min and 10-15 min.
TABLE I. Peak effects and per cent changes following injection of mephentermine and atropine (± standard deviation).

<table>
<thead>
<tr>
<th></th>
<th>Pre-injection</th>
<th>Post-injection</th>
<th>Per cent change</th>
<th>P value</th>
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</table>
| Mean arterial pressure (mm Hg) | M 81.6 ± 5.2 | M 123.0 ± 7.3 | 51.2 ± 13.3 | <0.01  
| Heart rate (beats/min)       | M 45.4 ± 4.4 | M 22.9 ± 7.3 | 22.9 ± 7.3 | <0.01  |
| Stroke volume (ml)          | M 61.8 ± 7.3 | M 140.6 ± 12.2 | 115.0 ± 15.4 | <0.01  |
| Cardiac output (l./min)    | M 135.2 ± 9.4 | M 192.8 ± 19.4 | 115.0 ± 15.4 | <0.01  |
| Systemic vascular resistance (dyne-sec-cm⁻²) | M 138.0 ± 19.4 | M 198.2 ± 23.4 | 115.0 ± 15.4 | <0.01  |
| Left ventricular minute work (kg-m) | M 138.0 ± 19.4 | M 198.2 ± 23.4 | 115.0 ± 15.4 | <0.01  |

M = Injection of mephentermine 0.75 mg/kg.
A = Injection of atropine 1-2 mg.
M-A = Repeat injection of mephentermine 0.75 mg/kg.
P value shows significance of change following injection of drug (n.s. = not significant).

RESULTS

Correlation between values of stroke volume obtained by the ballistocardiogram and by the dye-dilution method (90 determinations) was very good (r = 0.9146; P < 0.001).

Following the initial injection of mephentermine, mean arterial pressure (AP), systemic vascular resistance (SVR), and left ventricular minute work (LVW) were the only significant changes (table I). Administration of atropine 90 min later, on the other hand, significantly changed all variables except SVR. The repeat administration of mephentermine elevated AP and heart rate (HR), a different pattern from the pre-atropine injection of mephentermine. Maximum values of CO, LVW, AP, and HR produced by injection of mephentermine after atropine were significantly greater than those produced by mephentermine before atropine, although values of SV and SVR were significantly less. The following paragraphs describe the results in more detail. In addition, table II gives the time required for the attainment of maximum values.

Mean arterial pressure (fig. 2).

Mephentermine elevated AP from 81.6 to 123.0 mm Hg. The change was gradual, reaching a prolonged plateau. Atropine injected 90 min later produced a rapid and striking rise averaging 42.4 mm Hg; this peak value was 53.6 mm Hg above the initial control value. Subsequent injection of mephentermine produced a 25.6 mm Hg rise in AP, although the difference between the post-mephentermine value and the peak post-atropine value was very slight.

TABLE II. Time to maximum or minimum values following injection.

<table>
<thead>
<tr>
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<th>Min: sec ± SD</th>
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<tbody>
<tr>
<td>Mean arterial pressure</td>
<td>Mephentermine 4: 17.4 ± 1:53.4</td>
</tr>
<tr>
<td>Heart rate</td>
<td>Atropine 1:30.0 ± 1:07.8</td>
</tr>
<tr>
<td></td>
<td>Mephentermine (post-atropine) 1:38.8 ± 1:07.8</td>
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<tr>
<td>Stroke volume</td>
<td>Mephentermine 6: 22.0 ± 2:48.1</td>
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<tr>
<td></td>
<td>Atropine 6: 20.0 ± 2:48.1</td>
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<tr>
<td></td>
<td>Mephentermine (post-atropine) 6: 20.0 ± 2:48.1</td>
</tr>
<tr>
<td>Systemic vascular resistance</td>
<td>Mephentermine 2: 46.0 ± 2:35.3</td>
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<tr>
<td></td>
<td>Atropine 4: 46.0 ± 2:35.3</td>
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<tr>
<td></td>
<td>Mephentermine (post-atropine) 4: 46.0 ± 2:35.3</td>
</tr>
<tr>
<td>Left ventricular minute work</td>
<td>Mephentermine 5: 52.0 ± 3:52.7</td>
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<tr>
<td></td>
<td>Atropine 4: 54.0 ± 3:20.2</td>
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<td></td>
<td>Mephentermine (post-atropine) 2: 42.0 ± 1:11.9</td>
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**Fig. 2.** Mean arterial pressure as recorded from the five subjects. The intervals between injections were 90 min and 10-15 min.

**Fig. 3.** Heart rate (see fig. 2).

**Fig. 4.** Cardiac output (see fig. 2).

**Fig. 5.** Stroke volume (see fig. 2).

**Fig. 6.** Systemic vascular resistance (see fig. 2).

**Fig. 7.** Left ventricular minute work (see fig. 2).
Heart rate (fig. 3).
Mephentermine administration was followed by a slight, statistically insignificant, fall in HR. Atropine sharply increased HR, from 61.8 to 152.2 beats/min. Subsequent injection of mephentermine increased HR by 15.4 beats/min.

Cardiac output (fig. 4).
Injection of mephentermine did not change cardiac output, although administration of atropine almost doubled it. Subsequent injection of mephentermine slightly lowered CO; the difference was not statistically significant.

Stroke volume (fig. 5).
Stroke volume showed a slight, statistically insignificant increase with injection of mephentermine. Atropine lowered stroke volume by 26.8 ml, while the repeat administration of mephentermine did not change it.

Systemic vascular resistance (fig. 6).
Mephentermine approximately doubled SVR, which then slowly returned towards control values. Administration of atropine produced a moderate, but statistically insignificant, decrease in SVR, while a moderate, but insignificant, increase occurred with the repeat administration of mephentermine.

Left ventricular minute work (fig. 7).
Mephentermine increased LVW, but the change was very gradual. Atropine then produced a marked rise in LVW. Mephentermine subsequently increased LVW.

DISCUSSION
An analogue computer is more nearly ideal for the type of computation performed in these studies than is a digital computer. The signals—the e.c.g. and the b.c.g.—can pass directly into the machine without complicated conversion. Similarly, the direct output is in an easily scanned graphic form, rather than a confusing maze of numbers. The operations of integration, addition, multiplication, and square root extraction can be performed much more smoothly. Integration is more accurate. The overall accuracy of an analogue computer, although less than that of a digital computer, is more than ample for our purposes (four significant figures). Finally, for this type of work, the analogue computer is less expensive.

The ballistocardiograph-analogue computer method for calculating cardiac output proved to be highly accurate under the conditions of this study. For validation, ninety determinations of cardiac output by the dye-dilution method were performed, covering a twofold range in cardiac output. The correlation between values obtained with the two methods was very good and compares favourably with correlations obtained between dye-dilution and direct Fick methods (Hamilton et al., 1948; Werko, Lagerhof and Bucht, 1949; Doyle et al., 1953; Miller, Gleason and McIntosh, 1962). For example, Doyle and associates (1953) obtained a 0.73 correlation coefficient between the two methods. Miller, Gleason and McIntosh (1962) observed a difference between the two methods ranging from −20.0 to +28.4%. That the b.c.g. analogue computer method is accurate for determining cardiac output has also been confirmed in man in studies using other drugs: methoxamine (Smith and Whitcher, 1967a), halothane, fluroxene and nitrous oxide (Smith, N. Ty, unpublished data). The method admittedly is most accurate when healthy young subjects are given drugs which do not drastically alter the b.c.g. wave form.

Intravenously administered mephentermine increased arterial pressure and systemic vascular resistance, with no change in cardiac output, stroke volume, or heart rate. Some previous reports have described different effects of this agent, emphasizing its positive inotropic (Hodge and Dornhorst, 1966; Smith and Corbascio, 1970), chronotropic (Innes and Nickerson, 1965; Lewis and Weil, 1969), or vasodilating (Aviado, 1959, 1965; Udhoji and Weil, 1965) properties.

Four factors in our studies could account for these differences: homeostatic baroceptor reflexes, the larger amount of drug, the mode of injection, and the initial state of the circulation. The influence of the reflexes in altering the autonomic effects of mephentermine is indicated by the response to atropine, which unmasked some of the beta-adrenergic stimulating effects of mephentermine, with an increase in cardiac output and heart rate. Atropine also abolished the constrictor response to mephentermine. The repeat injection of the same large amount of mephentermine produced little change from peak effects of the atropine.

The large dose of mephentermine used in this study did give a dependable pressor response as indicated by the large increase in mean arterial pressure and the small standard deviation. Perhaps the less reliable pressor response observed clinically and reported by some investigators (Binder, 1958; Grady, Stough and Robinson, 1954; Mills et al., 1960) has been due to an inadequate dose. If, however, large
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amounts of mephentermine also inevitably produce vasoconstriction (Zaimis, 1968) then the price of reliability is too high.

Other investigators have also noted an increase in systemic vascular resistance with mephentermine in normal subjects (Andersen and Gravenstein, 1964; Li, Shimosato and Etsten, 1962). However, there is some disagreement on timing, Andersen and Gravenstein (1964) finding an increase during the first 20 min, with a subsequent return to control, and Li, Shimosato and Etsten (1962) observing no change for the first 20 min, vasoconstriction supervening subsequently. In the present study, systemic vascular resistance reached its peak within 3 min and remained significantly elevated for more than 1 hour.

The vascular actions of the drug in healthy subjects may be different from those in patients already in a state of vasoconstriction. Udhoji and Weil (1965) observed a decrease in systemic vascular resistance when large amounts of mephentermine were administered to patients in shock. Li and associates (1963) noted vasoconstriction only when vasodilatation was present in patients receiving spinal anaesthesia; otherwise, the pressor response arose from an increase in cardiac output.

The injection of atropine 90 min after the initial injection of mephentermine uncovered a surprisingly prolonged effect of the drug. Most of the values, except mean arterial pressure and left ventricular minute work, had returned to control, and neither of these was markedly elevated. However, atropine produced a dramatic response, increasing all variables except systemic vascular resistance.

In general, atropine made mephentermine a "better" pressor agent; not only was there a greater increase in arterial pressure, but the pressor response was brought about by an increase in flow, rather than resistance. This is a more useful way to raise blood pressure, since it causes a relatively smaller increase in myocardial oxygen consumption. However, heart rate was inordinately high and mean arterial pressure higher than necessary. Furthermore, a significant drop in stroke volume was seen. This decrease was probably due to the decreased time available for cardiac filling during the marked tachycardia. These findings suggest that judicious testing of combinations of much smaller amounts of atropine and mephentermine might lead to vasopressor therapy with haemodynamically useful properties.

These findings also bring up the increasingly important problem of drug interaction in anaesthesia. Atropine has now been shown to alter significantly the action of two vasopressors, namely methoxamine (Smith and Whitcher, 1967a) and mephentermine. Vasopressors and atropine are frequently used during the same procedure. The possibilities of other important interactions among the six to ten drugs routinely administered to patients are overwhelming.

The similarity in design between these studies and those previously reported on methoxamine (Smith and Whitcher, 1967a) allows a comparison of the two agents.* In general, mephentermine produced a greater increase in arterial pressure for a lesser disturbance in the rest of the circulation. Changes in all variables were less rapid, less drastic, and more prolonged. The delay from injection to peak action of mephentermine was four times that of methoxamine (1 min v. 4 min). This suggests that one must be prepared to wait longer for a peak effect with mephentermine and perhaps should avoid its use when a pressor response is urgently required—fortunately, a rare situation.

Each of our subjects described a sense of "relaxation" and "well-being", lasting for about an hour after initial injection of mephentermine. Andersen and Gravenstein (1964) described this response in three of six normal subjects, while Udhoji and Weil (1965) observed anxiety, restlessness, or seizures in three of eleven patients in shock and treated with mephentermine. Two of our subjects described an hour's period of analgesia beginning within 5 min of the initial injection: one subject in the antecubital fossa at the side of the indwelling catheter, the other in the low back, aching from prolonged immobility.

REFERENCES


* Three subjects, in fact, participated in both studies. Control values were similar with both sets of subjects.


EFFETS HÉMODYNAMIQUES AIGUS DE LA MEPHERMINE CHEZ L'HOMME

SOMMAIRE
Les effets circulatoires d'une injection unique de 0,75 mg/kg de mephentermine, ont été étudiés chez cinq sujets volontaires en parfaite santé. Quatre-vingt-dix minutes après cette première injection, une dose de 2 mg d'atropine a été administrée par voie i.v. et l'injection de mephentermine a été répétée. Le débit cardiaque a été mesuré, battement par battement, grâce à un système analogique comportant un ordinateur et un ballistocardiographe et vérifié à l'aide des débits cardiaques, déterminés en recourant à des méthodes de dilution de colorants. La première injection de mephentermine a entraîné une augmentation de la pression artérielle moyenne, de la résistance vasculaire périphérique et du travail/minute du ventricule gauche, sans provoquer de changements en ce qui concerne les autres paramètres. L'injection d'atropine a provoqué une brusque élévation de la fréquence cardiaque, du débit cardiaque, de la pression artérielle, ainsi que du travail du ventricule gauche, de même qu'une chute du débit systolique. La répétition de l'injection de mephentermine a déterminé des modifications considérablement moindres que l'injection initiale du même agent, quant à la circulation. L'administration d'atropine a ainsi permis de révéler les effets stimulants béta-adrénergiques de la meph-erminate de même qu'une durée d'action étonnamment prolongée de cette substance. Il a été suggéré d'étudier les effets de l'association atropine + mephentermine en vue d'examiner les possibilités d'amélioration d'une thérapeutique vaso-pressive. La mephentermine est relativement lente à agir, mais présente des pics d'action prolongés. Pour une augmentation donnée de la pression artérielle, elle entraîne des modifications au niveau des autres paramètres cardiovasculaires bien moins drastiques que la méthoxine.

AKUTE HÄMODYNAMISCHE WIRKUNGEN VON MEPHERMINE BEIM MENSCHEN

ZUSAMMENFASSUNG

EFFECTOS HEMODINAMICOS AGUDOS DE LA MEFENTERMINA EN EL HOMBRE

RESUMEN
Fueron investigados los efectos circulatorios de inyecciones intravenosas únicas de 0,75 mg/kg de mefentermina en cinco sujetos voluntarios sanos. Noventa min. después de la primera inyección fueron administrados 1–2 mg de atropina i.v. y se repitió la inyección de mefentermina. El gasto cardíaco fue medido a cada contracción con un sistema computador—ballistocardiográfico análogo, demostrado por

Septic shock or bacteraemic shock is an exceedingly lethal disease. It carries a mortality of up to 80 per cent.

There is little doubt about the primary lesion. The cause of the condition is toxema which results from the entry of substances contained in the cell walls of a large number of bacteria, mostly gram-negative, into the circulation of the human subject. When it comes, however, to the question of what damage this endotoxin does, there are widely diverging views.

For long it was believed that the initial effect was a peripheral vasoconstriction which led to tissue hypoxia. This tissue hypoxia led in turn to inadequate tissue perfusion hypoxia and the elaboration of excess lactate. This excess lactate produced an acidosis and it was argued that correction of the acidosis together with the administration of alpha adrenergic blockers to undo the vasoconstriction would reverse the condition. In fact this expectation has fallen down on two counts. First it seems that the main problem is not intense peripheral vasoconstriction, though arteriovenous shunts past the capillary bed may play a part in the condition. The amounts of lactic acid produced, too, are not really significant in terms of the acidosis to which they give rise. Far more severe degrees of acidosis can arise under other circumstances and the patient survive. Indeed the usual figure, certainly in experimental studies, is of the order of 5 millimoles of lactic acid per litre of blood and this would produce a base deficit of only 5 milliequivalents, an amount which few would regard as calling for treatment.

Today the term "cell suicide" is regarded as the most apt description of what happens in the patient who develops septic shock. This is combined, of course, with all sorts of disturbances involving intravascular clotting in the microcirculation and the activation of kinins.

Modern work has indicated, however, two points. First the circulation is by no means profoundly depressed in all the stages of septic shock. Indeed at some stages cardiac output may actually be increased, a situation which is effectively a high output failure. The most useful information, however, relates to the pathological changes which occur in the lungs. In these, small areas of haemorrhage and oedema are produced, apparently by the direct action of endotoxin on the lung tissues. This causes veno-arterial shunt with the result that the $P_{A\text{O}_2}$ tends to be well below normal and this indeed may be just as important in the production of peripheral hypoxia as is the peripheral vasoconstriction.

As far as treatment is concerned the only point on which there is uniform agreement is the value of the appropriate antibiotic, though even here a word of caution is necessary. It appears that in the presence of a bacteraemia due to gram-negative organisms the administration of the appropriate antibiotic may kill off so many organisms in the circulation itself that the amount of circulating endotoxin increases to a lethal level.

The second point on which there is fairly general agreement is the usefulness of steroids, and large doses of hydrocortisone, prednisolone, methylprednisolone or dexamethasone are used apparently with some success. The place of fluid replacement is somewhat hotly debated, some regarding it as a major therapeutic measure to be controlled by frequent determinations of the central venous pressure, but others feeling that the danger of over-transfusion and the precipitation of pulmonary oedema, especially in the presence of the diseased lungs, is quite considerable and that very great care should be used when fluids are given. There seems to be little evidence that a generalized increase in capillary permeability occurs with extravascular loss of protein-containing fluid, though there is evidence that the available oxygen does not somehow get to the tissues in the presence of endotoxin shock.

It will be apparent from the foregoing that current views concerning endotoxin shock have changed markedly over the last ten years. The present volume serves to bring together these ideas, as well as many more which are of very great importance to those who seek to treat patients of this kind. It is true that the conference of which it is an account took place in 1968, but the material presented in it was then well up to date. Further, much of it has, even now, not been widely disseminated. This book therefore can be commended without reservation to all who seek information on this most important subject. Not only does it provide information, it also provides at the end of each contribution a most useful list of references.

A. R. Hunter