BRITISH MEDICAL JOURNAL

LONDON SATURDAY 24 AUGUST 1974

Hazards of Genetic Experiments

In an unprecedented move the United States National Academy of Sciences last month called for a voluntary world-wide moratorium on certain types of genetic experiments with micro-organisms.[1] It did so because the hazards to human health are grave and unpredictable.

The Medical Research Council in Great Britain had also been considering for some time what action to take. Consequently, in view of the American warning it wrote to the units and individuals it supports in studies on the genetics of micro-organisms and asked them to refrain from research of this kind. In fact the M.R.C. is not supporting this sort of research, so that it was concerned to prevent its being undertaken rather than to stop something that had started. But the problem goes far beyond the M.R.C. Some 50 laboratories in Great Britain are so staffed and equipped as to have no difficulty in experimenting on "genetic engineering." It is thus an urgent matter that the dangers of some types of such work to the general population should be fully appreciated. The Government has, therefore, set up a committee under the chairmanship of Lord Ashby, F.R.S., to inquire into them.

Up to the 1940s bacteria were accepted as unicellular creatures that multiplied rapidly by simple fission. People who described nuclei or even nuclear-like material in microbes had a hard time at scientific meetings. But during the 1950s evidence increasingly showed that bacteria and viruses were capable of different kinds of fusion resembling the sexual modes of reproduction familiar in higher organisms. Besides simple fission, microbes clearly had a sex life of a kind.

The resulting recombinations were both interesting and useful—for example, in developing avirulent variants for live attenuated vaccines. Early in the 1960s warnings began to be heard that recombinant strains could be harmful as well as useful, and that it was conceivable that someone could unwittingly produce and release a laboratory-manufactured germ of greatly enhanced virulence. The phenomenon of transferable drug resistance gave impetus to detailed studies of how nuclear materials of various kinds could be transferred within and even between genera of microbes. This whole field of new and exciting research was eagerly cultivated, and biologically functional microbial plasmids became almost commonplace objects and tools of research.

Recent advances in techniques for the isolation and rejoining of segments of DNA now permit construction of biologically active recombinant DNA molecules in vitro. Such material has been shown to replicate and remain stable in *Escherichia coli*. The distinguished and responsible scientists who are the Committee of the National Academy of Sciences on Recombinant DNA Molecules have all agreed individually to renounce two types of experiment involving the new techniques until the potential hazards have been evaluated. They have also called for a committee to be established to define the hazards and to develop guidelines under which such research should be conducted. *E. coli* is commonly used to clone the recombinant DNA molecules and to increase their number. It is a normal and abundant inhabitant in the intestine of man and animals, and *E. coli* strains may exchange genetic material with other species and genera of bacteria, some of which are pathogens for man, animals, and plants. Thus we might have to face bacterial strains carrying new and vigorously replicating determinants for antibiotic resistance, toxin formation, or invasive capacity. We need a pause to examine at least whether such determinants already exist in nature.

Anxieties about tumours are also justified. Oncogenic DNA transferred to bacterial and viral populations in man and other species could possibly lead to an increased incidence of cancer and other diseases. Many fragments of animal DNAs linked to bacterial plasmid DNA or bacteriophage DNA could produce sequences common to RNA tumour viruses.

If the need for action is plain, where should responsibility lie for taking the initiative in Great Britain? At first thought the Medical Research Council and the Royal Society will come to many minds, and it is clear that these two organizations, other research councils, and the universities must all be involved. But the major issue is a question of preventive medicine on a national and international scale. Thus there are good reasons for suggesting that the Department of Health and Social Security, now equipped with a chief scientist, has a clear duty to take the lead in calling on its own expert advisers and the other interested bodies to consider what form any action should take. No doubt it would act in conjunction with Lord Ashby's committee. Stimulated by recent incidents the D.H.S.S. is even now considering what new safeguards are needed to prevent escapes of dangerous microbes from laboratories into the community. In view of the international hazards the World Health Organization should surely also turn its attention to the matter. This is not a question of banning research that may, according to how its results are used, bring great benefit or great disaster to man, such as we have seen

from atomic physics. What is at stake is whether the research itself can at present possibly be conducted safely. If highly invasive or oncogenic *E. coli* are manufactured, what means exist now to prevent their spread? Laboratory accidents may not be common, but they do occur.

[1] *Nature*, 1974, **250**, 175.

Hepatitis and Herpesvirus

Though the hepatitis viruses A and B are the common causes of acute viral hepatitis and of the very severe, though fortunately rare, cases of fulminant hepatitis, the liver may be affected by other systemic viral infections.[1] Goyette *et al.*[2] recently described the clinical course of a woman who succumbed from fulminant hepatic failure due to an overwhelming infection with herpesvirus hominis (herpes simplex). She became ill during the 28th week of her second pregnancy and may have acquired the infection from her firstborn, who had had a herpesvirus gingivostomatitis in the preceding weeks. The diagnosis was not suspected until necropsy showed a large yellow-tan coloured liver dotted with circular haemorrhagic rings. Histological examination showed typical inclusion bodies, and herpesvirus hominis was cultured from both the liver and other organs.

The prevalence of antibody in human sera suggests that most adults become infected by this virus early in life, often without any clinically obvious disease.[3 4] Localized lesions of mouth, lips, pharynx, eyes, or genitalia may, however, occur; and such primary infections are to be distinguished from local recrudescences of infection of the mouth, genitals, or eyes occurring later in life in people with both humoral and cellular immunity. The virus is thought to lie dormant in tissues but can be reactivated[4] by changes in the external or internal environment (exposure to sun, cold wind, fever, menstruation, nerve injury, emotion). Much less commonly, the primary infection with herpesvirus hominis gives rise to a generalized systemic illness with the liver prominently affected. This form of the illness is best known in neonates and young children.[5-9] In two reports[8 9] from South Africa there was an association with measles and malnutrition, but generally an obvious febrile herpetic infection, usually stomatitis, was accompanied by tender enlargement of the liver, hypoglycaemia, purpura, bleeding tendencies, and rises in the serum aminotransferases indicative of severe hepatitis.[9] Classical necrotizing lesions were usually present in the liver at necropsy and the adrenals and other organs were also often affected.

Reports[10-12] of primary generalized infection in adults are even less common, though since our last review[13] there have been a few more cases.[14-18] Hepatitis was mild in some of these, with slight tender enlargement only and no evidence of jaundice.[16] There is, however, one account of two patients suffering from extensive burns in whom there was evidence at necropsy of generalized herpesvirus infection and severe liver damage.[17] In three cases there were features of fulminant hepatic failure during life, though in two of these the diagnosis of a herpesvirus hominis infection was not made until after death.[14 15] In the third patient the diagnosis was confirmed during the 28th week of pregnancy by culture of a liver biopsy specimen.[12] That patient survived and was delivered of a macerated foetus. This and Goyette's case are the only two reports of a generalized herpesvirus infection during pregnancy, so it is difficult to substantiate Goyette's suggestion that pregnancy predisposes to such generalized infections because of depressed immunological responses. The differential diagnosis of a hepatitic-like illness in pregnancy must include (in addition to infection with viruses A and B) acute fatty metamorphosis, fortunately also rare. This condition, which characteristically occurs during the third trimester, may be suggested by a marked rise in serum alkaline phosphatase with only a modest increase in the aminotransferases.

In cases of fulminant hepatitis where herpesvirus hominis is suspected attempts should be made to confirm the diagnosis since specific chemotherapy is available. Scrapings from any vesicles found on the body can be examined by light microscopy for the typical intranuclear inclusion bodies, which on electronmicroscopy can be seen as virus particles. Immunofluorescent staining for the virus in a liver biopsy specimen would be specific, but biopsy may not be possible because of a prolonged prothrombin time. Vesicular fluid, blood, and any biopsy material obtained should also be cultured for the virus, though this will not give an immediate answer.

The decision to use one of the antivirus drugs that have been developed over the last few years when the diagnosis has not been established is a difficult one for the clinician. The thymidine analogue, idoxuridine, inhibits herpesvirus replication in vitro[19] and has been used with apparent success in herpes encephalitis.[20] Reports[21-23] of hepatotoxicity may be a sufficient reason to deter most clinicians from its use in a possible herpetic hepatitis. Another antiviral agent—cytarabine—has also been used to treat generalized primary infections[16] but may cause marrow suppression, and for neither drug is there as yet any controlled evidence of clinical value.[24 25]

[1] Zuckerman, A. J., in *Virus Diseases of the Liver*. London, Butterworth and Co. (Publishers) Ltd., 1970.
[2] Goyette, R. E., *et al.*, *Obstetrics and Gynecology*, 1974, **43**, 191.
[3] Andrewes, C. H., and Carmichael, E. A., *Lancet*, 1930, **1**, 857.
[4] Scott, T. F. McN., *American Journal of Ophthalmology*, 1957, **43**, 134.
[5] Zuelzer, W. W., and Stulberg, C. S., *American Journal of Diseases of Children*, 1952, **83**, 421.
[6] MacCallum, F. O., *Acta Virologica*, 1959, 3 (suppl.), p. 17.
[7] Wheeler, C. W., and Huffines, W. D., *Journal of the American Medical Association*, 1965, **191**, 455.
[8] Kipps, A., *et al.*, *South African Medical Journal*, 1967, **41**, 647.
[9] Becker, W. B., Kipps, A., and McKenzie, D., *American Journal of Diseases of Children*, 1968, **115**, 1.
[10] Kipping, R. H., and Downie, A. W., *British Medical Journal*, 1948, **1**, 247.
[11] Kilbourne, E. D., and Horsfall, F. L., *Archives of Internal Medicine*, 1951, **88**, 495.
[12] Flewett, T. H., Parker, R. G. F., and Philip, W. M., *Journal of Clinical Pathology*, 1969, **22**, 60.
[13] *British Medical Journal*, 1969, **2**, 204.
[14] Diederholm, H., *et al.*, *Acta Medica Scandinavica*, 1969, **186**, 151.
[15] Francis, T. I., Osuntokun, B. O., and Kemp, G. E., *American Journal of Gastroenterology*, 1972, **57**, 329.
[16] Juel-Jensen, B. E., and MacCallum, F. O., in *Herpes Simplex Varicella and Zoster*. London, Heinemann, 1972.
[17] Foley, F. D., *et al.*, *New England Journal of Medicine*, 1970, **282**, 652.
[18] Morris, J. A., and Nakumura, K., *American Journal of Tropical Medicine*, 1959, **8**, 723.
[19] Hermann, E. C., *Proceedings of the Society for Experimental Biology and Medicine*, 1961, **107**, 142.
[20] Nolan, D. C., Lauter, C. B., and Lerner, A. M., *Annals of Internal Medicine*, 1973, **78**, 243.
[21] Breedon, C. J., Hall, T. C., and Tyler, R. H., *Annals of Internal Medicine*, 1966, **65**, 1050.
[22] Dayan, A. D., and Lewis, P. D., *Lancet*, 1962, **2**, 1073.
[23] Silk, B. R., and Roome, A. P. *Lancet*, 1970, **1**, 411.
[24] Hirsch, M. S., Levin, M., and Chien, L. T., *Annals of Internal Medicine*, 1973, **78**, 779.
[25] *Postgraduate Medical Journal*, 1973, **49**, 572.

C.E.A. in 1974

Two years ago[1] in our review of research on the carcinoembryonic antigen we pointed out that the plasma C.E.A. test was non-specific, since moderate increases in the level could occur in a wide variety of malignant and non-malignant diseases of the gatrointestinal tract as well as in several other types of tumours. That seemed to preclude the test from being the