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, and chest radiography, chest-x-ray,
and urine culture were normal. Three days after
her temperature was normal and she was
transferred to a psychiatric hospital (Dr. J. G.
Henderson). She was treated with chlorpromaz-
ine and benztpine and continued on carbim-
azole 20 mg. daily. Two months later she was
more violent and disturbed 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 hyper-
thyroidism, 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.,
ANiTHOY J. HedLEY.
R. D. BewsHER.
Department of Therapeutics
and Pharmacology
University of Aberdeen.

References
1 Williams, R. H., Clute, H. M., Anglem, T. J.,
and EdRwards, R. H., Endocrinology, 1964, 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
Jackson 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 to show that it demolished the
theory that distension produces diverticula.
But nobody paid any attention, any more
than they did to the work of Edwards pub-
lished a decade later.

I think it is probable that the work of these
two eminent men should have been for-
gotten, when now, at length, their judgements
have been vindicated.—I am, etc.,
R. R. WILSON.
Department of Pathology,
St. Vincent’s 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 antihemophilic globulin
(cryo) is unusual. The only reported case is
that of Del Ducu and Eppes,5 who described
a 39-year-old man 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 at the Hospital for Sick Children,
Great Ormond Street, with dysarthria, blurring into
his right knee joint of two days’ duration.
He was given 18 units of cryo over 48 hours and
allowed to go home, i.e., the day after the injury
to his left knee caused a large haemarthrosis.
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 haemarthrosis 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 he was cold, moist, jaundiced skin, diffuse
subepicardial tachycardia, and purpuric rash on his
arms and legs. He was severely dehydrated.
Investigation confirmed the dehydration and showed
evidence of gross liver cell damage. He was
rehydrated, but continued to vomit.
Twenty-four hours later he developed
brown watery fluid which contained haemo-
globin. One litre of fresh frozen plasma
was transfused, and vitamin K (10 mg.
every six hours) was started for 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. By this time his haematocrit
level and 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 sub-
capsular surface was extensively mottled by
haemorrhage. 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 haemorrhages.
The stomach, duodenum, and jejunum main-
tained altered blood. There was a sub-
mucosal haemorrhage in the lower third of
the oesophagus. No obvious bleeding point
was found in the gastrointestinal tract.
The heart (428 g.) showed petechiae and a
large (4 x 1.5 cm.) subendocardial haemorrhage on the
left side of the intrav-
ventricular septum. Blood was present in the
trachea and main bronchi, and haemorrhage in the
submucosa of the hypopharynx. There was
no large occlusion of blood vessels. The
lungs were moist and densely 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
carried out on serum taken during the acute
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 agglutina-
tion.

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

Cryo represents a considerable advance
in the management of severe haemophilia.
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
strongly 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 Ducu, V., and Eppes, R. B., New English
Journal of Medicine, 1969, 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
passively needed, rather than 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 cer-
tainty is that suction from elastic recoil does
not measurably persist throughout diastole,
although, as Linden’s “suction” is only one
way of looking at a pressure difference and
it is likely that the pressures involved
are the same. The suction pressures
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 con-
ceive how Starling’s law of the heart could
otherwise remain valid and an adaptive
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 of diastole.

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 Later, mitral suction as the
result of outward movement of the valve
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 circumstance 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. 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.

REFERENCES
3. Cribb, D. G., British Heart Journal, 38, 266.

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 Hulgren and Hubis.2 Two of these patients developed incompetence around the prosthesis, and in neither was a third heart sound recorded. In a later study4 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. RAFFERY.
Cardiac Department, King's College Hospital, London S.E.5.

REFERENCES

Pyuria and Bacteriuria
SIR,—We agree with Dr. J. M. Littlewood (16 August, p. 416) that microscopic examination of fresh, unstrained 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 only 10 organisms 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 variable 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 12%),3 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 article5 seems more promising because it can be adapted for automation.

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.,
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R. H. R. WHITE.
The Children's Hospital, Birmingham.

N. M. JOHNSON.
School Health Service, City of Birmingham.

REFERENCES

Rheumatoid Arthritis: Extra-articular Manifestations
SIR,—Dr. F. Dudley Hart's Philip Ellinman 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.

—Lassitude, general malaise, and depression are often aggravated, and rehabilitation is almost unattainable until 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 intra-venous 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 haemolysis 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. Haemorrhage has been postulated as a minor factor, and Dixon et al.6 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 erythropoesis 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.
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REFERENCES

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. CRAWDUF.
Smooaks, 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.