pre-operative cholangiogram was performed, it seems probable that in part the difference in measurement in these cases was due to some mechanical dilatation of the duct when taking the operative cholangiogram, and that the diminution in size of the duct was more apparent than real. Certainly the results obtained provide no evidence that there is a clear tendency for a dilated duct to diminish in size after removal of calculi.

There was no evidence of any correlation between the continuation of symptoms after cholecystectomy and the size of the bile duct. Of the 15 patients with a bile duct of 12 mm. diameter or greater on post-operative cholangiography, 14 had either no symptoms or only mild ones not considered to be related to the biliary system. Similarly, of the 18 patients with symptoms possibly or probably due to some disorder of the biliary system, 15 had a common duct measuring 10 mm. or less on post-operative cholangiography. It is clear that the finding of a dilated common duct on cholangiography in a patient who has previously had a cholecystectomy is in itself of no significance. If there is evidence that at the time of operation the duct was definitely smaller, the enlargement presumably indicates obstruction to the duct, but this investigation provides no direct evidence on this point.

Summary and Conclusions

In a series of 73 patients undergoing cholecystectomy measurements were made of the diameter of the common bile duct as revealed on operative cholangiography, and on intravenous cholangiography performed 12 months or more after operation. At the time of this latter examination the patients were interviewed and placed in one of four categories according to their clinical symptoms.

There is a wide variation in the calibre of the normal common bile duct. It is suggested that, as seen on radiology, an image of 10 mm. diameter represents the usual upper limit of normal, and that an image of 12 mm. or greater is evidence of dilatation of the duct.

There is no evidence that the common bile duct becomes dilated after cholecystectomy.

There is no evidence that a dilated common bile duct diminishes significantly in calibre after cholecystectomy and removal of stones from the duct.

There is no correlation between the continuance of symptoms after cholecystectomy and the calibre of the common bile duct.

The finding of a dilated bile duct on intravenous cholangiography performed after cholecystectomy is of no significance in itself in the absence of information about the size of the duct at the time of operation.

All the patients in this investigation were admitted to the wards of the department of surgical studies, under the care of the director, Mr. D. H. Patey, or one of us (L. P. LeQ.). The operations were performed by members of the staff of the department. We are grateful to Mr. D. H. Patey for allowing us to review his patients and to include them in this report.

REFERENCES

- Benson, K. W. (1940). *Amer. J. digest. Dis.*, **7**, 1.
 Boyden, E. A. (1936). *Anat. Rec.*, **66**, 217.
 Cole, W. H., and Harridge, W. H. (1956). *Surg. Clin. N. Amer.*, **36**, 149.
 Don, C., and Campbell, H. (1956). *J. Fac. Radiol. (Lond.)*, **7**, 197.
 Oddi, R. (1887). *Arch. ital. Biol.*, **8**, 317. Cited by Boyden (1936).
 Samuel, E. (1957). *Ann. roy. Coll. Surg. Engl.*, **20**, 157.
 Sullens, W. E., and Sexton, G. A. (1955). *Ann. Surg.*, **141**, 499.
 Wise, R. E., and O'Brien, R. G. (1956). *J. Amer. med. Ass.*, **160**, 819.

NEW TECHNIQUE WITH HYDROXYDIONE

EXPERIENCES WITH "PRESUREN"

BY

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During his initial experiments to establish the existence of the "adaptation syndrome," Selye (1941a, 1941b) discovered that steroids had anaesthetic properties. He also reported that, while many steroids were hormones, pregnanedione could be regarded as a steroid anaesthetic without hormonal activity (Selye, 1941a, 1941b, 1942a, 1942b, 1943). Laubach *et al.* (1955) synthesized a soluble derivative of pregnanedione: 21-hydroxypregnane-3,20-dione sodium hemisuccinate ("viadril," "presuren"), which has become known by the contracted name of hydroxydione. Thus, for the first time, an anaesthetic became available which was chemically related to the heart tonics, the saponins, and certain substances manufactured in the body, such as the bile acids, corticosteroids, and the sex hormones. The first clinical trials of hydroxydione were conducted in the U.S.A. by Gordan *et al.* (1955), Murphy *et al.* (1955), and Howland *et al.* (1956), and these were followed by many others (Dauri, 1955; Burstein, 1956; Deligné and David, 1956; Dent *et al.*, 1956; Galley and Rooms, 1956; Gordan *et al.*, 1956; Harbord and Wild, 1956; Laborit *et al.*, 1956; Lerman, 1956).

The advantages claimed for this type of anaesthesia were: a high therapeutic index (wide safety margin); lack of respiratory depression if doses were kept within average clinical limits; quiescence of pharyngeal, laryngeal, and bronchial reflexes; the facility with which controlled respiration could be effected; and a less unpleasant recovery period for the patient (Galley and Rooms, 1956; Lerman, 1956). The disadvantages were the slow rate at which hydroxydione dissolved; a marked tendency to thrombophlebitis unless very weak solutions were used; the slowness of the induction resulting from the administration of such solutions by intravenous drip; and rises in pulse rate and occasional falls in blood pressure, particularly in elderly patients.

Recent Developments

Until recently the incidence of thrombophlebitis was minimized either by injecting 2.5% solutions into an exceedingly fast running drip (Murphy *et al.*, 1955) or by administering the substance in very weak solutions—for example, 0.5%—by means of an intravenous drip (Burstein, 1956; Galley and Rooms, 1956). Stedtfeld (1957) and Opderbecke (1957) reassessed the situation. Stedtfeld thought that post-operative vein reaction might be caused by chemical irritation, osmotic irritation, irritation due to solutions being at temperatures less than blood heat, the rate of injection (that is, the prolonged time during which weak solutions of hydroxydione remained in contact with the veins), or the large volumes necessitated by using an intravenous drip. After experiments on animals and a human volunteer he suggested warm physiological saline as the

ideal solvent, and gradually increased the strengths of the solutions he injected until 10% was used as a routine. Solutions of this strength were given as *rapidly as possible* in order to ensure that the endothelium of the arm veins was exposed to irritation for as short a time as possible. He claimed that this technique had virtually eliminated the incidence of thrombophlebitis.

More recently Grewe (1957 personal communication) and Grewe *et al.* (1957, 1958) introduced the use of 0.25% procaine solution (in water) as the solvent instead of saline. Even when given cold, hydroxydione-procaine solutions appeared to prevent the incidence of injection-pain sometimes experienced when hydroxydione was given without procaine. In this country, Landau (1958) has reported the use of 2.5% presuren brand of hydroxydione in warm normal saline by fairly rapid injection in a series of 120 patients.

Physical Differences Between two Brands of Hydroxydione

The original brand of hydroxydione used by us was dispensed as a soapy deposit clinging to the walls of the phial; more recently this brand has changed to a mixture of powder and soapy deposit. While the powder dissolves relatively rapidly the soapy deposit takes much longer, and even when warm solvents are used a great deal of froth is produced during the shaking necessary to effect solution. The powder in the phials shows an average particle size of 100 μ . Presuren brand hydroxydione is dispensed as a fine powder with no accompanying soapy deposit. It has an average particle size of 50 μ and dissolves readily in water, physiological saline, or procaine solutions even when these are at room temperature. As only gentle movement is required to effect solution, very little froth is formed and the hydroxydione can be drawn up into a syringe immediately. This rapid solubility and freedom from froth enables presuren to be made up and ready for use with almost the same facility as thiopentone. We have used presuren in a combined series of 346 cases (Table I).

TABLE I.—Distribution of Operations in a Combined Series of 346 Cases

Ophthalmic	6	Caesarean section	11
Mastoid region	11	Other lower abdominal (including pelvic)	52
Thyroid and neck	18	Bladder and urethra	29
Larynx and pharynx	6	Prostate	46
Major dental and mouth	5	Vagina and perineum	20
Thoracic	3	Limbs and torso (including mastectomy)	47
Gastric	28	Endoscopy	19
Biliary	22	Contrast radiographs	4
Other upper abdominal	6		
Renal and suprarenal	13		

Administration and Dosage

As solvents we have used cool and warm saline, cool and warm water, and cool procaine solutions. Because warm solvents appeared to have no effect on pain or discomfort during injection or on the incidence of post-anaesthetic thrombophlebitis they were soon given up. Presuren was given in two strengths, 5% and 10%. When made up in saline or water occasional pain or discomfort was experienced by patients during intravenous injection. This was referred to the upper arm, sometimes as far as the outer third of the clavicle, and in a child of 8 years as far as the praecordium. We tried to modify this by first giving pethidine and then hydroxydione into the same vein, with varying success. It was found that the finer the vein one used the greater the likelihood of pain or discomfort and that slowing the rate of injection was no preventive. The use of 0.25%

procaine solution as a solvent has prevented pain in all but two patients, and these had very fine veins. If fine veins have to be used we now use 0.5% procaine as the solvent (see Table II). Lignocaine may be substituted for procaine if so desired.

Originally, we injected presuren solutions at about the same speed as that at which we were accustomed to administer thiopentone. It was soon evident, however, that the more rapid the injection the less the incidence

TABLE II.—Effect of Presuren on Veins in 165 Consecutive Cases (A. H. G.)

Solvent	Injection Rate	No. of Cases	% Expressed of Column 3		
			Painless Injection	Post-operative Venous "Thrombosis"	
				Painful	Not Painful
Cool procaine 0.25%	Rapid	82	80 (97.5%)	2 (2.5%) Both fine calibre veins	22 (28%)
Cool procaine 0.5%	"	22 All fine-calibre veins	22 (100%)	0 (0%)	6 (27%)
Warm saline	{ Slow	7	6 (85.7%)	0	2
	{ Rapid	6	5 (83.3%)	1	4
Cool saline	{ Slow	8	6 (75%)	0	1
	{ Rapid	7	4 (57.1%)	1	5
Warm water	{ Rapid	5	4 (80%)	0	1
	{ Slow	7	4 (80%)	1	4
Cool water	{ Rapid	13	10 (77%)	0	4
	{ Slow	10	8 (80%)	2	7
Totals:					
Rapid injections—procaine as solvent		104	102 (98.1%)	2 (2%)	26 (26.9%)
Saline or water as solvent		61	47 (77%)	5 (8.2%)	29 (46%)
Rapid injections—water or saline as solvent		33	26 (78.8%)	0 (0%)	8 (24%)
Slow injections—water or saline as solvent		28	22 (78.6%)	5 (18%)	20 (71%)

of post-anaesthetic venous thrombosis. In most of our cases, therefore, we have injected into the vein as rapidly as possible through a wide-bore (12 s.w.g.) needle, never taking more than one second for each millilitre. After the injection is complete we have taken the following precautions to ensure the most rapid emptying of the arm vein: (a) the arm is held vertically for 30 seconds; (b) the patient is asked to open and close the fist in a rhythmic fashion; and (c) the arm is gently massaged in the direction of the shoulder. After lowering the arm a swab is gently held against the site of injection; the arm is not flexed with a swab in the antecubital fossa for fear of trapping some of the anaesthetic at this point and causing irritation. This fast-injection technique necessitates estimation of the dose before injection. In any case the drug acts far too slowly to allow the dosage to be estimated during injection as with thiopentone.

We are in general agreement with Landau (1958) that "an adequate level of basal narcosis without respiratory depression is obtained with a dose of from 6 to 8 mg./lb. (13.2 to 17.6 mg./kg.) and that this dose should be reduced to 5 mg./lb. (11 mg./kg.) in the aged, cachectic, or underweight patient." Such doses, by definition, would not be adequate without added cover from nitrous oxide and other adjuvants. We have found that the average time of induction is about three minutes—a little faster with doses above 500 mg. and a little slower when less than 500 mg. is given.

In contradistinction to the small series reported by O'Flanagan and McGuinness (1958), who used the drug

for psychotherapy, we have been able to induce sleep with doses as small as 400 mg. in adults. That some of their patients were able to converse after doses of 500 mg. may have been due to the unusually high reflex irritability accompanying psychotic states, and to the fact that no pre-anaesthetic sedation was used as in our own series.

Adjuvants and Premedication

In most cases basal narcosis with presuren has been augmented with nitrous oxide, pethidine, and the usual muscle relaxants (Table III). Cyclopropane and trichlorethylene have also been used; the former by itself and the latter in conjunction with nitrous oxide. Smaller doses of presuren can be given if cyclopropane is the adjuvant, and this mixture appears to have interesting potentialities, as is explained later.

TABLE III.—*Examples of Operations Performed Under Presuren, with Doses of Supplementary Drugs Used*

Operation	Sex and Age	Total Dose of Presuren (mg.)	Dose of Analgesic (mg.)	Dose of Relaxant (mg.)	Operating Time in Minutes (approx.)
Caesarean section and sterilization	F 28	500	P100	S150*	45
Retropubic prostatectomy and diverticulotomy	M 80	750	P50	C20	130
Resection of rectum	F 57	600	P90	C40	95
Total vaginectomy	F 52	750	P35	C15	170
Laryngopharyngectomy	M 47	1,000	P50	Nil	260
Thyroidectomy	F 23	800	P50	C10	80
Gastrectomy	F 48	800	P50	C25	65
Exploration of biliary tract	F 65	600	P35	C30	80
Partial nephrectomy	M 55	600	P50	C30	110

* Divided doses before and after delivery of foetus.
P=Pethidine. C=D-Tubocurarine chloride.
S=Suxamethonium (succinylcholine) chloride.

Most cases have been premedicated with papaveretum ("omnupon," "pantopon") and scopolamine except for the aged, who were given pethidine and atropine. Atropine alone was given before caesarean section and to patients with respiratory obstruction.

Larynx and Bronchi

When weak solutions of hydroxydione were administered and the induction time was in the region of 15 minutes it was usually found that by the time the patient was asleep a laryngoscope could be carefully introduced and the vocal cords displayed for intubation (Gordan *et al.*, 1955; Murphy *et al.*, 1955; Galley and Rooms, 1956; Lerman, 1956; Taylor and Shearer, 1956).

With the technique described in this report, sleep ensues within three minutes, but the larynx at this stage is not always quiescent, a further few minutes being required in these cases before intubation is attempted. This effect is mainly of academic interest, since muscle relaxants are normally used prior to intubation, but it would seem to indicate that, as with thiopentone, the rapid injection of hydroxydione occasionally fails to depress the laryngeal reflexes as rapidly as it induces sleep. Even so, hydroxydione has a considerable advantage over thiopentone in this respect. As is well known, thiopentone actually potentiates the laryngeal reflexes during induction, often causing spasm of the glottis. In a trial series using a 10% solution of hydroxydione one of us (L.H.L.) found that it was possible to intubate without muscular relaxants in 79.6% of 167 cases.

The "bucking" on endotracheal tubes, which is so irritating a feature after the recommencement of spontaneous respiration when thiopentone has been followed by suxamethonium (succinylcholine), is entirely absent when presuren is used as the basal narcotic.

Respiration

The two respiratory tracings in Fig. 1 compare the effect of the rapid injection of 500 mg. of presuren and thiopentone in healthy young subjects. It will be noted that thiopentone produces a hyperpnoea followed by a

FIG. 1.—Respiratory tracings, showing the effect of (A) thiopentone 500 mg. in a robust youth of 19, and (B) presuren 500 mg. in a girl of 15.

period of apnoea, and then, when spontaneous respirations occur, there is a resultant or residual hypopnoea. Presuren, when given at similar speed, produces its respiratory effects in slow motion. The initial increase in depth associated with falling asleep is less marked than with thiopentone. Apnoea is replaced by some minutes of hypopnoea, and then the respiratory amplitude steadily returns towards the pre-anaesthetic level.

Pulse Rate and Blood Pressure

After comparable doses of hydroxydione the rise of pulse rate is more marked when the substance is given in weak solution in bulk—that is, by intravenous drip. Most of the patients receiving rapid injections of 10% solutions showed little deviation in pulse rate from the normal unless cyclopropane or gallamine was used, the former slowing and the latter increasing the rate as with other anaesthetic combinations. This finding would seem to confirm the speculation of Taylor and Shearer (1956) that increases in pulse rate during hydroxydione anaesthesia might be due to the bulk of fluid used to facilitate the administration of clinical doses of weak solutions.

Doses of 500 mg. and under rarely cause a reduction in the blood pressure except in the cachectic or aged.

In the latter, doses above 500 mg. tend to be associated with falls of blood pressure proportionate to the dose given. We agree with Landau (1958) that this fall is more marked in hypertensive patients, as is also found with thiopentone anaesthesia.

Postural hypotension can sometimes be obtained by giving patients undergoing prostatectomy 500–600 mg. of presuren and, after tilting them head down, adding

FIG. 2.—Presuren supplemented by cyclopropane paradoxically produces controlled hypotension.

cyclopropane as the principal adjuvant. Under similar circumstances with nitrous oxide there is a tendency towards slight cyanosis of the face despite adequate oxygenation, as indicated by the colour of the blood in the wound. By changing over from nitrous oxide to cyclopropane the face becomes flushed and bright pink, the volume of the temporal pulse increases dramatically, the blood pressure falls, and bleeding from the wound is greatly diminished—a paradoxical finding, since cyclopropane usually increases bleeding (Fig. 2).

Veins

Table II illustrates the effect on veins of administering 10% presuren with varying solvents at different speeds. We can confirm that, using 0.25% procaine solution (in water) as the solvent, pain accompanying intravenous injection is absent unless a vein of very fine calibre is used. The use of 0.5% procaine in this way prevents pain even if very fine veins are used. Our observation (Fig. 3) that injection of hydroxydione solutions into the tubing of a blood transfusion slows the rate of the drip, which can be restored or even increased by injecting pethidine, procaine, or nikethamide solutions, suggests to us that pain during the intravenous injection of

hydroxydione in strong solution might be due, at least in part, to venous spasm. If this were so, it would be a further indication for mixing procaine with hydroxydione prior to administration, and the manufacturers of presuren might consider the advantages of adding procaine crystals to their phial.

With regard to post-operative vein irritation, Table II demonstrates that the incidence of thrombophlebitis is greatly reduced when the intravenous injection is given rapidly. It is interesting that, with the technique we have developed, the painless "thromboses" enumerated in Table II are for the most part not noticed either by the patient or by his attendants. This probably accounts for the variation in the recorded incidence of thrombophlebitis by different investigators. As with thiopentone, one either has to follow up every case oneself or enlist the aid of the most hard-hearted critic if the actual truth is to be discovered. Thiopentone has a post-anaesthetic thrombosis rate between 17 and 20%, but, being painless, largely goes unnoticed. Three of the painful thromboses here recorded were in veins of narrow calibre, two of them on the back of the hand. One of these also caused a mild oedema of the skin for 26 hours. It is best, therefore, to regard narrow veins as a relative contraindication to the administration of hydroxydione. Although the incidence of vein trouble is not greatly influenced by the dosage given, when it does occur its severity appears to be related to the dose—for example, patients who have 500 mg. or less may have a thickening of the vein found only on palpation, whereas those having more than this dose will, if they develop vein irritation, show stretches of frank thrombophlebitis. It will be found that about two-thirds of the "thrombosed" veins are still patent if a hypodermic needle is inserted.

Discussion

It should be noted that the dosage marked on the label of the presuren phial refers to the hydroxydione part and not to the entire molecule, which includes the sodium hemisuccinate moiety, as with the older brands of hydroxydione. It is important to realize this, because the dosage of presuren to be given is therefore smaller than one has hitherto associated with steroid anaesthesia.

FIG. 3.—Third hour of operation for laryngopharyngectomy. Effect on drip rate of drugs injected into the tubing of an intravenous blood-transfusion apparatus during progressive venous spasm. Aqueous solutions of ether and pethidine increase the drip rate: presuren slows the drip rate.

The manufacturers have certainly done a great service in marketing a product which is so readily soluble. In other ways presuren appears to behave differently from products with the same chemical formula, and we agree with Landau (1958) that these are probably due to physical differences, some of which have already been mentioned. By giving a 10% solution very rapidly steroid anaesthesia can now compete with the thiobarbiturates as a time-saver.

Where facilities permit, the disadvantage of a three-minute induction can be overcome by starting the anaesthetic while the previous operation is drawing to its close, as indeed one did in the days of ether and chloroform. In hydroxydione anaesthesia it should be noted that patients can be left with perfect safety after the induction dose has been given, owing to the fact that they fall asleep pleasantly and peacefully without losing control of their jaw muscles or becoming hypopnoeic. In fact, the anaesthetist or his assistant can give the injection to the patient in his bed and leave him in the care of ward attendants until he is to be fetched to the theatre. This, of course, is a procedure long since discarded with thiopentone because of its danger.

Owing to its slight effect on the respiratory exchange and the manner in which it depresses the laryngeal and bronchial reflexes presuren is ideal as an anaesthetic for laryngoscopy and bronchoscopy. On one occasion 450 mg. was given to a patient with marked stridor who was about to be operated upon for laryngectomy. Although the surgeon was at hand to perform a tracheotomy if a respiratory crisis occurred, his services were not required until an hour or two later in the normal course of the operation. When the larynx and trachea are irritable or a retrosternal goitre is present it is often difficult to anaesthetize for a thyroidectomy without the patient straining or coughing. Presuren eliminates this complication.

Caesarean section is yet another indication for presuren. A dose of 500 mg. followed by 50 mg. of suxamethonium, endotracheal intubation with a cuffed tube, and rhythmic inflation of the lungs with a nitrous

oxide and oxygen mixture enables the surgeon to make the skin and abdominal wall incisions and, if quick, to incise the uterus and extract the baby as well. Added doses of suxamethonium maintain relaxation if necessary, and directly the child is delivered intravenous pethidine can safely be given to augment the anaesthesia. A small dose of suxamethonium is often required before closure of the parietal peritoneum. All the babies delivered under this regimen have breathed either directly they were extracted from the uterus or shortly afterwards.

With carefully graduated doses, aged, cachectic, or poor-risk patients react extremely well to this form of anaesthesia. Unlike thiopentone, it is impossible to cause vasomotor collapse by injecting the anaesthetic too rapidly, owing, no doubt, to the relatively slow way in which hydroxydione produces anaesthesia. Hydroxydione is particularly suitable to permit the initial cleansing and subsequent dressings of extensive burns. Fit patients undergoing severe operations seem to stand the strain better and are more comfortable afterwards. Although an actual euphoria has been observed on but two occasions (Galley and Rooms, 1956) a post-anaesthetic sense of well-being is usual which enables patients to ignore or minimize their post-operative discomforts.

The paradoxical use of cyclopropane combined with presuren to produce postural ischaemia has already been mentioned. No doubt this is due to augmentation of the vasodilatation produced by each drug alone and the partial paralysis of vasoconstriction by presuren. If postural or controlled hypotension is required and more conventional means are employed it will be found that presuren greatly reduces the dose of the hypotensive drugs in general use (Fig. 4).

Summary

A new brand of hydroxydione, presuren, has been marketed which is readily soluble in cool water, physiological saline, or procaine solutions. Pain may be caused in a minority of patients when a 10% solution is injected intravenously, but this disadvantage can be eliminated by using 0.25% or 0.5% procaine or lignocaine as the solvent.

If this strong solution is injected rapidly and certain simple measures are instituted to make sure that the arm veins empty rapidly, the incidence of post-operative thrombophlebitis is not greatly in excess of that caused by the more conventional intravenous anaesthetics.

With reasonable doses respiratory depression is much less than with comparable clinical doses of thiopentone. In contradistinction to the latter, hydroxydione rapidly depresses the laryngeal and bronchial reflexes; this makes it the anaesthetic of choice for bronchoscopies and laryngoscopies.

Falls in blood pressure were roughly of the same magnitude, dose for dose, as when hydroxydione is given in weak solution by an intravenous drip; on the other hand, increase in pulse rate was very much less common.

Poor-risk patients appear particularly suitable for this type of anaesthesia. It

FIG. 4.—Excision of carcinoma from floor of mouth of thin but robust-looking man aged 64. Blood-pressure graph showing how presuren enables controlled hypotension (postural ischaemia) to be obtained with very small doses of a ganglion-blocking agent such as pentamethonium.

is also recommended for caesarean section, thyroidectomy, and patients exhibiting partial respiratory obstruction.

As was noted with the former methods of administering steroid anaesthesia, presuren minimizes the usual post-operative fatigue. It produces a sense of well-being during the recovery period, which enables patients to disregard most of the discomforts following operation.

We thank those registrars, house officers, and nurses, who assisted us in making clinical observations incorporated in this report. Our thanks are also due to Dr. med. J. Friebe and Mr. G. Stuart Blackie, of the Medical Scientific Department, Schering A.G. Berlin, for their co-operation throughout this trial; and Schering A.G. Berlin and their subsidiary company, Pharmethicals (London) Limited, for the generous supplies of presuren. The respiratory tracings were recorded on an apparatus constructed in the physics department, King's College Hospital, with the aid of grants to one of us (A. H. G.) from the University of London research grants committee and the King's College Hospital and Medical School joint research committee.

REFERENCES

- Burstein, C. L. (1956). *Curr. Res. Anesth.*, **35**, 476.
 Dauri, A. (1955). *Gazz. int. Med. Chir.*, **19**, 1516.
 Deligné, P., and David, M. (1956). *Anesth. et Analg.*, **13**, 667.
 Dent, S. J., Wilson, W. P., and Stephen, C. R. (1956). *Anesthesiology*, **17**, 672.
 Galley, A. H., and Rooms, M. (1956). *Lancet*, **1**, 990.
 Gordan, G. S., Guadagni, N., Picchi, J., and Adams, J. E. (1955). *Méd. et Hyg. (Genève)*, **13**, No. 297, p. 251.
 ——— (1956). *J. int. Coll. Surg.*, **25**, 9.
 Grewe, H. E., Piechowski, U., and Zuckert, D. (1957). *Zbl. Chir.*, **82**, 1671.
 ——— (1958). *Chirurg*, **29**, 121.
 Harbord, R. P., and Wild, W. N. (1956). *Proc. roy. Soc. Med.*, **49**, 487.
 Howland, W. S., Boyan, C. P., and Kuo-Chen Wang (1956). *Anesthesiology*, **17**, 1.
 Laborit, H., Huguenard, P., Douzon, C., Weber, B., and Guittard, R. (1956). *Arch. int. Pharmacodyn.*, **107**, 159.
 Landau, E. (1958). *Anaesthesia*, **13**, 147.
 Laubach, G. D., P'an, S. Y., and Rudel, H. W. (1955). *Science*, **122**, 78.
 Lerman, L. H. (1956). *Brit. med. J.*, **2**, 129.
 Murphy, F. J., Guadagni, N. P., and DeBon, F. (1955). *J. Amer. med. Ass.*, **158**, 1412.
 O'Flanagan, P. M., and McGuinness, O. L. (1958). *Lancet*, **1**, 196.
 Opderbecke, H. W. (1957). *Thoraxchirurgie*, **5**, 53.
 Selye, H. (1941a). *J. Immunol.*, **41**, 259.
 ——— (1941b). *J. Pharmacol. exp. Ther.*, **73**, 127.
 ——— (1942a). *Endocrinology*, **30**, 437.
 ——— (1942b). *Curr. Res. Anesth.*, **21**, 41.
 ——— (1943). *Ibid.*, **22**, 105.
 Stedtfeld, G. (1957). *Anaesthesist*, **6**, 140.
 Taylor, N., and Shearer, W. M. (1956). *Brit. J. Anaesth.*, **28**, 67.

Only 213 cases of plague were officially recorded in 1958, the lowest number since the beginning of the century, according to the World Health Organization. This continues the downward trend of the incidence of plague observed in recent years, especially since 1951, when 15,399 cases were reported (of which 8,230 were in India). The distribution of the 213 cases in 1958 was as follows. In continental Africa 6 cases were reported in the north-eastern part of Belgian Congo and 19 cases in the Central Province of Kenya. In Madagascar 21 sporadic cases were recorded in several local areas, most of which were situated in Tananarivo Province. In America active foci were located in Ecuador, Peru, and in the state of Bahia in Brazil. In Asia (outside continental China and the U.S.S.R.) a new focus (11 cases) was discovered in the Kurdistan-Miandoab area of Iran. The 26 cases reported in India were observed in three districts in the southern part of the country. Eighteen cases were reported in Burma, and 15 in Viet-Nam.

URINARY GLUCURONIC ACID EXCRETION IN LIVER DISEASE AND THE EFFECT OF A SALICYLAMIDE LOAD

BY

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of London, W.12

Bilirubin is liberated from the breakdown of haemoglobin in the reticulo-endothelial system and gives the indirect van den Bergh reaction (Lemberg, 1956). It is transformed to direct-reacting bilirubin by conjugation with one or two glucuronic acid molecules to form bilirubin mono- or di-glucuronide, and this occurs at the site of the carboxyl groups of the bilirubin molecule (Billing and Lathe, 1956; Schmid, 1956; Talafant, 1956; Schachter, 1957). The diglucuronide is almost certainly formed exclusively in the liver, the monoglucuronide in other sites also. Bilirubin diglucuronide is present in the bile in much greater amounts than monoglucuronide, and Bollman (1956) has shown that in hepatectomized dogs monoglucuronides of bilirubin can be found in the blood, while the diglucuronide disappears completely.

It has been suggested that some forms of severe congenital, non-obstructive, non-haemolytic jaundice are due to an inability to conjugate bilirubin with glucuronic acid (Arias and London, 1957; Schmid *et al.*, 1957; Axelrod *et al.*, 1957; Schmid, 1958; Peterson and Schmid, 1957).

Our purpose was to investigate the ability of the liver to perform this conjugation in congenital non-obstructive, non-haemolytic jaundice of the milder adult type (Gilbert's disease) (Gilbert and Lereboullet, 1902), in the Dubin-Johnson type of pigmentary hyperbilirubinaemia (Dubin and Johnson, 1954), and in various diseases of the liver. Salicylamide was chosen as the test substance because it is carried in the blood, like bilirubin bound to albumin, and is largely excreted conjugated with glucuronic acid (Goodman and Gilman, 1955); it is also non-toxic.

Material and Methods

Of the 40 subjects studied (see Table), 12 had no evidence of liver disease. Of the others, 14 suffered from portal cirrhosis; 3 from primary biliary cirrhosis; 6 from extrahepatic obstruction to the biliary passages—in one of these (Case 19) the obstruction was intermittent so that he was not jaundiced at the time of study; 4 had intermittent jaundice due to Gilbert's type of hyperbilirubinaemia—in every instance haemolysis had been excluded as the cause of jaundice, and an aspiration liver biopsy showed normal histology; and 1 suffered from the Dubin-Johnson type of hyperbilirubinaemia confirmed by the presence of large granules of unidentified brown pigment in liver biopsy sections.

The subjects received the general hospital diet—those with ascites were excluded, as significant amounts of conjugated substances, such as tetrahydrocortisone, can be found in ascitic fluid, and a falsely low urinary excretion might result (Englert *et al.*, 1957). Patients