there was no clinical or biochemical evidence of pancreatitis.

The pharmacology and toxicology of scorpion venoms have shown that the venom has a powerful effect not only on the somatic but also on the autonomic nervous system. Samaan and Ibrahim (1959), studying the action of purified samples of "scorpion toxin" on the salivary glands of dogs, concluded that small doses of toxin had no direct action on the salivary gland cell. On the other hand, the toxin stimulated the salivary centres of the central nervous system and enhanced the response of the peripheral neurosecretory salivary mechanism to chorda tympani impulses. The venom of scorpions contains a macromolecular protein fraction which is responsible for its neurotoxic properties. There is, however, little proof that acute pancreatitis is caused primarily by a purely neurogenic mechanism.

Apart from the protein fraction, the venom of scorpions contains numerous free amino-acids (Fisher and Bunn, 1957) and also an appreciable quantity of serotonin (Adam and Weiss, 1956). Diniz and Gonçalves (1960), using paper and starch zone electrophoresis, fractionated the venom of *T. serrulatus* and of *T. bahiensis* and showed that they were mixtures of proteins with toxic, smooth-muscle-stimulating, and hyaluronidase components and that they increased capillary permeability. It is possible that the venom of *T. trinitatis* acts on the pancreas through an enzymatic property. McHardy *et al.* (1963) thought that the intrapancreatic conversion of trypsinogen to trypsin was the most important if not the sole cause of pancreatitis. Trypsin increases the permeability of pancreatic blood vessels and causes oedema (Dragstedt, 1943). More work recently has shown that free trypsin in the pancreas releases kallikrin, another proteolytic enzyme found in the pancreas and the parotid glands; this acts on known precursors to produce a powerful hypotensive vasodilating polypeptide identical in physiological action to bradykinin.

Despite the high incidence of acute pancreatitis in this series (80%) the true incidence of *T. trinitatis* pancreatitis may be even higher when it is considered that normal values for amylase do not entirely eliminate the possibility of acute pan-

creatitis. Moreover, the scorpion does not always inject venom when it stings, since it can control its ejaculation so that this is total, partial, or non-existent (Junqua and Vachon, 1968). It is apparent that no immunity to the scorpion toxin develops following a sting, since pancreatitis occurred in seven patients who had been stung previously.

The scorpion sting is by far the most frequent cause of pancreatitis in Trinidad. Nevertheless, the venom of *T. trinitatis* has not been so widely recognized. The frequency of acute pancreatitis, however, is evident from this short study. Apart from being of clinical and public health interest, the venom of *T. trinitatis* may throw some light on the pathogenesis of acute pancreatitis.

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Preliminary Communications

Multiple Halothane Exposure and Hepatic Bromsulphthalein Clearance

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Summary: Multiple exposures to halothane have been shown to have delayed effects on bromsulphthalein (B.S.P.) clearance. Rats were exposed to repeated halothane anaesthetics, and their livers were subsequently isolated and perfused. B.S.P. retention in the perfusate of these isolated livers was greatly increased one to three weeks after the last halothane exposure. In similarly pre-treated animals at the same time period the B.S.P.-glutathione conjugating enzyme activity in homogenates of the livers was found to be depressed. These findings did not occur after multiple diethyl ether exposures or following a single exposure to halothane.

INTRODUCTION

The question of multiple exposures has become an extremely important one relative to the mechanism by which liver damage may be caused following halothane anaesthesia (Little, 1968). Attention has again been drawn to this problem by several recent reports (Trey *et al.*, 1968; Klatskin and Kimberg, 1969;

Rodriguez *et al.*, 1969), in addition to many previous individual surveys and case reports (Tygstrup, 1963; Sherlock, 1964; Morgenstern *et al.*, 1965; Griner, 1966; Subcommittee on National Halothane Study, 1966).

The controversy surrounding the possible role of halothane in the causation of postoperative liver dysfunction has centred on, among other factors, the inability of clinical and statistical surveys to eliminate the numerous potential causes of liver dysfunction during this period (viral hepatitis, blood transfusion, intraoperative hypotension and hypoxia, septicaemia, and the concurrent administration of potentially hepatotoxic drugs).

The present investigation was designed in an attempt to eliminate these other potential causes of liver dysfunction by the study of isolated perfused livers and liver homogenates from animals previously exposed to halothane on several occasions. Abnormalities of bromsulphthalein (B.S.P.) handling by the livers of such animals were observed, and the study was modified to confirm the findings and to attempt to isolate the abnormality present in the liver.

MATERIALS AND METHODS

ANIMALS

Male albino rats (weight 375-400 g.) of Wistar and Sprague-Dawley strains, housed in conditions of controlled temperature

and humidity and fed on a standard laboratory diet, were used as liver donors for both the isolated perfusion and liver homogenate experiments. The animals were allowed free access to water and food up to the beginning of the experiments. The animals were divided into three groups:

Group 1.—Control animals.

Group 2.—Animals exposed to multiple (3 or 5: see Results) 60-minute periods of 1% halothane vapour v/v (Vapor vaporizer, Dräger) in oxygen, on alternate days.

Group 3.—Animals exposed to multiple (3 or 5: see Results) 60-minute periods of 4% v/v diethyl ether vapour (E.M.O. vaporizer) in oxygen, on alternate days.

To achieve these periods of light surgical anaesthesia (Duncan and Raventós, 1959) in groups 2 and 3, batches of six animals were anaesthetized in an exposure chamber, anaesthetic mixtures being produced at a rate of 8 l./min., which is several times greater than the total average minute volumes of the rats. During the periods of anaesthesia there was no evidence of hypoxia or hypercarbia, as estimated by blood gas determinations on samples obtained by cardiac puncture from random animals. The animals regained full consciousness within minutes of the termination of the anaesthetic.

These animals showed no obvious ill effects after the anaesthetic exposures, continued to gain weight, and behaved normally until their use as liver donors at varying periods after the exposures.

ISOLATED LIVER PERFUSIONS

Isolated liver perfusions were performed according to the method of Miller *et al.* (1951) as modified by Fisher and Kerly (1964). The method, discussed in detail by the latter authors, involves the cannulation of the bile duct and portal vein followed by the removal of the liver and its subsequent perfusion in a sealed cabinet. The interior of the cabinet is humidified, and thermostatically controlled at a temperature of 38°C. The liver, mounted on a glass platform with the diaphragmatic surface down, is perfused via the portal vein. The outflow via the hepatic vein runs into a reservoir below this platform, from where it is recirculated by a finger pump to the glass "thin film" oxygenator above the liver. A 95% oxygen and 5% carbon dioxide mixture is passed into the oxygenator at a flow rate of 750 ml./min.

In the present perfusions the surgical procedure on the donor rats (in all groups) was performed under light diethyl ether and oxygen anaesthesia. The livers were not exposed to halothane or diethyl ether, however, during the perfusions in this series. Perfusate volume used was 100 ml., consisting of pooled Wistar and Sprague-Dawley albino rat blood obtained by cardiac puncture from multiple donors, diluted to a packed cell volume of 25% with a balanced salt-bicarbonate solution.* Perfusate pH (7.35-7.42). P_{O_2} (150-175 mm. Hg.), and P_{CO_2} (35-40 mm. Hg) were monitored at 15-minute intervals by the Astrup technique and kept within the given ranges. The portal vein pressure was 18 cm. perfusate, and the measured hepatic vein flow was constant (1.25-1.5 ml./g. liver wet weight/min.) during the period of B.S.P. estimation.

Apart from limited sampling of the perfusate for blood gas and acid-base estimations, the perfusate volume in these perfusions was kept constant. A different series of perfusions was undertaken to establish criteria of adequate perfusion and assess other metabolic effects of the anaesthetic agents (various criteria reflecting changes in carbohydrate and protein metabolism).

B.S.P. (supplied by Hynson, Westcott and Dunning, Inc., Baltimore) was added, at a dosage of 1.25 mg./100 g. donor

rat weight, to the perfusate reservoir 30 minutes after the beginning of the perfusion. At this time steady blood (1.25-1.5 ml./g. liver wet weight/min.) and bile flow (80-90 microlitres/g. liver/hour) were established. Perfusate samples were then withdrawn from the reservoir at 1, 3, 5, and 30 minutes after the addition of B.S.P.

B.S.P. concentration in the perfusate was measured spectrophotometrically, the samples having been subjected to a technique (Henry *et al.*, 1959) of acetone precipitation of proteins. This technique allows accurate B.S.P. estimations in the presence of haemolysis. Free plasma haemoglobin levels ranging from 50 to 75 mg./100 ml. were present in the perfusate during the period of B.S.P. estimations.

LIVER HOMOGENATES

In an attempt to establish which of the three mechanisms involved in the handling of B.S.P.—that is, hepatic uptake, conjugation, or excretion—was responsible for the findings from the isolated perfusion experiments, liver homogenates from livers of animals previously exposed to halothane and diethyl ether were used to estimate levels of hepatic B.S.P.—glutathione conjugating enzyme activity. The enzyme activity in the soluble supernatant fraction of liver was assayed by the method of Combes and Stakelum (1962), which involves incubating (for five minutes) homogenized aliquots of liver with B.S.P. and glutathione, and subsequently identifying the proportions of free B.S.P. and B.S.P.—glutathione by paper chromatography of the supernatant fluids.

Quantification of the B.S.P. on the chromatograms is performed by elution of the relevant bands of paper, the concentration of B.S.P. in the eluate being determined spectrophotometrically. In the present study aliquots of liver of 400-600 mg. were used (from freshly decapitated animals), and 0.5 mg. of B.S.P. and 4 mg. of glutathione were the quantities of substrates added for incubation. The data are expressed as milligrams of B.S.P. conjugated per gramme of liver wet weight per five minutes.

Duplicate slices of liver were assayed for glutathione content by the method of Grunert and Phillips (1951).

RESULTS

ISOLATED LIVER PERFUSIONS

The figures for B.S.P. percentage retention in the perfusate given in Tables I-IV represent the retention 30 minutes after the introduction of the dye to the perfusate reservoir.

The control figures in each table refer to B.S.P. estimations in isolated liver perfusions where the donor animal had not been previously exposed to an anaesthetic agent. These control animals were housed in the same conditions as the other groups, and control perfusions were interspersed at varying times among the perfusions of livers previously exposed to anaesthetic agents.

The results of perfusions performed at varying times after three halothane exposures (as described in Group 2 above) are set out in Table I. The statistically highly significant increased B.S.P. retention at one and three weeks after the halothane exposures did not occur at the same periods after diethyl ether exposure (see Table II).

The three-week interval following anaesthetic exposure was chosen to assess the effect of a single halothane exposure, and Table III shows that B.S.P. retention in this group did not differ significantly from the controls.

The fact that B.S.P. percentage retention values returned to the control perfusion range six weeks after the halothane exposures (see Table I) prompted the investigation from which data are presented in Table IV. Animals were exposed to halo-

*Plasmalyte-B (Baxter) containing (mEq/l) Na 130, Cl 109, K 4, Mg 3, bicarbonate 28.

thane on three occasions, and after an interval of six weeks were re-exposed to halothane on three further occasions (using the technique described under Group 2). This procedure resulted again in an increased B.S.P. percentage retention at the one-week and three-week post-exposure periods, but the figures do not differ significantly from those in Table I.

TABLE I.—Mean Perfusate B.S.P. Percentage Retention ($\pm$ S.D.) after Three Halothane Exposures

	Control (No Previous Halothane)	Interval After Exposure (Weeks)			
		1	3	4	6
Percentage retention ..	5 ± 3	18 ± 3	29 ± 6	14 ± 3	3 ± 2
n ..	5	3	3	3	3
P† ..	—	<0.001	<0.001	<0.005	N.S.

*Number of perfusions performed. †Refers to relevant values v. control (Student's *t* test).

TABLE II.—Mean Perfusate B.S.P. Percentage Retention ($\pm$ S.D.) after Three Diethyl Ether Exposures

	Control	Interval After Exposure	
		1 Week	3 Weeks
Percentage retention ..	5 ± 3	6 ± 2	3 ± 2
n ..	5	3	3

TABLE III.—Mean Perfusate B.S.P. Retention ($\pm$ S.D.) after a Single Halothane Exposure

	Control	3 Weeks After Exposure
Percentage retention ..	5 ± 3	6 ± 3
n ..	5	3

TABLE IV.—Mean Perfusate B.S.P. Percentage Retention ($\pm$ S.D.) after Three Halothane Exposures, Followed by a six-week Interval, and Three Further Halothane Exposures

	Control	Interval After 2nd Three Exposures	
		1 Week	3 Weeks
Percentage retention ..	5 ± 3	18 ± 2	21 ± 5
n ..	5	3	3

B.S.P.-GLUTATHIONE CONJUGATING ENZYME ASSAY

Results of estimations B.S.P.-glutathione conjugating enzyme activity in homogenates of livers from groups of animals, previously exposed to halothane and to diethyl ether, are presented in Table V. The control data represent similar estimations on animals which had never been exposed to an anaesthetic agent.

TABLE V.—B.S.P.-Glutathione Conjugating Enzyme Activity (Mean $\pm$ S.D.) after Multiple (5 $\times$) Anaesthetic Exposures (mg. B.S.P. Conjugated/g. Liver Wet Weight/5 Minutes)

	Controls	Interval After Exposure	
		2 Weeks	3 Weeks
After halothane { Enzyme activity ..	2.10 ± 0.62	1.49 ± 0.28	1.68 ± 0.40
n ..	26	5	10
After diethyl ether { Enzyme activity ..	2.10 ± 0.62	1.93 ± 0.36	1.70 ± 0.35
n ..	26	7	6

n = Number of animals investigated.

Statistical analysis of these results shows significant differences between the means of controls and those at two weeks after multiple halothane exposures ($P < 0.05$) and between controls and the three-week sample ($P < 0.01$). The control levels of enzyme activity and those following multiple diethyl ether exposures show no statistical difference. The glutathione content of duplicate slices of liver, at the two-week and three-week post-halothane exposure periods, does not differ significantly from the control levels (Table VI).

TABLE VI.—Liver Glutathione Content (Mean $\pm$ S.D.) Following Multiple (5 $\times$) Halothane Exposures (mg. Glutathione/g. Liver Wet Weight)

	Controls	Interval After Exposure	
		2 Weeks	3 Weeks
Glutathione levels ..	3.46 ± 0.58	3.84 ± 0.45	3.34 ± 0.20
n ..	6	6	3
P (v. control) ..	—	N.S.	N.S.

DISCUSSION

The present investigation shows what appears to be a delayed hepatic effect of multiple halothane exposure. Several studies showing increased B.S.P. retention in the early postoperative period following single and multiple halothane anaesthetics have previously been reported in man (Brindle *et al.*, 1957; Virtue *et al.*, 1958; Burnap *et al.*, 1958; Carson *et al.*, 1959; Griffiths and Ozguc, 1964; Joseph, 1964; Keéri-Szántó, 1965), in dogs (Brindle *et al.*, 1957), in sheep (Hull and Reilly, 1968), and in calves (Middleton *et al.*, 1966). During the immediate postoperative period raised B.S.P. retention has also been shown to occur following other anaesthetics: chloroform (Griffiths and Ozguc, 1964), cyclopropane (Prince *et al.*, 1965), and methoxyflurane (Keéri-Szántó, 1965). In these reports, however, the observations have been confined to the immediate postoperative period (up to seven days), and have not extended over the number of weeks reported in this communication.

The precise mechanism of the increased B.S.P. retention during the liver perfusions following previous halothane exposure in this study is not clear. There is considerable evidence (Combes and Stakelum, 1962) to support the view that the removal of B.S.P. from plasma is dependent on the simultaneous operation of two processes: (a) uptake into a hepatic storage compartment, and (b) excretion into bile.

It is now generally agreed (Combes and Stakelum, 1962) that the major pathway of B.S.P. metabolism in man, rat, dog, and other species involves conjugation with the tripeptide glutathione, composed of glutamic acid, cysteine, and glycine. Nevertheless, despite the observation that most of the B.S.P. excreted into bile is conjugated, the finding of free B.S.P. in bile leaves it uncertain whether conjugation is important for, or merely incidental to, hepatic uptake and biliary excretion of B.S.P. Combes and Stakelum (1961) identified in liver an enzyme that catalyses conjugation of glutathione with B.S.P. A depression of this enzyme activity has been shown in the present investigation to occur after multiple halothane exposures. This depression parallels the increase in B.S.P. retention seen in the perfused livers in similar circumstances. Impairment of B.S.P. conjugation may also be a reflection of low hepatic glutathione levels. Such levels did not occur in livers of animals reported here, where glutathione levels after halothane anaesthesia were within the normal range.

The enzyme shown to be depressed following multiple halothane exposure is not specific for the conjugation of B.S.P. This enzyme also catalyzes the conjugation of glutathione with other compounds (Combes, 1964), such as bromobutane, benzyl chloride, and *p*-fluoronitrobenzene. It is thus possible that the enzyme may be concerned with the conjugation of trifluoroacetic acid, which has been reported as a metabolite occurring during the biotransformation of halothane (Stier and Alter, 1966; Rehder *et al.*, 1967). The inference is that as a result of previous exposure to halothane certain enzymes are depressed, permitting accumulation of hepatotoxic metabolites, perhaps chlorinated derivatives which have yet to be identified. The possibility of enzyme changes of this nature resulting in hepatic injury following halothane has been suggested by Zimmerman (1968). The present findings, showing biochemical derangement following previous halothane exposure, are opposed to the criteria (Sherlock, 1964) which, in classifying halothane hepatotoxicity as a "sensitivity" or, allergic effect, exclude its reproducibility in experimental animals.

Two further mechanisms of interference with B.S.P. clearance merit attention. Alterations in the characteristics of serum albumin (Crawford and Hooi, 1968) and the relative deficiency of the hepatic cytoplasmic organic anion acceptor protein Y (Levi *et al.*, 1969) have been shown to interfere with B.S.P. uptake by the liver. The effect of halothane on these criteria would be of interest.

Finally, species variations are naturally a pertinent criticism of the type of study presented here. A mixture of Wistar and Sprague-Dawley rats (as supplied in these laboratories) have been used in this study. Wistar rats have been reported as having genetic variations in enzyme patterns (Javitt, 1965), but it should be emphasized that in this study the same animals were used as controls as were exposed to anaesthetic agents.

Despite such factors, these findings are regarded as significant in that they serve as a pointer to further directions in animal studies and possible application to comparable human situations.

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Medical Memoranda

Malabsorption and Schistosomal Involvement of Jejunum

British Medical Journal, 1970, 1, 671-672

Classically, *Schistosoma mansoni* worms inhabit the tributaries of the portal vein, especially the inferior mesenteric vein and the haemorrhoidal plexus (Manson-Bahr, 1960). The females pass their ova in the finer tributaries, especially at the rectosigmoid colon. The smaller immature ova excite a granulomatous reaction in the submucosa and the larger ova pass through the mucosa into the faeces, where they can be detected by low-power microscopy. Sadek (1965) reported finding *S. mansoni* ova in a biopsy specimen of the jejunum taken during laparotomy.

During the investigation of a case of malabsorption syndrome it was found that the jejunum was infested with lateral-spined *S. mansoni* ova.

CASE REPORT

A soldier aged 22 was referred in September 1967 because of bouts of distension of the abdomen and colic with diarrhoea for three months. There was a past history of infectious hepatitis, *S. haematobium*, and *Ancylostoma duodenale*, which had been treated during childhood.

In 1963 he noticed increased size of the abdomen, borborygmi,

and episodes of bulky, frothy, offensive diarrhoea with 30 to 40 motions a day, occasional tenesmus, and blood in the stools, which floated on water. In the three months before his admission the condition had become persistent. He had colicky pains, especially in the left iliac fossa, which were partially relieved by defaecation.

Shortly before admission he noticed puffiness of the face, oedema of the legs, and cramps in the muscles of these limbs. Two months earlier he had received antituberculosis drugs with no improvement. On admission he was alert and intelligent, but pale.

Investigations.—Tongue normal. Chvostek's sign negative. Thyroid: slight diffuse enlargement but no signs of thyrotoxicosis. Normal temperature. Respiratory, cardiovascular, nervous, and skeletal systems normal. Abdomen distended, with fullness in both flanks and pronounced gurgling but no shifting dullness. Liver enlarged 2 cm. below the costal margin, firm, and smooth; spleen enlarged 1 cm. below. No other masses. Rectal examination: no masses felt. Sigmoidoscopy: few tiny punched-out ulcers at 15 cm. Rectal biopsy showed *S. mansoni* ova in the mucosa and submucosa. Stools: frothy, bulky (three litres per 24 hours), with no blood or parasitic ova, but rich in *Giardia lamblia*. Chest x-ray picture normal. Blood picture: mild hypochromic anaemia. Faecal fat 30 g./72 hours. D-Xylose test (5-g. method): 0.3 g. excreted in five hours (abnormal). Serum calcium 6 mg./100 ml. Flat blood sugar curve. Thrombotest 70%. Serum alkaline phosphatase 10 K.A. units. Plasma proteins 5.8 g./100 ml. Electrophoresis: albumin 49%, α 1-globulin 3%, α 2-globulin 9%, β -globulin 12%, γ -globulin 27%. Needle liver biopsy: fatty infiltration of liver cells; no fibrosis. Jejunal biopsy (using the Crosby capsule): *S. mansoni* ova in the mucosa and submucosa with some granulomatous reaction and lymphocytic infiltration, but normal villi (Fig. 1). Small