Oncological Centres: Progress or Procrastination

It is now over a year since Sir Keith Joseph announced[1] that pilot oncology centres would be set up in the Manchester, South West Metropolitan, Leeds, and Wessex regions. These units were to spearhead a new approach to the problem of cancer—a concept that came originally from a D.H.S.S. committee headed by Sir David Smithers, which had strongly urged the advantages that would come from redeployment and reinforcement of effort in clinical cancer management. Further support came from Lord Zuckerman,[2] whose report to the Prime Minister on cancer research stated that these new centres would act as focal points for the treatment of rarer cancers, they would foster interdisciplinary co-operative effort in cancer management and research at both specialized and district hospital level, ensure that "the best available care becomes generally more available," and promote better understanding of the nature of cancer. The Government's announcements clearly implied that training would be provided and a career structure developed for those engaged in cancer research.

The centres were given a very wide range, including all aspects of patient care, statistics, clinical trials, public and professional education, and the build-up of appropriate research programmes. Indeed at first sight it looked as if any project with relevance to cancer could form part of the oncology programme, and the immense potential of the N.H.S. clinical services could, at least in theory, be recruited to help achieve the goal. In the past year detailed plans have been submitted to the D.H.S.S. and considerable enthusiasm for the scheme has been generated. Already in some regions projects have been launched as part of the new oncology enterprise.

What is now bedevilling the whole venture is that there has been no indication of the scale of the operation. Those engaged in planning for the regions are aware that success must depend on the generous voluntary help of clinicians—any form of coercion or direction might stifle the enterprise at the outset. Consequently doctors concerned with getting this help have had to adopt politicians' tactics, holding out promises of a brighter future and neatly side-stepping the question of the amount of money likely to be available. Indeed the sums of revenue money received so far do not even match up to the funds provided by charity for cancer research in these four regions. As details of the various proposals begin to be worked out it has become apparent that realistic schemes require the interplay of service and research within the N.H.S. and universities as well as integration with the cancer research charities and the Medical Research Council. So far, however, the Department does not appear to have set up its own co-ordinating machinery—and those working in the regions are finding that D.H.S.S. officials seem to be thoroughly confused, approaching each item piecemeal with little flexibility. Perhaps the Secretary of State would be well advised to appoint a co-ordinator who can appreciate the whole concept and help the scheme through its administrative difficulties. Furthermore, the sooner the D.H.S.S. makes a clear-cut policy statement saying what it intends to support, the sooner planners can stop wasting their time on schemes that are doomed from the outset.

It is absurd to suppose that Sir Keith Joseph gave the go-ahead without being well informed of the projected capital and revenue budgets likely to be required by the oncology centres. If the centres are to function as pace-setters for the country more beds and laboratories will be needed, as existing facilities already carry a heavy burden. The staff-patient ratios, particularly in the provinces, are low compared with those in centres doing high-quality work elsewhere in the world. Lord Zuckerman suggested that cancer research suffered more from a lack of talent than from lack of money. Nevertheless, it would be unrealistic to imagine that talented doctors and scientists will be attracted to work in cancer management or in research units until the problems of finance and career prospects have been resolved.

[1] *British Medical Journal*, 1972, **4**, 565.
[2] Lord Zuckerman, *Cancer Research*. London, H.M.S.O., 1972.

Babies' Blood Pressure Raised by Eye Drops

Drugs administered with the intention of producing a purely local action are sometimes absorbed in sufficient amounts to cause a systemic effect which is unwanted or even hazardous. Examples include adrenal suppression by topical corticosteroids given under occlusive dressings, tachycardia from inhalations of isoprenaline, hypertension from adrenaline and noradrenaline in dental local anaesthetics, and atropine toxicity from the use of this drug in eye drops to dilate the pupil.[1-4]

Recently a report has shown that the use of 10% phenylephrine eye drops to dilate the pupils of premature babies for ophthalmoscopy could cause a rise in blood pressure.[5] To confirm this, in a double-blind study, 12 infants of low birth weight were given one drop in each eye of either 10% or 2½% phenylephrine or normal saline. Normal saline and 2½% phenylephrine caused no significant change in blood pressure, but the 10% solution caused an average increase of 12 mm Hg systolic and 10 mm Hg of diastolic 30 minutes later. The increase lasted for about an hour. These increases are significant because the control blood pressure in these babies averaged only 55·7 mm Hg systolic and 32·4 mm Hg diastolic. This rise in pressure resulting from administration of only two drops would be unlikely to cause harm, but larger increases might result if a greater number of drops was given over a short period. The authors recommend that the strength of the ophthalmic solution of phenylephrine be restricted to 2½%, which is as effective in dilating the pupil and unlikely to raise the blood pressure.

It is interesting to inquire why these small doses instilled into the eye cause a systemic effect. Part of the answer must lie in the relatively high dose per unit weight in these small babies. A. Keys and A. Violante[6] studied the pressor responses to phenylephrine in adults and found that the dose required to raise the blood pressure was about 0·8 mg intravenously, 5 mg subcutaneously, and 250 mg orally. The oral dose corresponds to about 3·5 mg/kg in the adult. The ophthalmic dose in the babies weighing 907 to 2,438 g probably averaged about 5 mg/kg.

A second reason for the effect of the eye drops probably lies in the characteristics of the route of administration. Placing the same dose of phenylephrine on the skin of the abdominal wall of the babies caused local blanching of the skin but no rise in blood pressure. The mucosa in the eye, nose, and mouth is much thinner and more readily permeable to a drug than is the skin. A substantial amount of a drug such as glyceryltrinitrate can be absorbed directly from the buccal mucosa. This route

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can also produce a much greater effect for a given absorbed dose than would be the case if the drugs were swallowed. Many drugs, particularly sympathomimetic amines, are extensively metabolized on passing once through the gut wall or the liver.[7] A well-known example is isoprenaline, which has been given orally in doses of up to 90 mg at a time to treat heart block and which will increase the heart rate substantially if infused intravenously in a dose of 2 μg/min in an adult.[2] Isoprenaline is extensively conjugated as it passes through the mucosa of the gut,[6] and almost certainly the same is true of phenylephrine. As a result of their ability to by-pass these metabolic traps, drugs placed in the eye, nose, or mouth may exert a substantial pharmacological effect, much greater than would have been expected from the knowledge of the dose that is active when swallowed.

Thus the explanation of the rise in pressure in these infants of low birth weight appears to lie in three factors. Firstly, the dose was large in relation to their body weight; secondly, it was presented to a mucosa which is readily permeable to drugs; and, thirdly, this route would largely avoid the metabolic transformation which normally inactivates much of the dose. There is a moral here which is relevant for all drugs that are presented by a novel route, and not just in small babies. Drugs ought to be studied in both animals and man by all the routes by which they will be given, and doctors must consider the total dose that is to be dropped, sprayed, injected, or rubbed into the body, lest an unexpectedly large fraction of it should be absorbed.

[1] James, V. H. T., Munro, D. D., and Feiwel, M., *Lancet*, 1967, **2**, 1059.
[2] Conolly, M. E., *et al.*, *British Journal of Pharmacology and Chemotherapy*, 1972, **46**, 458.
[3] Boayes, A. J., Laurence, D. R., Lovel, K. W., O'Neil, R., and Verrill, P.J., *British Dental Journal*, 1973, **133**, 137.
[4] German, E., and Siddiqui, N., *New England Journal of Medicine*, 1970, **282**, 689.
[5] Borromeo-McGrail, V., Bordiuk, J. M., and Keitel, H., *Pediatrics*, 1973, **51**, 1032.
[6] Keys, A., and Violante, A., *Journal of Clinical Investigation*, 1942, **21**, 1.
[7] Rowland, M., *Journal of Pharmaceutical Sciences*, 1972, **61**, 70.

Problems with the Papillary Muscles

When a patient with ischaemic heart disease develops signs of mitral valve insufficiency it is usual to suspect dysfunction of the papillary muscles of the left ventricle. These specialized structures arise from the endocardial surface and terminate in chordae tendinae attached to both leaflets of the mitral valve. They are activated early in systole from the left main bundle and contract to tether the valve cusps while high pressure is developed within the ventricle.

The clinical signs of severe dysfunction consist of the acute, and often rapidly fatal, onset of pulmonary oedema.[1] A third heart sound may be noted, and there is a loud apical systolic murmur, usually full-length with mid-systolic crescendo. When the anterior cusp is affected the murmur is referred to the axilla or into the back. When the posterior cusp prolapses, the incompetence jet strikes the anteromedial wall of the left atrium close to the aortic root, and the murmur is referred to the aortic area and into the neck.[2 1] This condition is discriminated from aortic stenosis by the absence of an ejection click or valve calcification and the presence of a normal aortic second sound.

Pressure studies and cineangiography have shown that this acute form of mitral incompetence, in which sinus rhythm is usually maintained, is associated with a small left atrium, an increase in left atrial pressure at the same time as the murmur reaches maximum intensity, and rapid transit of the contrast medium to the pulmonary veins.[1 5] When the murmur is shorter and softer, the dysfunction and associated regurgitation are thought to be less. In these circumstances there may be no clinical deterioration and the signs are often transitory.[6]

Papillary function and ventricular function are closely related. In the dog combined malfunction produces mitral insufficiency.[7] A study of 14 patients with severe dysfunction showed that this occurred in the context of widespread coronary narrowing and poor left ventricular contraction during systole.[5] It has also been shown that as the ventricle dilates the papillary muscles become more tangential, and this may partly explain the mitral insufficiency of cardiac dilatation.[8]

The distinction between ischaemia and infarction may be fine. In dogs with subendocardial ischaemia mitral insufficiency may develop.[9] Healthy human papillary muscle has an excellent blood supply, but in advanced coronary narrowing the radial vessels supplying the subendocardial plexus are lost, and the alternative supply is not good enough for optimum muscle function.[8] Apparently normal papillary muscle removed at operation has been shown to have poor contractile characteristics.[10] There is a possibility of the damage being restricted to the tip of the muscle,[8] leading to chordal rupture. The clinical signs of this condition are as described above, but systolic clicks may also be heard.[11] The lack of extensive damage may account for the failure to confirm infarction in patients with chest pain who were later proved to have chordal rupture.[1]

Necropsy studies indicate a higher incidence of papillary lesions than could result from the acute syndrome described. In one series 25% of all necropsy subjects showed scars or acute infarcts of one or both muscles.[12] In another scarring was more common in persons who had been hypertensive.[13] A recent report from Denmark[14] details nine cases in which fatal infarction was confined to papillary muscle. In all but one the lesion was not apparent at necropsy to the naked eye but was detected by gross histochemical reaction and confirmed histologically. Most of the patients had left ventricular hypertrophy and all had died from pulmonary oedema. Four out of six in whom an electrocardiogram had been performed had had A-V conduction abnormalities. However, as three of these recordings were made in elderly, hypotensive, hypoxic patients immediately before death, the authors' contention that heart block is part of the syndrome of isolated papillary muscle infarction needs confirmation.

Papillary infarction need not be extensive to be serious. Because of its more distal blood supply the posterior muscle is usually the one involved. The problem may be rather more common in hypertensive patients with left ventricular hypertrophy—a situation in which subendocardial ischaemia is not unusual. Patients who recover and lose the signs of mitral insufficiency seem likely to have had minimal papillary damage and may have had associated dilatation or dysfunction of the ventricle. Transient symptoms of mitral insufficiency during anginal attacks seem likely to herald a poor prognosis and may indicate investigation with a view to coronary vein grafting. Troublesome residual insufficiency in a patient surviving infarction suggests, provided the ventricle itself is reasonably efficient, a need for mitral valve replacement.

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