Br. J. Anaesth. (1976), **48**, 119

CHANGES IN LIVER FUNCTION AFTER DIFFERENT TYPES OF SURGERY

R. S. J. Clarke, J. R. Doggart and T. Lavery

SUMMARY

Liver function tests carried out after minor surgical procedures, under anaesthesia lasting for 1 hr, showed no abnormalities. Tests after body surface operations under the same anaesthetic techniques showed transient derangements. After intra-abdominal procedures, liver dysfunction was more marked, although no patients with evidence of preoperative liver dysfunction or postoperative surgical complications were studied and none received blood transfusions. Measurements of the serum bilirubin concentration showed the most frequent abnormalities, but the pseudocholinesterase concentration decreased progressively after intra-abdominal surgery and b.s.p. retention increased significantly. Serum concentration of intracellular enzymes (LDH, s.g.o.t. and s.g.p.t.) increased within an hour of starting surgery, changes which were probably not related to liver function.

Several reviews have appeared which by their title suggest a relationship between anaesthesia and liver function (Dykes, 1970; Editorial, 1972). There is evidence connecting liver dysfunction with halothane (Sherlock, 1971; Reed and Williams, 1972) and particularly with a second administration a few weeks after the first (Mushin, Rosen and Jones, 1971; Inman and Mushin, 1974; Wright et al., 1975). On the other hand, there have been many studies which do not support this connection, or which suggest the alternative possibility of viral hepatitis as a possible cause (National Halothane Study, 1966; Walton et al., 1972; Simpson, Strunin and Walton, 1973). Since it is not possible to prove infective hepatitis as a cause in any individual case of jaundice, the pathologist attributes most deaths following surgery to anaesthesia (particularly if halothane has been given to the patient), unless there is strong evidence to the contrary (Sharpstone, Medley and Williams, 1971).

Other factors, associated with surgery, may cause jaundice, such as blood transfusion with the possibility of minor blood group incompatibilities, or sepsis in the alimentary tract, leading to portal venous spread to the liver (Lomanto et al., 1972). Maladministration of anaesthesia resulting in hypoxia or hypotension may cause hepatic damage (Vaizey, 1938). Handling of the liver also would appear to be a possible factor affecting liver function, in operations in the upper abdomen. Tissue trauma with myoglobin breakdown is inseparable from any type of surgery. The less easily defined surgical or traumatic stress which is responsible for other metabolic reactions, such as secretion of antidiuretic hormone from the posterior pituitary gland or cortisol from the adrenal cortex, might be expected to influence the liver also.

Previous work (Clarke et al., 1965, 1974) has shown that body surface surgery lasting approximately 1 hr, under nitrous oxide anaesthesia with intermittent doses of thiopentone, propanidid or Althesin, is followed by an increase in the serum bilirubin concentration. There was also a significant increase in the alanine aminotransferase concentration (s.g.p.t.) and a decrease in the serum pseudocholinesterase concentration, following the administration of either thiopentone or propanidid (Clarke et al., 1965). There were no such changes after brief minor gynaecological procedures under anaesthesia with nitrous oxide plus ketamine, ethanol, diazepam or Althesin (Clarke et al., 1974). The cause of the abnormalities in liver function tests in the groups having body surface surgery might be the longer duration of surgery, the greater total dose of intravenous anaesthetic or the type of surgery undertaken.

The present study is in two parts. First, four groups of patients, undergoing either minimal or body surface operations under anaesthesia with nitrous oxide plus intermittent doses of thiopentone or Althesin were studied to evaluate the role of the anaesthetic in the findings described by Clarke and his colleagues (1974). Some of the patients undergoing body surface surgery, recorded in the present study, were included in the earlier publication. Second, four groups of

R. S. J. Clarke, M.B., PH.D., F.F.A.R.C.S., Department of Anaesthetics, Queen's University of Belfast; J. R. Doggart, M.SC., PH.D., A.R.I.C.; T. Lavery, F.I.M.L.T.; Biochemistry Laboratory, Royal Victoria Hospital, Belfast.

TABLE I. *Details of patients anaesthetized with intermittent doses of i.v. anaesthetics plus nitrous oxide in oxygen (I)*

Type of surgery	Intravenous anaesthetic: Drug	Intravenous anaesthetic: Average total dose	No. of patients	Average age (yr)	Average weight (kg)
Minimal	Thiopentone	15.4 mg/kg	20	51	62
	Althesin	0.19 μlitre/kg	20	39	59
Body surface	Thiopentone	14.6 mg/kg	20	51	69
	Althesin	0.23 μlitre/kg	20	49	65

patients were studied having different types of surgical procedure for which the anaesthetic techniques, duration of anaesthesia and general management were almost identical. This study was designed to identify some of the non-anaesthetic factors in liver dysfunction following surgery. Some of this work has been described briefly by Clarke and Fee (1974).

METHODS

(I) Studies after intermittent intravenous anaesthesia

The four groups of patients are described in table I. All patients were premedicated with atropine 0.6 mg, and anaesthesia was induced with either thiopentone 5 mg/kg or Althesin 55–75 μlitre/kg. Maintenance was with 75% nitrous oxide in oxygen and further doses of the intravenous anaesthetic as required to prevent reflex movements. Surgical procedures have been grouped as minimal (cystoscopy, removal of a sebaceous cyst, or superficial biopsy) and body surface (herniorrhaphy, ligation and stripping of varicose veins, or total mastectomy). Regardless of the procedure, all anaesthetics lasted for 60–75 min. All patients had 12 hr of starvation before operation and an i.v. infusion of 500–1500 ml of compound sodium lactate solution B.P. (Hartmann's solution) was given during the course of the day. All were, in fact, able to take fluids by mouth on the evening after operation, followed by a light diet on the following day.

Blood samples for liver function tests were taken immediately before anaesthesia and at 6, 24 and 96 hr after the start of anaesthesia. Four estimations were made by the SMA-12/60 multiple analyser: bilirubin by an adaptation of the method of Jendrassik and Grof (1938), alkaline phosphatase (Morganstern et al., 1965), aspartate aminotransferase (s.g.o.t.) (Morganstern et al., 1966) and lactate dehydrogenase (LDH) (Hochella and Weinhouse, 1965). Alanine aminotransferase (s.g.p.t.) was measured by the method of King (1960) and the serum pseudocholinesterase concentration by that of Michel (1949).

(II) Studies after thiopentone–methoxyflurane–muscle relaxant anaesthesia

Four groups of patients were studied (table II), all of whom had the same anaesthetic technique, approximately the same duration of anaesthesia and different surgical procedures. All the patients were premedicated with atropine 0.6 mg and induction of anaesthesia was with thiopentone 5 mg/kg, followed by tubocurarine 0.5 mg/kg, 75% nitrous oxide in oxygen and methoxyflurane 0.2%. Small incremental doses of thiopentone or tubocurarine were given when required and controlled ventilation was maintained throughout. Methoxyflurane was discontinued approximately 10 min before the end of surgery and paralysis was reversed by the injection of atropine 1.2 mg and neostigmine 2.5 mg. The duration of anaesthesia was 60–75 min. The blood loss did not exceed 200 ml in any operation and blood was not administered. Starvation before operation and fluid replacement for the patients having minimal and body surface surgery were as in (I). Patients having intra-abdominal surgery had the usual restriction of oral feeding, and i.v. fluid therapy was continued until solid feeding had been restarted.

TABLE II. *Details of patients anaesthetized with thiopentone, tubocurarine, nitrous oxide in oxygen, and methoxyflurane (II)*

Group	Type of surgery	No. of patients	Average age (yr)	Average weight (kg)
1	Minimal	10	39	58
2	Body surface	10	37	66
3	Gastric	10	45	63
4	Biliary tract	10	48	64

TABLE III. *Results of liver function tests (mean ± SEM) before and after anaesthesia with i.v. thiopentone or Althesin plus nitrous oxide (I). Figures in heavy type are significantly different from the values recorded before operation*

Type of surgery	Intravenous anaesthetic	Time of sample (hr):	Bilirubin (mg/100 ml) 0	6	24	96	Alkaline phosphatase (u./100 ml) 0	6	24	96	LDH (u./ml) 0	6	24	96
Minimal	Thiopentone	Mean	0.53	0.51	0.48	**0.35**	8.0	8.5	8.9	7.8	283	275	291	296
		± SEM	0.055	0.047	0.051	0.048	0.76	0.66	0.67	0.38	12.2	12.6	13.1	25.5
	Althesin	Mean	0.68	0.68	0.62	**0.46**	11.4	11.0	9.9	12.0	346	294	313	305
		± SEM	0.050	0.044	0.061	0.050	2.16	1.91	1.86	2.68	18.4	19.7	15.8	12.4
Body surface	Thiopentone	Mean	0.60	0.68	**0.81***	0.55	7.8	9.0	8.1	8.4	312	309	269	268
		± SEM	0.040	0.059	0.068	0.058	0.43	0.84	0.51	0.74	20.2	20.0	13.7	22.4
	Althesin	Mean	0.69	0.81	**1.01***	0.59	8.6	9.0	8.0	8.1	320	303	314	287
		± SEM	0.057	0.083	0.114	0.074	0.48	0.67	0.83	1.05	18.8	27.4	26.5	17.8

Type of surgery	Intravenous anaesthetic	Time of sample (hr):	S.g.o.t. (u./ml) 0	6	24	96	S.g.p.t. (u./ml) 0	6	24	96	Pseudocholinesterase (u./100 ml) 0	6	24	96
Minimal	Thiopentone	Mean	23.3	26.9	23.7	19.8	22.8	22.5	24.3	17.4	93.6	91.6	94.7	94.9
		± SEM	1.55	1.94	1.56	1.69	2.69	3.45	4.15	2.42	4.38	6.72	5.09	4.69
	Althesin	Mean	31.2	32.1	31.1	30.3	31.0	31.1	31.0	34.1	98.0	92.7	93.9	97.6
		± SEM	2.88	3.17	2.34	3.27	7.97	7.28	7.13	7.32	7.95	7.80	7.43	10.33
Body surface	Thiopentone	Mean	21.8	**32.7***	23.4	20.3	19.8	27.0	23.8	26.5	88.8	95.3	86.5	**78.9***
		± SEM	1.88	1.78	2.20	1.81	3.39	11.93	4.42	5.04	4.13	4.41	4.41	3.86
	Althesin	Mean	31.1	42.1	35.4	30.7	26.7	31.6	31.9	32.0	101.8	95.3	**90.1***	**82.5***
		± SEM	1.43	5.98	6.17	4.05	2.97	4.31	6.25	5.72	5.34	4.48	4.69	4.83

*$P < 0.01$.

TABLE IV. *Details of patients, serum bilirubin and plasma haemoglobin concentrations in the patients receiving thiopentone, tubocurarine, nitrous oxide in oxygen and methoxyflurane (II). Conventions as in table III*

Group	Type of surgery	Average age (yr)	Average weight (kg)	Time of sample (hr):	Serum bilirubin (mg/100 ml) Total 0	Total 1	Total 6	Total 24	Total 96	Soluble fraction 0	Soluble fraction 24	Soluble fraction 96	Plasma haemoglobin (mg/100 ml) 0	1	6	24
1	Minimal	39	58	Mean	0.47	0.49	0.45	0.43	0.36	0.11	0.14	0.12	2.2	2.5	3.0	3.2
				±SEM	0.052	0.048	0.039	0.032	0.039	0.013	0.018	0.015	0.42	0.60	0.70	0.90
2	Body surface	37	66	Mean	0.60	0.66	0.74	**0.90***	0.46	0.17	0.23	0.13	5.6	6.2	4.4	6.0
				±SEM	0.047	0.091	0.098	0.091	0.063	0.047	0.042	0.018	2.58	2.12	1.36	2.95
3	Gastric	46	63	Mean	0.48	0.49	0.61	**0.78**	**0.89**	0.20	0.23	0.28	—	—	—	—
				±SEM	0.114	0.057	0.081	0.075	0.115	0.076	0.037	0.075	—	—	—	—
4	Biliary tract	48	64	Mean	0.50	0.67	**0.81***	**1.26***	**0.79***	0.13	**0.28***	0.16	7.0	7.1	5.9	6.7
				±SEM	0.058	0.060	0.123	0.229	0.089	0.031	0.024	0.017	2.9	2.1	1.9	1.7

*P < 0.01.

TABLE V. *Results of liver function tests (II) (continued from table IV). Conventions as in table III*

Group	Type of surgery	Time of sample (hr):	Alkaline phosphatase (u./100 ml) 0	1	6	24	96	LDH (u./ml) 0	1	6	24	96	S.g.o.t. (u./ml) 0	1	6	24	96
1	Minimal	Mean	9.4	8.7	9.0	8.9	9.3	360	333	363	423	358	24.5	28.6	28.5	23.6	24.3
		±SEM	0.93	0.90	0.99	0.75	0.97	34.0	16.2	29.3	32.9	36.8	2.59	2.88	3.65	2.48	2.63
2	Body surface	Mean	10.3	9.8	9.9	9.3	8.6	345	323	335	294	291	29.0	31.4	32.7	25.3	22.8
		±SEM	1.48	1.50	1.72	1.28	1.15	39.0	24.9	29.6	39.5	37.1	2.57	3.53	2.85	2.25	2.06
3	Gastric	Mean	7.6	7.8	7.7	7.2	7.4	287	**432***	**420***	**350**	350	23.4	**56.0***	**59.4***	**36.9***	36.7
		±SEM	0.50	0.49	0.50	0.49	0.58	22.3	40.0	42.4	28.7	37.8	2.69	5.67	5.32	2.90	6.59
4	Biliary tract	Mean	8.3	8.7	8.3	8.0	10.0	299	**394***	**387**	**367**	357	27.6	**54.0**	**54.9***	**42.7**	38.2
		±SEM	1.19	1.12	1.27	0.89	2.13	22.4	32.4	29.8	31.1	40.4	3.40	6.62	5.93	3.82	7.65

Group	Type of surgery	Time of sample (hr):	S.g.p.t. (u./ml) 0	24	96	Pseudocholinesterase (u./ml) 0	24	96	γGT 0	24	96	B.s.p. retention 0	24	96
1	Minimal	Mean	36.6	37.7	33.3	105	105	101	6.2	8.1	8.2	1.4	1.6	1.6
		±SEM	13.69	11.37	11.10	9.03	7.04	7.36	0.81	1.35	1.40	0.27	0.34	0.37
2	Body surface	Mean	44.8	42.9	45.1	118	116	107	12.1	13.0	11.9	2.6	**6.3**	5.9
		±SEM	11.67	10.78	13.69	9.40	10.08	8.53	2.67	3.38	2.64	0.58	1.98	1.75
3	Gastric	Mean	24.9	**58.2***	39.7	80	**70***	**55***	8.3	6.4	7.9	4.2	**17.7***	**18.3**
		±SEM	4.60	6.51	3.91	7.71	6.50	7.82	1.85	1.65	1.27	1.61	3.28	4.45
4	Biliary tract	Mean	29.1	**71.0***	63.6	120	112	**92***	13.2	15.8	22.8	2.4	**18.6***	**15.3***
		±SEM	7.27	12.08	18.49	9.62	8.37	6.31	3.09	3.04	5.93	0.81	2.59	2.87

*P < 0.01.

Patients recovering from surgery of the biliary tract had a "light diet" from about 48 hr and patients after gastric surgery the same diet from 96 hr. The caloric intake until oral feeding was started was about 500 cal/day, increasing thereafter to 1500 cal/day.

Blood samples for liver function tests were taken on the day before surgery and at 1, 6, 24 and 96 hr after the start of anaesthesia. In addition to the tests included in (I), bromsulphthalein (b.s.p.) retention was measured by the injection of 5 mg/kg of the dye into the antecubital veins of one forearm and sampling from the opposite forearm after 45 min (Mateer et al., 1943). Gamma-glutamyl transpeptidase (γ-GT) (Szasz, 1969), the direct or soluble bilirubin (Powell, 1944) and plasma haemoglobin concentration (Cripps, 1968) were measured. These latter tests, together with the s.g.p.t. and pseudocholinesterase estimations, were performed only on the day before surgery and at 24 and 96 hr after surgery. Comparison of data was by the paired Student t test, comparing the control data with the 1,- 6-, 24- or 96-hr values.

RESULTS

There was no significant difference between the minimal surgery group and the others in respect of liver function tests before operation.

(I) *Studies after intermittent intravenous anaesthesia*

Table III shows that in the group of patients having minimal surgery there was no significant adverse change in any of the tests over the first 4 day following surgery. This applied both to those patients who were anaesthetized with thiopentone and to those who received Althesin. However, there was a decrease in the serum bilirubin concentration to less than the control value on the 4th day after operation in those who received thiopentone and Althesin.

Patients having body surface operations had a progressive increase in serum bilirubin over the first 24 hr, decreasing to the control value or less by the 4th day after surgery. The increase following both agents was not significant at 6 hr, but was highly significant at 24 hr. In both anaesthetic groups the 96-hr values were less than those of the controls, but the difference was not significant.

Other tests showed a less consistent pattern, but there was a significant increase in s.g.o.t. between 0 and 6 hr following body surface surgery under thiopentone–nitrous oxide anaesthesia. The pseudocholinesterase concentration decreased progressively over the 96 hr after body surface surgery in both anaesthetic groups. After thiopentone only the decrease at 96 hr was significant. After Althesin there was a significant decrease at both 24 and 96 hr.

(II) *Studies after thiopentone–methoxyflurane relaxant anaesthesia*

The results of the liver function tests are shown in table IV. In group 1 patients, undergoing minimal surgery, there were no significant changes in any of

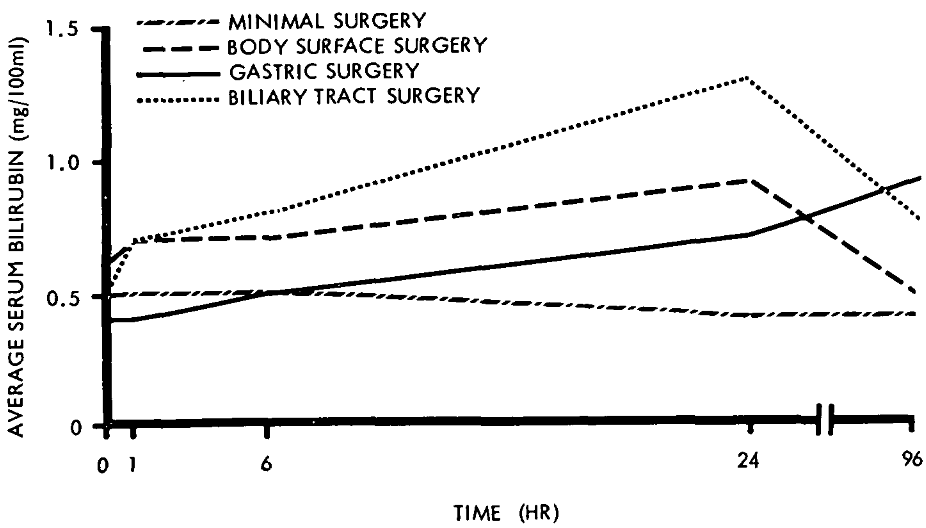

FIG. 1. Average serum bilirubin concentration before and after surgery in four groups of 10 patients. All were anaesthetized with thiopentone, methoxyflurane, tubocurarine and nitrous oxide in oxygen (II).

the tests. After moderate surgery the serum bilirubin concentration increased significantly over the first 24 hr (fig. 1). Thereafter it decreased to less than the control value and, although the 96-hr value was not significantly less than the control, in groups 1 and 2, the decrease was comparable with those observed in part (I). Attempts to fractionate the increase into soluble bilirubin (conjugated in the liver) and insoluble bilirubin (non-conjugated) showed only a small, non-significant increase in the soluble fraction.

The increase in bilirubin after gastric surgery was similar in magnitude to the other groups at 24 hr but increased further during the next 3 days. Again this was attributable mainly to an increase in the non-conjugated fraction.

After biliary tract surgery there was a steady and large increase in bilirubin concentration from the end of surgery. This was significant at 6 hr, reaching a mean value of 1.26 mg/100 ml at 24 hr, remaining increased at the 96-hr sample. In this group the soluble fraction had increased significantly at 24 hr after surgery but had decreased towards normal by 96 hr.

There was no significant change in the plasma haemoglobin concentration in any of the groups studied.

There were no significant changes in the other liver function tests in the patients undergoing minimal surgery (table V). After moderate surgery there was a small but significant increase in b.s.p. retention at 24 hr.

In the patients undergoing intra-abdominal surgery there were various enzyme changes which were often at the maximum value about the time at which surgery ended, decreasing to normal by 96 hr. After gastric operations, LDH and s.g.o.t. were increased markedly at 1, 6 and 24 hr (fig. 2). S.g.p.t. was not measured at 1 and 6 hr, but was increased at 24 hr. The pseudocholinesterase concentration decreased progressively from the control value, at 1 and 4 day and the b.s.p. retention was increased on both occasions on which it was measured.

The changes after surgery of the biliary tract were similar to those after gastric surgery, with increased LDH, s.g.o.t. and s.g.p.t. values at the same times after operation. The decrease in pseudocholinesterase was similar in extent but only statistically significant on the 4th day, and the b.s.p. rentention was increased to a similar extent at 1 and 4 days.

The alkaline phosphatase and γ-GT were not changed significantly in any of the groups of patients at any time.

DISCUSSION

It is clear from the studies of liver function after minimal surgery that certain anaesthetic techniques, maintained for 1 hr, have no deleterious effect on liver function. Thiopentone up to a mean total dose of 16 mg/kg and Althesin up to a mean total dose of 0.19 ml/kg (11 ml) together with nitrous oxide, cause no increase in the serum bilirubin concentration, liberation of intracellular enzymes or decrease in pseudocholinesterase concentration. The changes recorded by Clarke and his colleagues (1974) are therefore unlikely to be a result of the large total

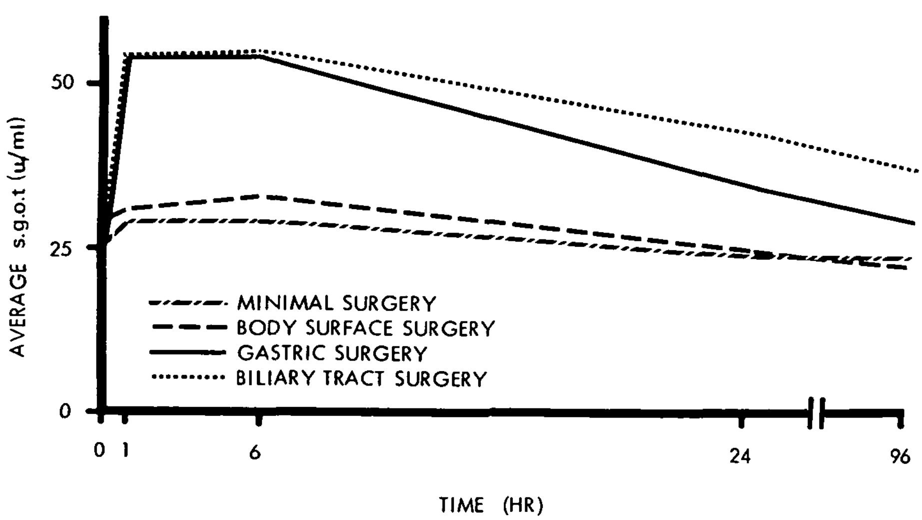

FIG. 2. Average s.g.o.t. concentration in four groups of patients before and after surgery. All were anaesthetized with thiopentone, methoxyflurane, tubocurarine and nitrous oxide in oxygen.

dose of intravenous anaesthetic but rather of a factor connected with the surgical procedure. The conclusions from the second part of the study, in which patients received thiopentone, pancuronium, nitrous oxide and methoxyflurane support the same conclusions. This information would merely add to the large number of negative findings (Kirwan et al., 1965; Kirwan, Dundee and Neill, 1965) if it were not for the positive findings in patients anaesthetized by the same technique and undergoing moderate or major surgery. The results in parts (I) and (II) from patients undergoing operations of moderate severity appear to be similar and will be discussed together.

The serum bilirubin concentration increased to a small but significant extent in groups of patients undergoing operations such as herniorrhaphy, vagotomy and gastroenterostomy, or cholecystectomy. However, the value was greatest in the patients having biliary tract surgery. On the whole the increase was mainly in the non-conjugated fraction, suggesting a hepatic or pre-hepatic cause rather than biliary tract obstruction (Sherlock, 1968). Bilirubinaemia may result from an increased rate of breakdown of erythrocytes but it has not been possible to detect any increase in circulating free haemoglobin by the methods used. However, any increase in haemoglobin could be cleared rapidly by the liver and converted to bilirubin. It would appear that a direct effect of the anaesthetic agent, causing haemolysis, can be excluded on the basis of both the present two groups of patients undergoing minimal surgery, and the earlier studies of Dundee (1955). Surgical trauma causing very transient haemolysis cannot be excluded as a factor, though in view of the changes in other liver function tests it is unlikely to be the sole factor.

The alkaline phosphatase concentration, which mainly reflects biliary tract obstruction (Sherlock, 1968), was unaffected in any of the groups studied. Similarly, the gamma glutamyl transpeptidase, a test which detects chronic liver disorders, acute drug sensitivity, and acute alcoholic damage, was unchanged. It has been shown that it is not as much affected by hepatitis as are the transaminases (Zein and Discombe, 1970; Keane et al., 1973). These two tests may have a general diagnostic value because marked alterations in a particular patient may be assumed not to be a result of reactions after operation or to hepatitis, but of a specific episode of drug intoxication.

The intracellular enzymes LDH, s.g.o.t. and s.g.p.t. were increased during and after both types of abdominal surgery. In general they returned progressively towards normal from the early peak. Since they are liberated when muscle is damaged, it is likely that direct trauma played an important part in the increase.

The pseudocholinesterase concentration, on the other hand, decreased mainly in the later postoperative period. It was affected in some of the groups having body surface surgery and in both groups having abdominal surgery. It is a test of hepatic synthesizing capacity and may be presumed to indicate a temporary derangement of this. It is the only test which does not appear to have returned towards control values and it is unfortunate that no later estimations were made.

B.s.p. retention showed a gradation of increase after operation from the small but significant change in group 2 to the high value (range 5–33%) in group 4. The figures suggest that the maximum effect occurs within the first 4 days, whereas pseudocholinesterase may not have reached its lowest value even in 96 hr. These changes are in agreement with earlier studies (Tagnon, Robbins and Nichols, 1948; Fairlie et al., 1951) which showed that surgery in the lower abdomen or body surface produce significant b.s.p. retention in the majority of patients. Surgery in the neighbourhood of the liver produced more definite hepatic dysfunction.

Before concluding that the surgical procedure is responsible for the various alterations in liver function described above, other possibilities should be considered. The type of patient in the groups being compared shows no pattern of age, weight or preoperative liver function tests which would account for the differing behaviour observed after operation. With such large batteries of tests some patients did, for instance, have an abnormally increased enzyme value in one test before operation. These patients were not excluded and subsequent tests usually suggested that this may have been purely a chance finding, not related to liver function in general. The preparation of all patients before surgery was similar and the duration of anaesthesia in the various groups was comparable also. All patients had i.v. fluid replacement during the operation, but none required or received blood transfusion.

After operation there were inevitable minor variations for, while all patients had adequate fluid replacement i.v. and later by mouth, the nutritional content varied. The patients having minimal and moderate surgery were usually able to have a light diet in the evening of operation and were eating almost normally on the following day. Patients having biliary tract surgery had a slower return to full feeding and patients recovering from gastric surgery were slower still. Measurements of total serum bilirubin have been made during fasting in both normal subjects and those with hepatic disease (Barrett, 1971). In both groups of patients there was an increase over a 2-day period to approximately twice the control value. In fact a small increase is apparent even after normal over-night starvation (Stengle and Schade, 1957). This increase amounted in one case to 278% (0.68–1.87 mg/100 ml) over 48 hr and was common to total and conjugated bilirubin. There is less information on changes in other liver function tests during a period of fasting, but measurements have been made in obese patients undergoing therapeutic starvation (Rosenthal et al., 1967). The periods of starvation were 14–30 day and there were no consistent changes in bilirubin, s.g.o.t., s.g.p.t. or LDH. However, there was a marked increase in b.s.p. retention in all patients. The relevance of these findings on starvation to those in the present study is uncertain because of the variable degree of caloric intake. However it might be said that while no patients were fasting completely after operation, the effects of starvation must be included with the effects of surgery in the study.

The alterations in liver function occurring after operation may be related to changes in splanchnic blood flow and oxygen consumption. These have been measured by Epstein and his colleagues (1966), Cooperman, Warden and Price (1968) and by Libonati and co-workers (1973). Libonati's group have shown that all anaesthetic techniques so far studied cause a greater reduction in splanchnic blood flow than in oxygen consumption. The least hypoxic effect appeared to be associated with halothane, with which the ratio of splanchnic blood flow to oxygen consumption was 0.85, and the greatest effect was associated with methoxyflurane (ratio 0.55), both agents being studied during both spontaneous and controlled ventilation. However, a technique using nitrous oxide, tubocurarine and moderate hyperventilation produced a ratio 0.59 which is very similar to methoxyflurane. They found no change in splanchnic lactate/pyruvate ratios which would support the suggestion of splanchnic hypoxia. In spite of these findings, although the type of anaesthesia used by the above workers was very similar to the type used in the present study, it is difficult to see that they have any bearing on the changes described following surgery, if only because they vary with the type of surgery being performed.

Other factors which may cause liver damage, such as hypoxia, hypotension and gastro-intestinal sepsis, have been excluded from this series and the cause of the derangements in liver function must be related to the surgical operation. Haemolysis may be a factor in the increase in serum bilirubin concentration, but the diminished b.s.p. clearance and the decrease in pseudocholinesterase suggest a generalized disturbance of liver function. Since these occur to some extent even after operations remote from the liver, it seems reasonable to conclude that it is the traumatic stress of surgery which is reponsible. This is known to cause increased sympathetic nervous activity, an increase in circulating cortisol, free fatty acids, blood sugar and antidiuretic hormone, and increased protein catabolism (Moore, 1959; Plumpton, Besser and Cole, 1969; Clarke, Johnston and Sheridan, 1970). Therefore, changes in liver function are to be expected. It is unfortunate that the knowledge that chloroform and other halogenated hydrocarbons are toxic to the liver has caused so much emphasis to be placed on the effects of anaesthesia as compared with those of surgical trauma.

It is difficult to evaluate the significance of the changes in liver function tests and it may be that these alterations are no more dangerous than the fluctuations in blood sugar concentration with and without food intake. However, it would seem to be important to know of consistent alterations in the various serum constituents, especially those related to surgery. A knowledge of the normal changes is particularly important in evaluating excessive alterations which may be related to anaesthesia.

REFERENCES

Barrett, P. V. D. (1971). Hyperbilirubin of fasting. *J.A.M.A.*, **217**, 1349.

Clarke, R. S. J., Dundee, J. W., Doggart, J. R., and Lavery, T. (1974). The effects of single and intermittent administrations of Althesin and other intravenous anesthetic agents on liver function. *Anesth. Analg.* (*Cleve.*), **53**, 461.

—— Fee, J. P. H. (1974). Changes in liver function after surgery. Abstract of paper given at the IV European Congress of Anaesthesiology. *Excerpta Medica*, **330**, 139.

—— Johnston, H., and Sheridan, B. (1970). The influence of anaesthesia and surgery on plasma cortisol, insulin and free fatty acids. *Br. J. Anaesth.*, **42**, 295.

—— Kirwan, M. J., Dundee, J. W., Neill, D. W., and Mitchell, E. S. (1965). Clinical studies of induction agents. XIII: Liver function studies after propanidid and thiopentone anaesthesia. *Br. J. Anaesth.*, **37**, 415.

Cooperman, L. H., Warden, J. C., and Price, H. L. (1968). Splanchnic circulation during nitrous oxide anesthesia and hypocarbia in normal man. *Anesthesiology*, **29**, 254.

Cripps, C. M. (1968). Rapid method for the estimation of plasma haemoglobin levels. *J. Clin. Pathol.*, **21**, 110.

Dundee, J. W. (1955). Thiopentone as a factor in the production of liver dysfunction. *Br. J. Anaesth.*, **27**, 14.
Dykes, M. H. M. (1970). Anesthesia and the liver. *Int. Anesthesiol. Clin.*, **8**, 175. Boston: Little, Brown & Company.
Editorial (1972). Postgraduate Educational Number: Anaesthesia and the liver. *Br. J. Anaesth.*, **44**, 909.
Epstein, R. M., Deutsch, S., Cooperman, L. H., Clement, A. J., and Price, H. L. (1966). Splanchnic circulation during halothane anesthesia and hypercapnia in normal man. *Anesthesiology*, **27**, 654.
Fairlie, C. W., Barss, T. P., French, A. B., Jones, C. M., and Beecher, H. K. (1951). Metabolic effects of anesthesia in man. IV: A comparison of the effects of certain anesthetic agents on the normal liver. *N. Engl. J. Med.*, **244**, 615.
Hochella, N. J., and Weinhouse, S. (1965). Automated assay of lactate dehydrogenase in urine. *Anal. Biochem.*, **13**, 322.
Inman, W. H. W., and Mushin, W. W. (1974). Jaundice after repeated exposure to halothane: an analysis of reports to the Committee on Safety of Medicines. *Br. Med. J.*, **1**, 5.
Jendrassik, L., and Grof, P. (1938). Vereinfachte photometrische Methoden zur Bestimmung des Blutbilirubins. *Biochem. Z.*, **297**, 81.
Keane, P. M., Garcia, L., Gupta, R. N., and Walker, W. H. C. (1973). Serum gamma glutamyl transpeptidase in liver disorders. *Clin. Biochem.*, **6**, 41.
King, J. (1960). A study of human transaminases. *J. Med. Lab. Technol.*, **17**, 1.
Kirwan, M. J., Dundee, J. W., Clarke, R. S. J., Mitchell, E. S., and Neill, D. W. (1965). Halothane hepatotoxicity: an investigation of the effects of short exposure. *Anaesthesia*, **20**, 59.
—— —— Neill, D. W. (1965). A comparison of the effects of chloroform and halothane on liver function. *Anaesthesia*, **20**, 66.
Libonati, M., Malsch, E., Price, H. L., Cooperman, L. H., Baum, S., and Harp, J. R. (1973). Splanchnic circulation in man during methoxyflurane anesthesia. *Anesthesiology*, **38**, 466.
Lomanto, C., Huvos, A. G., Fiocco, G. P., and Howland, W. S. (1972). Sepsis and postanesthetic hepatitis. *Anesth. Analg. (Cleve.)*, **51**, 264.
Mateer, J. G., Boltz, J. I., Marion, D. F., and MacMillan, J. M. (1943). Liver function tests. *J.A.M.A.*, **121**, 723.
Michel, H. O. (1949). An electrometric method for the determination of red blood cells and plasma cholinesterase activity. *J. Lab. Clin. Med.*, **34**, 1564.
Moore, F. D. (1959). *Metabolic Care of the Surgical Patient.* Philadelphia: Saunders.
Morganstern, S., Kessler, G., Auerbach, J., Flor, R. V., and Klein, B. (1965). An automated p-nitrophenylphosphate serum alkaline phosphatase procedure for the autoanalyser. *Clin. Chem.*, **11**, 876.
—— Oklander, M., Auerbach, J., Kaufman, J., and Klein, B. (1966). Automated determination of serum glutamic oxaloacetic transaminase. *Clin. Chem.*, **12**, 95.
Mushin, W. S., Rosen, M., and Jones, E. V. (1971). Posthalothane jaundice in relation to previous administration of halothane. *Br. Med. J.*, **3**, 18.
National Halothane Study (1966). *J.A.M.A.*, **197**, 775.
Plumpton, F. S., Besser, G. M., and Cole, P. V. (1969). Corticosteroid treatment and surgery. I: An investigation of the indications for steroid cover. *Anaesthesia*, **24**, 3.
Powell, W. N. (1944). A method for the quantitative determination of serum bilirubin with the photoelectric colorimeter. *Am. J. Clin. Pathol.*, **14**, 55.
Reed, W. P., and Williams, R. (1972). Halothane hepatitis as seen by the physician. *Br. J. Anaesth.*, **44**, 935.
Rosental, P., Biava, C., Spencer, H., and Zimmerman, H. J. (1967). Liver morphology and function tests in obesity and during total starvation. *Am. J. Dig. Dis.*, **12**, 198.
Sharpstone, P., Medley, D. R. K., and Williams, R. (1971). Halothane hepatitis—a preventable disease? *Br. Med. J.*, **1**, 448.
Sherlock, S. (1968). *Diseases of the Liver and Biliary System*, 4th edn. Oxford: Blackwell.
—— (1971). Progress report. Halothane hepatitis. *Gut*, **12**, 324.
Simpson, B. R., Strunin, L., and Walton, B. (1973). Halothane hepatitis—fact or fallacy? *Proc. R. Soc. Med.*, **66**, 56.
Stengle, J. M., and Schade, A. L. (1957). Diurnal–nocturnal variations of certain blood constituents in normal human subjects: plasma iron, siderophilin, bilirubin, copper, total serum protein and albumin, haemoglobin and haematocrit. *Br. J. Haematol.*, **3**, 117.
Szasz, G. (1969). A kinetic photometric method for serum γ-glutamyl transpeptidase. *Clin. Chem.*, **15**, 124.
Tagnon, H. J., Robbins, G. F., and Nichols, M. P. (1948). The effect of surgical operations on the bromsulfthalein retention test. *N. Engl. J. Med.*, **238**, 556.
Vaizey, J. M. (1938). Toxic jaundice following administration of pentothal. *Br. J. Anaesth.*, **15**, 55.
Walton, B., Dumonde, D. C., Williams, C., Jones, D. W., Strunin, J. M., Layton, J., Strunin, L., and Simpson, B. R. (1972). Failure to demonstrate increased lymphocyte transformation in patients with postoperative jaundice and physicians with alleged halothane sensitivity. *Br. J. Anaesth.*, **44**, 904.
Wright, R., Eade, O. E., Chisholm, M., Hawksley, M., Lloyd, B., Moles, T. M., Edwards, J. C., and Gardner, M. J. (1975). Controlled prospective study of the effect on liver function of multiple exposures to halothane. *Lancet*, **1**, 817.
Zein, M., and Discombe, G. (1970). Serum gamma-glutamyl transpeptidase activity as a diagnostic aid. *Lancet*, **2**, 748.

CHANGEMENTS DANS LES FONCTIONS HEPATIQUES APRES DIFFERENTS TYPES DE CHIRURGIE

RESUME

Les examens des fonctions hépatiques effectués après des interventions chirurgicales mineures sous anesthésie qui a duré une heure, n'ont fait ressortir aucune anomalie. Les examens effectués aprés des opérations sur la surface du corps, avec les mêmes techniques d'anesthésie ont montré des dérangements transitoires. Après les opérations intra-abdominales, les dérèglements du foie ont été plus marqués bien que l'on n'ait étudié aucun malade montrant des signes de dérèglement préopératoire du foie ou souffrant de complications chirurgicales postopératoires et il n'a été fait de transfusion sanguine à aucun d'eux. La mesure des concentrations de bilirubine dans le sérum montre les anomalies les plus fréquentes, mais la concentration pseudocholinestérase a progressivement baissé après la chirurgie intra-abdominale et la rétention de bromsulphthaléine a augmenté d'une manière significative. Les concentrations d'enzymes intra-cellulaires dans le sérum (LDH: déshydrogénation du lactate—SGOT: transaminase glutamooxalique sérique—SGPT: transaminase glutamopyruvique sérique) ont augmenté en l'espace d'une heure, après le commencement de l'intervention chirurgicale. Ces changements n'étaient probablement pas reliés à la fonction du foie.

UNTERSCHIEDLICHE ERGEBNISSE BEIM LEBERFUNKTIONSTESTS NACH VERSCHIEDENEN CHIRURGISCHEN VERFAHREN

ZUSAMMENFASSUNG

Bei Patienten, die während einstündiger Narkose, minimale chirurgische Verfahren erlitten hatten, wurden Leberfunktionsteste durchgeführt, deren Ergebnisse sich als normal erwiesen. Nach oberflächlichen Operationen beim indetischen Narkoseverfahren, ergaben sich vorrübergehende Störungen. Nach intra-abdominalen Operationen zeigten sich schwere Dysfunktionen, obwohl es sich hier weder um ein Patientengut mit prae-chirurgischen Leberdysfunktionen, noch um eines mit postoperativen Komplikationen handelte. Keine der Patienten hatten Bluttransfusionen erhalten. Obwohl im Serumkonzentrat sich die häufigsten pathologischen Befunde zeigten, war der allmähliche Abfall des Pseudocholinesterasekonzentrats nach intra-abdominaler Chirurgie bemerkbar, sowie auch der Anstieg der Bromsulphathaleinwerte. Die folgenden Intrazellularenzyme erhöhten sich im Serumkonzentrat, während der ersten postoperativen Stunde: Dehydrogenase Laktat, Serum Glutamin oxalazetische Transaminase, Serum Glutamin Pyruvat Transaminase. Es ist jedoch annehmbar, dass zwischen diesen Veränderungen und der eigentlichen Leberfunktion kein Zusammengang besteht.

CAMBIOS EN LA FUNCION DEL HIGADO DESPUES DE DIFERENTES TIPOS DE CIRUGIA

SUMARIO

Las pruebas de funcionamiento del hígado que se llevaron a cabo después de operaciones quirúrgicas menores bajo anestesia que duró una hora no mostraron anormalidades. Pruebas realizadas después de operaciones superficiales del cuerpo con las mismas técnicas de anestesia mostraron desarreglos temporales. Después de operaciones intraabdominales, el mal funcionamiento hepático fué más marcardo, aunque no hemos estudiado pacientes con pruebas de mal funcionamiento hepático pre-operativo o complicaciones quirúrgicas post-operativas y ninguno de ellos recibió transfusiones de sangre. Mediciones de concentraciones del suero de bilirubina mostraron las anormalidades más frecuentes, pero la concentración pseudocolinesterasa decreció progresivamente después de la cirugía intraabdominal y la retención de bromosulftaleina aumentó notablemente. Las concentraciones de suero de encimas intracelulares (LDH, s.g.o.t. y s.g.p.t.)—lactato dehidrogenasa, transaminasa oxalacética de suero glutámico, transaminasa pirurata de suero glutóámico—sufrió un incremento en el curso de una hora desde el comienzo de la operación, cambios que, probablemente, no estaban relacionados con la función del hígado.