

Swift M R & Hirschhorn K. Fanconi's anemia: inherited susceptibility to chromosome breakage in various tissues. *Ann. Intern. Med.* 65:496-503, 1966. [Depts. Neurology and Medicine, New York Univ. Medical Center, New York, NY]

This paper reported frequent chromosome breaks in lymphocytes, cultured skin fibroblasts, and possibly bone marrow in homozygotes with the rare autosomal recessive syndrome Fanconi anemia. It also called attention to the occurrence of two squamous cell carcinomas in one patient. [The SC¹® indicates that this paper has been cited in over 150 publications since 1966.]

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"In 1964, when I was a postdoctoral fellow in genetics with Kurt Hirschhorn in the department of medicine at New York University School of Medicine, Eleanor Ball asked me to see a patient on the dermatology service of Bellevue Hospital because a note from a previous hospitalization stated that the patient had 'wild chromosomes.'¹ This was my first encounter with a patient with Fanconi anemia (FA), which is one of a small group of rare autosomal recessive cancer-prone syndromes which are of considerable interest because of the insight they can offer into cancer predisposition and pathogenesis.

"In 1967, I was surprised when I, as a junior faculty member at NYU, was asked to discuss FA at medical grand rounds, since Hirschhorn and Fanconi himself had reviewed this rare disease very thoroughly in the previous two years. In seeking a fresh approach to this topic, I chose to explore the idea that heterozygous carriers of the FA gene, who are, according to the Hardy-Weinberg principle, common in the population, might express some of the cancer predisposition so manifest in homozygotes, and thus could constitute an important propor-

tion of persons in the general population who are genetically cancer-prone.

"The enthusiastic response of my colleagues to this theoretical proposal led me to design a small-scale family study to see if there was indeed an excess of cancer in the families of patients with FA.² Even now, however, it is not clear whether or not the FA heterozygote has an excess risk of cancer at certain sites, since in 25 FA families the mortality rates for blood relatives at those sites were only slightly higher than those in the general US population, while they were substantially higher than the rates in spouse controls from the same families.³

"A general principle then became evident: a substantial proportion of genes predisposing to common diseases might be identified and studied through the specific rare autosomal recessive syndromes they caused in homozygotes.⁴ It is surprising that this principle had not been recognized earlier, since Penrose in 1927 had proposed that the PKU heterozygote is predisposed to mental illness.⁵ Hypotheses about heterozygote predisposition to common diseases can be difficult to test if there is no laboratory procedure or clinical criterion to identify the gene carriers. By studying disease incidence in families of probands with selected autosomal recessive syndromes, we have extended the methods originally used for FA to identify genes for mental retardation, birth defects, diabetes, and heart disease, as well as cancer. From an accidental encounter with a patient with this rare recessive syndrome has evolved a general approach to analyzing genes for common diseases.

"It is likely that this article has been cited frequently because it was the first to show that chromosome breakage is found in all tissues studied and therefore represents something close to the primary defect in FA. It has also been cited because it was one of the first to call attention to the occurrence of squamous cell carcinomas in FA. There are recent articles documenting how frequently such cancers occur in FA homozygotes."⁶

1. Schroeder T M, Anshultz F & Knopp A. Spontane Chromosomenaberrationen bei familiärer Pannmyelopathie. *Humangenetik* 1:194-6, 1964. (Cited 185 times.)
2. Swift M. Fanconi's anemia in the genetics of neoplasia. *Nature* 230:370-3, 1971. (Cited 140 times.)
3. Swift M, Caldwell R & Chase C. Reassessment of cancer predisposition of Fanconi anemia heterozygotes. *J. Nat. Cancer Inst.* 54:863-7, 1980.
4. Swift M, Coben J & Plinkham R. A maximum-likelihood method for estimating the disease predisposition of heterozygotes. *Amer. J. Hum. Genet.* 26:304-17, 1974.
5. Penrose L S. Inheritance of phenylpyruvic amentia (phenylketonuria). *Lancet* 2:192-4, 1935.
6. Kennedy A W & Hart W R. Multiple squamous-cell carcinomas in Fanconi's anemia. *Cancer* 50:811-14, 1982.