SUBJECTIVE AND OBJECTIVE SENSORY RESPONSES TO INHALATION OF NITROUS OXIDE AND METHOXYFLURANE

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SUMMARY

An investigation, in volunteers, into the sensory effects of nitrous oxide and methoxyflurane showed that the subjective changes of reduction in visual awareness and heightened auditory awareness were not supported by objective measurement. Vision remained normal until the subjects became unresponsive, whilst hearing was in fact diminished. The analgesia produced by nitrous oxide was late in appearance relative to the other sensory changes and it disappeared very rapidly upon recovery. In contrast, analgesia appeared early with methoxyflurane and persisted well into the recovery period. The principal changes found were alterations in orientation in space, of intellectual attitudes, of mood and of emotional attitudes. The emotional attitudes were easily disturbed by extraneous noise or conversation and the need for a quiet approach not only to the induction of anaesthesia but also to the recovery from anaesthesia is stressed.

The use of nitrous oxide or methoxyflurane inhalation in non-operative situations such as obstetrical analgesia, ambulance transportation of the injured, or coronary care units, is increasing. The concentrations used have induced sleep in a number of patients. As sleep develops some of these patients appear to pass through all the stages of an anaesthetic induction, including the various subjective sensory stages. During laboratory tests of nitrous oxide uptake several of our subjects noted as they approached unconsciousness that they also experienced a number of subjective effects, and it was wondered if these could be objectively tested. Apart from this it is obviously important to know what subjective and objective effects are associated with inhalational analgesic techniques.

The subjective effects are: first, there is an immediate smell of the nitrous oxide or methoxyflurane followed, within three breaths, by an intensification of that smell accompanied by a slight metallic taste. Over the next five breaths, if breathing nitrous oxide, there is a loss of awareness of events going on behind the subject. Voices heard from behind the head cause a sudden surprised recall of the existence of this area. Next there is a slight loss of awareness of the peripheral fields of vision and of the peripheral surroundings whilst auditory stimuli seem louder, particularly if they originate close to hand, for example the noise of the expiratory valve. There is also mild tinnitus at this stage. There is then a feeling of cutaneous warmth accompanied by a slight apprehension and nausea as well as a curious feeling of clumsiness and thickening of the fingers together with a "greying out" of colour. By the 20–25th breath (if breathing 80% nitrous oxide, 20% oxygen) this fades, to be replaced by a mixture of emotions, particularly of pleasure and anger. Intense paranoia occasionally develops, all conversation being interpreted as referring to the subject, and any suggestion of anything being in the slightest amiss creates a wave of intense hostility.

By the next five breaths these feelings fade, peripheral vision now constricts to a narrow tunnel field and the desire to concentrate attention on this field is overwhelming. The ability to concentrate appears enhanced and during this phase auditory contact is lost. Mental concentration now becomes desirable for its own sake and visual contact is lost; however, the subject is unaware of this but is now in a world of his own and feels he can solve at least some of the world's problems. Sharp painful stimuli are perceived as pain almost up to this point.

Thinking now becomes circular and, particularly on the second or third gaseous experience, a regretful awareness that it will be difficult to recall these
thoughts later now develops. There is also an intense feeling of “déjà vu”, that is the subject recalls the same problems with the same clarity as before and deduces the same conclusions only to forget them until next time. The amnesia, though, is not quite complete; the subject can recall that he dealt brilliantly with some problem but cannot remember what the problem was. Concentration continues until consciousness is lost, although the subject is unaware that this is impending or when this happens.

During recovery there is a reversal of this process, but it progresses very much more rapidly. Emotional instability and lability are pronounced and either anger or amusement is extremely easily provoked.

With weaker concentrations of nitrous oxide, the progress of these various psychological changes is identical but takes place at a very much slower pace.

During inhalation of 0.35–1% methoxyflurane the same sequence of events takes place, albeit very much more slowly. However, when subjective consciousness is lost, as judged by the subject’s previous experience of nitrous oxide, the subject can make normal rational movements; thus he may solemnly hand the anaesthetic apparatus to an attendant taking care that it does not fall to the ground, and then withdraw the hand to the resting position. The subject is totally amnesic about such movements and on recovery is surprised to realize he has made them. Emotional lability appears to be much reduced with methoxyflurane as compared with nitrous oxide, and disturbances of taste or the sensation of nausea are all much less pronounced.

Painful stimuli (prickpicks) are felt as touch stimuli at a very early stage during methoxyflurane inhalation. Pain is not felt during recovery until a considerable period (at least 10 minutes) after the regaining of full consciousness following a period of exposure to the agent of less than 5 minutes duration. Pain sensation then returns abruptly, when the subject is suddenly and surprisingly aware of the painful punctures in his fingers. In contradistinction, on recovery from nitrous oxide pain perception returns very quickly, i.e., with five to ten breaths.

Although Burns, Robson and Welt (1960) have presented an account of some of the sensory effects of low concentrations of nitrous oxide, the principal subjective sensations such as loss of peripheral vision, colour sense, and alterations of hearing when near-anaesthetic concentrations are used, do not appear to have been objectively tested. It was, therefore, decided to investigate objectively the changes in sensory modalities up to the point of objective loss of consciousness in order to determine whether the subjective changes that were experienced were in fact real.

METHODS

Two agents, nitrous oxide and methoxyflurane, were used because of their current popularity in inhalational analgesic therapy and because in all these situations a near-anaesthetic gas concentration is or may be used.

Six anaesthetists and five technicians, all familiar with the techniques of anaesthesia, took part in this study. They sat in the upright posture and were given either nitrous oxide or methoxyflurane to breath from a Boyle apparatus using a facepiece and a simple Magill attachment with a 10 l./min fresh gas flow. Methoxyflurane was supplied from a Pentec vaporizer. The technique of administration of nitrous oxide and methoxyflurane closely imitated that used in clinical practice, that is, the strongest mixture that the subject would tolerate was initially given and the concentration increased as he became accustomed to the smell. The objective was to produce unconsciousness as rapidly as is usual in clinical practice and yet not to proceed so fast that the transitions occurred too quickly for the subject to give his responses to the various tests. No attempt was made to maintain a particular concentration of anaesthetic. We were interested to observe the effects just as consciousness was being lost and, by imitating clinical practice, it was felt that any observed changes would more closely resemble those experienced by patients. The administration was continued up to the point at which the subject became unresponsive or was unconscious, as judged by two observer anaesthetists. Concentrations of nitrous oxide were therefore varied between 40% and 80% depending upon the subjects’ known sensitivity to this agent. Methoxyflurane concentration was started at 0.35% and increased to 1%. The carrier gas was oxygen, the concentration of which was never less than 20% and in the case of methoxyflurane 99% or above.

Although not all subjects took part in each test, all experienced a number of gaseous inductions. Only one sensory modality was tested at each gaseous induction. No subject was given the same anaesthetic at an interval of less than 1 week. The subject was asked to indicate his response by finger signals except
during the colour vision test when the subject spoke the numbers into the facepiece. Two anaesthetists were always in attendance at each induction for reasons of safety and to determine when conscious-
ness was objectively lost.

The following modalities were tested: (1) hearing; (2) vision (both peripheral and colour); (3) vibration sense; (4) proprioception; (5) sharp pain; (6) two point discrimination.

**Hearing.**

It was not possible to test the full range of frequen-
cies in drowsy subjects and frequencies of 1000 and 4000 Hz were chosen as representing the middle and upper end of the frequencies of normal hearing. A Peters’ audiometer was used to produce sound of known frequency and loudness. Testing took place in a soundproof room. The subject’s hearing was tested, first whilst breathing oxygen from a facepiece and then whilst breathing the anaesthetic mixture. Only one ear was tested at each experiment. Although all the subjects had clinically normal hearing as judged by the audiometer, all individual changes had to be referred to the subject’s own control level of sound perception because within the clinical range of normality there is a wide variation between an individual’s auditory threshold. The reproducibility of the level of perception, after an initial short practice and learning session, in any one individual on any particular day was found to be within 1–2 db. In the audiomeric test the subject sat, wearing earphones, facing the investigator but could not see the controls and dials of the machine. The test sound was pro-
duced as short bursts of pure tone sounds of the particular frequency being studied, starting with the quietest and gradually increasing in loudness. When the subject first heard the sound he signalled to the investigator. A practised audiometrist can determine the threshold of sound for any particular, frequency in a comparatively few seconds.

In this investigation repetitive determinations of the auditory threshold were made at approximately 10-second intervals and the first of each pair of frequencies was chosen at random. The results were recorded as decibel changes from the subject’s control level. Six subjects were involved in this part of the study.

**Vision.**

Ishihara charts were used to investigate colour vision. All subjects had normal colour vision before the investigation was started. Random cards were taken from the basic set of 92 charts, after ensuring that each aspect of colour vision was covered, and were presented briefly to the subject, who identified the numbers verbally. Presentation was in a well-
illuminated room and was continuous up to the point of unconsciousness.

Visual fields were tested using a perimeter in a darkened room. The moving spot was a white disc 2 mm in diameter, as was the central white disc. Only the lateral half of the visual field could be tested, the facepiece obscuring the medial half of the visual field. Again testing was continuous up to the point of unresponsiveness, the lateral half of the visual fields being continually scanned.

**Position sense and vibration sense.**

Vibration sense was repetitively tested using a standard tuning fork applied to the lateral malleolus. Position sense was tested using a finger, care being taken to avoid pressure on the finger in the direction of the movement.

**Pain.**

This was tested using a sharp pin applied to the pulp of the finger or thumb. Testing took place up to the loss of consciousness. Seven subjects took part in this part of the study.

**Two-point discrimination.**

This was tested in two sites, the back of the fore-
arm and the fingertips, using the standard apparatus that is employed in neurological examination. In nearly all subjects tests were performed at 10-second intervals and there were not less than five subjects per test.

**RESULTS**

**Hearing.**

Despite all the subjects’ claims that hearing improved during the inhalation of the anaesthetic agent the results of objective testing did not confirm that this was so but indicated that hearing remained unchanged almost to the point of unresponsiveness when in all except one subject there was a small loss in auditory acuity. This happened very quickly, often too quickly to determine the perceptive level of the second of the two sounds being presented. Failure of response occurred long before the subject appeared unconsciousness as judged by the two observing anaesthetists.
The transition was frequently very abrupt occurring over a 2–3 second period, that is the time taken to change from one degree of loudness to another, or from one frequency to another. All values are expressed as changes in decibels from the control levels when measured whilst breathing oxygen.

<table>
<thead>
<tr>
<th>Frequency (Hz):</th>
<th>1000</th>
<th>4000</th>
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<tbody>
<tr>
<td>Nitrous oxide</td>
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<tr>
<td>Subject 1</td>
<td>-5</td>
<td>-5</td>
<td>-10</td>
<td>-15</td>
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<td>Subject 2</td>
<td>-10</td>
<td>?*</td>
<td>-5</td>
<td>-10</td>
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<tr>
<td>Subject 3</td>
<td>-15</td>
<td>-5</td>
<td>-70</td>
<td>-5</td>
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<tr>
<td>Subject 4</td>
<td>-10</td>
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<td>0</td>
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<tr>
<td>Subject 5</td>
<td>-5</td>
<td>-10</td>
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<td>Subject 6</td>
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On subsequent questioning all these subjects stated that they felt the stimuli, that it was still painful, but felt too euphoric to bother about it or indeed to co-operate with the investigation.

Peripheral sense and vibration sense.

There was no observable change in the perception of these modalities with either nitrous oxide or methoxyflurane at any stage until consciousness was lost.

Two-point discrimination.

There was a very marked reduction in two-point discrimination as unconsciousness approached. The fingertip discrimination distance doubled whilst on the back of the arm discrimination increased from 5 cm to more than 15 cm. The loss in discrimination was slight at first but rapidly increased as unconsciousness approached.

DISCUSSION

The principal subjective sensations in the production of unconsciousness are an increased auditory perception, a "greying out" of colour perception, and tunnel vision as well as psychological changes. These subjective sensations have been well documented from the earliest studies of nitrous oxide. Thus Humphry Davy (1800) on inhaling nitrous oxide noted that "indignation and pride were the first feelings produced by the sight of the persons about me. . . . "Vivid ideas poured rapidly through my mind" (p. 460); "Sublime emotion connected with highly vivid ideas" (p. 462); "I existed in a world of newly connected and newly modified ideas; I theorised, I imagined that I had made discoveries" (p. 408); "I endeavoured to recall the ideas; they were feeble and indistinct".

The description is not unlike that recorded in the opening paragraphs of this article.

Henrie, Parkhouse and Bickford (1961) found that in 17–22% of their subjects breathing 17–30% nitrous oxide in oxygen for 10 minutes or more, there was a tendency to perseverate or experience "déjà vu" phenomena. They also found that there was a marked reduction in the ability to recall events that had occurred during the inhalation of nitrous oxide and that late recall was even more affected, effects not dissimilar to the "feeble and indistinct" ideas that Humphry Davy found in trying to recall his memories.

Davy noted a subjective increased awareness of sound: "My hearing became more acute" (p. 458); "I distinctly heard every sound in the room" (p. 487).
He also noted a subjective improvement in vision. Our subjects noted an apparent "grey-out" of vision. Westerland, Pittinger and Reger (1961) have also noted subjective shrinking fields of vision and diminished visual activity, but did not investigate this further. Burns, Robson and Welt (1960) found little difference in visual threshold with low concentrations of nitrous oxide, but made no attempt to measure colour perception, or peripheral field of vision. For the reason that colour perception depends upon good visual acuity it was decided to use this particular test to see if the subjective sensations could be detected objectively. However, neither the subjective visual sensation of diminished colour vision or of tunnel vision could be verified by objective testing. Both sensations remaining stubbornly normal with both agents up to near loss of consciousness.

The audiometric tests used showed that, contrary to the subjective impression, hearing is diminished as unconsciousness approaches. The results indicate that the change occurs very abruptly during the induction of anaesthesia whether using nitrous oxide or methoxyflurane and is complete very rapidly, that is within a few seconds. Its occurrence does not seem to be related to the alveolar concentration because it did not develop until the subjects had been breathing the inhaled concentration well beyond the time (2 minutes plus) at which the alveolar concentration would be in near-equilibrium with the inhaled mixture. The reduction in hearing did not occur until the alveolar concentration was always above 40% whereas Burns, Robson and Welt (1960) record auditory loss on inhaling 25% nitrous oxide continuously. If the reduction of hearing is dose-related, as suggested by Westerland, Pittinger and Reger (1961), then there is a substantial time-lag between the attainment of a particular alveolar concentration of the anaesthetic agent and the change in hearing. This time-lag is greater than perhaps can be explained on the basis of simple pharmacokinetics; for example, it occurred after the brain had been exposed to an arterial nitrous oxide tension above 25% for a substantial time.

The results of the tests of analgesia were somewhat surprising and implied that the analgesic properties of nitrous oxide, where sharp pain is concerned, leave much to be desired. Analgesia could not be demonstrated with this agent until the subject was almost unconscious. It may be that, like hearing, there is a great time-lag between the time taken to reach an analgesic concentration of nitrous oxide in the alveoli and the time taken to reach an effective level of analgesia. An alternative explanation may lie in the clinical observation that patients hyperventilate when given nitrous oxide mixtures to inhale for alleviation of pain. Our subjects were trained not to hyperventilate. Perhaps, therefore, the observed difference between the levels of nitrous oxide required to produce analgesia in the present work and those reported to be effective clinically could be accounted for by the concomitant reduction of cerebral arterial carbon dioxide tension produced by hyperventilation causing enhancement of the analgesic effect of nitrous oxide. Such hyperventilation would, in addition, considerably increase the rate of uptake of nitrous oxide. However, methoxyflurane proved, under the conditions of this study, to be a much more effective analgesic than nitrous oxide. The delay in the return of appreciation of pain from punctures after methoxyflurane inhalation until after a long period of full recovery was particularly noticeable.

The contrast between the trained and the untrained observer when painful stimuli was being applied was very striking and it may be that the euphoriant effect of nitrous oxide contributes significantly to the apparently clinical satisfactory use of nitrous oxide as an analgesic.

There has recently been considerable interest in the relief of pain by inhalational means, both during the transportation of patients in pain and for the relief of pain in patients with myocardial infarction. The use of 50% nitrous oxide in oxygen (Entonox) is currently popular. It is suggested that methoxyflurane is worth evaluation in these situations. Methoxyflurane requires simpler apparatus than does Entonox, although the loss of the additional oxygen concentration might be a disadvantage. The use of methoxyflurane is also less likely to produce emotional lability than is nitrous oxide and is less likely, particularly with intermittent use, to produce periods of unconsciousness, with the hazards of repetitive anaesthetic inductions. Major, Rosen and Mushin (1967, 1968) have reported favourably on the use of methoxyflurane in obstetrics. This agent is in some circumstances nephrotoxic and it may not be advisable to use it for the treatment of patients in pain associated with blood loss or low cardiac output states when renal perfusion may be impaired.

Whilst none of these tests used in this study can be considered quantitative and, therefore, not capable of precise statistical evaluation, nevertheless the most striking feature was the uniform consistency in response for all the subjects for all the tests. The subjects were trained observers and experienced in
the psychological sensations produced by these agents and could concentrate their attention on the tests whilst partially under the influence of the drugs. No attempt was made, or could be made, to conduct the investigation under double-blind conditions. Whenever possible, however, the subject was positioned so that he could not see the test equipment. We were not concerned to discriminate between the effects of nitrous oxide and methoxyflurane when examining their effects on healthy subjects. Discrimination between the two agents would require a much greater degree of elaboration of experimental technique than was available. Thus for the colour vision test the ambient lighting and the composition of that light would need to be rigidly controlled in order to determine whether any fine shades of colour perception were dulled with one agent more than the other. In addition a greater number of volunteer trained subjects would be needed for such an evaluation than were available.

Nevertheless, within the limitation of these conditions, the findings that the apparent reduction in peripheral visual field, the apparent monochromatic vision and the apparent increased hearing could not be confirmed by objective testing were unexpected. All the subjects were definite in their statements that these changes in apparent sensory perception were very great. The cause of these differences remains obscure but may be related to loss of distraction from sensory input of other modalities. Combinations of stimuli were not tested because the subjects found it difficult to concentrate on the tests, especially when the stage of unconsciousness was being approached.

These subjective psychological responses stress the need for a very gentle quiet approach during gaseous induction and indicate that if it is desired to speak to the patient during induction, it will startle the patient less if the voice does not come from behind the patient’s head. Furthermore, because the patient may interpret all discussions as referring to him it would seem desirable that all unnecessary conversation be stopped during anaesthetic induction. Precisely the same desiderata also apply during recovery from anaesthesia and the likelihood of a disturbed period of recovery may be reduced by using the same quiet approach during this phase also.

REFERENCES

REACTIONS SENSORIELLES SUBJECTIVES ET OBJECTIVES A L’INHALATION DU PROTOXYDE D’AZOTE ET DU METHOXYFLURANE

SUMMARY
Les études effectuées sur des volontaires et se rapportant aux effets sensoriels du protoxyde d’azote et du méthoxyflurane, ont démontré que les changements subjectifs de la réduction de la vigilance visuelle et de la vigilance auditive n’ont pu être confirmés par des mesures objectives. La vision reste normale jusqu’à ce que les sujets deviennent sans réaction alors que l’ouïe était effectivement diminuée. L’analgésie produite par le protoxyde d’azote était apparemment tardive par rapport à d’autres changements sensoriels et elle disparaissait très rapidement à la récupération. Avec le méthoxyflurane, au contraire, l’analgésie se manifestait très tôt et persistait assez longtemps dans la période de récupération. Les altérations de l’orientation dans l’espace, des attitudes intellectuelles, des attitudes émotionnelles et des humeurs étaient les principaux changements. Les attitudes émotionnelles étaient facilement troublées par les bruits extérieurs ou la conversation et il fallait s’autreindre à une approche calme non seulement pour l’induction de l’anesthésie mais aussi au moment de la récupération de l’état vigil.

SUBJEKTIV UND OBJEKTVIE SENSORSCHIE REAKTIONEN AUF DIE INHALATION VON LACHGAS UND METHOXYFLURANE

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REACCIONES SENSORIALES SUBJETIVAS Y OBJETIVAS POR INHALACION DE OXIDO NITROSO Y METOXIFLURANO

RESUMEN

Una investigación llevada a cabo en personas voluntarias, acerca de los efectos sensoriales del óxido nitroso y metoxiflurano, mostraron que los cambios subjetivos de la reducción de la percepción visual y la exaltación de la capacidad auditiva no tenían un fundamento según las medidas objetivas. La visión permanecería normal hasta que los individuos perdieran la capacidad de respuesta, mientras que la audición disminuía en efecto. La analgesia producida por el protxido de nitrógeno aparecía tarde en relación a los otros cambios sensoriales y desaparecía rápidamente en el momento de la recuperación. Por el contrario, la analgesia se presentaba muy pronto con metoxiflurano y persistía de modo apreciable durante la fase de recuperación. Los principales cambios consistieron en alteraciones de la orientación en el espacio, actitudes intelectuales, emocionales o cambios de humor. Las actitudes emocionales se afectaban fácilmente por los ruidos extraños o la conversación y la necesidad de un acceso tranquilo, no sólo para la inducción de la anestesia, sino también para la recuperación de la misma.

BOOK REVIEW

Catecholamines (British Medical Bulletin, Vol. 29, No. 2, May 1973). Published by the Medical Department, the British Council, 97–99 Park Street, London, W1Y 4HQ.

Instead of becoming an overworked area, as seemed possible a decade ago, the role of the “catecholamines” in both physiology and disease has expanded enormously in recent years. Quite new facets have emerged, to a degree which is illustrated well in this Bulletin, mainly from the collaboration of biochemists with pharmacologists. A few of these are referred to below, and it should also be mentioned that “catecholamine” has apparently become a generic term for many substances which are not amines of catechol.

All examinees in pharmacology know now that the actions of noradrenaline released at the sympathetic nerve endings are terminated not so much by enzymatic destruction but by recapture back into the nerve terminals. There will be some awareness, also, of the techniques of fluorescence histochemistry (most recently used to map out catecholamine-containing pathways in brain), and of the chemical research-tool, 6-OH-dopamine, which in the neonatal animal can prevent the development of most of the sympathetic nervous system (not, however, the adrenal medulla).

While fluorescence histochemistry has also demonstrated the axonal transport of noradrenaline-containing vesicles to the nerve terminals at rates of 10 mm/hr, the “downward” movement of synthesizing enzymes seems to be of greater quantitative importance, and it is interesting to find that their activity in catecholamine biosynthesis is stimulated by an increase in nerve impulse traffic.

The field covered includes the prostaglandins, the E-type of which can antagonize catecholamines and can be released on adrenergic stimulation.

Still uncertain in detail, but likely to become clearer in the near future, is the activity of motile proteins—microtubules and microfilaments—in the release of adrenergic transmitter (stimulus-secretion coupling). Incompletely understood is the place for monoamine oxidase in normal physiology, one possibility being that it is sited to destroy potentially toxic amines which are ingested. There is evidence to favour a role for noradrenaline as a central inhibitory transmitter—or does it excite inhibitory neurones or constrict the blood supply?

It seems now that several of the hypotensive agents in clinical use have central actions, although with less certainty than the effects on medullary vasomotor neurones of clonidine (which is thought to stimulate inhibitory alpha-adrenergic receptors). Some doubt is cast on the “false transmitter” basis of action of alpha-methyldopa, since the metabolic product (alpha-methylnoradrenaline) itself has high pressor activity.

Some three sections of the Bulletin are concerned directly with clinical practice. An important statement is that about 75% of individuals with diastolic pressures above 110 mm Hg are not being treated because they remain undiscovered. Most anaesthetists know of the frequency of untreated hypertension from their preoperative measurements of arterial pressure, and some may have remarked on the fact to cardiologists, whose answer could be that time does not permit a follow-up.

There are 16 contributions in this issue, most of them by well-known investigators. Recent laboratory findings are presented in considerable detail, which may overwhelm the non-specialist reader, and there is a fair amount of overlap especially between the earlier sections. However, in a substantial introduction W. D. M. Paton summarizes the contents in rather more detail than this reviewer has done. This Bulletin is an essential item of reference for medical libraries.

R. A. Millar