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.

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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.

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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

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