## Comment

Self monitoring of blood glucose concentrations has had a major impact on the management of diabetes and when used with either intensified conventional treatment or continuous subcutaneous insulin infusion allows euglycaemia to be achieved.[3] The technique has been notably free of problems except for one reported case of dextrose contamination of the finger tips.[4]

Healthy skin will tolerate repeated puncture without ill effects. In diabetes, however, several adverse factors may be compounded and lead to tissue necrosis. Impaired blood supply, neuropathy, abnormal synthesis of collagen, and the fact that more intensive monitoring is required as the disease progresses lead to an increased risk of infection initially followed by impaired healing, which impedes recovery. As in our patients, the creation of shunts in the forearm for vascular access in haemodialysis may further compromise blood flow to the fingers. Impaired peripheral sensation, often present in these patients, may aggravate matters since the patient may continue to use an obviously damaged but pain free site. The increased risk of infection during immunosuppressive treatment after renal transplantation may be another compounding factor.

In case 1 problems occurred in only one finger, which may represent an unfortunate lapse of aseptic technique; the increased risk of infection in diabetes, however, was shown by the poor outcome despite prompt antibiotic and surgical treatment. The ease of prevention compared with the difficulty of eradicating established infection must be emphasised to diabetics using this self monitoring technique. Our second patient had more severe vascular disease, neuropathy, and visual impairment that led to her sometimes having to use several sticks for a single capillary blood sample. She also took at least four and often seven readings a day. These factors all contributed to the occurrence of sepsis on several fingers and emphasise the increased likelihood of problems when a partially sighted patient obtains capillary blood samples from fingers with decreased sensation. Advice should also be given to diabetics with haemodialysis shunts to avoid getting samples from the fingers of the arm containing the shunt and on the appropriateness of using the side of the finger rather than the finger pulp.

Although we use self monitoring in many of our diabetics and all of our diabetics with renal failure, who usually have associated neuropathy, this complication is rare. Nevertheless, it is important to prevent these lesions and to give careful attention to ulcers when they appear.


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3 Reeves ML, Seigler DE, Ryan EA, Skyler JS. Glycemia control in insulin-dependent diabetes mellitus: comparison of outpatient intensified conventional therapy with continuous subcutaneous insulin infusion. *Am J Med* 1982;**72**:673-80.

4 Kinmonth AL. Home blood glucose monitoring: a sticky artefact. *Br Med J* 1981;**282**:272-3.


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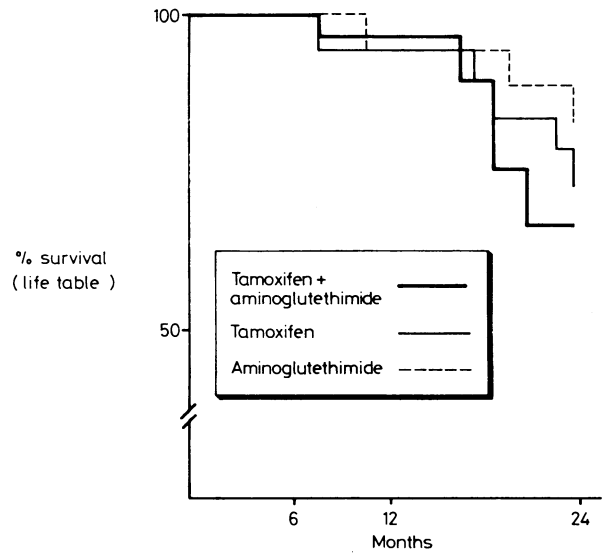
# Combination treatment with tamoxifen and aminoglutethimide in advanced breast cancer

Tamoxifen and aminoglutethimide are effective drugs in the endocrine treatment of advanced breast cancer with response rates of around 30%.[1 2] They act by different mechanisms,[1 2] and by analogy with combination chemotherapy we studied their efficacy in combination in the treatment of advanced breast cancer. We compared our results with those obtained in a previous trial comparing the two drugs as single agents.[2]

## Patients, methods, and results

Sixty two consecutive patients with histologically proved advanced breast cancer were treated with tamoxifen 10 mg by mouth twice daily in combination with aminoglutethimide 250 mg by mouth three times daily (increasing to four times daily after two weeks if toxicity permitted) with hydrocortisone 20 mg twice daily. Standard criteria for staging disease and for defining objective response were used as previously described.[2] Median age was 56 years (range 31-77 years); six patients were premenopausal, eight perimenopausal, and 48 postmenopausal or postoophorectomy.

Twenty three of the 62 patients (37%) achieved an objective response and seven showed stable disease for at least three months. Responses were seen for all sites of disease, including soft tissue (12/25 patients), bone (8/29), lung (5/16), and liver (2/6). The figure shows the duration of the response calculated by life table analysis compared with that for tamoxifen and for aminoglutethimide used as single agents.[2] Median duration of response was




Duration of response from start of treatment (life table analysis) obtained with combined tamoxifen and aminoglutethimide compared with responses obtained with tamoxifen alone and aminoglutethimide alone.[2]

16 months, which is not significantly different from the duration of response obtained with each agent alone. Median survival of patients who responded has not yet been reached, but at 24 months after the start of treatment the predicted survival rate for combination treatment was 67%, compared with 75% for tamoxifen alone and 82% for aminoglutethimide alone. Side effects were similar to those previously described for aminoglutethimide alone[2] and included initial lethargy or drowsiness (35%), a self limiting rash (27%), nausea (11%), and depression (18%). Four patients (6%) could not tolerate treatment.

## Comment

This study suggests that a combination of tamoxifen and aminoglutethimide has no advantage over either agent used alone in terms of the rate or duration of response. Indeed, our results reflect the consistent reporting of similar rates and durations of response obtained with all major forms of endocrine treatment used alone in advanced breast cancer.[3]

In the absence of therapeutic benefit combined endocrine treatment has disadvantages. It is more expensive and likely to be associated with increased toxicity. More importantly, the opportunity offered by sequential treatment for a second response after relapse with first line treatment is lost. This might eventually be reflected in a shortened overall survival with combination endocrine treatment, although such a disadvantage would take time to emerge and has not so far been seen.

Different combinations of endocrine treatment might possibly be more effective than this one, although reports so far are not encouraging. Two Danish trials failed to show any benefit for tamoxifen combined with medroxyprogesterone acetate or diethylstilboestrol over tamoxifen alone.[4] Preliminary data from a triple combination trial with tamoxifen, aminoglutethimide, and danazol show a higher response rate but no difference in duration of response or survival compared with tamoxifen alone,[5] and a trial of combined aminoglutethimide and danazol showed a significantly inferior rate of

response and survival compared with aminoglutethimide alone (R Murray, personal communication). Further studies are required, but we doubt whether combination endocrine treatment is likely to confer appreciable advantage in this disease.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# Clinically apparent rubella reinfection with a detectable rubella specific IgM response

Subclinical reinfection with rubella may occur, particularly if seroconversion has been induced by rubella vaccine.[1] Verified reinfections in which the patient has developed a rubelliform rash, however, have been reported infrequently. Traces of rubella specific IgM have been detected in reinfection in people with vaccine induced seroconversion after experimental challenge,[2] but there is only one report of its detection in a reinfection after seroconversion due to natural infection.[3] Indeed, the absence of detectable rubella specific IgM has become accepted as a characteristic of rubella reinfection.[4]

We report a case of confirmed, clinically apparent rubella reinfection in an immunocompromised patient with presumed previous natural infection and in whom a rubella specific IgM response was detected.

## Case report

A 19 year old woman was diagnosed as having acute lymphoblastic leukaemia in April 1982. Remission induction chemotherapy with standard agents achieved a complete remission by the fourth week. Central nervous system prophylaxis (radiotherapy and intrathecal methotrexate) for four weeks was followed by maintenance treatment.

Seven days after beginning maintenance treatment (22 July) she presented feeling generally unwell with aching limbs, espisodes of shivering, and loose stools. She was feverish (39 C) and had conjunctival injection but no arthropathy or lymphadenopathy. Soon after admission a fine macular rash appeared over her arms and back. The white cell count was $3{\cdot}4\times10^9$/l (neutrophils 20%, lymphocytes 66%, monocytes 14%). The illness was clinically diagnosed as rubella and questioning disclosed contact with a child with a rubelliform rash three weeks previously. The patient gave a serologically unconfirmed history of rubella as a child and denied having been vaccinated against rubella. The illness resolved within three days.

Sera collected in April 1982, on the day of admission, and at later intervals were available (table). The six sera were evaluated for rubella specific antibodies by haemagglutination inhibition, radial haemolysis, and IgM capture radioimmunoassay. The results showed a haemagglutination inhibition titre of 100 IU and a haemolytic zone of 12 mm for the serum collected in April. These values are accepted as indicative of previous primary rubella. Both of these assays showed a substantial, prompt rise in amount of detectable antibody at the onset of the illness. Antibody capture radioimmunoassay is a sensitive assay for rubella specific IgM,[5] values exceeding 3·3 arbitrary units rarely being found without supporting evidence of recent rubella infection (personal observation). Rubella specific IgM was not detected in this patient's serum before her illness but a peak of 6·1 arbitrary units was found in the acute phase. The value declined over subsequent weeks. Rubella specific IgM was also detected by gel filtration and haemagglutination inhibition.

## Comment

This patient's illness was clinically diagnosed as rubella and, though she was immunocompromised as a result of her chemotherapy and acute lymphoblastic leukaemia, it was symptomatically mild and of short duration. Even in immunocompromised patients, however, clinically apparent reinfections have been reported infrequently.

The other uncommon feature of the illness was the detection of rubella specific IgM using a sensitive quantitative assay. The detection of rubella specific IgM is established for reinfections in people with vaccine induced seroconversion but there is only one report of its occurrence in a reinfection in a person with natural seroconversion.[3] In that report the patient also had a clinical illness and the diagnosis of a reinfection, rather than a primary infection, was based on the presence of rubella antibody detected by haemagglutination inhibition in a sample of serum taken before the illness. It is now accepted that haemagglutination inhibition titres may be due to residual non-specific inhibitors in the serum and not be indicative of rubella specific antibody. In our patient, preillness rubella specific antibody was detected by radial haemolysis in addition to haemagglutination inhibition.

Although our patient had disturbed immunological function, the results obtained do indicate that rubella specific IgM may be detectable in reinfections when previous seroconversion is due to natural infection. The amount of rubella specific IgM, however, was smaller than seen in primary infections.


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*Results of evaluation for rubella specific antibodies in six samples of serum*

| | 14 April | 22 July | 26 July | 2 August | 16 August | 29 October |
|---|---|---|---|---|---|---|
| Radial haemolysis for rubella specific IgG (zone in mm) | 12 | 15 | 17 | 17 | 17 | 17 |
| Antibody capture radioimmunoassay for rubella specific IgM (arbitrary units) | 1·0 | 6·1 | 5·6 | 5·0 | 4·0 | 2·9 |
| Haemagglutination inhibition (IU) | 100 | 800 | 800 | 800 | 800 | 800 |