Non-linearity and Safety Standards for Ionizing Radiation

For a couple of decades now the recommendations of the International Commission on Radiological Protection have been based on the working hypothesis that harmful consequences of radiation exposure, such as genetic damage and cancer, increase in frequency in simple proportion to the radiation dose in the exposed tissues. Thus one major I.C.R.P. principle is to use average dose in a tissue as the basis of reference, ignoring any non-homogeneity of irradiation at the cellular level either in space or in time. If, as is often supposed, a linear hypothesis like this may overestimate risk but will not underestimate it then it is clearly a suitably conservative working theory to be going on with until more exact dose-response relationships are established. It is not, however, self-evident that linearity is always conservative when irradiation of tissue is highly non-homogeneous—for example, after inhalation of radioactive dust into the lung. Would the consequent spotty irradiation be more or less likely to cause cancer than if the whole tissue were to be exposed to the same average dose? All safety standards for radioactive contamination of the atmosphere depend on the answer for the lung, and, furthermore, the relative importance of homogeneous and non-homogeneous irradiation of tissue is a general problem for radiological protection as a whole.

Factors concerned include the number of cells irradiated, which decreases the more spotty the irradiation; the dose each irradiated cell receives (*not* the average dose per cell, which begs all the questions), which may increase the more spotty the irradiation; the relationship between dose and the probability per cell of producing the effect of concern (lung cancer in the example mentioned); and the extent to which other cellular effects of irradiation may interfere with the development and expression of the effect (for example, cell death or sterilization might prevent a very early cancer from growing). A clear head, mathematical facility, and extensive computations are essential ingredients in providing an answer, and an attempt has recently been made by Mayneord and Clarke.[1] In the absence of hard information, representative but not necessarily realistic numbers had to be used for the radiosensitivities of cells, and the results of the computations cannot be better than the ideas and the facts on which they are based. One noticeable point is that the expression $e^{-\lambda D}$ is used throughout for sterilization of cells by the less densely ionizing radiation such as *x*-rays and beta particles without acknowledgement that a shoulder is commonly to be found on the cell survival curve.[2] Nevertheless, a useful and reassuring conclusion is reached. Exposure of skin and lung to particulates containing beta-emitters may be an important practical problem in running nuclear power stations, and it turns out that the I.C.R.P. conventions are satisfactory. The difference in frequency of effect to be expected according to I.C.R.P. concepts as compared with more realistic calculations for a spotty distribution is too small to matter, even when the dose response function for carcinogenesis is assumed to be quite non-linear, for instance dependent on the square or even higher powers of the dose.

The corresponding "hot particle" problem for alpha-emitters, especially plutonium, has been a matter of great interest in the last year or two.[3] The inhomogeneity of irradiation is considerably more pronounced than for beta-emitters, and this introduces additional mathematical difficulties. The problem has been briefly and tentatively considered elsewhere[4]; perhaps a similarly rigorous mathematical analysis can be made for these alpha-emitters too.

[1] Mayneord, W. V., and Clarke, R. H., *British Journal of Radiology*, 1975, Suppl. 12.
[2] Mole, R. H., *British Journal of Radiology*, 1975, **48**, 157.
[3] Medical Research Council, *The Toxicity of Plutonium*. London, H.M.S.O., 1975.
[4] Mayneord, W. V., and Clarke, R. H., *A Mathematical Investigation into the Carcinogenic Risks Associated with Particulate Sources of Activity*. 1974, C.E.G.B. Report No. RD/B/N2878.

Candida Endocarditis

Candida endocarditis is an uncommon but grave disease, the gloomy prognosis of which became increasingly clear as reports and surveys gathered volume after the first documented[1] clinical account in 1940. Spontaneous infection seldom occurs, and in most patients the condition arises as a complication of open heart surgery, drug addiction, or antibiotic therapy for bacterial endocarditis.

A recent review[2] of the possible modes of infection and the diagnostic features of the condition stressed that the onset is often silent without fever or other systemic manifestations. The clinical picture—as with bacterial endocarditis—depends on the mechanical effects on the affected valve (natural or artificial), which may be obstructed with vegetation, and on the occurrence of embolism. The diagnosis rests primarily on positive blood cultures in Sabouraud's medium, the growth taking a minimum of ten days to appear and often three weeks or longer. Negative cultures for bacteria do not imply that the infection is fungal, nor does failure to obtain a growth of fungus exclude this diagnosis. Serological tests[3] with rising titres of candida precipitins or agglutinins provide earlier evidence of infection, but opinions differ as to their reliability.[2 4 5] Occasionally proof may be obtained by a biopsy of marrow or from material removed at embolectomy, which should be preserved for microscopy and culture.

Antibacterial agents are valueless in fungal endocarditis, for which the most widely used drug is amphotericin B. This is said to be fungistatic rather than fungicidal; it requires intravenous administration and is slowly excreted by the kidneys. There are many side effects, of which the nephrotoxic action is the most serious. A more recent antifungal agent, 5-fluorocytosine, has the advantage of oral administration. Its half life in the body is four to eight hours, and like amphotericin B it is fungistatic and excreted mainly in the urine. Marrow depression and hepatic damage have been reported.[6]

Earlier surveys,[7–11] usually from cardiac surgical centres, emphasized the high mortality of the condition, Kay and colleagues in 1968 finding only six survivors out of 52 patients in accounts in English language journals. A useful report[12] from the same unit in Los Angeles has brought the story up to date with a total of 116 patients with fungal endocarditis (candida species in 91, aspergillus in 15, other or unidentified organisms in 10). In order of frequency the aortic valve was infected most often (58%), then the mitral (30%), aortic and mitral together (10%), and tricuspid (9%). To these 116 patients the authors added a further 15 of their own with candida endocarditis. Their analysis of the outcome of the disease in relation to the treatment employed showed a mortality of 100% with no treatment and a mortality of 82% when either chemotherapy or surgery was used alone. The encouraging part of their report lies in the considerably better

results obtained when antifungal drugs were combined with surgery. Taking nine patients managed this way from published reports together with 11 of their own the mortality was 20%.

The Los Angeles team advocate surgery within 48 hours of diagnosis (thus minimizing the time during which the organism may grow into the myocardium), with removal of the infected valve and irrigation of the infected site with a solution of amphotericin B (1 g per litre of Ringer's solution) for a period of 15 minutes before the prosthetic valve is inserted. After operation they recommend a prolonged course of amphotericin B given intravenously in a dose of 10 mg increasing to 50 mg if tolerated, three times weekly, possibly up to a total dose of 2 500 mg.

Experience of this condition has shown that its diagnosis constitutes a surgical emergency, and that few patients will survive with chemotherapy alone.

[1] Joachim, H., and Polayes, S. H., *Journal of the American Medical Association*, 1940, **115**, 205.
[2] Seelig, M. S., *et al.*, *Progress in Cardiovascular Diseases*, 1974, **17**, 125.
[3] Ouchterlony, O., in *6th International Congress for Microbiology*, vol. 11, p. 276. Rome, 1953.
[4] Remington, J. S., Gaines, J. D., and Gilmer, M. A., *Lancet*, 1972, **1**, 413.
[5] Hellwege, H. H., Fischer, K., and Blaker, F., *Lancet*, 1972, **2**, 386.
[6] Record, C. O., *et al.*, *British Medical Journal*, 1971, **1**, 262.
[7] Kay, J. H., *et al.*, *Journal of the American Medical Association*, 1968, **203**, 621.
[8] Braimbridge, M. V., *Lancet*, 1969, **1**, 1307.
[9] Chaudhuri, M. R., *Journal of Thoracic and Cardiovascular Surgery*, 1970, **60**, 207.
[10] Engelman, R. M., *et al.*, *Annals of Surgery*, 1971, **173**, 455.
[11] Seelig, M. S., *et al.*, *Journal of Thoracic and Cardiovascular Surgery*, 1973, **65**, 583.
[12] Turnier, E., *et al.*, *Chest*, 1975, **67**, 262.

Restrictions on Coroners' Juries

A Bill is to be introduced into the House of Commons to abolish the duty of coroners' juries to return verdicts of murder or manslaughter against a named individual and the coroner's duty to commit that person for trial. Lord Wells-Pestel, speaking for the Government, announced this in the Lords last week.[1]

Everyone with a concern for justice will welcome this long overdue proposal. It is a centuries-old duty of a coroner's jury in cases of murder, manslaughter, and infanticide to name the person they consider to have been guilty of the crime, and the coroner has a consequential duty to commit him for trial. The Brodrick report[2] did no more than reflect the common opinion today in its condemnation of this procedure. The difficulty of ensuring a fair trial for a person who has already had a verdict of guilty hung round his neck has long been acknowledged. Furthermore, the coroner's jury often reaches its verdict on evidence that would never be allowed in a criminal court.

Several recent cases have focused attention again on this mediaeval anachronism, not least the one concerning two doctors discussed by our Legal Correspondent in the *B.M.J.* three weeks ago.[3] The inquest was on a boy of 2 years who had died after an operation for peritonitis. Both doctors told the coroner they had diagnosed gastroenteritis. After a three-day inquest the jury returned a verdict of manslaughter and the coroner committed the two doctors for trial on the charge.[4] When the trial came on the Crown offered no evidence against them and they were discharged. But the ordeal to which they had been subjected included having to face in the coroner's court what the Medical Defence Union[3] described as "a mass of evidence which was highly prejudicial and clearly inadmissible in any criminal court or even in a civil court."

It is to prevent the repetition of injustices of this kind that the Bill deserves a swift passage.

[1] *House of Lords Hansard*, 23 July 1975, col. 324.
[2] *Report of the Committee on Death Certification and Coroners*, Cmnd. 4810. London, H.M.S.O., 1971.
[3] *British Medical Journal*, 1975, **3**, 108.
[4] *British Medical Journal*, 1975, **2**, 287.

Aetiology of Optic Neuritis

The aetiology of optic neuritis continues to cause uncertainty. The proportion of patients whose first symptom of neurological disease is optic neuritis and who later develop symptoms and signs of definite multiple sclerosis has variously been reported[1 2] to lie between 11·5% and 85%. In a further large series of studies of cases of optic neuritis reported from Finland, 50% were reported to develop probable multiple sclerosis during an average follow-up period of 10 years.[3 4] If, then, only a proportion of patients with optic neuritis later develop indications of multiple sclerosis it would be helpful for prognosis to have some test to distinguish them.

Many centres have reported that antibodies to measles (and to a lesser extent other viruses) are increased both in frequency and in level in the serum of patients with multiple sclerosis when compared with controls. Similarly, patients with multiple sclerosis[5–7] have a higher incidence and higher levels of measles antibodies in the cerebrospinal fluid and a decreased ratio of serum/C.S.F. antibody levels. Link *et al.* (1973)[8] were able to divide their patients with optic neuritis into two groups on the basis of the presence of oligoclonal IgG in the C.S.F., which is commonly found in multiple sclerosis patients. The implication is that multiple sclerosis is likely to develop in patients with optic neuritis whose C.S.F. shows changes like those found in multiple sclerosis. Such a postulate cannot, however, be accepted until proved by careful follow-up. Arnason *et al.*[9] studied HL-A and other antigens in patients with optic neuritis and multiple sclerosis and suggested that the two conditions had differing genetic backgrounds; but a recent study has been unable to confirm these findings.[10]

These theoretical possibilities should not be allowed to obscure the practical points of importance. By no means all cases of optic neuritis are due to multiple sclerosis, and a number of other causes, particularly in the older patients, should be remembered. These include diabetes, pernicious anaemia, optic nerve compression, chronic meningitis, and vascular diseases including arteriosclerosis and arteritides.[3 11–13] It is also worth remembering that multiple sclerosis has an overall prognosis which is relatively milder than was once believed,[14] and that patients with multiple sclerosis originally presenting with optic neuritis have an even better prognosis for mortality and disability.[15–17]

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[4] Nikoskelainen, E. Dissertation to the Medical Faculty of the University of Turku, 1975.
[5] Winchester, J. S., and Hambling, M. H., *Journal of Medical Microbiology*, 1972, **5**, 137.
[6] Salmi, A. A., *Annals of Clinical Research*, 1973, **5**, 319.