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 $\mu\text{g.}/100\text{ ml.}$ 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.,

ANTHONY J. HEDLEY.
P. D. BEWSHER.

Department of Therapeutics
and Pharmacology,
University of Aberdeen.

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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.

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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

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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.

Important circumstantial evidence in support of the theory of passive dilatation of the ventricle is provided by consideration of the abnormal but characteristic ventricular cardiographic silhouettes after mitral valve replacement using low-profile disc and central-flow homograft valves. As a result of some preliminary observations we would distinguish the "turnip" heart outline that characterizes the disc valves from the "pear" heart of the homograft valve, and suggest that the shape adopted by the ventricle is determined by the grossly abnormal filling patterns in each case.⁵ It seems logical that the reduction in cardiac output that is uniformly observed in these patients is related directly to these changes.—I am, etc.,

KENNETH REID.

Nuffield Department of Surgery,
Radcliffe Infirmary,
Oxford.

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SIR,—It is interesting that Dr. H. Ikram and others (16 August, p. 413) have confirmed the observations that were made in our paper of 1966.¹ We studied the phonocardiograms of 26 patients whose mitral valves had been replaced with prostheses. On no occasion was a third heart sound recorded, although we did record diastolic sounds similar to those found by Hultgren and Hubis.² Two of these patients developed incompetence around the prosthesis, and in neither was a third heart sound recorded.

In a later study³ a catheter was passed across a mitral valve prosthesis from the ventricle to the atrium, thereby creating severe mitral incompetence. The phonocardiogram taken during this episode did not show a third heart sound.

There would now seem to be a considerable body of published evidence that the third heart sound does not occur in the absence of a sub-valve apparatus.—I am, etc.,

EDWARD B. RAFTERY.

Cardiac Department,
King's College Hospital,
London S.E.5.

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Pyuria and Bacteriuria

SIR,—We agree with Dr. J. M. Littlewood (16 August, p. 416) that microscopic examination of fresh, unstained urine for the presence of bacteria is a useful and undervalued clinical skill; indeed, we stated in our article (12 July, p. 81) that we had made this observation in nine out of ten bacteriuric girls. As he pointed out, heavily infected urine is usually turbid. However, we have

also seen optically clear urine containing significant numbers of bacteria, and a specimen giving a colony count of 100,000 per ml. would contain only one organism per high-power field, or less than one in each small square of a Fuchs-Rosenthal counting chamber. The reliability of this method is therefore questionable when infection is light or the urine is dilute.

Like Dr. Littlewood, we also commented at some length on the disadvantages of screening for pyuria—though in our hands it gave a false-negative rate of 25% (assuming that the true prevalence of bacteriuria in British schoolgirls is 1.2%),¹ not 40%. However, any method which relies upon microscopic examination is likely to be too time-consuming and costly for screening on a large scale, and the chemical method to which we referred in our article² seems more promising because it can be adapted for autoanalysis.

Dr. Littlewood suggests that urine microscopy should be carried out by school medical officers at the medical examination. One of our stated objectives was to assess whether this would be feasible, but we concluded in our last paragraph that it would be premature to introduce it until better techniques are established and the real health hazards of asymptomatic bacteriuria have been evaluated. We are therefore grateful to him for reiterating our plea for further research into the natural history. However, we believe that careful follow-up of bacteriuric girls with anatomically normal urinary tracts, randomly allocated to treatment and control groups, by a limited number of paediatric departments with a declared interest in the field is likely to make a greater contribution to knowledge than the disclosure of large numbers of cases in the country as a whole.—We are, etc.,

S. R. MEADOW.

Department of Paediatrics,
Guy's Hospital,
London S.E.1.

R. H. R. WHITE.

The Children's Hospital,
Birmingham.

N. M. JOHNSTON.

School Health Service,
City of Birmingham.

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Rheumatoid Arthritis: Extra-articular Manifestations

SIR,—Dr. F. Dudley Hart's Philip Ellman lecture (19 July, p. 131) will give great pleasure to anyone requiring a concise summary of the extra-articular manifestations of rheumatoid arthritis. However, I should be most grateful if you would allow me to make a comment. Dr. Hart mentions "a new Parkinson's Law . . ." that there is an inverse frequency between the occurrence of rare diseases and their appearance in print in learned journals. Surely the commonest manifestation of rheumatoid arthritis is anaemia; but this topic is hardly discussed.

It is thought that some 25% of rheumatoid patients show a normocytic hypochromic anaemia, the severity of which usually depends on the activity of the primary disease

process.¹ Lassitude, general malaise, and depression are often aggravated, and rehabilitation is no doubt delayed unless this often readily treatable tissue defect is corrected. In fact, very little is known about the aetiology of this anaemia. The serum iron is usually low, and the iron-binding capacity normal. Dr. Hart stresses the fact that many of the apparent systemic manifestations of rheumatoid arthritis are, in fact, side-effects of the various treatments. Undoubtedly salicylate-induced gastrointestinal blood loss is of prime importance, but there are no doubt other aetiological factors. Various suggestions have been put forward and they all play a minor role. For instance, there may be a failure of intestinal absorption of iron (as suggested by patients who respond to intravenous iron therapy after proving refractory to oral therapy), or defect in the iron transport mechanism may exist. Thirdly, there may be an increased absorption of iron by non-bone marrow tissue preventing its utilization. Increased blood destruction as a cause is unlikely, although hypersplenism as occasionally seen in Felty's syndrome may be a factor, but most anaemic rheumatoid patients show no evidence of increased haemolysis. Red cell life-span measurements are also non-contributory.² Haemodilution has been postulated as a minor factor, and Dixon *et al.*³ have shown an increased plasma volume in rheumatoid arthritis patients, as compared to controls. Marrow hypoplasia is never very evident, but in those cases where none of the above factors operate decreased erythropoiesis is the remaining possibility.

For the many patients where treatment is required oral iron, parenteral preparations, or even transfusions are necessary. Surely any paper dealing with rheumatoid arthritis should contain at least mention and discussion, if not prominence, of such an important, common, and fascinating manifestation.—I am, etc.,

A. CALIN.

Guy's Hospital,
London S.E.1.

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Care of Aged Doctors

SIR,—Having seen one elderly woman doctor suffer in the way Dr. Kenneth Hazell describes (16 August, p. 412) from apparent lack of more suitable facilities, may I ask: (i) What is the size of the problem? (ii) What happens to those in other professions similarly afflicted? (iii) What help can the B.M.A.'s Benevolent Fund perhaps provide?—I am, etc.,

J. P. CRAWFORD.

Sevenoaks, Kent.

SIR,—I am entirely in agreement with Dr. Kenneth Hazell (16 August, p. 412), and feel that something should be done about his suggestion.—I am, etc.,

W. J. McKEAND.

Eastbourne, Sussex.