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Pointers

Rubella: Testing of three live attenuated vaccines produced antibody levels lower than those from natural infection (p. 271). Chronic viraemia detected in 10 out of 12 babies congenitally infected with rubella (p. 289).

Kidney Disease in Pregnancy: Nineteen patients with nephrotic syndrome were studied through 31 pregnancies. Problems encountered in antenatal period, but in long-term follow up 15 had shown no deterioration of renal function (p. 276).

"Awareness" during Anaesthesia: Investigation of 150 obstetric patients suggests that premedication has an important function in light anaesthesia, as 17·3% had unpleasant "recall," and 6·6% recalled pain (p. 280).

Acute Appendicitis: Nearly half the children admitted to hospital with appendicitis do not have it, though distinction on clinical grounds can be very difficult (p. 284).

Digoxin Intoxication: Plasma digoxin concentration, measured by inhibitory effect on ^{86}Rb uptake by human red cells in vitro, can be useful in diagnosis of intoxication (p. 286).

Urine Specimens: Suprapubic aspiration of bladder shown to be safe and reliable method of collecting specimen, which can be kept at 4° C. or room temperature for up to 10 days before culturing (p. 293).

Epilepsy and the Pill: Low oestrogen/progestogen contraceptive had no effect on frequency of fits in 20 epileptic women on regular anticonvulsant therapy (p. 294).

Primary Hepatic Pregnancy: Report of case (p. 296).

Current Practice: Severe measles in the tropics (p. 297). Today's Tests: Schilling test (p. 300).

Community Nurse Team: Bristol experiment with nurses attached to doctors working from new health centre shows this system has potential (p. 306).

Computers: Conference of the British Computer Society opened by Mr. David Ennals (p. 309).

Personal View: Professor Lars Werkö (p. 311).

L.M.C. Conference: Representatives rejected detailed proposals of the Green Paper at special meeting (*Supplement*, p. 37).

G.M.S. Committee: Government to be asked for assurance on freedom to prescribe (*Supplement*, p. 47).

Police Surgeons: Agreement reached (*Supplement*, p. 53).

Treatment of Advanced Breast Cancer

Some patients with advanced cancer of the breast obtain worthwhile remissions of the disease when its hormonal environment is altered. This may be achieved pharmacologically by the administration of hormones (androgens, oestrogens, progestogens, or corticosteroids) or more drastically by ablation of endocrine glands. An operation of this kind is considered at some stage in the management of most patients and may take the form of bilateral adrenalectomy plus oophorectomy[1] or a direct attack on the pituitary.[2]

Hypophysectomy for advanced mammary cancer was performed originally through a frontal route. The operation can be done through an incision in a skin crease of the forehead; the bone flap is small, and it is not necessary to shave more than 1 to 2 in. (2·5 to 5 cm.) of scalp. In Great Britain some of the best results have been obtained by this procedure and then packing the pituitary fossa with wax impregnated with radioactive yttrium-90 after removal of the gland.[3] When the results of transfrontal hypophysectomy were compared with those of adrenalectomy plus oophorectomy,[4] hypophysectomy appeared marginally the more effective, but for practical purposes there was little to choose between the two methods. Transfrontal hypophysectomy, however, requires the services of a major neurosurgical team and is beyond the scope of many units dealing with mammary cancer, whereas any competent general surgeon can carry out adrenalectomy.

Both procedures are major operations, and many patients may be considered unfit for either of them. A more simple and more widely applicable method of ablation is by implantation of the pituitary with rods of yttrium-90.[5,6] The dimensions of the pituitary fossa are measured from radiographs and the dose of irradiation necessary to destroy the gland is calculated. The yttrium is inserted under *x*-ray control either through the external nares or through tiny incisions on each side of the bridge of the nose. In skilled hands the operation can be done quickly and with a minimum of surgical trauma. The operative mortality and serious morbidity are very low indeed,[7] and patients can usually leave hospital within four to five days of operation. Unfortunately ablation is often incomplete, and careful post-mortem studies in one series of patients suggested that only 71% of patients had had more than 95% of the gland destroyed.[7]

The development of a combined transnasal and transethmosphenoidal surgical approach to the pituitary[8,9] may prove eventually to be the best solution to the problem. This operation, which can be performed quickly and simply by an experienced otolaryngologist, allows a clear view of the recesses of the fossa and gives results comparable to those of other methods.[10] The initial morbidity from persistent leakage of cerebrospinal fluid and meningitis has been reduced greatly by experience and refine-

ments of technique,[11] and the operative mortality (approximately 5%) is similar to that of other methods.

The ideal method of endocrine ablation is not yet known. But carefully controlled comparative clinical trials are already in progress in some of the major centres concerned with this problem.

Despite the many methods of treatment now available, there is no rational plan for the management of patients with advanced breast cancer. A. P. M. Forrest,[7] surveying 211 patients, found that most of them had received at least three different forms of treatment and that 25% had received five or more. The order in which treatments were given followed no definite pattern. As the rate of response to any form of treatment is low, many surgeons prefer to use major endocrine ablation as a last resort after simpler methods—the administration of hormones—have failed. But during hormone therapy many patients either die or become so ill that major ablation is out of the question. In one series a third of the patients died while taking hormones[12]; in another series 43% became unfit for major ablation while receiving treatment with androgens.[13] In spite of this the results of three prospective clinical trials suggest that, from the point of view of survival, there is no advantage to be gained from early endocrine ablation,[4 14 15] and as the morbidity from simple forms of treatment is less than that from major ablation it seems reasonable at present to reserve major surgery until simple methods have failed. Oophorectomy in premenopausal women, or oestrogens (stilboestrol or ethinyl oestradiol) in postmenopausal women, may be followed at a later stage by whichever form of major ablation is most readily available.

In each of these three prospective trials fewer than 30% of the patients showed clear objective evidence of response. The corollary is that some 70% of them were subjected, unnecessarily, in the terminal stages of their illness, to unpleasant forms of treatment which proved to be of no value to them. Patients who respond to treatment obtain a remission which lasts on average for 18 months to two years and occasionally for five years or even longer.[16] Pain from osseous metastases is relieved, lytic lesions recalcify, and pathological fractures may heal. When endocrine ablation is effective it brings dramatic relief, bedridden women may return to a normal way of life, and when they relapse finally death is usually swift. But a method is needed greatly to distinguish those patients who are likely to respond to treatment from those who are not.

Certain factors are known to influence the patient's response. These include the latent interval between treatment of the primary disease and the appearance of metastases, the sites of the lesions, the relation to the menopause, the response to previous endocrine therapy, and the amounts of certain steroid hormones excreted in the urine. Patients with a long latent interval are more likely to respond to endocrine ablation than those with a short one.[11 17] Visceral deposits, particularly those of brain, lung, and liver, seem less likely to regress than skeletal ones.[11 18 19] Premenopausal women fare better than postmenopausal women and those within five years of the menopause fare worst of all. Major ablation is likely to be particularly effective in premenopausal women who have responded previously to oophorectomy. R. D. Bulbrook and his colleagues[20] studied the amounts of various urinary steroids excreted by patients with advanced cancer of the breast who were subsequently treated either by adrenalectomy or by hypophysectomy. They found that in those patients who tended to benefit from operations the urinary levels of aetiocholanolone were high and the levels of total 17-hydroxysteroids were low. Conversely, if aetiocholanolone was low and the 17-hydroxysteroids were high patients were unlikely to respond. In order that these estimations could be used for purposes of prediction they combined them in a formula termed a "discriminant function." The formula was 80–80 (17-OHS (mg./24 hrs.))+aetiocholanolone (μg./24 hrs.). When the preoperative levels of the steroids were substituted in the formula and the result was a positive number, a successful response to operation was likely. If it was negative, an operation was likely to fail. These estimations are tedious to perform and require a skilled steroid chemist, but results from several other centres appear to confirm those of Bulbrook and his colleagues,[16 21] and the subject merits a more detailed study. Recent work suggests that the discriminant function may predict the response to hypophysectomy more effectively than that to adrenalectomy.[22 23]

None of the factors mentioned or any combination of them enable us, at present, to predict for certain whether any individual patient will respond to ablation or not. Before we can answer the question, "What is the place of hypophysectomy in the treatment of breast cancer?" we need more prospective comparative clinical trials, more fundamental studies of the endocrine status of the patients, and a detailed discriminant analysis of the many factors which may influence response.

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Screening for Inborn Errors of Metabolism

The term "screening" is commonly used to describe the investigation of a group of apparently healthy people for specific diseases. A screening procedure should be relatively simple and inexpensive, should give no false negative and few false positive results, and should detect a disease for which early treatment has value. Economic, social, and ethical

[1] *Screening for Inborn Errors of Metabolism.* Report of a W.H.O. Scientific Group. *Wld Hlth Org. techn. Rep. Ser.*, 1968, No. 401. 8s. net.