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

antigenic type has a survival advantage. Years ago, therefore, influenza viruses were passaged in eggs in the presence of antiserum or in mice which had been immunized against the same virus. Certainly new serotypes were recovered, but they did not correspond to the new serotypes which occurred in the general population.

Fazekas de St. Groth has devoted many years to the study of the haemagglutinin antigens of the influenza virus and has pointed out that, as these viruses evolve, the new strains are able to evoke antibody not only against themselves but also against their predecessors, whereas the preceding viruses (necessarily in view of current theories) do not evoke antibody against the viruses that follow them. He calls the first viruses of a series "junior" and the last "senior."[2] He has advised the Pasteur workers and collaborated with them, and they have together employed improved techniques of passage and selection, using carefully prepared and selected antibodies. They believe they have now produced the "senior" strain of the series starting with the Hong Kong strain, and have made an experimental vaccine with it which is antigenic in man. They have shown that it evokes antibody against the A/England/42/72 strain, and they believe that it will prevent influenza against all the future members of this series. At the end of the series we shall presumably start a new series, and they are not claiming that their strain will protect against this. Though Fazekas de St. Groth believes in the existence of "bridging" strains between these series, most workers believe there is a much more radical break, possibly due to recombination between human and animal strains.

Two important practical questions arise. Have the workers at the Pasteur Institute successfully anticipated natural evolution? And, if they have done so, was it a lucky chance or is it a success that they will be able to reproduce at will? It would be helpful to know in this connexion whether the techniques of selection they are using always give the same final mutant when starting with a given strain. It is therefore important that the antigenic composition of this interesting strain should be checked in other influenza virus reference laboratories and that it is compared with the new influenza viruses as they emerge over the next few years. If it turns out that the expectations of its producers are fulfilled, then they will have forged a valuable new tool for making enough vaccine soon enough to have a real impact on epidemic influenza.

Even so, there will be serious questions still to answer, such as how to predict the major shifts of antigen type and whether widespread vaccination with a laboratory-grown "senior" strain would have the effect of hurrying up the evolution of the virus in nature.

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Advice on Heart Transplants

The Department of Health rarely offers advice on clinical matters, but the letter to heart surgeons from the Chief Medical Officer (see p. 431) is one of the exceptions to this general principle. A group of experts on transplantation called together by the C.M.O. has in effect recommended that no heart transplants should be undertaken in Britain for the time being, and this seems to be the explanation for the recent press reports[1] that the possibility of such an operation was considered and rejected at a London hospital earlier this month.

The first rush of heart-transplant operations after Professor C. Barnard's pioneer work[2] in 1967 caused widespread public disquiet, and since 1970 only a very few centres throughout the world have continued to carry them out. The most encouraging results have come from N. E. Shumway's group in the U.S.A., which has been able to achieve 60% two year survival among those patients surviving the immediate postoperative period.[3] Not unreasonably, cardiac surgeons in Britain are anxious to try to match these results, so the C.M.O.'s letter must have been a disappointment to them. There are, however, good reasons for advocating a voluntary embargo on cardiac transplantation at present. Good as Shumway's results are, the procedure is still experimental and carries a high peri-operative mortality. The attitude implicit in the letter—that development of the techniques of cardiac transplantation should be further advanced before more attempts are made in Britain—is certainly one that will receive considerable support. Two other arguments should also be considered. Firstly, at a time when resources of money and staff are severely limited heart transplantation cannot yet justify priority; and, secondly, there is a real probability that resumption of heart transplants now might prejudice public opinion at the very time when the supply of donor organs for kidney operations is at last beginning to improve. When the potential benefit to a handful of patients is weighed against the possible ill effects on hundreds of patients with renal failure, the decision seems clear cut.

There are some occasions when the Department of Health can usefully give a lead to the profession in a matter of clinical judgement; soon after the start of professional disquiet about amphetamines, for example, it asked doctors to try wherever possible to find alternatives to their prescription, and this request was generally followed. The suggestion that resumption of heart transplantation in Britain should be deferred for the time being is equally deserving of support by the profession.

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