for any published account of these misfortunes, which are presumably theoretical.

I have used the gingival sulcus route of administration of oxytocin with complete success, and, may I dare to suggest, much greater comfort, satisfaction, and safety to the patients.¹ Ritchie and Brudenell have also published papers describing the satisfactory use of oxytocin administered by absorption through the buccal mucous membrane.^{2,3}

It would be interesting to know why absorption of a drug through the buccal mucosa is more dangerous than giving the same drug intravenously.—I am, etc.,

Croydon,
Surrey.

T. G. E. WHITE.

REFERENCES

- White, T. G. E., *Journal of the Royal College of General Practitioners*, 1968, 18, 198.
- Ritchie, J. M., and Brudenell, J. M., *British Medical Journal*, 1966, 1, 581.
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Porton Jet Injector

SIR,—We were somewhat perturbed by the implication of Dr. W. G. White (23 August, p. 472). From the earliest design and development work done at Porton it was never intended that the instrument should be used for intramuscular injection, and we have always stressed the difficulties and, indeed, the undesirability of attempting to give intramuscular injections with this type of instrument.

There are many obvious reasons for this, which I do not wish to expand upon in a short letter, but for the present I wish to stress my opinion that neither this nor any similar instrument that I have handled can be relied upon to deliver an accurate or accurately emplaced dose below the deep fascia.—I am, etc.,

H. M. DARLOW.

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Salisbury, Wilts.

Thrombocytopenia with Multiple Autoantibodies

SIR,—The cyclical aspect of the thrombocytopenia in the interesting case described by Dr. O. Brey and his colleagues (16 August, p. 397) need not be stressed. The patient had established and dangerous platelet deficiency; the physiological variation in the low platelet count was not important.

I have recently investigated two similar patients, both of whom were cured by splenectomy. One patient relapsed after four years, however, and despite continuous steroid cover she died 18 months later of uncontrolled intestinal bleeding. Not unexpectedly, splenuli were found post mortem. The patient of Dr. Brey and his colleagues had a high serum globulin and the added interest of hyperthyroidism. The overaction of the thyroid appeared to be only temporary. Was the goitre perhaps painful at first and the lesion therefore de Quervain's thyroiditis? My colleagues and I have submitted for publication elsewhere an example of this syndrome associated with sarcoidosis. Did their patient have evidence of sarcoid changes?

The discovery of mitochondrial antibodies may be particularly relevant. Primary biliary

cirrhosis is possibly chronic sarcoidosis. Reversion of the Kveim test by time is usual. Thus the autoimmunity is a result and not the cause of the disease. Differences in severity of the primary inflammation rather than differential absorption of antibodies, I suspect, accounts for the inconstant immune titres.—I am, etc.,

G. A. MACGREGOR.

Chilworth, Surrey.

Do Cervical Smears Save Lives?

SIR,—Your leading article (7 June, p. 585) stated that the answer to the question why 10 years' mass population screening programme for cervical cancer in British Columbia has not significantly reduced mortality from the disease is simply because the deaths were mostly occurring in the 25% of the population that did not come forward for routine cytological screening. This explanation is overoptimistic if not misleading.

The initial experience of cytological cancer screening in Singapore and Malaysia has shown a disappointingly low pick-up rate of 2-4 early cervical cancers out of 1,000 gynaecological and obstetrical patients screened. This despite the fact that cancer of the uterine cervix is the commonest malignant tumour among women here.

The incidence of cervical cancer among Singapore women is one of the highest in the world, computed at 52.5 per 100,000 women aged 35-64 years.¹ Ashley² put forward the idea that there may be two types of cervical cancer, and supported this with epidemiological data on carcinoma-in-situ and invasive carcinoma of the cervix from the United States and the United Kingdom. One, the slowly progressive carcinoma-in-situ or early invasive carcinoma among women in the fourth decade of life is usually detected by vaginal cytology and amenable to treatment with good prognosis. The other, the more rapidly growing invasive carcinoma among women in the fifth decade of life, is diagnosed in the late stages of the disease, is difficult to treat, and has a poor prognosis. This proposition may well prove to be true.

Thus cervical smears should continue to be used, but we should realize the limitation so far as saving lives is concerned.—I am, etc.,

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Kuala Lumpur,
Malaysia.

LAWRENCE CHAN.

REFERENCES

- Doll, R., *British Journal of Cancer*, 1969, 23, 1.
- Ashley, D. J. B., *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1966, 73, 382.

Nalorphine in Opiate Poisoning

SIR,—In the treatment of opiate drug poisoning the total dose of nalorphine is stated to be 60 mg./hr.¹ or 40 mg.² The reason advanced for this restriction in dosage is that nalorphine itself may cause respiratory depression.³ We believe, however, that the total dose and rate at which nalorphine is given should be dictated not by arbitrary figures of total dosage over standard intervals of time but rather by the condition of the patient. The following report illustrates this point.

A 40-year-old woman was admitted to the Regional Poisoning Treatment Centre with a history of having taken 20 tablets of Diconal (that is, 200 mg. of dipipanone, equivalent to 100 mg. of morphine), together with 10 Mandrax tablets (methaqualone and diphenhydramine), five hours before admission. She was deeply unconscious; unresponsive to any painful stimulus; shocked and apnoeic; her pupils were fixed and dilated. Endotracheal intubation and hand ventilation served to correct the anoxia, and the pupils became pinpoint in size. There was no improvement in her level of consciousness or shock despite correction of her anoxia. Nalorphine 20 mg. was given intravenously, and her spontaneous minute volume improved from apnoea to 4½ litres. Over the next hour her minute volume could only be satisfactorily maintained by an infusion of nalorphine, and a total dose of 105 mg. was given intravenously in that period. The pupils became normal in size and her level of consciousness improved so that she responded to minimal painful stimulus. Full reversal of her conscious level was, no doubt, prevented by the Mandrax. (Serum methaqualone 1.5 mg./100 ml.) A total dose of 170 mg. nalorphine was given over a period of four hours, 105 mg. of which was given during the first hour. This succeeded in reversing the dipipanone-induced respiratory depression without itself producing any respiratory complications.

It may be concluded that in gross opiate overdosage it may be both safe and therapeutically necessary to give nalorphine in incremented doses in excess of that previously considered safe. The indication for further medication should be the clinical state of the patient. Care should be taken on the one hand not to undertreat, with resulting continuing respiratory depression, and, on the other, not to overtreat, with resulting nalorphine-induced respiratory depression.—We are, etc.,

N. WRIGHT.

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REFERENCES

- Matthew, H., and Lawson, A. A. H., *The Treatment of Common Acute Poisonings*, 1967, p. 111. Edinburgh, Livingstone.
- British National Formulary*, 1968, p. 224. London, British Medical Association and The Pharmaceutical Society of Great Britain, 1969.
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Psychosis and Antithyroid Drug Therapy

SIR,—We were interested to read the report by Drs. C. F. Herridge and I. Abey-Wickrama (19 July, p. 154) of acute psychosis in a patient treated with antithyroid drugs. Our recent experience with a similar patient provides an interesting comparison, since it suggests that the psychotic illness is not necessarily related to the onset of hypothyroidism.

A 27-year-old married woman was admitted to a general medical ward with suspected thyrotoxicosis. The diagnosis was confirmed by radioiodine tracer studies and a serum protein bound iodine (P.B.I.) level of 15.6 µg./100 ml. There was no personal or family history of psychiatric illness. Treatment was started with carbimazole 60 mg. daily in divided doses, and at the time of discharge three weeks later she was still clinically hyperthyroid; the serum P.B.I. was 6.1 µg./100 ml. She was advised to continue carbimazole 60 mg. daily for a further

seven days and then reduce the dose to 45 mg. daily.

Eleven days later she was readmitted with an acute psychotic illness characterized by paranoid delusions. She was febrile and her pulse rate varied between 110 and 145. Clinically she was considered to be euthyroid and the serum P.B.I. was 4.3 µg./100 ml. Serum urea, electrolytes, full blood count, electrocardiogram, chest x-ray, and urine culture were normal. Three days later her temperature was normal and she was transferred to a psychiatric hospital (Dr. J. G. Henderson). She was treated with chlorpromazine and benztropine and continued on carbimazole 20 mg. daily. Two months later she was mentally normal and during her illness she remained clinically and biochemically euthyroid.

Subtotal thyroidectomy was carried out two months after her discharge (Mr. W. Michie), and at her most recent review, 10 months after operation, she was euthyroid and normal in all other respects.

At the time of her first admission this patient was considered to have severe hyperthyroidism, and the treatment rapidly altered her thyroid state towards normal. There was no evidence of hypothyroidism at any time during her illness. It is suggested that her psychiatric disturbance may have been due to either the acute change in her metabolic state, induced by the antithyroid drug, or to the drug itself. Similar findings have been reported previously.¹—We are, etc.,

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P. D. BEWSHER.

Department of Therapeutics
and Pharmacology,
University of Aberdeen.

REFERENCE

- ¹ Williams, R. H., Clute, H. M., Anglem, T. J., and Kennedy, F. R., *Journal of Clinical Endocrinology and Metabolism*, 1946, 6, 23.

Diverticular Disease of the Colon

SIR,—It seems to me unfortunate that in a recent article (24 August 1968, p. 475) and a leading article (9 August, p. 311) on diverticular disease of the colon no mention should have been made of the work of H. C. Edwards. As long ago as 1932 he won the Jacksonian prize for his work on diverticula of the intestine, later published in the *Lancet*,¹ the *British Journal of Surgery*,² and later still as a book.³ In these publications Edwards brought forward much evidence to show that diverticular disease is a result of irregular or abnormal contraction of the muscle. He also referred to the work of A. P. Stout⁴ as pointing to the same conclusion. Stout's paper, written in 1923, dealt with diverticula of the appendix. It was a pioneering effort in that it demolished the theory that distension produces diverticula. But nobody paid any attention, any more than they did to the work of Edwards published a decade later.

I think it is regrettable that the work of these two eminent men should have been forgotten, when now, at length, their judgements have been vindicated.—I am, etc.,

R. R. WILSON.

Department of Pathology,
Stobhill General Hospital,
Glasgow N.1.

REFERENCES

- ¹ Edwards, H. C., *Lancet*, 1934, 1, 221.
- ² Edwards, H. C., *British Journal of Surgery*, 1934, 22, 88.
- ³ Edwards, H. C., *Diverticula and Diverticulitis of the Intestine*, 1939. Bristol, Wright.
- ⁴ Stout, A. P., *Archives of Surgery*, 1923, 6, 793.

Serum Hepatitis in a Haemophiliac

SIR,—Serum hepatitis after the use of cryoprecipitated antihæmophilic globulin (cryo) is unusual. The only reported case is that of Del Duca and Eppes,¹ who described a 39-year-old haemophiliac who developed transient jaundice 60 days after receiving 28 units of cryo for dental extraction. He recovered rapidly after one day of nausea and vomiting. We report a second case with a fatal outcome.

A 41-year-old male haemophiliac presented in January 1969 with spontaneous bleeding into his right knee joint of two days' duration. He was given 18 units of cryo over 48 hours and allowed to go home. Two weeks later an injury to his left knee caused a large hæmarthrosis. Sixty ml. of blood was aspirated with strict aseptic technique under cover of 6 units of cryo. Sixty units of cryo were given over the next two weeks, but the hæmarthrosis was slow to resolve, and for the next two months he had twice weekly physiotherapy under cover of 6 units of cryo, receiving a total of 162 units in all.

In May 1969 he presented with rigors and generalized abdominal pain associated with a skin rash over his arms and legs. Next day he developed nausea and continuous vomiting and passed dark urine and stools. On admission to hospital four days later he looked ill with cold, moist, jaundiced skin, diffuse upper abdominal tenderness, and a purpuric rash on his arms and legs. He was severely dehydrated. Investigations confirmed the dehydration and showed evidence of gross liver cell damage. He was rehydrated, but continued to vomit. Twenty-four hours later the vomit contained brown watery fluid which contained hæmoglobin. One litre of fresh frozen plasma was transfused, and vitamin K₁ (10 mg. every six hours) was added to the intravenous fluids. He continued to vomit blood-stained fluid and his condition gradually deteriorated. Apart from confusion and jaundice there were no signs of liver failure. Serum bilirubin was then 20.5 mg./100 ml., Hb 16.4 g, packed cell volume 45%, and blood urea 133 mg./100 ml.

At this point he vomited fresh blood for the first time. He continued to vomit blood for the next 12 hours: 8 pints (4.5 l.) of blood and six units of cryoprecipitate were given without improvement. Because of his rapid deterioration exchange transfusion of three units of blood was performed. He died 72 hours after admission.

Post-mortem examination (Dr. A. H. Cruickshank) revealed a small liver (1,370 g.). The capsule was wrinkled and the subcapsular surface was extensively mottled by hæmorrhage. The cut surface showed mottling with alternate areas of pallor and congestion. The common bile duct was patent, the portal and hepatic veins normal. The gall bladder did not contain any stones. The spleen was moderately enlarged (540 g.) with scattered subcapsular hæmorrhages. The stomach, duodenum, and jejunum contained altered blood. There was a submucosal hæmorrhage in the lower third of the oesophagus. No obvious bleeding point was found in the gastrointestinal tract. The heart (428 g.) showed subepicardial petechiae and a large (4×1.5 cm.) subendocardial hæmorrhage on the left side of the intraventricular septum. Blood was present in the trachea and main bronchi, and hæmorrhage in the submucosa of the hypopharynx. There was no laryngeal obstruction. The lungs were moist and deeply congested. Both kidneys showed a pale jaundiced cortex. Histology of the liver showed extensive hepatocellular damage. Complement fixation

tests for viruses (Dr. Bruce White) were performed on serum taken during the actual illness and on stored serum taken in January 1969. Apart from a rather high titre for cytomegalovirus (1/64) both specimens were normal. Serum used successfully as a source of SH antigen gave a weak positive agglutination.

The clinical and necropsy findings here are fully compatible with the diagnosis of serum hepatitis.

Cryo represents a considerable advance in the management of the severe haemophiliac. This and other centres have used many thousands of units without mishap and we do not know of a similar case in Britain. It is important to re-emphasize the potential danger of cryo to ensure its use only when strictly needed. A check should be kept of the source of cryo to trace any serum hepatitis which may occur in future.

We are grateful to Dr. T. Black for permission to report this case.

—We are, etc.,

J. A. WHITTAKER.
M. J. BROWN.

Royal Infirmary,
Liverpool.

REFERENCE

- ¹ Del Duca, V., and Eppes, R. B., *New English Journal of Medicine*, 1966, 275, 965.

Origin of the Third Heart Sound

SIR,—While wanting to agree with Drs. M. I. M. Noble and K. B. Saunders (16 August, p. 413) that the major part of ventricular filling probably represents a passive process as the heart muscle dilates, these authors have not demonstrated that diastolic suction due to elastic recoil does not occur briefly at the moment of mitral valve opening in very early diastole, as seems to be the case. What they have shown with certainty¹ is that suction from elastic recoil does not measurably persist throughout diastole, although, as Linden² states, "suction" is only one way of looking at a pressure difference and it is likely that the pressures involved are small. The sensitivity of the methods used therefore for measuring these differences is all important. It is only to be expected that elastic recoil pressure effects are small, for ventricular filling, since it is hard to conceive how Starling's law of the heart could otherwise remain valid and an adaptive exercise response occur. Although it is likely that elastic recoil pressure effects are small, this does not diminish their importance as a means of controlling the critical boundary layer as the mitral valve opens.³

It is legitimate to consider the geometry of the adjacent atrial and ventricular chambers as a diffuser whose main function is pressure recovery during diastole. By controlling the boundary layer of fluid entering the ventricle at this critical moment of time, full expansion of the jet is achieved and pressure recovery throughout almost doubled, though the amount of lateral suction that needs to be applied is slight.⁴ Lateral suction as the result of outward movement of the ventricle wall certainly does occur to a major extent throughout diastole with respect to fluid entering the ventricle, and is responsible for continued control of the boundary layer.