of postmenopausal women cannot be excluded—for example, stress, parity, and diet, also the persistence of enzymic activity in the ovaries[2 3] or possibly in the uterine body.

I found that hysterectomized and oophorectomized women tolerate continuous treatment for a longer period than "normal" women. Intermittent therapy (thrice weekly) with all forms of oestrogenic substances is the treatment now used in this clinic. This therapy is based on empirical rules.

It would be a great asset if we could evaluate the menopause in a more precise manner to establish or confirm oestrogen lack as the cause of the various postmenopausal symptoms, and research is proceeding along these lines in this clinic.—I am, etc.,

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Decline of the Necropsy

SIR,—The writer of your leader "Decline of the Necropsy" (24 April, p. 181) must surely have had his tongue in his cheek. In compliment to my clinical colleagues it should be made clear that the decline of the hospital necropsy has arisen since surgeons now send their specimens to the pathologist while the patient is still alive, and advances such as antibiotic therapy have converted necropsies on medical patients to studies in degeneration rather than infection.

As for "hack operations"—firstly, these frequently involve the honour and liberty of the subject; insurance, compensation, and legacies; and the reputation of one's colleagues. The same cannot be said of routine hospital necropsies.

Secondly, the principle envisaged by your writer could be extended further. Surgeons might be released from removing normal appendices in nursing homes, gynaecologists from performing routine abortions in private clinics, and physicians from fussing over private neurotics anywhere; these gentlemen would not then be "condemned to neglect more important hospital duties." Moreover there is no reason why a barrister should waste his valuable time attending court for a plea in mitigation in respect of some peculiarly revolting villain; solicitors should not be asked to conduct conveyancing; indeed one can continue ad infinitum.

Although admittedly I must now eschew the higher flights of chemistry and virobacteriology nonetheless a fundamental interest in haematology has not prevented me from considering myself a better "pathologist" because on occasion I look at sections and even make postmortem examinations. Indeed, I have come to the view that apart from the occasional (very occasional) surgical biopsy it is the coroner's necropsy alone in which the full skill, learning, and responsibility of the pathologist (as distinct from technical and scientific procedures) is seen to full advantage.—I am, etc.,

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Blue Valve Syndrome

SIR,—Your leading article "Blue Valve Syndrome" (8 May, p. 294) gives a rather incomplete picture of a condition which must, by now, be familiar to all pathologists interested in the heart. This is presumably the condition originally described in 1958 by Fernex and Fernex,[1] which is not uncommon in general hospital necropsy material, at least in this region.[2] Apart from the familial cases, this abnormality is seen mainly in the elderly and was found in 1% of necropsies on patients over 50 in this hospital.

It may well be that the condition proceeds to intractable heart failure, but this process probably takes many years. Histories of loud mitral systolic murmurs for 20 years before the final illness are not uncommon, and about a third of the cases that I have seen died of non-cardiac disease. Clinicians should be aware that mucoid degeneration predisposes to "spontaneous" rupture of the chordae tendinae as well as to endocarditis (both infective and non-bacterial thrombotic), but apart from these complications the mitral incompetence seems to be relatively well tolerated in the age group in which it is most often found.

Finally, may I protest against perpetuating this new term "blue valve syndrome". It seems to have been coined on the basis of a single case by authors[3] whose review of the literature was confined to four American papers. In my experience of over 50 cases the colour is more accurately described as pearly-grey and emphasis on the occasional blue tinge would only add to the number which are incorrectly labelled rheumatic valvular disease. There is undoubtedly a place for a short, recognizable name for this comparatively common condition but Fernex and Fernex's original term "mucoid degeneration" is as short, and considerably more accurate than the term "blue valve".—I am, etc.,

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Beta-adrenergic Blocking Drugs

SIR,—Your leading article on "Beta-adrenergic Blocking Drugs" (30 January, p. 243) raises some fundamental questions in this rapidly expanding field. The first is the distinction between intrinsic sympathomimetic activity and selectivity. There is good pharmacological evidence, in both animals and man, that practolol has a cardioselective action. However, it is quite possible that an agent with intrinsic sympathomimetic activity could achieve a selective effect if sympathetic tone were higher in the heart than in the bronchial smooth muscle. It has been shown for agents with intrinsic sympathomimetic activity that where sympathetic tone is low, no change in function results, but where tone is high beta blockade occurs.[1] This is supported by the comparative study on airway function in asthmatics done by Connolly and Batten.[2] It would appear from their study that a drug does not have to be cardioselective to have less effect on airway resistance. In any case whether drugs are cardioselective and/or have intrinsic activity, they may still provoke asthmatic attacks in sensitive subjects, and at present there is no beta-blocking drug which is free from side effect.

The leading article comments on a paper in the same issue by Sandler and Pistevos (p. 254). In this paper, considerable falls in blood pressure were seen after intravenous oxprenolol given for the treatment of dysrhythmias after myocardial infarction. It is unfortunate that oxprenolol was administered as bolus injections in amounts up to 6 mg. As the drug is approximately equipotent with propranolol, it is not surprising that a bolus injection might cause hypotension. The main therapeutic conclusion is that any effective beta-blocking drug when given intravenously should be injected slowly with extreme caution, as there is no known beta-blocking drug which would be free from the risk of provoking hypotension in such a situation.

Another major problem in evaluating the newer beta-blockers is obtaining an accurate estimate of their beta-blocking potency versus propranolol in man. This is especially true of the cardioselective drug practolol, where the standard test, which is prevention of isoprenaline tachycardia, becomes difficult to interpret.

In the therapeutic situation practolol has been evaluated extensively in angina. In only one published study so far[3] where practolol has been compared with propranolol in the same patients it seems that practolol was approximately one tenth as potent as propranolol. In the same symposium, Prichard[4] also stated that the maximum effect that could be obtained in angina with practolol was less than that which could be obtained with propranolol. Therefore it becomes difficult to interpret the frequency of side-effects such as bronchospasm and heart failure, because part of the apparent therapeutic advantage of practolol may be due to the fact that it is being used in doses which do not produce the same degree of beta blockade.

It would seem to me that there is a strong case for doing double-blind cross-over trials in angina, using the newer drugs oxprenolol and practolol, in an attempt to assess their relative potency, and side effects due to beta blockade, such as hypotension and bronchospasm.—I am, etc.,

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Breath-activated Aerosol

SIR,—I should like to report a small study of a new breath-activated, pressurized inhaler. This device (Autohaler) has been developed in an attempt to overcome the problems which some patients experience in synchronizing the delivery of a metered dose of bronchodilator drug with the beginning of a deep inspiration.[1] To obtain maximum benefit from a pressurized inhaler, the dis-

charge of the inhaler must coincide with the start of a deep inspiration.[2] The importance of teaching patients the correct technique of using these inhalers has been stressed.[2-4]

The Autohaler consists of a plastic case incorporating a spring-loaded-dose release mechanism which is triggered by the negative pressure of inspiration. This mechanism operates a renewable cartridge consisting of a conventional pressurized aerosol vial and a washable mouthpiece. It is claimed that the new device ensures that the dose is released automatically within the first 5% of inspiration and that the breath-activated "trigger mechanism" is capable of being operated by an inspiratory effort equivalent to a flow as low as 20 l./minute. The possibility that a patient with considerable respiratory disability may not be able to trigger the firing mechanism was investigated.

Twenty-six patients who all had severe degrees of airways obstruction with a forced expiratory volume in one second (FEV_1) of less than 1 litre were instructed how to use the Autohaler. They were then asked to take at least two puffs from an Autohaler containing placebo only and their ability to operate the mechanism was assessed (Table). In addition, if the patient had used a conventional inhaler in the past, he was asked to compare the Autohaler with this previous inhaler—*as a device only*—and his preference was recorded. The results of this simple evaluation of Autohaler are shown in the table.

Patient	FEV_1	Ease of "Triggering"*	Preference†
1	350	A	3
2	900	A	3
3	500	A	3
4	700	A	2
5	700	A	3
6	850	A	3
7	600	A	3
8	650	A	0
9	750	A	3
10	900	A	3
11	550	A	2
12	600	A	3
13	450	A	0
14	850	A	0
15	950	A	3
16	900	A	3
17	400	A	3
18	600	A	3
19	450	B	0
20	750	A	1
21	750	A	0
22	450	B	1
23	650	A	3
24	450	A	3
25	950	A	3
26	650	A	0

*A Without any difficulty
B Difficult
†0 No previous experience
1 Not as good
2 As good
3 Better than ordinary inhaler

This new breath-activated device would seem to offer a number of advantages over conventional pressurized bronchodilator inhalers. It is capable of being operated by patients with considerable respiratory disability and appears to overcome the problem of synchronizing release of the drug with the beginning of inspiration. The manufacturers also claim that as it cannot be "test fired" it should prove economical in use. However, this new inhaler could have its dangers, simply because it provides an easier and probably more efficient way of administering potentially dangerous sympathomimetic amines and propellant gases.[5] Its simplicity may persuade the unwary doctor to prescribe this, or similar devices, for patients previously regarded as being not intelligent enough, or more important, not old enough to use a conventional inhaler, and it is in these groups—the unintelligent and the very young—that excessive use of pressurized aerosols may be expected.—I am, etc.,

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Ampicillin Rashes in Glandular Fever

SIR,—Dr. T. Pastor (24 April, p. 222) has raised several questions regarding the occurrence of rashes in almost all patients with glandular fever who are given ampicillin. Reports of this intriguing phenomenon first appeared in 1967,[1-3] and there have been several reports since, almost all referring to only one or two cases. The cause of this phenomenon is quite unknown and it is not even certain whether the eruption is an allergic or a toxic manifestation. Glandular fever is characterized by production of abnormal antibodies and abnormal lymphocytes, and since both antibodies and lymphocytes are concerned in allergic responses it is tempting to assume such a reponse to ampicillin. On the other hand, there is almost invariably some impairment of liver function in patients with glandular fever[4] and it has been suggested that this may lead to production of toxic metabolites of ampicillin such as penicillamine, which is said to cause similar rashes.[5] However, if this latter were the case, one would expect a high incidence of ampicillin rashes in patients with infective hepatitis treated with this drug. Although many patients must be given ampicillin during the prodromal phase of infective hepatitis a high incidence of ampicillin rashes has not been reported in this condition as far as I am aware.

Whether the "hypersensitivity" to ampicillin in patients with glandular fever is permanent or temporary is, likewise, not known. There is, quite rightly, a reluctance deliberately to expose patients to the risk of a recurrence of what is usually an extremely florid skin reaction associated almost invariably with fever. There is, too, the spectre of sudden death due to anaphylaxis, though anaphylactic reactions to ampicillin have only rarely been reported. Ampicillin has on at least two occasions been continued for several days after patients with glandular fever developed what were almost certainly rashes due to the ampicillin and the rash has cleared in each case before the ampicillin was discontinued.[2 6] This, of course, may have been because of the development of a temporary latency with regard to "hypersensitivity"—a well-known phenomenon of true penicillin allergy—and must not be taken to indicate that ampicillin may be given subsequently with impunity. One of the patients included in my own series of patients with glandular fever and ampicillin rashes was inadvertently given ampicillin a year later and, within a day or two, developed another florid maculopapular eruption.

While one cannot, because of lack of evidence, say whether one should assume patients with glandular fever who develop ampicillin rashes to be subsequently allergic to ampicillin there is, to my mind, convincing evidence that one need not consider such a patient to be allergic to penicillin G or penicillin V. Thus patients with glandular fever given penicillin G or penicillin V do not have a higher incidence of rashes than untreated patients,[7] and several patients who developed rashes due to ampicillin during an episode of glandular fever have subsequently been given penicillin without ill effect (personal observation). Knudsen[8] gives good reasons for believing that the maculopapular erythemas most commonly associated with ampicillin therapy in general are not true penicillin rashes and I would certainly support this view. In fact, my experience with glandular fever had led me earlier to make the suggestion that many rashes due to ampicillin and, probably, other post-1959 semisynthetic penicillins are not true 6-aminopenicillanic acid hypersensitivity reactions.[7]—I am, etc.,

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Henoch-Schönlein Nephritis

SIR,—May I be allowed to comment on your leading article (15 May, p. 352) on "Henoch-Schönlein Purpura and the Kidneys"? The paper by Dr. S. R. Meadow and his colleagues (of whom I am one), to which you referred several times, has not yet been published and the majority of your readers—save those few who heard an abbreviated version presented before the British Paediatric Association last month—are not in a position to judge the accuracy of your statements or the soundness of your opinions.

The mortality of Henoch-Schönlein nephritis is compared in adults and children: "This relatively high mortality rate is in strong contrast to the situation found in children; only two of Meadow's 87 cases with renal disease died." Actually three out of 88 have died; moreover, no mention is made of four additional children with active nephritis and declining renal function, two of whom are already in early chronic renal failure two and five years after onset. This appreciably modifies the view that one must take of the ultimate mortality in children, which is probably not very different from that reported in adulthood. Progressive glomerulonephritis of any kind is a relatively infrequent occurrence in children but Henoch-Schönlein purpura is nevertheless one of the commoner individual causes.

Secondly, you state that we have "recorded several striking successes" with cyclophosphamide therapy in severely affected children. This is untrue; our results fail to reveal any definite advantage for either cyclophosphamide or azathioprine over con-