

MEAN VALUES OF S.T.I. AND STANDARD DEVIATION (S.D.) IN TEN HEALTHY VOLUNTEERS

Variable	Absolute values (mean±S.D.)	Successive measurements	
		S.D.Δ%	Least significant difference (P≤0.05)
P.E.P. _c	125.0±13.1	9.46%	19.0%
L.V.E.T. _c	400.5±8.8	2.58%	5.2%
P.E.P./L.V.E.T.	0.317±0.038	11.08%	22.2%

Least significant differences at 95% confidence level between two consecutive measurements in the same individual are given in right-hand column.

Tracings were made and interpreted in the way described by Weissler et al.⁵ In order to estimate the variation between two consecutive measurements in the same person, the successive difference variation was used as statistical test. The relative difference (Δ%) was calculated by expressing the difference between two successive measurements A and B as a percentage of the average (A+B)/2. Two successive measurements would, with 95% probability, be expected to be separated by no more than 2 standard deviations. We found that in a particular patient the pre-ejection period index (P.E.P._c) must change by at least 19%, left-ventricular ejection time index (L.V.E.T._c) by 5.2% and P.E.P./L.V.E.T. by 22% to become significant at the 95% confidence level (see table). The measurements did vary in individuals regardless of the time elapsed between recordings.

Thus in monitoring S.T.I. values in patients on cardiotoxic drugs such as doxorubicin, P.E.P._c or P.E.P./L.V.E.T. must increase by at least 20% to reflect unequivocally a drug-induced negative inotropic effect.

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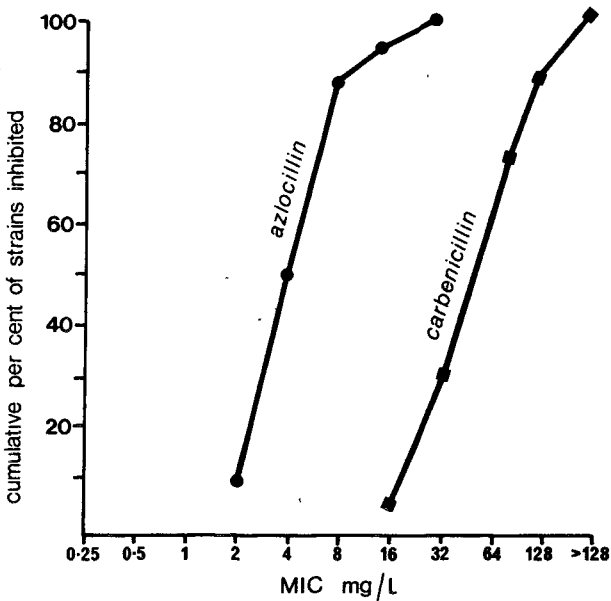
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IN-VITRO ACTIVITY OF AZLOCILLIN AGAINST PSEUDOMONAS

SIR,—The activity of azlocillin, a new semisynthetic broad-spectrum ureidopenicillin, was evaluated in vitro against 104 strains of *Pseudomonas aeruginosa* and compared with carbenicillin.

Fresh consecutive clinical isolates of *Ps. aeruginosa* from different patients were tested on the direct sensitivity test agar (D.S.T. Oxoid) containing 5% lysed blood by the disc diffusion method, using NCTC 10662 as the control organism and inoculating to give a semiconfluent growth. Four antibiotics—azlocillin (0.03 mg), carbenicillin (0.10 mg), gentamicin (0.01 mg), and tobramycin (0.01 mg)—were tested by this method. The minimum inhibitory concentrations (M.I.C.s) were determined by the agar-incorporation technique using the same medium as above, the concentration of both azlocillin and carbenicillin ranging between 0.25 and 128 mg/l. 10 µl of broth containing 10 000 colony-forming units was spotted on the plate with the help of a multiple inoculator. 99% reduction of the original inoculum was taken as the M.I.C.

By both disc diffusion and agar incorporation techniques 12 strains of *Ps. aeruginosa* were found to be resistant to carbenicillin with M.I.C. greater than 128 mg/l, but none was resistant to azlocillin, gentamicin, or tobramycin. The M.I.C. for carbenicillin was 4–8 times greater in vitro than that for azlocillin (see figure). None of the strains was inhibited by less than 2 mg/l of azlocillin. Azlocillin is inactivated by β-lactamase but this may be counteracted to some extent by the very high in-



In-vitro activity of azlocillin and carbenicillin against 104 strains of *Ps. aeruginosa*.

trinsic molecular activity of azlocillin. Also there was a significant difference between M.I.C. and M.B.C. (minimum bactericidal concentration) with increasingly heavier inoculum but the clinical relevance of this is not known for certain.¹

The peak blood levels attainable have been reported as 166 mg/l² and 431 mg/l, respectively, after 2 and 5 g of intravenous azlocillin (the only route by which it can be administered at present);³ all of our strains should, therefore, be susceptible to this compound.

Carbenicillin is a useful antibiotic, especially when in combination with an aminoglycoside such as gentamicin, for the treatment of systemic infection caused by *Ps. aeruginosa*. However, the administration of very large doses of carbenicillin on its own to treat sepsis may lead to side-effects.^{4,5} If the in-vitro activity of azlocillin is reflected in vivo, and provided the emergence of resistance does not become a major problem, it will no doubt have a place in treating pseudomonas infection.

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ALLERGIC REACTION TO BITE OF FLY LARVA OF FAMILY THEREVIDÆ

SIR,—A boy of 10 was pushing his hand through soft sand in West Glamorgan when he found a fly larva of the family Therevidæ (Diptera). On trying to remove the larva from his hand he was bitten between the little finger and the next. The bite left a white area with two small red punctures in the centre. The area became swollen and the boy became so ill that he was taken to hospital where it was thought that the reaction was partly allergic and partly psychological. The boy suffers from asthma and hayfever.

The larvae of Therevidæ normally favour sandy soil where they are voracious predators of earthworms and beetle larvæ. A fully grown larva of the genus *Thereva*, to which the present specimen almost certainly belongs, is about 3 cm in length, active, and whitish in colour with a distinct brownish head capsule. There is no previous record of their biting man but

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there are two cases¹ of their involvement in cases of intestinal myiasis presumably arising from their accidental ingestion in food originating in the soil. The only similar case of which I have heard is of a larva of a horse-fly (*Tabanidae*) biting a finger during a demonstration but this produced no ill-effects. Although likely to be of rare occurrence, it is possible that many soil-dwelling fly larvæ of predaceous habit, and with consequently well-developed mouthparts, could be capable of piercing the skin. Allergic reactions to such bites are also a possibility though they will not be as common as reactions to bites and stings of certain adult insects such as ants, bees, and wasps which inject "venom".

The study of allergic reactions to the stings and bites of insects has been neglected in Britain but is receiving considerable research attention in the United States^{2,3} where fatalities from insects exceed those from poisonous snakes.³ I would welcome any information on unusual allergies or fatalities resulting from insect bites or stings for use in the current revision of a standard text.⁴

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LEVAMISOLE IN CROHN'S DISEASE

SIR,—Reports of two uncontrolled studies on the treatment of Crohn's disease with levamisole were encouraging.^{5,6} We report here the results of a small double-blind trial of levamisole in patients with active Crohn's disease who had received no previous medical treatment or no specifically immunosuppressive treatment for at least 3 months. The aim of the trial was to assess whether levamisole would maintain a steroid-induced remission.

All patients gave informed consent and were treated initially with 'Synacthen', 2 mg intramuscularly daily for three days and then prednisolone, 60 mg daily. In addition patients were allocated to receive either levamisole or placebo in a double-blind fashion and in a dose of 50 mg daily for 1 week, twice daily for 2 weeks and three times daily thereafter. Steroids were reduced according to clinical response and the patients were followed up fortnightly and later monthly or every 2 months for a total of one year. Clinical, hæmatological, and biochemical assessments were scored in a pre-arranged manner.⁷ A relapse, as judged by two doctors independently, was recorded as a failure.

Seventeen patients entered the trial. Only two of the seven treated with levamisole successfully completed the year's trial and steroid therapy had been withdrawn by 3 and 7 months. Three patients relapsed at 2, 3, and 7 months whilst still taking prednisolone. One patient was withdrawn at 3 months because of a drug rash and one because of non-compliance. Both were still on steroids but neither had relapsed.

Four of ten control patients completed a year's follow-up having stopped steroid therapy at 4, 5, 6, and 7 months. Three patients relapsed while still taking steroids at 3, 4, and 5 months and one further patient at 8 months who had stopped steroid therapy 1 month previously. One patient was withdrawn at 3 months because of itching and one patient died following a mesenteric embolus. Levamisole had no apparent steroid-sparing effect and there was no difference in the disease-activity score between the two groups.

We have now abandoned this trial. We failed to show any

benefit of levamisole treatment in this admittedly small study. If we could predict that levamisole might reduce a relapse-rate of 40% over one year by half, forty recurrences would need to be observed and approximately one hundred and thirty patients entered into the trial. This would give a 50% chance of showing a statistically significant result;⁸ to improve the chances would require more patients, longer follow-up, or a better treatment. Secondly, azathioprine has already been shown to have a steroid-sparing effect⁷ and to reduce the relapse-rate in the long term.⁹

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LYMPHOMA AND RHEUMATOID ARTHRITIS

SIR,—Dr Barrett and colleagues¹⁰ asked rheumatologists or epidemiologists to reveal if the incidence of lymphoproliferative disorders in patients with autoimmune diseases is higher than that in the general population. We have studied the incidence of malignant neoplasms in patients with rheumatoid arthritis (R.A.) using two separate nationwide data registers covering the whole Finnish population—namely, the Social Insurance Institution's population data register with information on medication for certain chronic diseases (including R.A.) and the Finnish Cancer Registry with data on all cancer patients diagnosed in Finland. The follow-up of 11 483 male and 34 618 female patients with R.A. yielded a total of 213 911 person-years.¹¹ The observed number of cancers was higher than expected in men (407 *vs.* 354.1) and much as expected in women (795 *vs.* 783.8). An increased risk of leukæmia, lymphomas, Hodgkin's disease, and myeloma was found; 130 cases were observed, only 59.6 expected ($p < 0.001$).

There seems to be an excess risk of leukæmia, lymphomas, and myeloma in patients with R.A. The continuous immunological stimulation in R.A. could cause proliferation and malignant transformation of some clones of immunologically competent cells.¹² Immunodeficiency in patients with autoimmune diseases might also be involved.¹⁰ The pathogenetic pathways of lymphoproliferative neoplasms in R.A. patients are, however, far from clear.

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FLOPPY MITRAL VALVE

SIR,—Your editorial of Jan. 20 is a scholarly piece with which I find no disagreement. I would point out, however, that "floppy valve" was a term originated by a cardiovascular surgeon, Dr Raymond Read¹³ (born and educated in England, now residing in the United States), who was not cited in your editorial. Indeed Hurst's textbook refers to myxomatous degeneration of either the mitral or aortic valve as Read's syndrome.¹⁴

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