be remembered. Many of our patients in executive or general administrative positions have been off work for only half a day after quite extensive hand surgery. Married women have been able to undergo treatment yet able to manage their young children with minimal disturbance to family life. We suspect that many surgeons do not realize the upset that admission to hospital can cause to a whole family, with the breadwinner often having to stay at home, unpaid, to look after the dependants. This applies particularly to the self-employed man who previously avoided necessary treatment because of his difficult business situation.

The fact that 1,500 patients have been treated in this unit without serious mishap reflects the high standards of surgery. The fact that the unit is managed and run entirely by the sister-in-charge (with a consultant as adviser only) and has run so well reflects a new relationship between the nursing staff and doctors which might apply to those special investigative units now required for the practice of modern medicine.

Such a surgical unit appears to work well within a metropolitan area where no great distance of travel is involved, though about 10% of all the patients lived more than 20 miles (32 km) from the hospital. We have not used premedication in any patient and doubt its requirement, and this means that patients can use their own transport, within the physical disability of the operative site; such features are of course discussed at the first interview.

The friends of Hammersmith Hospital provided curtains and a carpet for the waiting room and furniture for the recovery room. We are grateful for their financial assistance.

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For Debate . . .

The Halothane Dilemma: A Case for the Defence

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"Circumstantial evidence is a very tricky thing—it may seem to point very straight to one thing, but if you shift your own point of view a little, you may find it pointing in an equally uncompromising manner to something entirely different."—*The Boscombe Valley Mystery*, Sir Arthur Conan Doyle.

There is still much dispute about whether a clear-cut cause-and-effect relationship between halothane anaesthesia and liver damage has been established. Arguments in favour of the existence of "halothane hepatitis" seem partly to be based on concepts which are sometimes difficult to accept, since they make assumptions about the antigenic features and metabolism of halothane which are not justified by current knowledge.

It is the purpose of this review to make a critical appraisal of the available data and to assess the present situation.

Historical Review

When halothane (Fluothane) was introduced in 1956 it was suggested that its chemical similarity to other halogenated hydrocarbons might make it apt to cause liver damage.^{1,2} This was not borne out by the results of animal experiments^{3,4} or the early clinical trials in man.⁵⁻⁷ Clinical reports of liver damage, however, thought to be due to halothane subsequently appeared in the literature,^{8,9} and these prompted a

number of retrospective surveys of liver dysfunction occurring after anaesthesia and surgery.¹⁰⁻¹²

The largest of these (the United States National Halothane Study)¹⁰ reviewed the incidence of fatal massive hepatic necrosis occurring within six weeks of anaesthesia in some 850,000 patients undergoing surgery in 34 hospitals. About 250,000 of these patients received halothane. Eighty-two cases of fatal massive hepatic necrosis were recorded of which all but nine could be explained on the basis of either the patient's known disease or the surgical procedure or a recognizable postoperative complication. Hence nine cases were attributed to the anaesthetic agent; seven of these nine unexplained cases had received halothane and four of the seven had previously received halothane within six weeks of the final operative procedure. Reports on four of these seven cases, however, had already been published, and two others were known to the participating hospitals before the start of the study. So from this extensive review only one new case of massive hepatic necrosis associated with halothane was elicited. The committee concluded that "unexplained fever and jaundice in a specific patient might reasonably be considered a contraindication to its subsequent use." Later Dykes and Bunker² drew attention to the fact that "there was not a single patient in the National Halothane Study who was jaundiced after the administration of halothane, who died after a second administration, and who was found at necropsy to have suffered massive or intermediate hepatic necrosis."

A statistic from this study concerning the incidence of fatal massive hepatic necrosis attributed to halothane is widely quoted. The overall incidence of massive hepatic necrosis was approximately 1 in 10,000—that is, 82 in 850,000—regardless of the anaesthetic agent used; but in only nine of these patients—of whom seven received halothane—was it felt that massive hepatic necrosis could be attributed to the anaesthetic agent itself. Therefore at worst the true incidence of massive hepatic necrosis associated with halothane in this series was

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seven out of 250,000 or about 1 in 35,000, and not, as is sometimes stated, 1 in 10,000. It must also be recognized that the knowledge of the "pre-existence" of six of these seven cases may have prejudiced the validity of this statistic.

From this and other studies^{11 13-15} it became clear that in modern anaesthetic practice the number of cases of liver damage attributable to anaesthetic agents was small. It is important also to remember that all anaesthetic techniques, including spinal anaesthesia,^{16 17} have been incriminated. Statistically, halothane appears to be no worse than any other agent¹¹ and in some instances better.^{10 12} Postoperative jaundice, however, a readily observed feature of liver damage, has increasingly been recognized over the past two decades regardless of the anaesthetic agent used. This has been attributed to the increasing use of blood transfusion, increasing complexity of operative procedures, and the multitude of other drugs now part of modern medical practice.^{12 18}

MULTIPLE ADMINISTRATION OF HALOTHANE

Since liver damage occurring after anaesthesia and surgery has increased, and because halothane is now used in over 70% of all anaesthetic procedures in countries where it is widely available, it is hardly surprising that despite the reassurance of these early surveys further clinical reports, retrospective studies, reviews, and leading articles have attempted to link halothane, particularly after multiple administrations, with liver damage. The data, however, in some of these studies are difficult to interpret—for example, Trey and his colleagues^{19 20} were not able to give the number of patients who were subjected to halothane in relation to the number who died with massive hepatic necrosis, and much of their information is, it would seem, second hand. An example of the risk of relying on such reports can be seen in a recent paper²¹ in which eight patients were described as surviving an attack of jaundice after halothane anaesthesia. From the case histories given, two of these patients, in actual fact, did not receive halothane; one was given methoxyflurane (Penthane) and the other fluoroene (Fluoromar).

Hughes and Powell²² described a greater than 2% incidence of severe liver damage in a small series of patients subjected to multiple halothane anaesthetics. Had this liver damage been directly related to the administration of halothane one might reasonably expect this to have been confirmed by other centres, since up to the present time halothane had been used for more than 50 million anaesthetics.

In a series of 11 cases reported by Sharpstone and his colleagues²³ unexplained postoperative fever occurred in nine and jaundice in three patients after a previous halothane anaesthetic. All of these patients subsequently received further halothane anaesthetics and six died of massive hepatic necrosis; it was concluded that halothane was responsible. No other diagnosis appears to have been thought likely, yet five of these patients were suffering from malignant disease, one had cholelithiasis with a subphrenic abscess, and one had cirrhosis of the liver. This latter patient²⁴ developed a severe urinary infection after his initial halothane anaesthetic, yet his postoperative fever was described as "unexplained."

PATTERNS OF FEVER AND JAUNDICE

Sharpstone and his colleagues support the view that unexplained postoperative fever or jaundice after halothane should be an indication to avoid further halothane anaesthesia. Trey and his colleagues,¹⁹ however, showed that postoperative fever is as common after the use of other anaesthetic agents as it is after halothane. Dykes²⁵ confirmed this finding and also described a variety of postoperative raised temperature patterns regardless of the anaesthetic agent used. Furthermore, in a retrospective survey¹⁴ in which eight patients were found who had become jaundiced after halothane anaesthesia

four of these patients were again subjected to halothane anaesthesia and in no instance did the jaundice recur.

A recent review article by Sherlock²⁶ concludes that "halothane hepatitis" can be differentiated from viral hepatitis on clinical, morbid anatomical, and immunological grounds. Again, unfortunately, the arguments put forward are unconvincing. The author's clinical criteria are based on the occurrence of unexplained postoperative fever, an association with multiple exposures to halothane, a number of non-specific changes in liver function, and jaundice which may or may not be present. The lack of specificity and significance of postoperative fever has already been emphasized. The morbid anatomical changes described appear to depend for recognition on "the experience of the pathologist." The immunological differences seem to rest mainly on the finding of antimitochondrial antibodies and induced lymphocyte stimulation. Both these tests, however, are non-specific. Her statement that a negative test for hepatitis-associated antigen (Australia antigen) rules out coincidental viral hepatitis is not supported by other expert opinion.^{27 28}

Among evidence for the postulate of hypersensitivity to halothane Deborah Doniach,²⁹ mentioned reports of rashes, bronchospasm, joint pains, unexplained fever, leucocytosis, and eosinophilia. These features may have been reported in association with liver damage after halothane anaesthesia, but is their relationship correlated or casual? She recommended a systematic search for early evidence of eosinophilia, yet eosinophilia was not found in any of 11 cases reported by Sharpstone and his colleagues.²³ From the available evidence clearly some of these abnormalities do occur from time to time, but further investigation will be required before firm conclusions can be drawn.

ADVERSE REACTIONS TO DRUGS

Reports on adverse reactions to drugs occurring in Great Britain have been collected by the Committee on Safety of Drugs since 1964, and to date 126 cases of jaundice associated with anaesthesia have been reported, of which only 103 pertain to halothane³⁰—though a recent publication³¹ stated that in Great Britain halothane forms a part in nearly 90% of all general anaesthetics.

Mushin and his colleagues³¹ reported a statistical comparison of three groups of patients—54 patients reported to the Committee on Safety of Drugs during the period 1964-9 and 74 patients from the literature, all of whom had become jaundiced after multiple halothane anaesthetics, and a control group of general surgical patients. In the first two of these groups there was an apparent "excess" of patients who had had two anaesthetics within one month, from which the authors concluded that "halothane should if possible be avoided in patients who have had it before, particularly if this was within the previous four weeks."

The authors based their study on the hypothesis that "halothane hepatitis" is caused by sensitization, and therefore no clinical details of the patients were provided. It is important to note that all cases of jaundice associated with halothane reported to the Committee on Safety of Drugs are included. The crux of the matter, however, is whether or not these cases of postoperative jaundice were unexplained. Firstly, the United States National Halothane Study¹⁰ reported 82 cases of fatal postoperative hepatic necrosis, but the expert panel decided that an adequate explanation other than the anaesthetic agents existed for all but nine of these. Extrapolation from these data suggests that only some 10% of postoperative liver damage is likely to be attributable to anaesthetic agents. Secondly, we are currently engaged in a study of postoperative jaundice occurring in Great Britain and Eire, and to date in most cases investigated the jaundice may well be due to factors other than the anaesthetic agents used.

For these reasons it is highly unlikely that all of the cases

reported to the Committee on Safety of Drugs were unexplained, and the "excess" figure of 68% of the total cases of jaundice reported to the committee who became jaundiced after two operations in a month—with an alleged cause-and-effect relationship with halothane—should be considerably reduced. Furthermore, the two groups of cases collected from the literature and reported to the committee were limited to anaesthetics repeated within 10 years. Under these circumstances it is misleading to include in the calculations the 23% of patients in the control group who had received their first anaesthetic more than 10 years previously. Appropriate calculation shows that 13% of the control group, rather than the 7% stated, received two anaesthetics within a month. Hence the apparent excess of patients who became jaundiced after two operations in a month, with an alleged cause-and-effect relationship with halothane, may not exist. Nevertheless, the high mortality and incidence of jaundice after operations repeated within a month is a matter of concern.

In contrast to these reports, studies by Dykes¹⁴ and Gronert³² and their colleagues, and an earlier study by Mushin and others,¹¹ failed to show an association between liver damage and multiple exposures to halothane. Furthermore, cases have been reported where postoperative liver dysfunction might have been attributed to halothane had not other aetiological factors subsequently come to light.^{33 34} Finally, it must be borne in mind, as Dykes and Walzer³⁵ showed, that a small but definite proportion of surgical patients can be expected to be suffering coincidentally from hepatic dysfunction not suspected preoperatively but revealing itself during the postoperative period.

Present Position

In countries where it is readily available halothane is used in over 70% of all anaesthetic procedures. Thus it is to be expected that halothane will have been administered in most cases where postoperative liver damage occurs. In the United States National Halothane Study¹⁰ the great majority of cases of massive hepatic necrosis were attributed to causes other than the anaesthetic agent used. Even so, there remains a few cases where no adequate explanation exists, and concern is felt particularly about two groups of patients—firstly, overweight, middle-aged patients, female rather than male, with a vague history of indigestion; and secondly, patients subjected to multiple halothane anaesthetics, often for minor surgical procedures.

If halothane is directly concerned in causing liver damage at least four possible mechanisms must be considered: a direct toxic effect; a normal or abnormal metabolite; a relation to viral hepatitis; or hypersensitivity—(a) direct, (b) a normal or abnormal metabolite.

DIRECT TOXIC EFFECT

For a drug to be classified as a hepatotoxin it should fulfil criteria which include the following conditions.³⁶ (a) Liver damage of a distinct histological pattern appears after a predictable and usually brief latent period following exposure to the offending agent. (b) The damage is elicited in all exposed individuals and can be reproduced in experimental animals. (c) Damage is dose-related and other tissues are often affected.

None of these conditions is met by halothane. Large quantities have been ingested by man without ill effect.^{37 38}

NORMAL OR ABNORMAL METABOLITE

As halothane is metabolized by man^{39 40} and many other species a metabolite could act as a hepatotoxin either in the form of a free radical or as a cumulative toxic substance.

Alternatively a metabolite could act as a hapten, leading to a hypersensitivity response (see below).

If the causal agent were a normal metabolite it should fulfil the criteria laid down for a hepatotoxin (see above). In addition to this, if it were an abnormal metabolite one might expect a genetic or familial association, but none has been shown. By contrast, in malignant hyperpyrexia which may be triggered by halothane the genetic and familial links are already clearly established, despite the fact that only about 170 cases have been reported in the world literature.⁴¹

At present none of the known metabolites of halothane has been shown to be hepatotoxic in animals.⁴² Though enzyme induction⁴³ and genetic and environmental factors⁴⁴ influence the normal rate of metabolism of halothane in man there is no published evidence that any of these changes is associated with liver damage.

RELATION TO VIRAL HEPATITIS

The incidence of viral hepatitis (infectious and serum) in the world is unknown. The disease, however, appears to be becoming more prevalent and affecting an older age group—for example, Harville and Summerskill⁴⁵ reported that 80% of their patients were over 40, an age group particularly associated with the halothane dilemma.

Until recently no satisfactory diagnostic test for viral hepatitis existed, but the advent of the hepatitis associated antigen⁴⁶ (Australia antigen) initially led to the expectation that this problem had been overcome. Unfortunately, it is now becoming clear that hepatitis associated antigen is probably concerned only in serum hepatitis⁴⁶; the test is not technically straightforward and the percentage of positive results therefore varies widely from laboratory to laboratory. Even in confirmed cases the test may be positive for only a relatively short period of time. Furthermore, viruses other than those responsible for infectious and serum hepatitis may give rise to jaundice—for example, cytomegalic virus,⁴⁷ for which again there is no satisfactory easy test. Therefore a negative hepatitis associated antigen does not appear to rule out viral infection.

Some indication of the size and difficulty of this problem was given in a paper² by Dykes and Bunker, who estimate that in the United States of America some 200-300 patients each year are likely to be subjected to anaesthesia while incubating viral hepatitis. The potential effects of anaesthesia on such patients, or those with chronic active hepatitis, is not clear. Recently it has been suggested that carriers of viral infection,⁴⁷ who are normally symptom-free, may manifest clinical signs postoperatively owing to non-specific depression of their normal immunological responses by surgery and anaesthesia.⁴⁸ Perhaps halothane depresses immunological responses more than other anaesthetic agents?

Since the signs and symptoms of viral hepatitis are similar to those described in cases of alleged "halothane hepatitis," it has been suggested that all such cases are, in fact, viral in origin.⁴⁹ On the other hand it has recently been claimed⁵⁰⁻⁵² that it is possible, on either clinicopathological or morbid anatomical grounds alone—by the use of light and electron microscopy—to differentiate between liver damage due to viral infection and that allegedly caused by halothane. Unfortunately in all of the above studies the clinical history and biochemical findings were available to the pathologist. In contrast, where liver sections were unlabelled and clinical histories were not available the panel of expert pathologists associated with the National Halothane Study was unable to distinguish between massive hepatic necrosis occurring after viral hepatitis compared with that alleged to occur after halothane anaesthesia.⁵³ Hence until liver damage in patients with alleged halothane hepatitis can be clearly distinguished from that seen in viral hepatitis, or unequivocal diagnostic tests are devised for the possible viruses involved, it will

remain impossible in any individual case to exclude a viral cause.

HYPERSENSITIVITY

For a drug to act as an antigen in a hypersensitivity response certain criteria should be satisfied. (a) The drug should be a large or a reactive small molecule or be capable of combining with proteins or other molecules in a body or be metabolized to a substance which can do the same. (b) Rashes, eosinophilia, arthralgia, fever, or other signs of hypersensitivity are commonly seen. (c) There is usually a history of previous exposure to the antigen. (d) Hypersensitivity once established is usually long-standing, though delayed hypersensitivity tends to diminish with time.

Halothane is a small, chemically unreactive and poorly water-soluble molecule. Neither halothane nor any known metabolite of halothane combines with proteins; it has been suggested that halothane may combine with mitochondria,⁵⁴ but this is speculative. The various stigmata of hypersensitivity have been neither consistently nor commonly observed. Attention has already been drawn to the difficulty in interpretation of rashes, fever, and eosinophilia associated with surgery and anaesthesia.

Clinically, drug hypersensitivity usually occurs after a history of previous exposure. Hypersensitivity responses do, however, occur after a single exposure—for example, after chlorpromazine—but it should be noted that chlorpromazine binds with mitochondria⁵⁵ and could therefore act as a hapten. Furthermore, genetic links have been shown.⁵⁶ Once drug hypersensitivity is established further exposure leads to a reaction in a high percentage of cases—for example, about 40% with chlorpromazine.⁵⁶ The sequence, halothane→liver dysfunction—further halothane→no damage, has been reported in all of four patients by Dykes and his colleagues.¹⁴ It has been suggested,⁵⁷ however, that “halothane hypersensitivity” does not persist for longer than two to three months, and the interval between successive halothane administrations was longer than this in two of these four patients. It is also of interest that Burns⁵⁸ recently reported the cases of two patients who were subjected to three halothane anaesthetics within three months. In each case jaundice occurred after the second anaesthetic but not the third.

Several tests are claimed to show the presence of an immunological response to halothane; these include the presence of antimitochondrial antibodies in relatively high titre, and induced lymphocyte stimulation. Tests for antimitochondrial antibodies have been positive in some but not all of the patients with alleged “halothane hepatitis.”^{54 59 60} It must be stressed that antimitochondrial antibodies may be found in a variety of liver disorders not associated with surgery or anaesthesia.^{54 60} The administration of carbon tetrachloride to rats has also been found to produce antimitochondrial antibodies,⁶⁰ suggesting that the production of these antibodies may merely result from liver damage; the implication being that liver damage releases tissue-specific antigen to which the subject may not have acquired a full immunological tolerance.

Stimulation of lymphocytes by specific antigen in clinical hypersensitivity and by plant mitogens may result in increased uptake of tritiated thymidine by the cultured cells. Paronetto and Popper⁵⁹ used this test to study 15 patients with alleged “halothane hepatitis” and showed increased uptake—that is, lymphocyte stimulation in 10, and inhibition in three others. Some of the positive levels of stimulation, however, were only marginally higher than the upper limit of the normal controls, and the highest levels were recorded in two patients after single exposure only—one to halothane and one to methoxyflurane. If these findings are valid the implication is that halothane itself is the antigen, since it was used to provoke the lymphocyte stimulation in these patients. The increased

stimulation was short-lived and occurred only while the patients were jaundiced. This raises the question, as with antimitochondrial antibodies of whether lymphocyte stimulation or inhibition is non-specific to some types of liver dysfunction rather than indicative of the cause. It is of interest, therefore, that Park and his colleagues⁴⁸ recently showed that immediately after surgery induced lymphocyte stimulation is noticeably depressed. Nevertheless after a few days this returns to the preoperative level and thereafter rises. Possibly, therefore, Paronetto and Popper⁵⁹ may have shown the “normal” response of lymphocytes after surgery and anaesthesia and that hence the liver dysfunction in their patients was coincidental.

A few anaesthetists, other operating-room personnel, and one worker manufacturing halothane are also alleged to have developed hypersensitivity. One case was recorded in detail⁶¹; an initial illness diagnosed as viral hepatitis was followed by recurrent attacks of hepatitis allegedly due to halothane, culminating in an attack of hepatitis after direct challenge with halothane. Review of the case history, however, shows that though this person frequently relapsed soon after re-exposure, on at least one occasion he was exposed to halothane for a long time without adverse effect. Chronic active hepatitis is perhaps an alternative possible diagnosis in this case. At all events it must be recognized that this person was not challenged with anaesthetic agents other than halothane. Furthermore, tests for smooth-muscle antibody⁶² and hepatitis-associated antigen were not reported subsequently.

The evidence against hypersensitivity in operating-room personnel must also be borne in mind. Firstly, halothane is present even in the atmosphere of well-ventilated North American operating rooms;⁶³ secondly, halothane has been detected in the blood⁶⁴ and expired air^{63 64} of operating room personnel and metabolites of halothane have been found in their urine⁶³; yet, thirdly, in more general terms a survey⁶⁵ of the causes of death of 441 American anaesthesiologists provided no evidence of a higher incidence of liver disorders in this group compared with a general population sample. In view of the large number of operating-room personnel exposed to halothane throughout the world it is surprising that so few alleged reactions to halothane have been reported.

Conclusion

The scientific evidence for the existence of “halothane hepatitis” is incomplete. If it does exist it is rare. It is not yet possible conclusively to rule out viral infection as a cause of liver damage in any individual case. It would seem reasonable to expect that halothane, like all other known anaesthetic agents, must carry some small risk of causing postoperative liver dysfunction.

The need now is for more accurate and detailed information about all cases of liver dysfunction occurring after any anaesthetic procedure, so that the extent of the problem as a whole may be determined and attempts made to elucidate its mechanism.

Meanwhile the verdict against halothane remains, as in Scottish law, not proven.

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Clinical Problems

Vasectomy

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Vasectomy as a method of contraception must be considered from two different aspects—the problem of the population explosion and the personal one of the married couple. The global problem of population control is scarcely recognized, even in those countries with a rapidly increasing population. The greatest single obstacle to the economic and social advancement of the majority in the developing world is rampant population growth. In India, where over 8 million men have already had a vasectomy, a million new lives are added to the population every month. The Philippine Islands currently have a population of 37 million; at the present rate of growth

these islands would have to support over 100 million people in 35 years' time unless some form of population control is instituted. Sixteen centuries were required to double the world population after the birth of Christ, but the present population will double in 35 years. A child born today in a world of 3 billion people will expect to see an increase to 15 billion, and his grandchild will live in a world of 60 billion.¹

Predicting population changes is a favourite sport of professional demographers. The population of North America, with a growth rate of 1.1% per year, could double in the next 63 years. Latin America could double its population in 24 years. Europe has an average growth rate of 0.8%, which gives a doubling time of 88 years. The populations of France, Switzerland, and the Netherlands could double in 60-80 years; those of Italy in 100 years; United Kingdom 117 years; Czechoslovakia, Austria, and Ireland 140 years; West Germany 175 years; and East Germany 700 years. The population of the Soviet Union could double in 70 years. If the world's population

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