

Editorial/Van die Redaksie

New directions in the management of early breast cancer

Until recently most doctors believed that they understood the basic principles of the management of breast cancer. The essence was that operable cancers were treated by mastectomy and inoperable lesions by radiotherapy, with additional oophorectomy in premenopausal women and oestrogen supplementation in postmenopausal women. The past decade, however, has seen the progressive erosion of these precise and time-honoured concepts. Indeed, the armamentarium of the registrar in training is currently an extensive resource of denunciations and denials of all previously held beliefs rather than a confident base of convictions. We find that the disease is no longer divided into 4 stages, but is categorized by a wider-ranging (and more precise) TNM system. An increasing opinion is that mastectomy is no longer required for early breast cancer and that lesser procedures are satisfactory. Chemotherapy has been extended to all stages of the disease, in ever-proliferating acronymic combinations. Given these radical departures from previously established dogma, what is the best treatment for early breast cancer at present? Is mastectomy really necessary and are lesser procedures safe? When and to whom should chemotherapy be administered? Most important of all, what is the best treatment for our patients?

Radical mastectomy was the operation of choice for curable breast cancer for over half a century, and dissenters (like Keynes¹ and Peters²) were regarded as irresponsible and heretical. In the 1950s the controlled clinical trial became a powerful and popular research tool in all branches of medicine and not least in breast cancer. In a search for better survival figures, early trials tested treatments more extensive than radical mastectomy, adding super-radical resection or extended radiotherapy to the operation, but these more extensive procedures were found to be no better than radical mastectomy.^{3,4} A subsequent series of trials progressively tested lesser procedures against the established radical mastectomy and it soon became clear that simple mastectomy (preserving the chest muscles) gave the same results as radical mastectomy. It also became evident that axillary irradiation was unnecessary when axillary dissection had been performed and vice versa. Axillary dissection was useful for prognostication and reduction of nodal recurrence but did not influence the incidence of subsequent distant metastases.⁵⁻⁷ By the early 1970s

opinion had therefore swung away from the classic procedure to simple mastectomy with preservation of the chest muscles. A logical extension of this reasoning was to question whether mastectomy was necessary at all: why not merely remove the lesion and its surrounding tissue, retain the breast and irradiate it? There were several reports (outside of controlled trials) of patients treated by local excision of the lesion and irradiation which attested to the safety of this procedure.⁸ Many centres subsequently undertook controlled trials to test procedures less extensive than mastectomy followed by radiotherapy. The outcome of one of these has been published and has been received with great interest and acclaim. Veronesi⁹ in Milan reported a comparison of removal of a quadrant of the breast (with overlying skin and underlying fascia) followed by radiotherapy in women with cancers of 2 cm or less with classic radical mastectomy in women with similar lesions. He found that survival and recurrence rates were similar in both groups.

Veronesi has gone on to suggest that there might be a variety of therapeutic choices for women with operable breast cancer: firstly, segmental mastectomy with axillary clearance followed by radiotherapy might be the therapeutic choice for women with lesions less than 2 cm in diameter and in whom the size of the breast and location of the tumour make this procedure technically feasible. Secondly, total mastectomy and axillary clearance might be the treatment of choice for the older patient (in whom postoperative radiotherapy would be undesirable or inconvenient) or for patients with larger tumours. Thirdly, radical mastectomy might be the treatment of choice in those patients in whom it is desirable to remove the pectoral muscles because the tumour is attached to the muscle or in cases of treatment failure when mastectomy is being undertaken as a local 'rescue palliation'.

Veronesi has emphasized that not only is the surgical technique a specialized one, but the essential adjuvant radiotherapy requires special expertise. We endorse this view and suggest that these newer techniques be performed either by or in conjunction with recognized centres in this country. The general practitioner should continue to refer patients with suspicious breast lumps to specialists with such an affiliation.

The last decade has seen a massive investigation into the role of chemotherapy as an adjuvant to surgery in various stages of the disease. Metastatic and local recurrence after

surgery was seen to be due to pre-existing micrometastatic deposits and combination chemotherapy was the systemic attack. When the results of the chemotherapeutic trials were pieced together it became evident that adjuvant chemotherapy for early breast cancer delayed recurrence at a 10-15% level in premenopausal women with positive axillary nodes.¹⁰⁻¹² Whether the survival rate was improved at all remains a controversial issue.^{10,11,13} Indeed, it may be that chemotherapy delays recurrence but does not significantly improve survival. It is unlikely that there will be any shattering breakthrough using currently available drugs, and we have a feeling that a plateau has been reached. Also, many problems await resolution and future trials of adjuvant chemotherapy will consist of therapeutic manipulations aimed at reducing toxicity and defining the role of adjuvant chemotherapy in postmenopausal women, in women without axillary lymph node involvement and in women in whom endocrine manoeuvres and irradiation are used concurrently. The 'magic bullet' drug is still awaited. Should our patients with early breast cancer be offered adjuvant chemotherapy if the advantage is merely a delay in recurrence of the order of 10 - 15%? The answer is yes, if they have axillary node involvement (with its serious prognostic implication) and if chemotherapy can be

administered in one of the recognized centres in this country.

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Magnesium deficiency — a cardiac disease risk factor?

In recent years interest in the development of magnesium-related research has given rise to the foundation of the International Magnesium Society and a journal devoted to the mineral, *Magnesium Bulletin*. Magnesium depletion in man usually results from inadequate dietary intake of magnesium salts or increased excretion of the ion in urine or faeces. Clinical evidence of deficiency may include tetany, dysphagia, anaemia and cardiac arrhythmias.¹

Ionic magnesium is a co-factor for the function of many enzymes, of which the sodium and adenosine triphosphatase responsible for maintaining electrolyte balance across myocardial cell membranes is of major interest. Evidence suggests that simple potassium replacement regimens during periods of depletion due to disease or drugs may be insufficient to restore intracellular potassium levels to normal when magnesium deficiency is also present.² An argument can therefore be made for dietary magnesium supplementation in certain patients.

The incidence of magnesium deficiency in South Africa is unknown, although the low magnesium content of drinking water in some areas and the widespread use of preparations such as laxatives and diuretics, which increase magnesium losses, suggest that this question deserves attention.

An interesting parallel exists between some areas of the RSA and parts of Finland, in which water supplies are relatively magnesium-deficient and sudden death, apparently from cardiac causes, is common.³ Whereas Finnish studies have been fairly detailed, and the concept of magnesium deficiency as a major cardiovascular risk factor is gaining ground on pathophysiological and epidemiological evidence, no satisfactory studies have been carried out in South Africa. Careful epidemiological and clinical studies are needed to determine whether any link exists between magnesium deficiency and sudden death in South Africa and, if it exists, to determine why such deaths show an apparent racial bias. In addition, it might be wise to include magnesium and other elements in all future basic investigations of cardiac arrhythmias and the essentials of myocardial metabolism.

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Drugs in pregnancy and behavioural teratogenesis

'One of the first duties of the physician is to educate the masses not to take medicine.'

Sir William Osler, 1849-1919

The press, both medical and lay, has fostered an awareness of the dangers of drug use during pregnancy. The first trimester is widely recognized as the period of greatest risk to the offspring as it is during this period that cell multiplication is most rapid and the bodily organs are defined. During the further months of pregnancy, development of the fetus proceeds at a less hectic tempo, as the organism and its organs consolidate and grow.

However, the emphasis in most reports of adverse effects of drugs during pregnancy is chiefly on the gross anatomical deformities that occur; the thalidomide tragedy, with the birth of infants with rudimentary limbs, gave immense impetus to the awareness campaign, but did stress the anatomical deficits — most thalidomide babies were fortunately spared central nervous system involvement.

The potential of drugs for producing behavioural and intellectual impairment has not achieved the same prominence. Such repercussions of drug therapy are often not associated with any overt anatomical congenital abnormalities, and may well only become apparent months after the birth of the baby. Animal studies have

indicated that a wide variety of drugs do impair the behavioural and intellectual development of the offspring exposed to certain drugs *in utero*. Evidence that similar events occur in humans is accumulating.

Drugs such as tranquillizers, analgesics, anti-emetics, anti-epileptics, antidepressants, cannabis, vitamin A, sex steroids and others have been shown to produce deficits in behavioural development in many animal species. Drugs administered immediately before or during parturition have also been shown to take their toll.

The fact that the central nervous system has not matured by the time the baby is born, and that it continues to organize itself for a long time after, must serve to stress the vulnerability of this system during the whole of pregnancy, and beyond into neonatal and infant life.

The responsibility of the practitioner in educating the pregnant patient to avoid all unnecessary exposure to body-foreign and medicinal substances for the full span of pregnancy and into the breast-feeding period is great. The prescriber's responsibility in avoiding all non-essential medicines for the same time interval is likewise great and deserves special emphasis.

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