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ÜBERSICHT

The minute Chromosome (Ph¹) in chronic granulocytic Leukemia*

Recently a consistent specific chromosome abnormality has been demonstrated in association with one form of human leukemia, chronic granulocytic leukemia. This abnormality, the Philadelphia chromosome (Ph¹), was named for the city in which it was discovered, and its existence has since been confirmed by workers in several countries. It is a minute chromosome, apparently derived from a chromosome 21 through the loss of a portion of the long arm of this small acrocentric autosome.

The Ph¹ chromosome may be present in the leukemic cells of every case of typical chronic granulocytic leukemia. The few cases in which it has not been observed probably represent instances in which adequate samples of dividing myeloid cells were not obtained. Since the chromosome is not present in all of the patient's cells, but only in the leukemic ones, its demonstration requires that dividing leukemic cells be obtained from peripheral blood (by culture methods) or from bone marrow.

The Ph¹ chromosome has not been observed in any other form of leukemia or in any normal individual. Its consistency and specificity with respect to chronic granulocytic leukemia suggests that it is the cause of the neoplastic state in this disease. It has been suggested that the pathogenesis of chronic granulocytic leukemia may be as follows: A mutagenic agent damages a chromosome 21 in a myeloblast in an individual's marrow so as to produce a cell containing the Ph¹ chromosome. The genetic alteration in this cell confers upon it a slight competitive growth advantage over adjacent normal myeloblasts. As a result of this advantage, progeny of the abnormal cell,

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bearing the Ph¹ chromosome, eventually overgrow the normal hematopoietic tissues and produce the clinical and hematological picture of chronic granulocytic leukemia.

From a clinical standpoint, the Ph¹ chromosome has proved of little value as a diagnostic tool. Its presence is limited to typical cases of chronic granulocytic leukemia. It is not found in the myeloproliferative syndrome (polycythemia vera, myelofibrosis, myeloid metaplasia) or other atypical myeloid disorders which may present diagnostic problems. The fact that it is not found in these atypical disorders indicates that they are fundamentally different from chronic granulocytic leukemia, although some hematologists have considered such disorders to be variants or precursors of the latter disease.

The Ph¹ chromosome is the first example of a consistent specific chromosome change associated with a human neoplasm. Such chromosome changes as have been observed in other leukemias and in solid tumors have not been consistent from case to case. It is generally felt that such inconstant changes may play a role in the *progression* of malignant tumors in individual patients, but that they probably do not represent the genetic change which *initiated* the neoplasm. The fact that a consistent chromosome abnormality has been observed only in chronic granulocytic leukemia does not rule out the possibility that the initial change in other tumors may involve the chromosomes; it may simply mean that the fundamental alteration in the genetic apparatus is too small to be demonstrated by our present, relatively crude techniques. No general statement as to the significance of chromosome alterations in the initiation of neoplasia will be possible until more refined techniques have been utilized to examine a wide spectrum of primary malignant tumors.

Meanwhile, since chronic granulocytic leukemia is the one human neoplasm in which chromosome studies reveal a specific *genetic* difference between the normal and malignant cells, and since it involves numerous gene loci, it seems logical that this disease should be most intensively studied for a specific therapeutically-exploitable *immunological* or *biochemical* difference. Unfortunately, although a specific biochemical abnormality has already been demonstrated in the cells of chronic granulocytic leukemia, decreased alkaline phosphatase, it has not been possible to utilize this difference for therapeutic purposes.

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