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Influenza, Pregnancy, and Leukaemia

After the discovery of the fetal abnormalities caused by maternal rubella there were several investigations of the effects of other viral infections in pregnancy. Some of these studies found no evidence of any harm to the fetus, while others showed a slightly increased incidence of abortion or of malformations, usually not as severe and certainly never as frequent as those after rubella infection. Now it seems that influenza in pregnancy may not be as harmless as has been thought. At page 485 of the *B.M.J.* this week Mrs. Jean Fedrick and Dr. Eva Alberman report that seven children out of 1,959 born in March 1958 to mothers who had apparently had an influenzal infection in pregnancy developed leukaemia or Hodgkin's disease, whereas only six cases occurred among 14,791 children born in the same week to mothers not giving this history. They also show a very strong correlation between the mortality from these diseases among children born in a particular year and sickness absence from influenza in the preceding winter.

An association between childhood cancer and viral infection in pregnancy was first suggested in 1958, when Alice Stewart, J. Webb, and D. Hewitt[1] reported a total of 10 such infections (rubella, mumps, herpes zoster, and infectious hepatitis) among their cancer cases and only one in a control. This particular study was at first criticized on the grounds that a mother whose child had developed cancer was more likely to recall events during her pregnancy than was a control. However, while the claim that *x*-ray examinations in pregnancy could cause childhood cancer has been vindicated the results relating to viral infections seem to have been ignored. But Fedrick and Alberman's report extends these earlier findings in two new and important ways: the evidence of the role of influenza in the genesis of leukaemia and Hodgkin's disease and the suggestion that it causes these neoplasms and no others.

These discoveries raise questions and have implications of wide importance. Firstly, what else may be caused by influenza in pregnancy? Another British study[2] of that particular epidemic found a higher incidence of both malformations and abortions. A higher incidence of malformations was also reported from Ireland.[3] On the other hand two American studies showed no adverse effects.[4 5] A study of the 1951 epidemic, which was caused by a different strain of virus, found an increased mortality before the age of 2 years, but this was among a small sample of infants and the causes of death were not remarkable.[6] Last year in his annual report[7] the Chief Medical Officer pointed out that there had been only two occasions since 1945 when perinatal mortality had not decreased from one year to the next. In both cases the increase could be attributed to unusually high neonatal mortality in the April-June quarter, and each time there had been an epidemic of influenza in the preceding winter; a further note on this subject appeared in our correspondence columns last week.[8] None of these studies had, however, concerned the long-term follow-up of the very large numbers of infants in the National Child Development Study, and further reports from this group should be able to show unequivocally whether influenza in pregnancy affects intrauterine or postnatal growth and perinatal or child mortality.

It should, then, be possible to determine many of the effects of influenza in pregnancy from existing data. But this cannot be said when the problem is approached from the other aspect—what proportion of childhood leukaemia or Hodgkin's disease is caused by influenza in pregnancy? In this particular week's births seven of 13 cases appear to have been so caused, but the 1957 epidemic was of a new strain and exceptionally widespread. When there is less influenza the proportion will almost certainly be lower. The second part of Fedrick and Alberman's paper suggests that overall it is small. A stronger statement might have been possible had the authors determined the dates of birth of children dying of leukaemia rather than imputing them. This work also suggests that other influenza epidemics, as well as that of 1957-8, may have given rise to leukaemia and related disorders. What other incidents in pregnancy, and in particular what other viral infections, must be looked at again as possible causes not of all cancers but of leukaemia and Hodgkin's disease? With the advantage of hindsight it may be asserted that the only reason why this discovery was not made sooner was that earlier workers did not follow up enough infants for sufficiently long periods. Large groups of infants exposed to these various hazards now need to be identified and traced, and this will not be easy. It may not be premature to suggest that those responsible for antenatal care should actively seek histories of minor illnesses of which they might not otherwise learn.

The findings also have implications for medical practice, but it is important to re-emphasize that any clinical decision is based on a balance of probabilities. Nine times a very small risk of leukaemia is still a very small risk of leukaemia, and such a small risk does not justify termination of pregnancy. In any event, several of the influenza infections reported occurred far too late in pregnancy for this even to have been considered. Nor should pregnant

patients who develop influenza, or are exposed to it, necessarily be vaccinated. Though the influenza vaccine used in Britain contains killed influenza virus it may also contain active or latent members of the avian-leucosis group of viruses. Doctors would do well to bear in mind that the protection from available vaccines is far from complete, and that any reduction in the risk of subsequent leukaemia would be very small. The local and other reactions of vaccination in fact probably outweigh the benefits. At the same time it seems reasonable to add influenza to rubella as an illness which should wherever possible be kept away from pregnant women.

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[2] Pleydell, M. J., *British Medical Journal*, 1960, **1**, 309.
[3] Coffey, V. P., and Jessop, W. J. E., *Lancet*, 1959, **2**, 935.
[4] Wilson, M. G., Heins, H. L., Imagawa, D. T., and Adams, J. M., *Journal of the American Medical Association*, 1959, **171**, 638.
[5] Walker, W. M., and McKee, A. P., *Obstetrics and Gynecology*, 1959, **13**, 394.
[6] Manson, M. M., Logan, W. P. D., and Loy, R. M., *Rubella and other virus infections during pregnancy*. Ministry of Health. Reports on Public Health and Medical Subjects, No. 101, London, H.M.S.O., 1960.
[7] Department of Health and Social Security. *On the State of the Public Health. Annual Report of the Chief Medical Officer, 1970*. London, H.M.S.O., 1971.
[8] South, J., *British Medical Journal*, 1972, **2**, 464.

Progress in Behaviour Therapy

To the non-specialist who tries to keep abreast of progress in psychiatry the field of behaviour therapy presents particular difficulties. Because the techniques of treatment are based on psychological principles much of the literature can be assessed thoroughly only if the reader has some knowledge of psychology. Indeed, some of the most important papers appear in journals of psychology and much of the rest in one of the specialist journals which are devoted exclusively to behaviour therapy. These difficulties have been mitigated to some extent by accounts of the subject[1] [2] written for the general reader and by others presenting a thorough, though more specialized, review of recent advances.[3] [4]

Lately much work has been devoted to consolidating earlier advances in forms of treatment now widely used. In Wolpe's method of systemic desensitization the physician presents scenes producing fear while the patient relaxes. There is good evidence that this treatment is effective for phobic states but is progressively less potent as the component of generalized, background anxiety becomes more prominent. Some modification of treatment has therefore been sought, especially for patients with severe agoraphobia, who frequently present with generalized anxiety as well as their phobias. For these patients rapidly acting intravenous barbiturates have been used as an aid to relaxation during desensitization treatment.[5] More recently good results have been claimed with a modification of treatment in which anxiolytic drugs are given at first in large doses and then in progressively smaller ones from week to week.[6] The value of both approaches is still uncertain.

Other psychiatrists have turned to an alternative technique known as flooding (implosion) treatment, in which fear-producing mental imagery is presented continuously for long periods. There are some reasons for thinking that this may be suitable for patients who are very anxious, for the technique does not depend on relaxation, which is a requirement for desensitization. Indeed anxiety is deliberately allowed to mount up during treatment sessions. So far there is no certain evidence that flooding is superior to desensitization. However, the fact that it leads to results which are at least as good as those of desensitization is of some interest, for the treatment breaks all the rules on which desensitization is based and consequently makes us question some of our assumptions.

Studies such as these also indicate that it may not be possible to understand solely by reference to conditioning principles all the changes which desensitization and flooding bring about. A. Bandura[7] has argued cogently for greater recognition of the role of cognitive processes in behaviour therapy. For example, modification of behaviour can lead to a change in attitudes, and greater self-control may be acquired by mental rehearsal in everyday life of events which took place during treatment sessions. On this view simple conditioning and cognitive processes are not mutually exclusive but interact with one another. Thus, changes in conditioned emotional responses can lead to change of attitude, while that in turn may affect the future emotional response to the same events. Some such idea is required, for example, to explain why the effects of aversion therapy can apparently last for months or years, while the effects of aversive conditioning in the laboratory dissipate quickly.

Aversion therapy is a third form of behaviour therapy. Nowadays the aversive stimuli are usually mild shocks from a battery-operated shock-box, and they are associated repeatedly with parts of the behaviour pattern which the patient wishes to control. A recent investigation by R. Hallam and colleagues[8] adds to the growing evidence that this form of behaviour therapy also depends on factors other than simple conditioning. Patients presenting with alcoholism or for sexual deviations were studied. Evidence for conditioned anxiety was sought during and after treatment both by questioning patients and by measuring heart rate and skin conductance. No evidence was found of conditioned anxiety responses developing during treatment, even in those patients who improved clinically. Indeed when findings were compared with those of control patients who were treated with group therapy, the only change which could be attributed specifically to aversion therapy was the development of a feeling of revulsion for drink—and the authors were unable to explain how this came about.

Studies such as this are raising important questions about the ways in which simple conditioning procedures become converted into the complicated psychological and social changes which are assessed when it is decided whether a psychiatric patient has improved. Clinicians may feel that this admission of ignorance about the action of behaviour therapies is far healthier than the confident statements which were being made ten years ago that behaviour therapy followed the rules of "modern learning theory."

[1] Meyer, V., and Chesser, E. S., *Behaviour Therapy in Clinical Psychiatry*. London, Penguin, 1970.
[2] Wolpe, J., *The Practice of Behaviour Therapy*. London, Pergamon, 1969.
[3] Yates, A. J. *Behaviour Therapy. New York*, John Wiley and Sons, 1970.
[4] Franks, C. M., *Behaviour Therapy: Appraisal and Status*. New York, McGraw Hill, 1969.
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[6] McCormick, W. O., and O'Gorman, E. C., *Psychological Medicine*, 1971, **1**, 339.
[7] Bandura. A., *The Principles of Behaviour Modification*. New York, Holt Rinehart and Winston, 1969.
[8] Hallam. R., Rachman, S., and Falkowski, W., *Behaviour Research and Therapy*, 1972, **10**, 1.