those treated with porcine calcitonin for periods of up to two years have been found to have circulating antibodies. Reports on the possible antigenicity of salmon calcitonin are awaited.

Side-effects of treatment are usually slight. They include nausea, flushing, tingling, and erythema and pruritus at the site of injection. Only rarely have they been so severe as to necessitate stopping treatment, but it is probably wise to skin-test allergic patients before treating them with preparations of animal hormones.

At present calcitonin therapy should be considered for patients with Paget's disease who have bone pain not controlled by simple analgesics; widespread disease, especially if complicated by high-output cardiac failure; progressive deformity; fractures, especially in weight-bearing bones; or compression of nerves by bony overgrowth.

Hypercalcaemia is often due to increased resorption of bone, and several workers have reported that calcitonin is a safe and effective method of lowering the serum calcium. It has been used sucessfully in patients with hypercalcaemia due to disseminated malignant disease,[8] hyperthyroidism,[5] hyperparathyroidism,[4] idiopathic hypercalcaemia of infancy,[9] and vitamin D intoxication in both children and adults.[4] Alternative methods of treatment of hypercalcaemia are also effective, particularly sodium phosphate, but this is best avoided if the kidneys are impaired; calcitonin is then the treatment of choice. Preliminary studies have shown some symptomatic and biochemical improvement in one patient with osteogenesis imperfecta tarda treated with salmon calcitonin,[6] but confirmation on further patients is required. Whether calcitonin will prove to be of value in the treatment of idiopathic osteoporosis is still uncertain. Reports of short-term studies in man are conflicting, and results of long-term trials are awaited.[1]

There is no doubt that calcitonin therapy represents an advance in the management of Paget's disease. It is also of value in the treatment of hypercalcaemia associated with increased bone resorption, particularly if renal disease is present.

[1] Foster, G. V., Byfield, P. G. H., and Gudmundsson, T. V., *Clinics in Endocrinology and Metabolism*, 1972, 1, 93.
[2] Cunliffe, W. J., *et al.*, *Lancet*, 1968, 2, 62.
[3] Woodhouse, N. J. Y., *et al.*, *Lancet*, 1971, 1, 1139.
[4] West, T. E. T., Joffe, M., Sinclair, L., and O'Riordan, J. L. H., *Lancet*, 1971, 1, 675.
[5] Bijvoet, O. L. M., Veer, J. V. der S., and Jansen, A. P., *Lancet*, 1968, 1, 876.
[6] Goldfield, E. B., Braiker, B. M., Prendergast, J. J., and Kolb, F. O., *Journal of the American Medical Association*, 1972, 221, 1127.
[7] Woodhouse, N. J. Y., *Clinics in Endocrinology and Metabolism*, 1972, 1, 125.
[8] Foster, G. V., *et al.*, *Lancet*, 1966, 1, 107.
[9] Milhaud, G., and Job., J. C., *Science*, 1966, 154, 794.

Locally Advanced Breast Cancer

In Great Britain breast cancer remains the commonest malignant disease of women. In spite of intense propaganda on early diagnosis many women still present with advanced lesions. Often this means wide dissemination, with metastases to liver, lung, and especially bone. Palliative treatment depends mainly on hormone therapy, cytotoxic drugs, and radiotherapy for especially painful sites of secondary deposits. But from time to time patients present with locally advanced carcinoma of the breast. The features of the disease may include fixation to underlying muscle, infiltration or ulceration of the skin, satellite nodules, and fixed axillary lymph nodes, but without clinical or radiological evidence of widespread metastases. These women form a special group as regards treatment, since their eventual death is made all the more miserable by the ulceration, discharge, odour, and bleeding of the fungating primary tumour. The medical attendant will achieve much if he can at least ensure that she dies with the local disease under control.

Mastectomy alone in the advanced cases has a deservedly bad reputation for rapid local recrudescence of disease.[1] The conventional treatment advised for advanced local breast cancer is radiotherapy. Though the tumour mass may shrink remarkably and ulceration heal, local recurrence is unfortunately common.[2 3] P. Helman and M. B. Bennett[4] combined radiotherapy with intra-arterial cytotoxic therapy and noted worthwhile palliation with this rather elaborate technique.

Recently J. Sonneland[5] reported a rather unconventional method of dealing with this problem in a woman of 87 with a fungating carcinoma of the breast. The surface of the carcinoma was destroyed by means of zinc chloride paste fixative. Six applications were made over a ten-day period, after each of which a leathery dead peel was excised at the bedside. There was little discomfort, and at the end of this treatment underlying pectoral muscle was reached, biopsy of which showed no evidence of malignancy. A split-thickness skin graft was then applied, and the patient was given stilboestrol by mouth. She died 18 months later of an unrelated condition, and the careful necropsy failed to disclose any residual malignant disease. This technique of chemosurgery has been used over the centuries, and it is still difficult to assess its exact role or indeed its advantages, if any, over conventional excisional surgery, diathermy coagulation, or cryosurgery. However, this apparently first reported case of the use of chemosurgery in the primary treatment of ad-advanced breast carcinoma is encouraging enough to warrant further serious consideration.

A more conventional approach to this problem has been a combination of radiotherapy and mastectomy. E. D. Montague[6] found that simple mastectomy followed by radiotherapy was better than radiotherapy alone for local control of large tumours in pendulous breasts. However, when ulceration was present, in 13 out of 33 patients treated by simple mastectomy and radiotherapy the tumour recurred as against 16 out of 55 treated simply by radiotherapy. Recently T. A. M. Stoker and H. Ellis[7] have reported on 24 patients with stage III breast cancer treated during 1962-70 by supervoltage radiotherapy to a maximum tumour dose of approximately 6,000 rads followed 4 to 16 weeks later by either simple mastectomy (in four cases), simple mastectomy with axillary clearance (11 cases), or radical mastectomy in nine cases in which the pectoral muscle was involved. The wound underwent primary healing in every patient. Three patients have developed local recurrence of their tumours, two within two years of surgery, and both of these have been subsequently controlled by hormone therapy or endocrine surgery. One recurrence was associated with disseminated disease and occurred shortly before death. Seven patients are dead, and in 6 of these cases no local tumour was present at the time of death. One patient was lost to follow up at one year, at which time she was well, and the remaining 14 are alive with local disease at present controlled. The mean survival time of the seven patients who died was 13 months after operation. Twelve of the patients have survived three years or more after mastectomy, and three of these have no

signs of disseminated disease. This report suggests that toilet mastectomy after radiotherapy may be a reasonable procedure in selected cases, especially of large tumours in pendulous breasts when an adequate margin of skin can be preserved. Clearly this important subject remains sub judice. Stoker and Ellis consider that a multicentre controlled trial should be instituted to establish whether or not post-irradiation toilet mastectomy improves the quality of survival in patients with locally advanced carcinoma of the breast compared with those treated by supervoltage radiotherapy alone.

[1] Cade, S., *American Journal of Roentgenology*, 1949, **62**, 326.
[2] Atkins, H. L., and Horrigan, W. D., *American Journal of Roentgenology*, 1961, **85**, 860.
[3] Edelman, A. H., Holtz, S., and Powers, W. E., *American Journal of Roentgenology*, 1965, **93**, 585.
[4] Helman, P., and Bennett, M. B., *British Journal of Surgery*, 1968, **55**, 419.
[5] Sonneland, J., *American Journal of Surgery*, 1972, **124**, 391.
[6] Montague, E. D., *American Journal of Roentgenology*, 1967, **99**, 995.
[7] Stoker, T. A. M., and Ellis, H., *British Journal of Radiology*, 1972, **45**, 851

Prolonged Levodopa Therapy

Levodopa has been administered continously to many thousands of patients with Parkinsonism over the last three years, so it is now becoming possible to assess long-term effects. Experience confirms that it is the most potent therapeutic agent available, though it does not help all patients, and it does not appear to halt the inexorable advance of the disease in cases of idiopathic Parkinsonism. But it ameliorates symptoms, and in some patients at least this benefit has been sustained over several years. However, many patients who had previously obtained substantial benefit from levodopa are now experiencing a gradual deterioration in motor performance. This is a familiar story in the treatment of many other chronic diseases, in which major therapeutic advances are followed by the realization that doctors often palliate but seldom cure.

Levodopa has proved to be safe despite many dose-dependent adverse reactions at the start of treatment when the dose is being adjusted to an optimal level. But with long-term treatment two new problems have emerged. One, which has been termed "oscillation in performance" or the "on-off phenomenon,"[1 2] comprises rapid transient deterioration of the Parkinsonian motor deficit, which develops over minutes and usually persist for 1-6 hours. These episodes then clear spontaneously. Hypokinesia, tremor, and rigidity may be exacerbated over the period of deterioration. Hypotonia is common and has also been reported. These oscillations in performance are commonest in patients who have been on levodopa for over a year. They usually occur in the afternoon, and they may be repeated in cycles. Their mechanism is not understood.

The second new problem with levodopa is a group of endocrine disturbances which have been detected by metabolic investigation but which have not so far caused clinical symptoms. Administration of levodopa over a year has been found to result in a rise of growth hormone in the plasma, an increase in serum cholesterol, a decrease in glucose tolerance, and a delayed but exaggerated insulin response.[3] It appears that these changes take some time to become established, as similar investigations after shorter periods of levodopa therapy have failed to show the same abnormalities.[4]

The action of levodopa on growth hormone and glucose tolerance presumably stems from the formation of catecholamines, which are likely to influence endocrine function at the periphery and through the central nervous system. Peripheral actions of catecholamines can impair glucose tolerance in man,[5 6] and perfusion of catecholamines through the central nervous system leads to the release of growth hormone in animals.[7 8] Studies on the urinary metabolites of orally administered levodopa in Parkinsonian patients indicate that dopamine is formed in much larger quantities than the other catecholamines.[9] It may therefore be significant that a tubero-infundibular fibre system, which terminates in the median eminence of the hypothalamus (intimately concerned with the control of pituitary function), contains high concentrations of dopamine and is very likely to employ this catecholamine as a neurotransmitter.[10-13]

From a practical viewpoint the findings of these metabolic disturbances should lead physicians to be aware that, though the evidence is at present unconfirmed, diabetes mellitus and acromegaly may emerge as late complications of levodopa therapy. However, to put matters in perspective, M. D. Yahr and R. C. Duvoisin[14] have pointed out that from a clinical experience of 800 Parkinsonian patients receiving levodopa for up to five years they have not encountered a single new case of diabetes mellitus or acromegaly. Furthermore, there was no change in the insulin requirements of those patients who were diabetic before starting levodopa.

[1] Cotzias, G. C., Papavasiliou, P. S., and Gellene, R., *New England Journal of Medicine*, 1969, **280**, 337.
[2] Barbeau, A., Mars, H., and Gillo-Joffroy, L., in *Recent Advances in Parkinson's Disease*, ed. F. H. McDowell and C. H. Markham, p. 204. Philadelphia, F. A. Davis, and Oxford, Blackwell, 1971.
[3] Sirtori, C. R., Bolme, P., and Azarnoff, D. L., *New England Journal of Medicine*, 1972, **287**, 729.
[4] Van Woert, M. H., and Mueller, P. S., *Clinical Pharmacology and Therapeutics*, 1971, **12**, 360.
[5] Karam, J. H., Grasso, S. G., Wegienka, L. C., Grodsky, G. M., and Forsham, P. H., *Diabetes*, 1966, **15**, 571.
[6] Porte, D., and Williams, R. H., *Science*, 1966, **152**, 1248.
[7] Müller, E. E., Dal Pra, P., and Pecile, A., *Endocrinology*, 1968, **83**, 893.
[8] Müller, E. E., Pecile, A., Felici, M., and Cocchi, D., *Endocrinology*, 1970, **86**, 1376.
[9] Calne, D. B., Karoum, F., Ruthven, C. R. J., and Sandler, M., *British Journal of Pharmacology*, 1969, **37**, 57.
[10] Fuxe, K., *Acta Physiologica Scandinavica*, 1963, **58**, 338.
[11] Fuxe, K., *Zeitschrift für Sellforschung und Mikroskopische Anatomie*, 1964, **61**, 710.
[12] Fuxe, K., and Hokfelt, T., *Acta Physiologica Scandinavica*, 1966, **66**, 245.
[13] Lichtensteiger, W., and Langemann, H., *Journal of Pharmacology and Experimental Therapeutics*, 1966, **151**, 400.
[14] Yahr, M. D., and Duvoisin, R. C., *New England Journal of Medicine*, in press.

Novel Attack on Influenza

We are all acutely aware that influenza vaccination has not prevented yet another epidemic of influenza, and so the report that workers at the Institut Pasteur in Paris have made a substantial step forward is of unusual interest. No scientific report has yet reached us, but an article has appeared in *Le Monde*, and this has been the subject of comment on the radio and in other newspapers.

It appears that the French workers have tried to manipulate influenza A viruses in the laboratory in order to reproduce the sort of antigenic shifts which led to the emergence of the A/England/42/72 type and the present influenza epidemic.[1] It is generally thought that what happens is that the virus passes among individuals of whom many carry antibody against it, so that a virus with a new