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Serum enzyme changes after major lung surgery —with and without halothane

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The postoperative changes in serum aspartate aminotransferase (SGOT), serum alanine aminotransferase (SGPT), and lactate dehydrogenase (LDH) levels after major lung operations were studied in patients some of whom received halothane and some of whom did not. There were no differences between the two groups of cases. It seemed possible that the rises in SGOT and LDH which occurred quite frequently were an indication that tissue autolysis was occurring in the body.

Retrospective statistical studies have largely discounted the risk of the development of massive hepatic necrosis as a complication of halothane anaesthesia (National Halothane Study, 1966; Mushin, Rosen, Bowen, and Campbell, 1964; Vickers and Dinnick, 1965; Henderson and Gordon, 1964). This form of investigation, however, involves a collection of data from a large number of sources with the inevitable accompanying variability in the material. One of the conclusions of the National Halothane Study was that prospective investigations of the toxicity of halothane would now be justified, and the present paper attempts this assessment.

The most obvious method of detecting minor liver damage is the determination of the transaminase content of the serum of patients in the postoperative period, for such enzymes do not appear in appreciable quantity unless liver cells have been destroyed and are undergoing autolysis. A certain amount of work in this field has already been carried through (Ayres and Williard, 1960; Lawrence and Schulkins, 1956), including enzyme studies on patients to whom chloroform had been given (Fote, 1960; Reichard, Wiqvist, and Yllner, 1960; Griffiths and Ozguc, 1964; Imray, Kennedy, and Kilpatrick, 1964; Rollason, 1964), and, more recently, studies in patients who had been anaesthetized with halothane (Rollason, 1964; Tornetta and Boger, 1964; Beckman, Brohult, and Reichard, 1966). Most of these studies have been informative up to a limited point, but it clearly emerges that changes in serum transaminase levels in the postoperative period are governed more by the operative procedure than by the anaesthetic agents themselves.

It had also been suggested some years ago that when carbon dioxide retention occurred (Morris, 1960) or when the blood pressure fell during anaesthesia (Morris and Feldman, 1963) halothane liver damage was much more likely to occur, and in the National Halothane Study there were a few cases where it was impossible to exculpate halothane. Because of these facts, I have made a comparative study of the serum enzymes in the postoperative period after major lung surgery. Since hypotension and carbon dioxide accumulation were likely to be present frequently, I limited the investigations to those undergoing thoracotomy for lung resection (see Table I).

TABLE I

NATURE AND DURATION OF OPERATIONS PERFORMED

Operation	Halothane Anaesthesia	Anaesthesia without Halothane
	No. of Cases	No. of Cases
Pneumonectomy ..	5	7
Lobectomy	8	6
Sleeve resection ..	5	2
Thoracotomy only ..	5	4
Other intrathoracic ..	4	4
Total	27	23
Mean duration of operation	156 min. (range 70–240)	162 min. (range 80–270)
Mean minimum blood pressure	75 mm. Hg (range 50–110)	77 mm. Hg (range 50–120)

METHODS

CHOICE OF LIVER FUNCTION TEST Since the primary purpose of this study was to obtain evidence of destruction of liver cells appearing in the postoperative period, conventional tests of liver function such as

thymol turbidity and zinc sulphate flocculation (which demonstrate a deficiency of sufficient surviving liver cells) were not used. Similarly, those tests such as the serum alkaline phosphatase determination and the prothrombin time, which indicate biliary obstruction, seemed unlikely to be of any great value. Facilities were not available for the bromsulphthalein excretion test.

When liver cells autolyse, the enzymes in them, including serum aspartate aminotransferase (SGOT), serum alanine aminotransferase (SGPT), and lactate dehydrogenase (LDH) appear in the serum in increased quantities (Arturson and Persson, 1959; Baron, 1963; Bodansky, 1962; West and Zimmerman, 1959; Wróblewski and LaDue, 1955a). Whilst the work was in progress it became apparent that LDH consists of a group of isoenzymes (Vesell and Bearn, 1961). The acetone-stable fraction of LDH is that which appears following autolysis of liver cells, and also that which is liberated by breaking down red cells, and the concentration of this enzyme was determined in the last 24 cases.

TIMING OF THE TESTS Fote (1960) and Reichard *et al.* (1960) had shown that, following the administration of chloroform for delivery, there is a rise in the concentration of serum enzymes derived from the liver, possibly the result of cellular autolysis, within 48 hours. A previous study (Hunter, 1964) had shown little or no rise in SGOT or SGPT 48 hours after 15 neurosurgical operations with or without hypothermia involving the administration of trimetaphan and/or halothane to the point of producing an arterial pressure of 50 mm. Hg for periods varying from 15 to 20 minutes. Attention has been drawn to the fact that the clinical manifestations of so-called halothane hepatotoxicity may not appear until nearly a week after exposure to the drug (Lindenbaum and Leifer, 1963). With these facts in view, enzyme estimations were made on the patients of this series on the second or third, on the fourth or fifth, and on the seventh postoperative days. This lack of uniformity was dictated by the fact that either the second or fifth postoperative day invariably fell within the week-end. A number of results had to be rejected because of haemodialysis. Occasionally, too, for reasons unconnected with the investigation or because the patient died, fewer than the full three specimens were available. Those for whom only a single postoperative specimen was available are excluded from this study. Those from whom only two specimens were obtained are retained and it is because of them that the numbers are irregular.

THE TECHNIQUE OF ANAESTHESIA Patients were premedicated with 10 mg. morphine and 0·6 mg. atropine. Anaesthesia was induced with sufficient thiopentone to abolish the eyelash reflex, usually some 200–300 mg. This was followed by 40–60 mg. suxamethonium, depending on the patient's weight. After inflation of the lungs and the spraying of the inside of the trachea with a long spray containing 4% lignocaine, a double-lumen tube was passed—Carlens', White's, and Robertshaw's tubes were all used, the pattern being dictated by the surgeon's needs. In those who were subsequently to be anaesthetized with halothane this was initially a supplement to nitrous oxide and oxygen. Immediately after transfer to the operating theatre the patient was connected to a Blease ventilator and curarized. The ventilator was then set to deliver some 8 to 12 l./min., depending on the patient's size. The flow of the nitrous oxide was cut off, the oxygen flowmeter was set to 5 l./min. and the Fluotec vaporizer to 1 to 1·5%. The machine then delivered to the patient a mixture of halothane, oxygen, and air in the manner described by Robertshaw (1963). The actual concentration of halothane in the inhaled gases was of the order of 0·25–0·75% and represented the minimum dose of anaesthetic which would immobilize the patient. The halothane was turned off half way through the closure of the chest and nitrous oxide and oxygen was substituted. At the end of the operation residual curarization due to tubocurarine was reversed with neostigmine and atropine. The patients all awoke promptly at the end of the procedure.

Alternate patients were anaesthetized in exactly the same way but without the use of halothane. In three no supplement to nitrous oxide and oxygen was required. In three other cases supplementary pethidine was given. In the remainder a technique of neuroleptanalgesia (with relaxants also) was employed in which 2–4 mg. dehydrobenzperidol and 1–2 mg. phenoperidine were injected intravenously immediately before or immediately after the induction dose of thiopentone. Further doses of phenoperidine were given as necessary to make the patient immobile during surgery. There is no suggestion that any of these agents has any effect on any of the serum enzymes studied. In one patient it was necessary to use nalorphine to restart breathing at the end of the procedure.

BIOCHEMICAL METHODS The SGOT and SGPT were determined by Reitman and Frankel's (1957) method. The results are expressed in Sigma-Frankel units. The normal range for SGOT is 5–40 units and that for SGPT 5–35 units. The LDH was measured by the method of Berger and Broida (1964), and the acetone-stable lactate dehydrogenase (ASLDH) by the method of Latner and Turner (1963). A normal figure for LDH was 250–500 BB units. Values in excess of 750 units are definitely of pathological significance. The acetone-stable component of the LDH gives a normal value of 50 units, but the normal range is not fully defined.

RESULTS

The number of patients in whom abnormal serum levels developed are shown in Table II. There were no more among those who received halo-

TABLE II

NUMBER OF PATIENTS WITH ABNORMAL SERUM ENZYME LEVELS

Anaesthetic	No. of Cases	SGOT >40 Units	SGPT >35 Units	LDH >750 Units	ASLDH >90 Units
Halothane	27	9	3	9	11
Nitrous oxide-oxygen and non-volatile supplement ..	23	8	2	9	10

TABLE III

SERUM ENZYME LEVELS AFTER MAJOR THORACIC OPERATIONS

Anaesthetic	Enzyme	Means and Standard Deviations		
		Specimen 1	Specimen 2	Specimen 3
Halothane ..	SGOT (SF units)	33·0±13·3 (27)	28·9±14·5 (24)	26·9±14·7 (20)
Nitrous oxide		37·6±11·4 (23)	32·3±20·3 (22)	21·3±10·5 (18)
Halothane ..	SGPT (SF units)	13·9±8·3 (27)	17·0±10·3 (25)	18·6±12·0 (18)
Nitrous oxide		14·0±4·8 (23)	17·2±13·2 (22)	15·7±9·1 (18)
Halothane ..	LDH (BB units)	636±226 (27)	592±240 (22)	551±292 (19)
Nitrous oxide		579±241 (23)	576±223 (22)	590±270 (18)
Halothane ..	ASLDH (BB units)	140±46 (14)	100±40 (14)	94±56 (11)
Nitrous oxide		103±78 (15)	108±69 (10)	113±61 (12)

Figures in parentheses indicate the number of cases in each group.

thane than among those who did not. This point is emphasized by the mean serum enzyme levels in the two groups of patients presented in Table III. From these it will be seen that abnormal figures for SGOT and LDH occurred in some cases while there were minimal changes in SGPT. It is also interesting that the trend of SGOT, LDH, and ASLDH was downwards during the period of the investigations while that of SGPT was very slightly upwards. Of the enzymes studied, change in SGPT is that which is most likely to indicate hepatic disturbance. Beckman *et al.* (1966), using other tests of liver function, demonstrated a change similar to that noted here in relation to SGPT, though in their series the standard deviations are so great that the differences are not statistically significant.

There was a very wide variation both in LDH and ASLDH. The variation was approximately equal in both groups of cases, and probably indicates little more than the fact that LDH is subject to many influences, presumably because this enzyme is widely distributed through the organs, the muscles, and the red cells of the human body. Again there were no significant differences between those who received halothane and those who did not.

Preliminary normals for the type of patients in my series were established by withdrawing specimens from 11 patients immediately after the induction of anaesthesia. The results in these patients are shown in Table IV. They indicate that the raised postoperative serum enzyme levels are not a perpetuation into the postoperative period of an abnormality which was present before operation.

Since it appeared from these results that the postoperative figures in both groups of cases were more or less identical, the findings were pooled for further study. Scatter diagrams were plotted for SGOT against SGPT (Fig. 1). There was obviously no relationship between the two serum enzyme levels. SGOT was plotted against LDH (Fig. 2). Here there appeared to be some correlation although the scatter was very wide indeed. LDH and ASLDH (Fig. 3) were plotted one against the other and, though there appeared from inspection of the figures to be a relationship between the two, in fact the scatter diagram did not confirm this.

TABLE IV

PREOPERATIVE SERUM ENZYME LEVELS IN 12 CASES OF THE SERIES AND THE POSTOPERATIVE LEVELS IN THESE CASES

Enzyme	No. of Cases	Preoperative Level (Mean± S.D.)	Postoperative Levels (Means±S.D.)					
			Specimen 1		Specimen 2		Specimen 3	
			Cases	Level	Cases	Level	Cases	Level
SGOT (SF units)	11[1]	13±5·3	12	32±12	11	33±27[2]	12	25±11
SGPT (SF units)	12	7·3±4·5	12	14±5	11	16±17[2]	11	16±10
LDH (BB units)	12	307±100	12	463±185	11	446±210	11	425±115
ASLDH	12	55±14	11	81±42	8	84±32	11	96±36

[1] A twelfth case gave an SGOT level of 115 units. This result was excluded as a presumptive technical error. The postoperative values were 36, 8, and 17.

[2] This group includes a single patient whose second SGOT was 105 and second SGPT was 66. Unfortunately, the third specimen was not obtained from this patient, but his clinical course was uneventful. It seems likely that these figures were due to an incident in which near cardiac arrest occurred in the postoperative period.

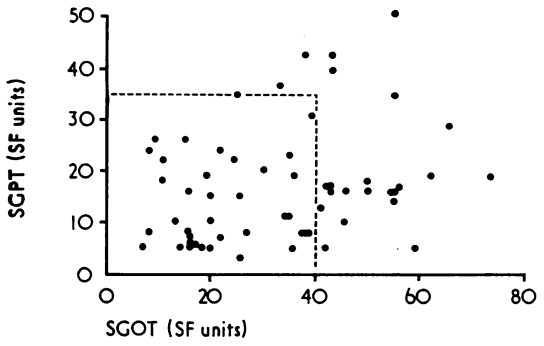

FIG. 1. *Scatter diagram to show relationship between SGOT and SGPT (prepared by plotting points for all abnormal values and for 20 unselected determinations within normal limits).*

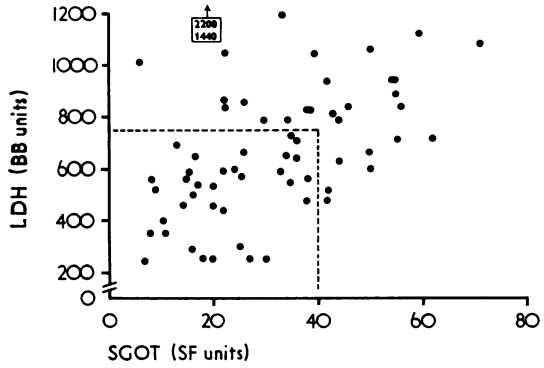

FIG. 2. *Scatter diagram to show relationship between SGOT and LDH (prepared by plotting points for all abnormal values and for 20 unselected determinations within limits).*

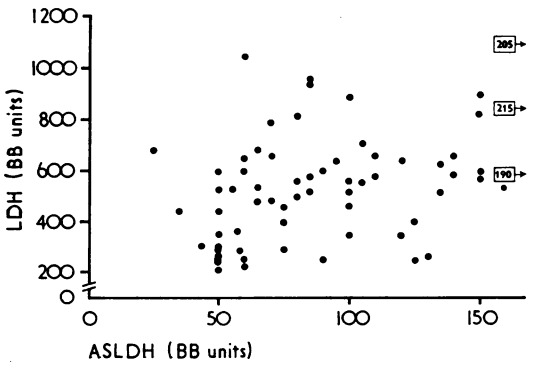

FIG. 3. *Scatter diagram to show relationship between LDH and ASLDH (prepared by plotting points for all abnormal values and for 20 unselected determinations with values within normal limits).*

The calculated correlation co-efficients were as follows:

SGOT and SGPT	0·42±0·17
SGOT and LDH	0·34±0·16
LDH and ASLDH	0·64±0·28

DISCUSSION

The basic finding of this study is that there is quite often a rise in the SGOT, LDH, and ASLDH levels and little if any change in SGPT in the blood in the postoperative period in those who have undergone thoracotomy and major lung surgery. There is, however, no difference in the frequency and the extent of the rise between patients who receive halothane and those who do not. Not only is there no statistically significant difference between the two forms of anaesthesia but the values obtained in these two groups are so similar that they very strongly suggest that the responses are identical.

High values for SGOT have been noted in the postoperative period by other workers (Lawrence and Schulkins, 1956; Thoma, Krohn, and Futch, 1963) especially after procedures in which there has been extensive red cell destruction—for example, cardiac operations (Walker and Morgan, 1964). By contrast, however, the author (unpublished, 1965) has noted relatively low values for SGOT and SGPT, too, in the postoperative period in four patients, anaesthetized with methoxyflurane, after gynaecological procedures such as pelvic floor repair and radical vulvectomy, perhaps because extravasation into tissues is much less marked and bleeding occurs mainly to the exterior. However, although this confirms the observations of Lawrence and Schulkins (1956), my observations were made on only four patients.

CARBON DIOXIDE RETENTION The results of this study do not support the suggestion of Morris and Feldman (1963) that a raised P_{CO_2} and hypotension could aggravate halothane hepatic damage. We did not monitor P_{CO_2} changes either in the blood or in the expired air of these patients. One lung anaesthesia, however, was regularly employed, and in an appreciable number of cases there were technical difficulties in maintaining an adequate respiratory exchange at some point during the operation. It is therefore virtually certain that in both groups of cases some degree of carbon dioxide retention occurred during anaesthesia. Further, several cases in both groups

had postoperative sputum retention, and some rise in P_{CO_2} at this time was likely to have occurred.

HYPOTENSION Blood pressures were taken every 10 minutes by palpation. In both groups of cases moderate falls in blood pressure occurred in relation to the giving of tubocurarine, to blood loss or cardiac tamponade by direct pressure of a retractor. The mean minimum systolic blood pressure in those receiving halothane was 75 mm. Hg, with a range of 50 to 110. In those anaesthetized by other means the mean minimum blood pressure was 77 mm. Hg, with a range of 50 to 120. This observation confirms in passing that there was no essential difference between the material in the two groups and in addition it suggests that it is possible to use halothane in association with hypotension without the production of evidence of liver damage.

DURATION OF EXPOSURE Although some workers have found disturbances of serum enzymes after a very short exposure to chloroform (Fote, 1960; Reichard *et al.*, 1960) not all accept this. Most of the cases of serum enzyme disturbance which have followed the administration of this agent have occurred after administrations lasting an hour or more (Glover, 1961), as indeed have many cases of acute yellow atrophy (Siebecker and Orth, 1956).

A review of these facts, however, suggests that the period of exposure to halothane must be important. In this series the mean period was 120 minutes, with a range of 25 to 210 minutes. The mean total duration of operation in those receiving halothane was 2 hours 36 minutes (range 70 to 240 min.) and in those anaesthetized by other methods the mean duration of operation was 2 hours 42 minutes (range 80 to 270 min.). It would therefore seem that an appreciable exposure of the patients to the anaesthetic occurred; further the exposure was comparable in duration with that of some of the cases reported by other workers in whom liver disturbances have followed. This analysis of the result also makes clear that the material in the two groups was truly comparable.

The concentrations of halothane used in my patients were low, being between 0·25 and 0·75%. The patients were artificially ventilated, and so I think that blood levels of the drug were relatively higher than they would have been in patients spontaneously breathing such concentrations of halothane. In fact, the doses of halothane used were at least sufficient to prevent movement and coughing in response to surgical stimuli, for no other agent was used and the depth of curarization was unusually light. On the other hand, the amount of surgical stimulation produced by major thoracic surgery is not severe, and it may well be that when halothane alone is used for surgical procedures requiring more profound anaesthesia, it might produce different effects.

PREOPERATIVE TRANSAMINASES The basic conclusion of this study is that high transaminase and lactate dehydrogenase levels are to be expected in the postoperative period after thoracotomy for lung cancer. The question arises whether the abnormality was present before the operation. This is of special importance for a number of reasons: a raised lactate dehydrogenase has been described as a manifestation of hepatic secondaries from lung cancer (Wróblewski and LaDue 1955b, 1955c; West and Zimmerman, 1958; Hinton, 1965; Gault, Cohen, Kahana, Leelin, Meakins, and Aronovitch, 1967), and chronic respiratory insufficiency has been shown by Refsum (1963) to be capable of causing liver damage—perhaps by causing anoxia or by back pressure in the hepatic veins, severe enough to raise the serum transaminase levels. It was not possible to obtain truly preoperative specimens in the patients of the present series. Blood was, however, withdrawn from 11 patients shortly before the operation began. The serum transaminase and lactate dehydrogenase levels in these specimens were very much lower (Table IV) than those in the postoperative period for these particular patients. Further, the postoperative values obtained showed no evidence that the patients in this small group differed in any way from the remainder of the series.

When this work was begun some three years ago, it appeared that the determination of SGOT and SGPT was the best readily available method of assessing liver damage. Since this work began, two other factors have had to be taken into account. First, the ornithine-carbamoyl transferase and the iso-citric dehydrogenase determinations have become more widely used, and are regarded as more specific (Sterkel, Spencer, Wolfson, and Williams-Ashman, 1958). The latter was used by Tornetta and Boger (1964), who observed some increases in the postoperative period in those anaesthetized with the aid of nitrous oxide, droperidol, and fentanyl. Reichard *et al.* (1960) used the determination of ornithine-carbamoyl transferase and believed that they had

shown that halothane did in fact cause liver damage. In a more recent study, however, Beckman *et al.* (1966) note that the serum concentration of this enzyme rises with almost all forms of anaesthesia and further that maximum serum concentration of the enzyme may be delayed by as much as nine days. They do not, however, regard this as evidence of liver damage but rather as a response of tissues to trauma. It is also interesting that these particular workers do not appear to have noted a difference in the pattern of response to SGOT and SGPT. That which most seriously casts doubt on the usefulness of the present findings is an observation by Blackburn, Ngai, and Lindenbaum (1964) that one patient who developed frank liver failure showed no difference whatever in SGOT and SGPT during the entire period of his illness. Perhaps the fact that in the present study LDH and ASLDH were also investigated may to some extent compensate for this difficulty.

The last question is the significance of the rises in serum enzyme activity. It is clear from Figs 1 and 2 that there is little real connexion between the changes in the different enzymes unless it be that SGOT rarely rises with a normal LDH. Probably the rises in serum enzyme content reflect tissue autolysis, but it is by no means clear what tissues are involved. There was some suggestion that LDH rose more often than the other enzymes, but presumably this merely reflects the wide distribution of LDH in the tissues of the body.

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REFERENCES

Arturson, G., and Persson, B.H. (1959). Serum transaminase activity as an index of liver cell destruction. *Acta chir. scand.*, **117**, 221.

Ayres, P. R., and Williard, T. B. (1960). Serum glutamic oxalacetic transaminase levels in 266 surgical patients. *Ann. intern. Med.*, **52**, 1279.

Baron, D. N. (1963). Clinical enzymology with particular reference to liver disease. *Proc. roy. Soc. Med.*, **56**, 173.

Beckman, V., Brohult, J., and Reichard, H. (1966). Elevations of liver-enzyme activities in serum after halothane, ether and spinal anaesthesias. *Acta anaesth. scand.*, **10**, 55.

Berger, L., and Broida, D. (1964). *The Colormetric Determination of Lactic Dehydrogenase*. Sigma Technical Methods Bulletin No. 500.

Blackburn, W. R., Ngai, S. H., and Lindenbaum, J. (1964). Morphologic changes in hepatic necrosis following halothane anesthesia in man. *Anesthesiology*, **25**, 270.

Bodansky, O. (1962). New functional principles in diagnostic aspects of liver disease. *Bull. N.Y. Acad. Med.*, **38**, 711.

Fote, F. A. (1960). Hepatic effects of chloroform anesthesia in obstetrics. *Amer. J. Obstet. Gynec.*, **79**, 1142.

Gault, M. H., Cohen, M. W., Kahana, L. M., Leelin, F. T., Meakins, J. F., and Aronovitch, M. (1967). Serum enzymes in patients with carcinoma of lung: lactic-acid dehydrogenase, phosphohexose isomerase, alkaline phosphatase and glutamic oxaloacetic transaminase. *Canad. med. Ass. J.*, **96**, 87.

Glover, W. (1961). Communication to Research Grants Committee, Manchester Regional Hospital Board.

Griffiths, H. W. C., and Ozguc, L. (1964). Effects of chloroform and halothane anaesthesia on liver function in man. *Lancet*, **1**, 246.

Henderson, J. C., and Gordon, R. A. (1964). The incidence of postoperative jaundice with special reference to halothane. *Canad. Anaesth. Soc. J.*, **11**, 453.

Hinton, J. M. (1965). Serum lactate dehydrogenase in bronchial carcinoma. *Thorax*, **20**, 198.

Hunter, A. R. (1964). Comment on paper by Bunker, J. P., and Blumenfield, C. M. Liver necrosis after halothane anesthesia: cause or coincidence. *Survey of Anesthesiology*, **8**, 27.

Imray, J. McG., Kennedy, B. R., and Kilpatrick, S. J. (1964). The effect of brief chloroform administration on liver function. *Anaesthesia*, **19**, 33.

Latner, A. L., and Turner, D. M. (1963). Clinical application of the effect of acetone on serum lactate dehydrogenase. *Lancet*, **1**, 1293.

Lawrence, S. H., and Schulkins, T. (1956). Serum transaminase levels following prolonged surgical anesthesia. *Anesthesiology*, **17**, 531.

Lindenbaum, J., and Leifer, E. (1963). Hepatic necrosis associated with halothane anesthesia. *New Engl. J. Med.*, **268**, 525.

Morris, L. E. (1960). Comparison studies of hepatic function following anesthesia with halogenated agents. *Anesthesiology*, **21**, 109.

—— and Feldman, S. A. (1963). Influence of hypercarbia and hypotension upon liver damage following halothane anaesthesia. *Anaesthesia*, **18**, 32.

Mushin, W. W., Rosen, M., Bowen, D. J., and Campbell, H. (1964). Halothane and liver dysfunction: a retrospective study. *Brit. med. J.*, **2**, 329.

National Halothane Study (1966). *J. Amer. med. Ass.*, **197**, 775.

Reichard, H., Wiqvist, N., and Yllner, S. (1960). Chloroform anaesthesia in obstetrics. Its effect on the serum activity of ornithine carbamyl transferase, glutamic oxalacetic transaminase, and glutamic pyruvic transaminase. *Acta obstet. gynec. scand.*, **39**, 661.

Reitman, S., and Frankel, S. (1957). A colorimetric method for the determination of serum glutamic oxalacetic and glutamic pyruvic transaminases. *Amer. J. clin. Path.*, **28**, 56.

Refsum, H. E. (1963). Arterial hypoxaemia, serum activities of GO-T, GP-T and LDH, and centrilobular liver cell necrosis in pulmonary insufficiency. *Clin. Sci.*, **25**, 369.

Robertshaw, F. (1963). Personal communication.

Rollason, W. N. (1964). Chloroform, halothane, and hepatotoxicity. *Proc. roy. Soc. Med..*, **57**, 307.

Siebecker, K. L., and Orth, O. S. (1956). A report of seven administrations of chloroform for open thoracic operations. *Anesthesiology*, **17**, 792.

Sterkel, R. L., Spencer, J. A., Wolfson, S. K., and Williams-Ashman, H. G. (1958). Serum isocitric dehydrogenase activity with particular reference to liver disease. *J. Lab. clin. Med.*, **52**, 176.

Thoma, G. W., Krohn, W., and Futch, E. D. (1963). Variations of serum transaminases in the early postoperative period. *Texas St. J. Med.*, **59**, 402.

Tornetta, F. J., and Boger, W. P. (1964). Liver function studies in droperidol-fentanyl anesthesia. *Anesth. Analg. Curr. Res.*, **43**, 544.

Vesell, E. S., and Bearn, A. G. (1961). Isozymes of lactic dehydrogenase in human tissues. *J. clin. Invest.*, **40**, 586.

Vickers, M. D., and Dinnick, O. P. (1965). Post-operative hepatic morbidity with special reference to the role of halothane. *Anaesthesia*, **20**, 29.

Walker, W. F., and Morgan, H. G. (1964). Plasma-transaminase levels in cardiac surgery with extracorporeal circulation. *Lancet*, **1**, 683.

West, M., and Zimmerman, H. J. (1958). Serum enzymes in disease. I. Lactic dehydrogenase and glutamic oxalacetic transaminase in carcinoma. *Arch. intern. Med.*, **102**, 103.

—— —— (1959). Serum enzymes in hepatic disease. *Med. Clin. N. Amer.*, **43**, 371.

Wróblewski, F., and LaDue, J. S. (1955a). Lactic dehydrogenase activity in blood. *Proc. Soc. exp. Biol. (N.Y.)*, **90**, 210.

—— —— (1955b). Serum glutamic oxalacetic transaminase activity as an index of liver cell injury: a preliminary report. *Ann. intern. Med.*, **43**, 345.

—— —— (1955c). Serum glutamic-oxalacetic-transaminase activity as index of liver-cell injury from cancer: a preliminary report. *Cancer (Philad.)*, **8**, 1155.