

service to expand where it can; from looking seriously at why it has not expanded elsewhere; and from putting things right in time to attract potential new consultants when they become ready.

<sup>1</sup> Department of Health and Social Security, *Health Trends*, 1978, **10**, 61.

<sup>2</sup> Turner, J M, and McDowall, D G, *Anaesthesia*, 1973, **28**, 551.

<sup>3</sup> *Basic Medical Education in the British Isles, Report of GMC Survey*. London, Nuffield Provincial Hospitals Trust, 1977.

<sup>4</sup> Vickers, M D, and Rosen, M, *British Medical Journal*, 1978, **1**, 1491.

<sup>5</sup> Hunter, A R, *Anaesthesia*, 1978, **33**, 427.

<sup>6</sup> Royal Commission on the NHS, *Doctor Manpower 1975-2000: Alternative Forecasts and Their Resource Implications*. Research Paper No 4, p 37. London, HMSO, 1978.

## Polypeptide hormones inside cells

The idea of polypeptide hormones entering cells seems revolutionary. The first stage in the action of a polypeptide hormone is binding to a specific receptor site on the surface of the target cell.<sup>1</sup> Until recently this interaction was thought to represent the limit of cell penetration by the hormone: all its effects were assumed to result from binding to the localised receptor on the plasma membrane. The belief that polypeptide hormones do not enter cells has now been challenged in a series of recent studies based on new techniques. Will this also revolutionise our ideas about cellular mechanisms?

One of the methods used in these investigations relies on electron microscopic autoradiography to localise <sup>125</sup>I-labelled hormones in target tissues. This technique has shown that insulin can enter intact liver cells<sup>2</sup> and cultured lymphocytes,<sup>3 4</sup> and that human chorionic gonadotrophin can enter ovarian cells.<sup>5</sup> Image intensification (with a highly sensitive light-amplifying television camera) has shown fluorescently labelled insulin and epidermal growth factor inside cultured fibroblasts.<sup>6</sup> These findings raise the possibility that certain actions of polypeptide hormones could be mediated through a direct effect inside the cell of the hormone itself, of the hormone-receptor complex, or of the degradation products rather than through events localised on the surface of the cell.

Exactly how polypeptide hormones—which have molecular weights ranging from a few thousand to nearly 40 000—penetrate cells remains unknown, but there is some evidence that they enter the cells as hormone-receptor complexes.<sup>5</sup> The surfaces of hormone target cells are probably turned over quite rapidly,<sup>7</sup> and this process is likely to cause plasma membrane components, including hormone receptors, to be taken into the cell and to be shed from it. Hormone bound to receptors might, then, be expected to pass into the cell as part of the process of the turnover of the cell surface. Alternatively, the movement into the cell could depend on specific endocytosis of hormone-receptor complexes,<sup>8</sup> particularly in the case of insulin, where such movement has been reported to occur fairly rapidly.<sup>3 6</sup> The eventual fate within the cell of hormone, hormone receptors, and other membrane components is probably in the lysosomes,<sup>8</sup> where they are broken down into amino-acids to be used again by the cell for the synthesis of macromolecules.

Though there is now substantial evidence that polypeptide hormones, particularly insulin, enter target cells there is nothing to show that this process is important in stimulating the cells. Among the possible roles that have been suggested

for this passage into the cells are degradation of hormone and receptor and direct long-term actions on the nucleus. The intracellular effects of many polypeptide hormones (with the notable exception of insulin<sup>1 9</sup>) are, however, known to be mediated by a mechanism depending on adenylate cyclase-cyclic adenosine monophosphate (AMP), localised on the plasma membrane.<sup>1 10</sup> In this system, binding of the hormone to the receptor leads to activation of adenylate cyclase, and it is the resulting increases in cyclic AMP concentrations that mediate the hormone's various intracellular effects. Until some clear function for intracellular polypeptide hormones can be established, therefore, we should perhaps be cautious about assuming that the process has a general importance in physiological terms.

<sup>1</sup> Rees Smith, B, *Advances in Clinical Chemistry*, 1977, **19**, 91.

<sup>2</sup> Gordon, P, *et al*, *Science*, 1978, **200**, 782.

<sup>3</sup> *Science*, 1978, **202**, 260.

<sup>4</sup> Carpentier, J L, *et al*, *Journal of Clinical Investigation*, 1978, **61**, 1057.

<sup>5</sup> Conn, P M, *Nature*, 1978, **274**, 598.

<sup>6</sup> Schlessinger, J, *et al*, *Proceedings of the National Academy of Sciences of the United States of America*, 1978, **75**, 2659.

<sup>7</sup> Doljanski, F, and Kapeller, M, *Journal of Theoretical Biology*, 1976, **62**, 253.

<sup>8</sup> Silverstein, S C, Steinman, R M, and Cohn, Z A, *Annual Review of Biochemistry*, 1977, **46**, 669.

<sup>9</sup> Czech, M P, *Annual Review of Biochemistry*, 1977, **46**, 359.

<sup>10</sup> Pastan, I H, Johnson, G S, and Anderson, W B, *Annual Review of Biochemistry*, 1975, **44**, 491.

## Prognosis of optic neuritis

Optic neuritis presents a characteristic clinical picture and has an excellent short-term prognosis with most patients recovering vision completely. The long-term prognosis is less certain, for the crucial question is the risk of developing multiple sclerosis. A recent paper in *Brain*<sup>1</sup> has highlighted some of the problems in estimating this possibility. The reported risk varies from a figure as low as 13% in a series from America<sup>2</sup> to as high as 87% in one from Australia.<sup>3</sup> In three large British studies<sup>1 4 5</sup> the risks were estimated to be 40%, 51%, and 78% respectively, the highest figure being the calculated probability of a patient developing multiple sclerosis within 15 years of an episode of optic neuritis. Indeed, the major factor in the variation of the figures quoted is the length of follow-up; for as McAlpine, Lumsden, and Acheson<sup>6</sup> wrote over ten years ago: "The longer the period of observation the higher will be the percentage of cases of retrobulbar neuritis which develop signs of multiple sclerosis."

In their review Compston and his colleagues<sup>1</sup> discussed some of the factors which might be useful in predicting this risk. Clinical factors—age, sex, degree of visual loss, and bilateral lesions—do not seem important, but recurrent attacks of optic neuritis and onset of symptoms in winter appear to be associated with an increased risk of developing multiple sclerosis. Until now investigation has proved unhelpful: surprisingly, a pleocytosis in the cerebrospinal fluid in optic neuritis does not necessarily indicate an increased risk of multiple sclerosis.<sup>5</sup> Nevertheless, the presence of oligoclonal immunoglobulins in the CSF may prove a useful predictor, and this warrants further study.<sup>7</sup> Another line of investigation which seems worth pursuing is the human leucocyte antigen (HLA) make-up of patients with optic neuritis. Compston *et al*<sup>1</sup> found that the risk of multiple sclerosis was higher in patients with optic neuritis who were