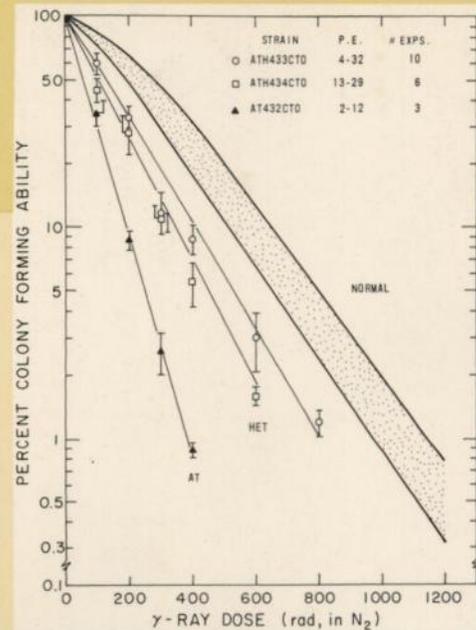
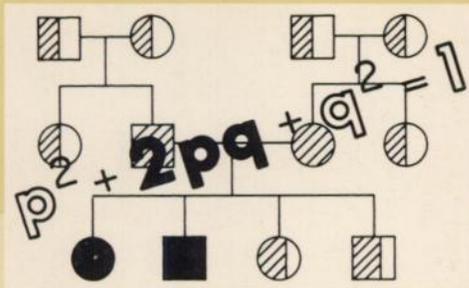
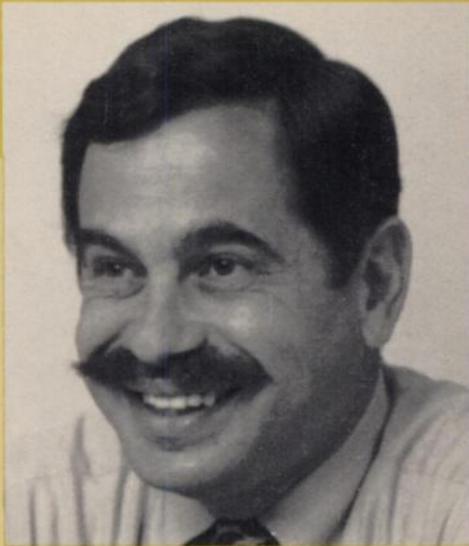




# Cancer Research

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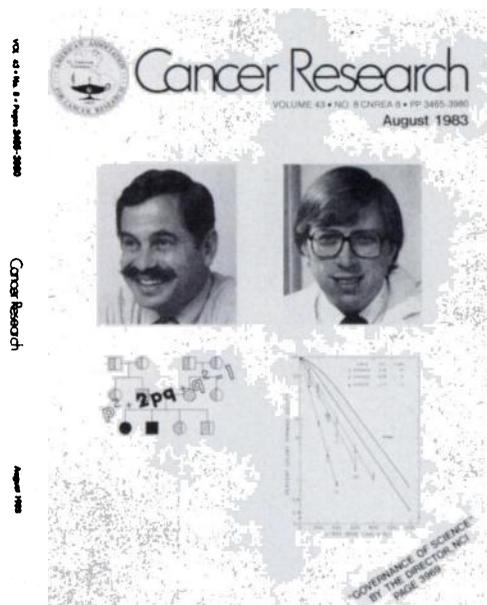
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"GOVERNANCE OF SCIENCE"  
 BY THE DIRECTOR, NCI  
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# COVER LEGEND

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Although genetic predisposition is widely recognized to play an important role in many cancers, it has been difficult to identify and characterize the genes involved. In 1971, Dr. Michael Swift proposed that genes which cause certain autosomal recessive syndromes associated with cancer (e.g., Fanconi's anemia) may also be cancer predisposing in heterozygotes (Nature, 230: 370, 1971). Since heterozygous carriers of these genes are relatively common, according to the genetic principle known as the Hardy-Weinberg principle (*lower left*), he argued that a substantial proportion of human cancer predisposition might be identified through these autosomal recessive syndromes.

Swift has studied the incidence of cancer in families of patients with Fanconi's anemia, ataxia-telangiectasia (AT) (Cancer Res., 36: 209, 1976), and xeroderma pigmentosum (XP) (J. Natl. Cancer Inst., 62: 1415, 1979). In families of XP patients, Swift found an excess

of skin cancers and suggested that some XP heterozygotes are predisposed to skin cancer. The most striking cancer excess was in the AT families. Since AT heterozygotes may comprise 1% or more of the population, he stated that genes for AT may be of substantial importance in genetic predisposition to cancer.

When the lymphoma in AT homozygotes is treated with conventional doses of radiotherapy, a marked acute radiation reaction may occur (Cunliffe *et al.*, Br. J. Radiol., 48: 374, 1975). *In Vitro* study of skin fibroblasts from patients with AT exhibit marked radiosensitivity as indicated by impaired clonal survival (Taylor *et al.*, Nature, 258: 427, 1975). Dr. Malcolm C. Paterson of Atomic Energy of Canada, Ltd., showed in 1976 that susceptibility to  $\gamma$ -radiation was due to a DNA repair defect (Nature, 260: 444, 1976). This finding was the  $\gamma$ -ray analogue of the DNA repair defects in XP cells after exposure to ultraviolet light (UV). The DNA repair defects in these two genetic disorders are nonoverlapping. The DNA in fibroblasts from patients with XP is repaired normally after exposure to  $\gamma$ -radiation. DNA in fibroblasts from patients with AT is repaired normally after exposure to UV. These observations are important in understanding the fundamental biology of carcinogenesis and possibly aging. Paterson (Cancer Res., 39: 3725, 1979) and others subsequently reported that, in AT heterozygous cells, DNA repair is intermediate between normal and the marked reduction seen in cells from homozygotes, even though carriers are clinically normal (*lower right*).

These clinical and laboratory findings demonstrate how genetic and environmental factors may interact in cancer pathogenesis.

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M. B. S.